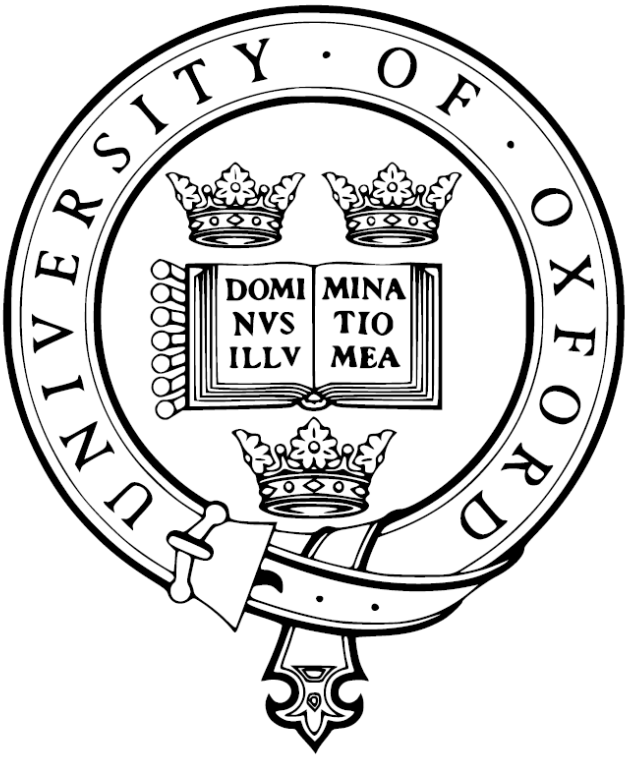
Catalytic Reductive Cyclisation of Amides Using Vaska's Complex



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

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Trinity Term 2020

In memory of my grandparents, Christiane (Mamie) and Claude (Papou).

Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2016 until December 2019, under the supervision of Professor Darren J. Dixon. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



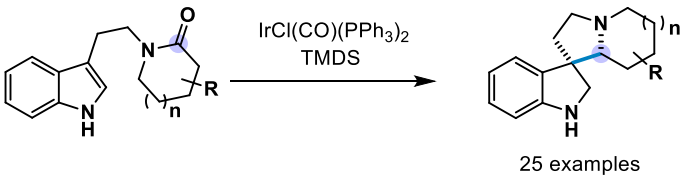
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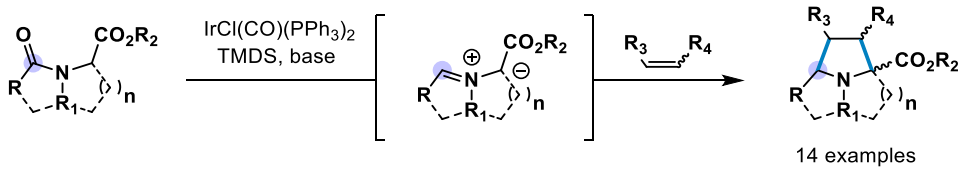
Abstract

Chapter 1 introduces tertiary amines, and the main strategies available for their synthesis. Vaska's complex is introduced, and its recent use for the reduction of tertiary amides and lactams is exhaustively described.

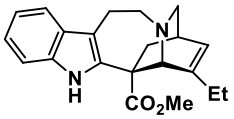
Chapter 2 details the development of a spirocyclisation methodology from indole-tethered tertiary amides and lactams. The selectivity observed and the broad substrate scope make it a method of choice for the synthesis of spirocyclic indolines.



Chapter 3 describes the development of a cycloaddition methodology, based on accessing azomethine ylides from tertiary amides and lactams, and reacting these 1,3-dipoles with a range of dipolarophiles, generating polycyclic amines. It is of value for the synthesis of polysubstituted pyrrolidine ring-containing amines.



Chapter 4 details the investigations towards the design and application of a synthetic sequence leading to the total synthesis of a pentacyclic alkaloid, catharanthine. Previous syntheses are described, before model studies establish the feasibility of an IMDA cascade sequence triggered with Vaska's complex. The natural product synthesis is then described.



Chapter 5 details our efforts towards making the previously described methodologies amenable to large scale, and why they should be particularly attractive for industrial applications. Finally, preliminary results for the synthesis of new Vaska-type Iridium complexes for the reduction of non-tertiary amides functional groups are described.

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Coming to the end of these four years, there are many people I would like to thank.

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Of these people, I should thank again Mix, Jamie, Thomas, Tanya, Connor, Yao, Ben, and Darren, your help in proofreading this work was precious. Finally, I know these acknowledgements are – as can be life – a little rambling and incoherent. It is so you can read the first word of each line to be transported back.

I'll now switch to French for the last people I need to thank.

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Abbreviations

(+)	Dextrorotary
(−)	Levorotatory
δ	NMR chemical shift
Δ	Heat
ν_{max}	Infrared absorption maximum
Ac	Acetyl
AIBN	Azobisisobutyronitrile
app	Apparent
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bpy	2,2'-Bipyridine
br	Broad
Bz	Benzoyl
cat	Catalytic
Cbz	Carboxybenzyl
cod	1,5-Cyclooctadiene
COSY	COrrelation SpectroscopY

cy	Cyclohexyl
δ	Delta
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCE	1,2-Dichloroethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
$dFCF_3$	3,5-Difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl
DIBAL-H	Diisobutylalumnium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dr	Diastereomeric ratio
dt	Doublet of triplets
dtbbpy	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
dtd	Doublet of triplet of doublets

dtdd	Doublet of triplet of doublet of doublets
E	Entgegen
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ent	Enantiomer
epi	Epimer
ES	Positive electrospray
et al.	*et alia*
equiv.	Equivalents
fac	Facial
FCC	Flash Column Chromatography
FT	Fourier transform
g	Grams
GII	Grubbs catalyst 2nd generation
HAT	Hydrogen Atom Transfer
hept	Heptuplet
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HGII	Hoveyda–Grubbs catalyst 2nd generation
HMBC	heteronuclear multiple bond coupling
HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography

HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coupling
HWE	Horner–Hadwsworth–Emmons
IBX	2-Iodobenzoic acid
IMDA	Intra Molecular Diels Alder
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	Coupling constant
LDA	Lithium Diisopropylamide
m	Multiplet
m	Meta
M	Molar
M	Mega
m/z	Mass to charge ratio
MOM	Methoxymethylether
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
n	Nonuplet
N	Normality
NIS	*N*-Iodosuccinimide

NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	Nucleophile
o	Ortho
p	Para
p	pentet
Piv	Pivaloyl
PMHS	Polymethylhydrosiloxane
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
ppy	Polypyrrole
prep	Preparative
pyr	Pyridine
q	Quartet
qd	Quartet of doublets
qt	Quartet of triplets
quant.	Quantitative
R	Rectus
R	Unspecified organic group

RCM	Ring-Closing Metathesis
rr	Regioisomeric ratio
Red-Al	Sodium bis(2-methoxy)aluminium hydride
rt	Room temperature
s	Singlet
S	Sinister
sept	Septuplet
STAB	Sodium triacetoxyborohydride
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
tdd	Triplet of doublet of doublets
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin layer chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl

T_3P	Propanephoponic acid anhydride
Ts	*para*-Toluenesulfonyl
TS	Transition state
tt	Triplet of triplets
UV	Ultraviolet
w	Weight
Z	Zusammen

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Chapter 1 : Introduction

1.1 Amines and amides

1.1.1 Nitrogen: from stars to life

All matter of the macroscopic world exists as an assembly of atoms, almost entirely made in the burning cores of stars all over the universe. Nuclear fusion of hydrogen produces the gigantic amount of energy that allow us to observe their light, billions of light-years away from Earth. The hydrogen, generated in the first minutes after the Big Bang, is consumed in processes such as the proton-proton chain, the triple-alpha process, or CNO cycles, generating most of the small elements ($6<Z<26$) of the periodic table. This last set of fusion reactions, the CNO cycles, are responsible for the production of helium and energy in diverse forms, from hydrogen. Nitrogen atoms are made in large number in the CN cycle of the CNO reactions - mostly in stars whose core is slightly hotter than our Sun's - and is the 7th most abundant element of the universe.[1]

It has been crucial for life's emergence on earth, where, through the nitrogen cycle, nitrogen gas in the atmosphere is converted into ammonia by bacteria in the soil, which is in turn transformed and incorporated in amino acids and proteins, essential building blocks for life. It is thus unsurprisingly part of the four basic organic elements: with hydrogen and oxygen constituting the water in our body, and carbon comprising lipids, carbohydrates, and amino acids, proteins, and nucleic acids when associated with nitrogen atoms.

1.1.2 Nitrogen-containing molecules: structure and reactivity

Among the organic compounds incorporating nitrogen atoms, two classes in particular are of great importance.

On one hand there are amines, formal derivatives of ammonia where the hydrogens atoms have been replaced by a carbon-based substituent. The lone pair of electrons centred on the nitrogen atom, combined with an electronegativity lower than that of chalcogens or halogens, makes amines Lewis and Brønsted basic. Amines exist in the human body at the *N*-terminus or side chain of amino acids or in neurotransmitters: histamine **1** is involved in the inflammatory response, epinephrine **2** (also known as adrenaline) regulates visceral functions such as heart and respiration rate in hazardous situations, while serotonin **3** is often associated with the feeling of well-being and happiness.

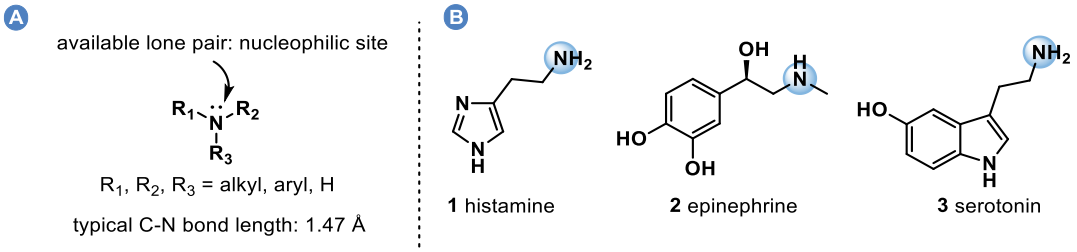


Figure 1. **A**. General amine structure and **B**. amine neurotransmitters

On the other hand, there are amides, comprised of an electron-withdrawing carbonyl placed adjacent to a nitrogen atom, which allows for the delocalisation of the nitrogen lone pair of electrons. This leads to partial double-bond character (C–N bond length of 1.33 Å vs 1.47 for amines) making the C–N bond of an amide remarkably strong, at the expense of reduced intrinsic basicity (and consequently, reactivity), making the amide carbonyl the least electrophilic in carboxylic acid derivatives reactivity scale (see **Figure 2**) This structural motif is famous for its essential role in living bodies: proteins are macromolecular polymers comprised of amino acid units linked by peptide bonds (another name for the

C–N bonds of an amide functional group) and can range from fifty to hundreds of thousands of amino acids building blocks. Smaller assemblies also exist, and are called polypeptides (for instance tripeptide glutathione **4**).

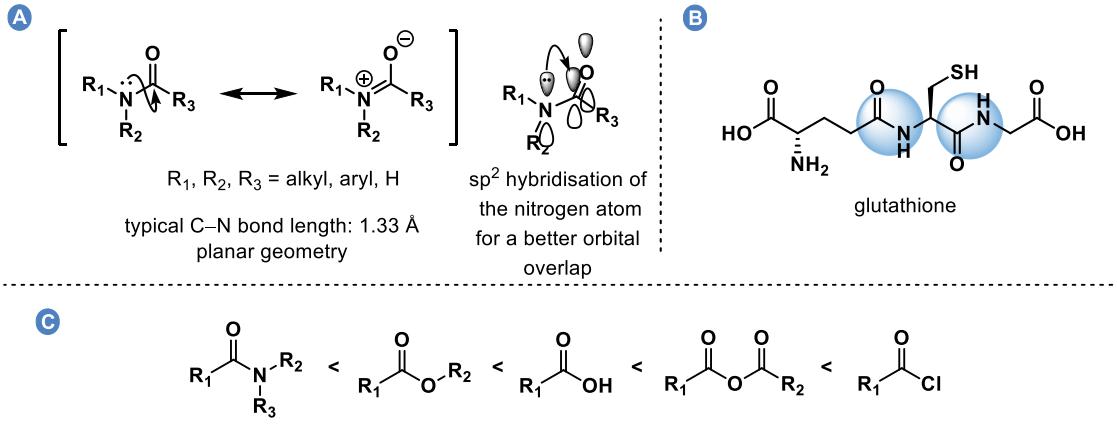
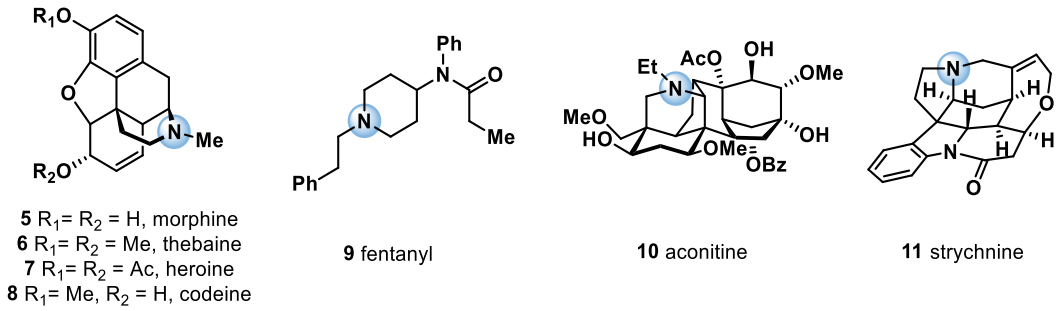


Figure 2. **A**. General amide structure **B**. Glutathione, a tripeptide **C**. Reactivity scale of carboxylic acid derivatives towards nucleophilic attack

1.1.3 Occurrence of tertiary amines in nature and in synthetic organic chemistry

Amines, in particular tertiary amines (possessing three alkyl/aryl group on the nitrogen atom) are exceptionally important compounds in traditional medicine, as they generally display bioactivity against a wide range of diseases and conditions. They have played an historic role in all civilizations, from the Mayas to the Chinese, the Romans, ancient Greeks, and as far back as the Assyrians: extracted from plants, traditional medicines have been using them for the preparation of remedies for thousands of years. Certain classes of alkaloids (naturally occurring compounds containing a basic nitrogen atom, very often a tertiary amine functional group), such as the opiate family, have been reported to be consumed as recreational drugs as early as 3000 BC,[2] almost concurrently with the invention of writing itself. From naturally abundant morphine **5**, present in large quantities in opium (extracted from poppies), and its

numerous derivatives (**6**-**8**, **Figure 3**), to the very recent potent man-made fentanyl **9**, opioids, for instance, have shaped many aspects of modern society.



5 R_1= R_2 = H, morphine
6 R_1= R_2 = Me, thebaine
7 R_1= R_2 = Ac, heroine
8 R_1= Me, R_2 = H, codeine

9 fentanyl

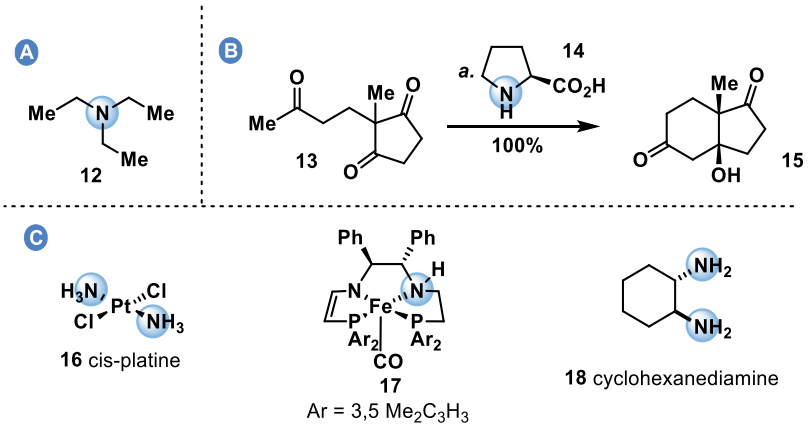
10 aconitine

11 strychnine

Figure 3. Tertiary amines in naturally-occurring and synthetic organic compounds

Even today, when they are not used directly as active pharmaceutical ingredients (such as aconitine **10** for the treatment of rheumatisms, neuralgia, or even strychnine **11** for eye disorders), alkaloids are a fantastic source of inspiration for the design of drug leads.[3] In some natural product families, they are embedded in a complex polycyclic structure making them attractive targets for total syntheses.

In synthetic organic chemistry, the Brønsted and Lewis basicity of amines leads to a range of uses as soluble organic bases (triethylamine being arguably the most common), but also in applications ranging from organocatalysis (for secondary amines in particular, see L-proline **14** in the Hajos-Parrish-Eder-Sauer-Wiechert reaction **Scheme 1**, **B**)[4] to transition metal catalysis, where they can be useful ligands for transition metal complexes, such as in cis-platin, or in Fe and Cu-based catalysis (**Scheme 1**, **C**).[5, 6]



Reagents and conditions: (a) **14** (3 mol%), DMF, rt, 20 h, 100%

Scheme 4. Amines in organic chemistry: **A**. Brønsted base, **B**. organocatalyst, **C**. ligand

1.2 Synthesis of tertiary amines

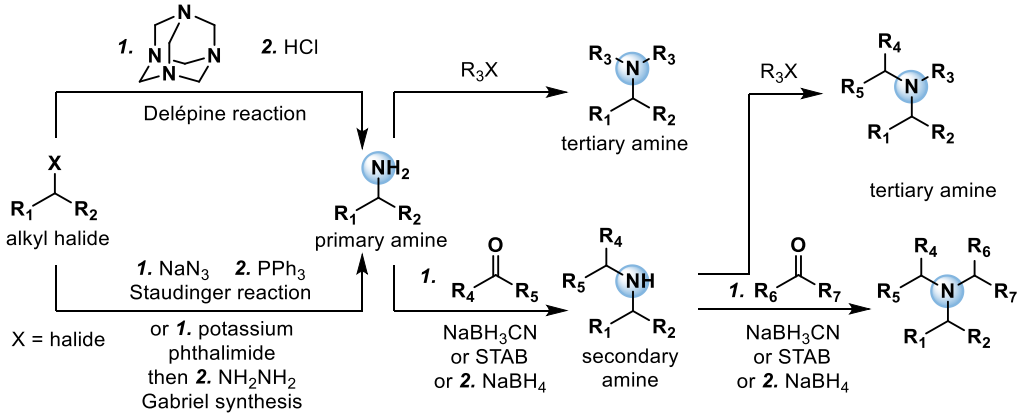
Amines, in particular tertiary amines thus find use in our everyday life, as drugs, but also agrochemical products, or dyes. In organic synthesis, their desirability for their unique basic properties resulted in numerous strategies being developed to access them, whether to make simple amine building blocks, or for their incorporation at a late stage in a complex structure.

The following section will describe, non-exhaustively, the main strategies for the synthesis of amines (in particular, tertiary amines) from other functional groups.

1.2.1 Early approaches

A number of named reactions were developed in the first half of the 20th century for the introduction of a primary amine, often from an alkyl halide: the Delépine reaction for instance is a direct approach,[7] while the Gabriel amine synthesis or the Staudinger reaction proceed via a phtalimide or an azide respectively (**Scheme 2**).[8,9] These produce a primary amine, which can be alkylated through direct *N*-

alkylation (though polyalkylation might be an issue), or very commonly by condensation with an aldehyde or ketone, followed by a borohydride-mediated reduction. Over the past three decades, *N*-arylation reactions have been made possible by reactions such as Buchwald-Hartwig or Chan-Lam couplings.[10,11]

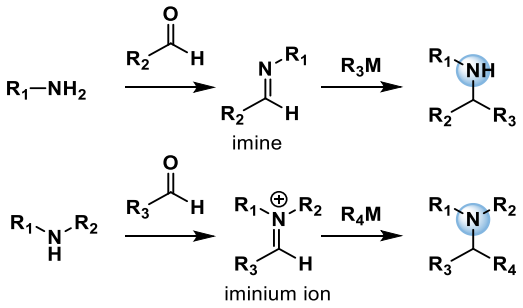


Scheme 2. Traditional named reactions approach for the synthesis of primary amines, and tertiary amines downstream

1.2.2 Imine/Iminium ion as electrophiles

A very common access point to α-branched secondary and tertiary amines is the interception of an imine or an iminium ion during condensation of an amine and an aldehyde (ketones are seldomly used due to decreased reactivity both in the ketimine formation and its subsequent reaction) with a carbon-based nucleophile such as a Grignard or an organolithium reagent. This strategy is especially useful early in a synthesis, to rapidly assemble building blocks and increase complexity in a convergent approach.[i]

[i] A modern twist of this type of assembly is the reductive generation of an α-amino radical from the imine in order to allow coupling to an electrophilic coupling partner in an umpolung approach.[12]

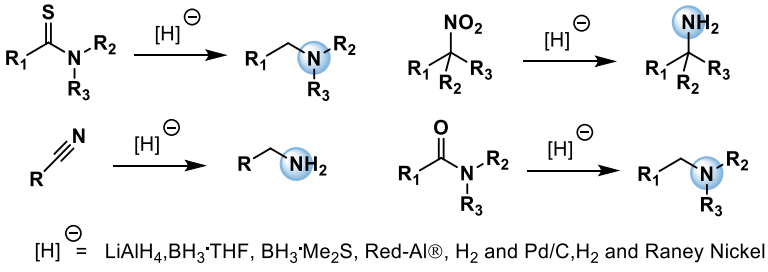


Scheme 3. Imines and iminium ions as amine precursors

1.2.3 Reductive approach

In line with the Staudinger strategy, where the azide is introduced as a nucleophile and subsequently reduced, thioamides, nitriles or nitro groups can also be incorporated in a structure (via cyanides or nitronates, respectively in a nucleophilic substitution, or a Henry reaction for example), and reduced to the corresponding amine. The reduction conditions usually require the use of super-stoichiometric metal-hydride reagents, such as (but not limited to) $LiAlH_4$, BH_3·THF, BH_3·Me_2S, Red-Al, or hydrogen in conjunction with Raney nickel or palladium on charcoal.

Finally, tertiary amides or lactams can be reduced to the corresponding amine using any of the above hydride reagents. This method is particularly powerful as it can allow direct access to tertiary amines. This approach does however usually require particularly harsh conditions, typically elevated temperatures in ethereal solvents with a less than ideal safety profile.



Scheme 4. Reduction of nitro, nitrile, and amides for the synthesis of amines

The fact that amides contain the least electrophilic carbonyl in the carboxylic acid derivative series (see **Figure 2**, **C**) means that a chemoselective reduction of amides over other carbonyl-containing compounds (including ketone, aldehydes, and carboxylic acid derivatives) is not possible without prior protection of the more reactive functional group, or subsequent reoxidation to the carbonyl, damaging the redox-economy principle.

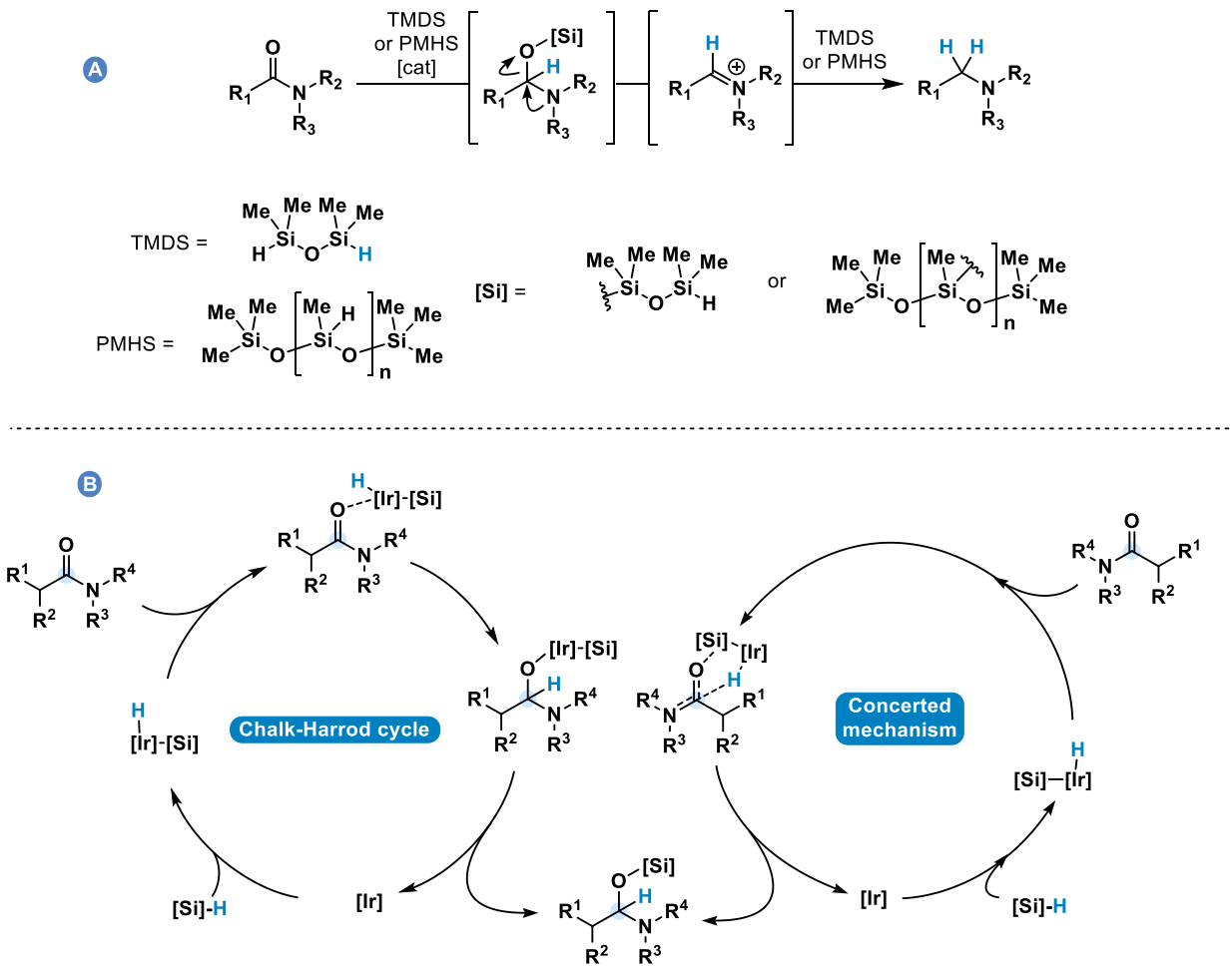
1.2.4 Transition metal-catalysed reduction of amide functionality

In the latter part of the 20th century (namely the 1980's and the 1990's), the acceleration of transition metal catalysis research - combined with the emergence of silane reagents - allowed the development of the hydrosilylation reaction for ketones, esters, and aldehydes carbonyls. This reaction can be catalysed by several transition metals: Cu,[13] Ir,[14] Mo,[15] Rh,[16] Ru,[17] Ti,[18] and Zn were all found to be viable.[19]



Scheme 5. General ketone or aldehyde hydrosilylation

Advances in the field then allowed new reactivity that could target the amide carbonyl, and the transition metal-catalysed reduction of amides to amines was developed mainly in the 2010's. Co,[20] Cu,[21] Fe,[22] Mo,[23] Rh,[24] Ru,[25] and Zn were however all shown to be able to catalyse this transformation.[26] In these examples, use of a "dual silane" containing two proximal Si–H bonds imparted increased activity.[27] Particularly, tetramethyldisiloxane (TMDS, see **Scheme 6**, **A**) and its polymeric counterpart poly(methylhydroxysilane) (PMHS) have emerged as reagents of choice.[28]



Scheme 6. Amide exhaustive reduction with silane reagents and a transition metal catalyst.

Among these transition metal complexes, one catalyst stood out as it was particularly chemoselective for tertiary amides over all other carbonyls: Vaska's catalyst, an iridium complex.[29] Due to the mild reaction required for the hydrosilylation (in particular reactions are run at rt where other systems required higher temperatures), it is also the first complex to grant access to intermediates in the reduction. All other catalytic systems only afforded the fully reduced amine product due to the instability of these intermediates at the high temperature required for their formation.[30]

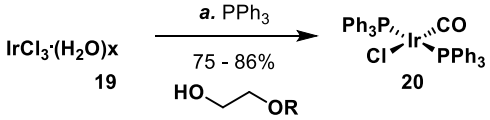
Though the mechanism is not fully elucidated, two possibilities exist (**Scheme 6**, **B**). On one hand, a traditional Chalk-Harrod mechanism could, after oxidative addition of the active Iridium species in the reactive Si–H bond, coordination of the amide species, and reductive elimination, give rise to the silylated hemiaminal species. On the other hand, the mechanism could also be a concerted or semi-concerted hydride delivery and O–Si bond formation, due to the partial positive and negatives charges that would

exist after oxidative addition on the Silicon and Hydrogen atom respectively. In both of these mechanisms, the lewis basicity of the amide is key and explains the chemoselectivity of the transformation.

1.3 Use of Vaska's complex in the reduction of amides

1.3.1 Vaska's catalyst

In 1961, the research into transition metal was booming, and Estonian-American chemist Lauri Vaska was trying to synthesize new Iridium complexes by reaction between the hydrated form of $IrCl_3$ **19** and various ligands (PPh_3, $AsPh_3$, $SbPh_3$). He first reported the formation of hydrido complexes of iridium when reacted in alcohol at room temperature,[31] and when the reaction was heated, he observed the incorporation of a carbonyl, originating from the alcoholic solvent, in the iridium complex **20**.[32]



Reagents and conditions: (a) PPh_3 (excess), R=$CH_2CH_2OCH_3$, 190 °C, 2 h, 86%, R=H, 190 °C, 7 h, 75% R=CH_2CH_2OH, 240 °C, 2 h, 76%, R=$CH_2CH_2OCH_2CH_2OH$, 270 °C, 4 h, 83%.

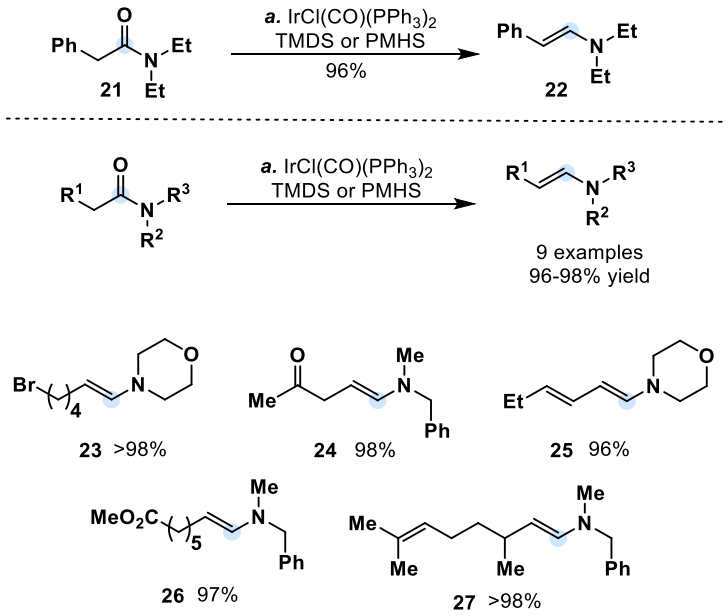
Scheme 7. Original synthesis of Vaska's complex

Interestingly, this complex was shown to undergo oxidative addition with HCl, leading Vaska to rapidly study its interaction with other simple diatomic molecules. Remarkably, he showed in 1963 that the complex can reversibly bind oxygen by forming a singular μ_2 side-on adduct.[33] In 1962, he reported an oxidative addition of the iridium complex with molecular hydrogen to form the dihydride.[34] Three years later, the complex was shown to have some catalytic activity in the hydrogenation of ethylene.[35]

Unfortunately for him, in a similarly serendipitous discovery, Wilkinson reported in 1965 the synthesis of $RhCl(PPh_3)_3$,[36] which became the eponymous catalyst, and this complex showed extraordinary properties for its use in hydrogenation and hydroformylation reactions that outshadowed most other complexes showing moderate activity, such as Vaska's complex. In the next five decades, Vaska's complex shines in inorganic chemistry as a tool to teach the concept of oxidative addition, but showed very few applications in organic chemistry… until 2009.

1.3.2 Discovery of new reactivity with Vaska's complex for the reduction of tertiary amides

In 2009, Nagashima, in his pursuit to uncover transition-metal complexes able to exhaustively reduce amides to amines, was testing the performance of a few commercial catalysts in the reduction of diethylhomobenzoylamide **21**.[29] The intrinsic predisposition of this model substrate to capture the iminium ion intermediate in the reduction as the conjugated enamine **22** (see **Scheme 8**) led to the identification of Vaska's complex as a potent catalyst, even at 0.05 mol% loading. The authors then reported a broad scope in the enamine formation, tolerating traditionally sensitive functional groups such as alkenes, ketones, and esters. Most of the enamines are produced in quantitative yields.

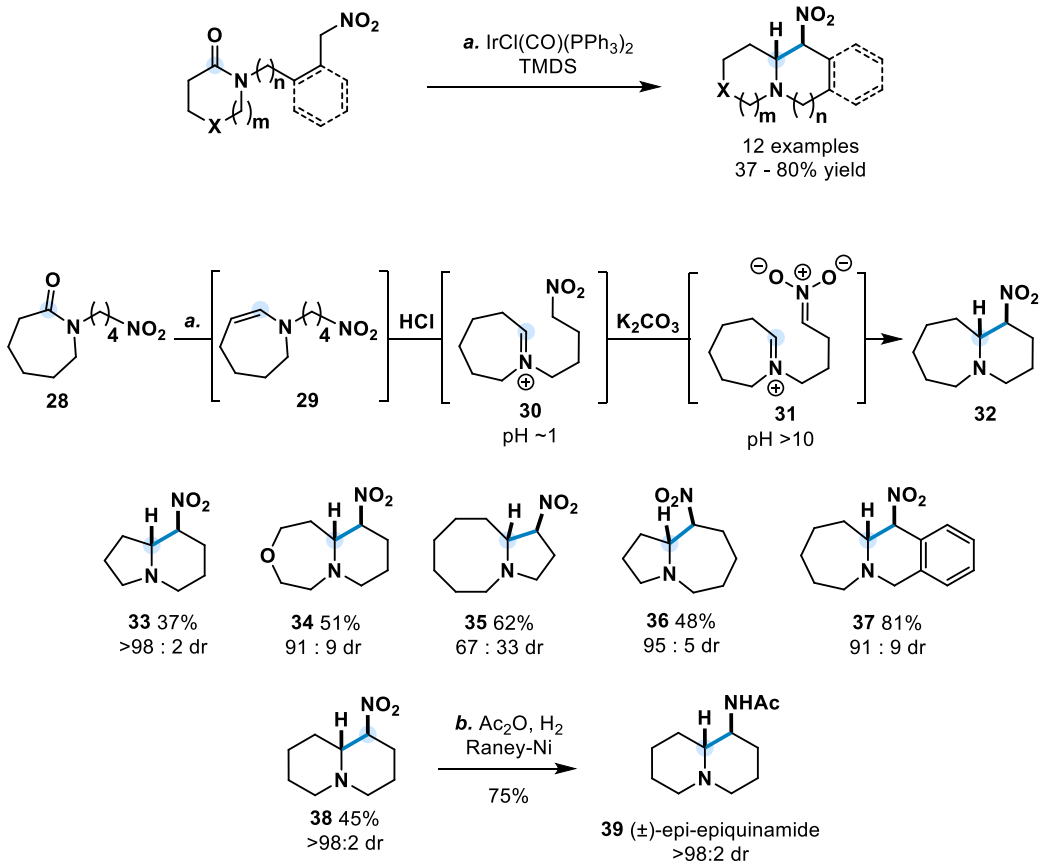


Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (0.05 mol%), TMDS or PMHS, PhMe, rt, 30 min.

Scheme 8. Application of Vaska's complex to a chemoselective partial reduction of amides to enamines.

This initial report caught the attention of a few synthetic groups in the world, and five years later, two studies demonstrated the possibility to intercept the iminium ion with carbon-based nucleophiles.

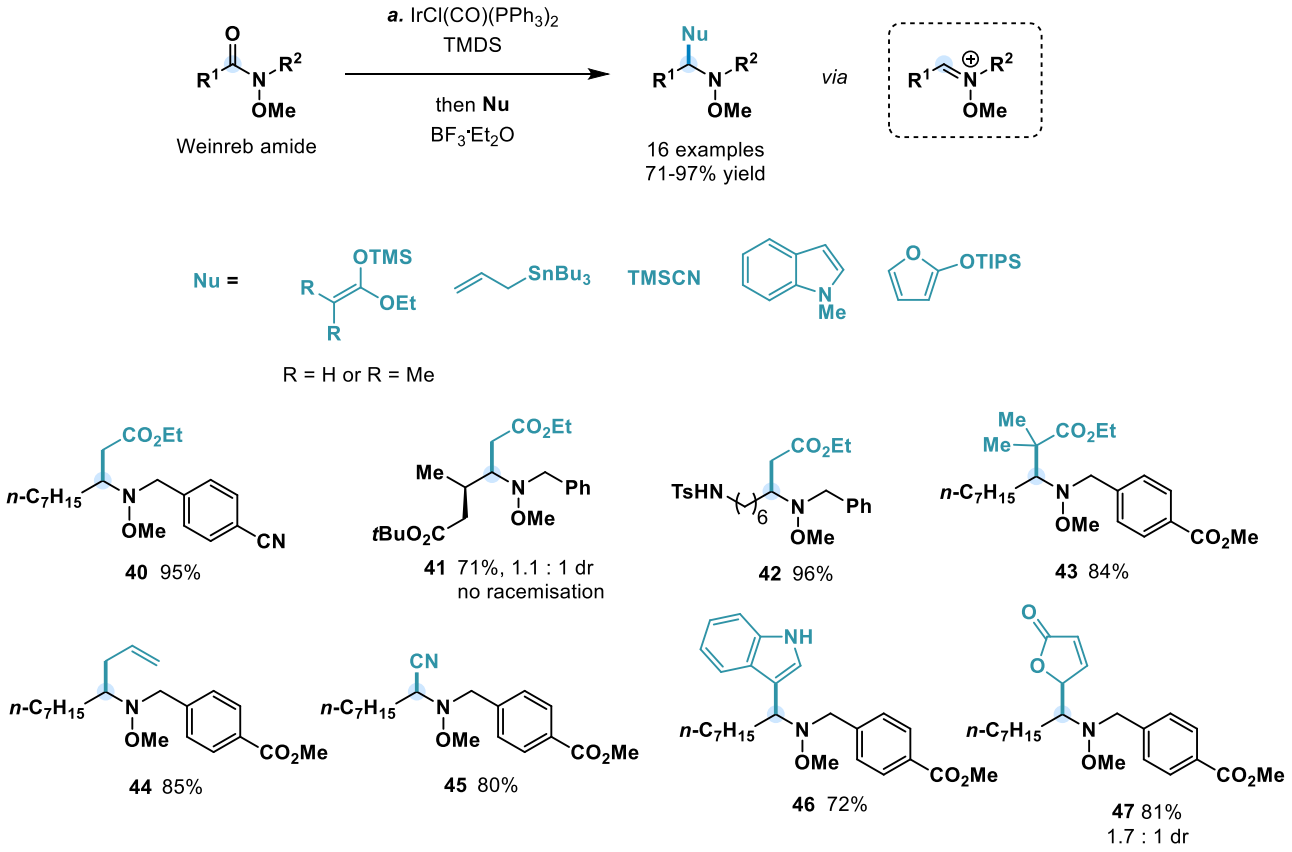
In 2014, Dixon *et al*, after gaining an interest in amide reduction for a key step in their synthesis of manzamine A,[37] aimed at the development of a cyclisation based on the use of nitroalkane tethered amides. Upon reduction to the enamine **29** and acidification, the iminium ion **30** could be generated. Subsequent basification unveiled the nucleophilic properties of the nitronate, and nucleophilic attack of the iminium ion allowed the formation of a C–C bond, producing an α-branched β-nitro amine product **32**.[38] Various ring-size were tolerated and formed (**33**–**37**), and epi-epiquinamide **39**, a natural product could be made by a one-pot reduction and acylation of one of the cyclised amine products.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (0.05 mol%), TMDS, PhMe, rt, 10 min, then HCl, then K_2CO_3 (b) Ac_2O, Raney-Ni, H_2, MeOH, 40 h, rt, 75%, >98 : 2 dr.

Scheme 9. Dixon's intramolecular nitro-Mannich, intercepting the intermediate iminium ion.

A few months later, Sato and Chida disclosed a report in which Weinreb amides could be activated with Vaska's complex and TMDS, and an external nucleophile could be added on a second phase of the reaction, facilitated by $BF_3{\cdot}Et_2O$ as a Lewis acid for the *N*-methoxy iminium ion generation. This resulted in couplings of a wide variety of nucleophiles with the iminium ions,[39] allowing for a reductive functionalisation of *N*-methoxyamines in very good yield, with great functional group tolerance [(nitriles, esters, sulfonamides for instance), 40–47].



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (5 mol%), TMDS, PhMe, rt, 30 min, then nucleophile, $BF_3{\cdot}Et_2O$, rt, 1 h.

Scheme 10. Sato and Chida's methodology, based on the interception of the intermediate iminium ion with various nucleophiles.

Together, these three reports sparked a growing interest in the synthetic community,[ii] and resulted in the publication of more than 20 reports (over the past five years), using this catalytic system to:

- selectively and exhaustively reduce a tertiary amide or lactam in a densely functionalized molecule, often in the end-game of natural product synthesis

[ii] At the time where the work described in this thesis started, these were the only three reports using the Vaska's complex-TMDS catalytic system for the reduction of amides. Since then, 25 publications described its use in a key-step of a natural product total synthesis, or as the main feature of a newly developed methodology.

- generate and subsequently intercept an iminium ion species arising from the silylated hemiaminal in an intra- or intermolecular C–C bond formation event
- generate an enamine species – and possibly design a cascade sequence downstream

The reports following these approaches will be described and discussed in the next section.

1.3.3 Exhaustive reduction of amides to amines in natural product syntheses

Due to its extraordinary chemoselectivity, Vaska's complex, in conjunction with TMDS, is particularly useful as a reductant in the late stages of alkaloid total synthesis where molecules are densely functionalized, often with esters or ketones either present in the target, or necessary for the carbon skeleton construction.[iii]

Having developed methodologies based on the iridium complex, Sato and Chida recognised its potential in the last step of their neostenine total synthesis (see **Scheme 11**, **A**).[40] Reduction of lactam **48** to the silylated hemiaminal with excess (10 equiv.) TMDS, followed by addition of TFA to force iminium ion formation, and final TMDS-mediated reduction, delivered natural product **49** in 78% yield. A lactone present in the starting material was not affected by the reductive conditions.

A year later, Dixon *et al* used the catalytic system in their synthesis of the *strychnos* core **51** (partial reduction with Vaska's catalyst and TMDS,[41] followed by ionisation with AcOH and final $NaBH_3CN$-mediated reduction) and as the final step of their (–)-himalensine A (**53**) total synthesis (ionisation and final reduction with formic acid, see **Scheme 11 B, C**).[42] As a testimony of the exquisite chemoselectivity of the catalytic system, in these two reactions, a variety of carbonyl-containing functional groups were untouched: two ketones, an ester, and an enone.

[iii] This section will be limited to instances where Vaska's complex is used to produce a fully reduce amine product. See section 4.3.4 of this chapter for its use as a functionalisation tool.

This approach to himalensine A *via* its lactam precursor **52** was also used in 2019 by Xu and Guao, although with different triggers for the iminium ion formation (TFA and AcOH respectively) and terminal reductant (Et_3SiH, $NaBH(OAc)_3$ respectively).[43, 44]

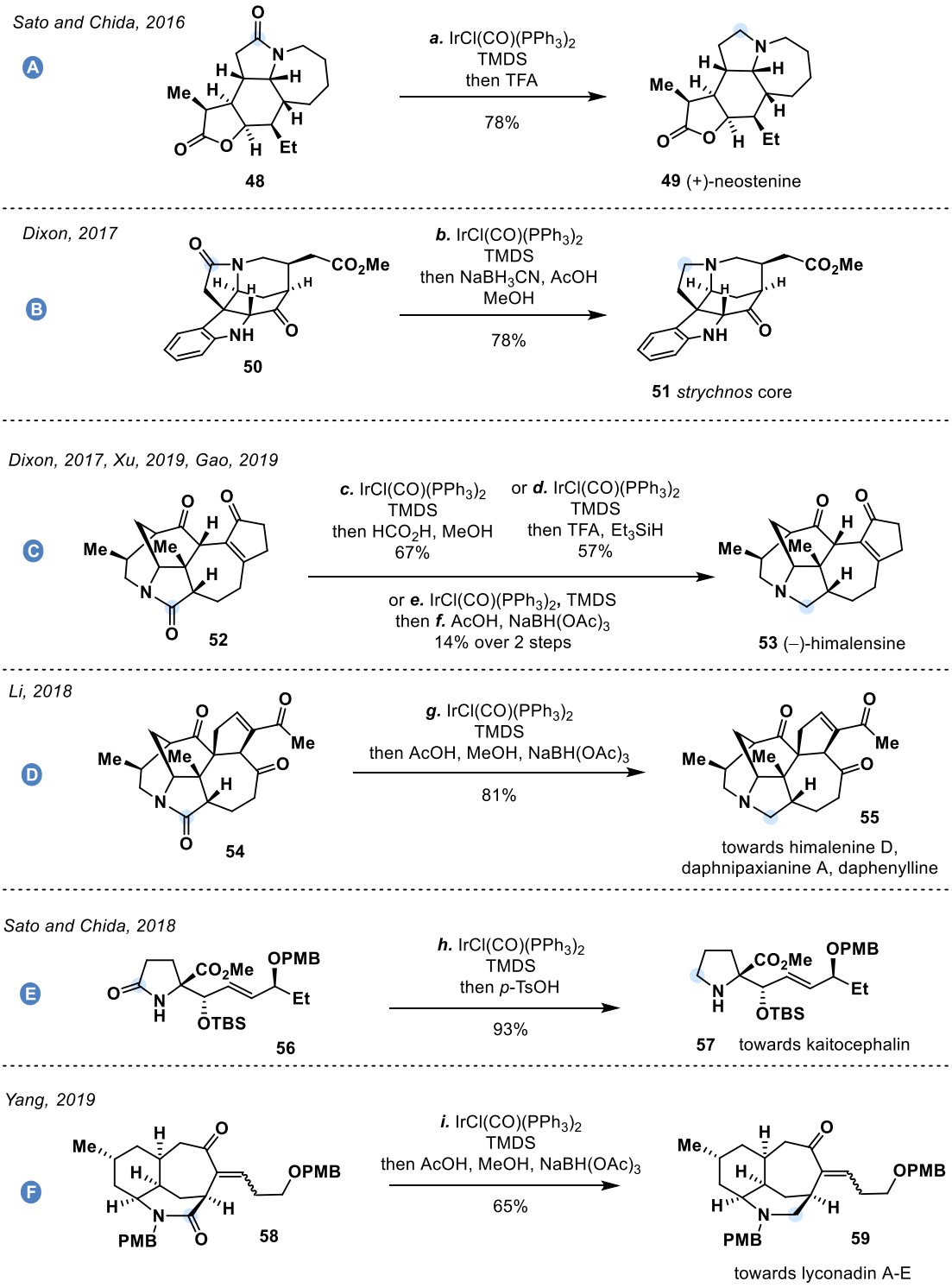
In the same natural product family, Li *et al* could access no less than three amine-containing natural products with the late-stage reduction of lactam **54** (see **Scheme 11**, **D**).[45]

Impressively, in 2018, Sato and Chida performed an unprecedented exhaustive reduction of secondary lactam **56**.[iv, 46] Vaska's complex is usually selective for tertiary amides and lactams, but using a large excess of TMDS (15 equiv.) followed by addition of *p*-TsOH, secondary amine **57** could be obtained in high yield, setting the stage for the end of their total synthesis of kaitocephalin (see **Scheme 11**, **E**).

Finally, in 2019, Zang *et al*, using the same reaction conditions as Li's, could access **59**, en route to five related alkaloids of the same family, lyconadins A-E (see **Scheme 11**, **F**).[47]

It is interesting to note that ionisation of the silylhemiaminal in all these instances has been performed with a Brønsted acid (TFA, AcOH, HCO_2H, or *p*-TsOH). Although not always necessary – some of these reaction conditions simply use a large excess of TMDS – the use of an additional mild hydridic reductant ($NaBH_3CN$, $NaBH(OAc)_3$, Et_3SiH, or HCO_2H) was often required.

[iv] This is, to the best of our knowledge, the only instance of a secondary amide or lactam being successfully reduced with Vaska's catalyst.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS (10 equiv.), CH_2Cl_2, rt, 90 min, then TFA, 2 h, 78%; (b) $IrCl(CO)(PPh_3)_2$ (0.5 mol%), TMDS (2 equiv.), CH_2Cl_2, rt, 60 min, then $NaBH_3CN$ (0.5 equiv.), AcOH (1 equiv.), MeOH, 12 h, 78%; (c) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS (11 equiv.), CH_2Cl_2, rt, estimated 60 min, then AcOH (excess), MeOH, 60 °C, 10 h, 67%; (d) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS (excess) CH_2Cl_2, rt, estimated 60 min, then TFA (excess), Et_3SiH, rt, 48 h, 67%; (e) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS (excess), CH_2Cl_2, rt, estimated 60 min, then HCl, 60 min; (f) AcOH (2 equiv.), $NaBH(OAc)_3$ (2 equiv.), rt, 1 h, 14% over 2 steps; (g) $IrCl(CO)(PPh_3)_2$ (5 mol%), TMDS (2.5 equiv.), CH_2Cl_2, rt, 60 min, then AcOH (1.1 equiv.), $NaBH(OAc)_3$ (2 equiv.), MeOH, rt, 12 h, 81%; (h) $IrCl(CO)(PPh_3)_2$ (2 mol%), TMDS (15 equiv.), CH_2Cl_2, rt, 45 min, then *p*-TsOH (1.2 equiv.), rt, 5 h, 93%; (i) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS (2.5 equiv.), CH_2Cl_2, rt, estimated 60 min, then AcOH (1.1 equiv.), $NaBH(OAc)_3$ (2 equiv.), MeOH, rt, 1 h, 65%.

Scheme 11. Exhaustive reduction of lactams to cyclic amines in natural product syntheses.

This approach has been increasingly used as it allows introduction of the nitrogen atom at an early stage in the synthesis as an amide or a lactam, which will be mostly unreactive during the carbon skeleton construction steps. Final chemoselective reduction at a late stage unveils the amine, without having to resort to protecting group chemistry, or functional group oxidation. Consequently, we expect this efficient strategy to become a mainstay in alkaloid syntheses.

1.3.4 Reductive functionalisation of amides for the synthesis of α-functionalised amines

The Dixon, Huang, and the Sato and Chida groups, are responsible for the development of no less than ten methodologies based on Vaska's catalyst between 2015 and 2018.[38-39, 48-54, 57] All of these strategies are based on the silylhemiaminal intermediate (see **Scheme 6**), and its interception in a subsequent reductive functionalization reaction. All of these methods are comprised of a partial reduction step, whose conditions vary very little: the amide substrate is reduced in presence of 1 to 5 mol% of the iridium complex, and 2 to 3 equivalents of TMDS, in a non-polar aprotic solvent (typically toluene or dichloromethane).

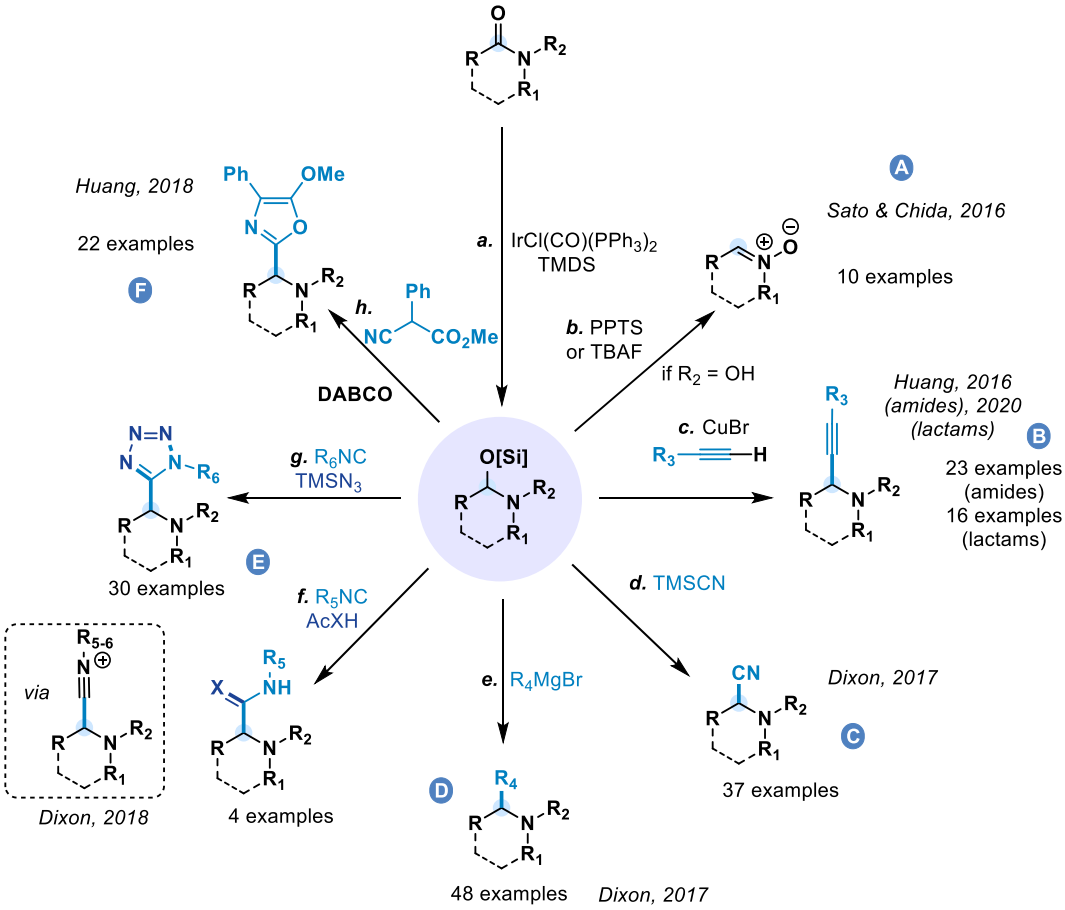
In 2016, Sato and Chida reported the use of the iridium complex as a convenient reductive approach to nitrone synthesis from *N*-hydroxy amides, with PPTS or TBAF as a late additive to the reaction mixture (**Scheme 12**, **A**).[48]

The same year, Huang developed a copper co-catalysed methodology allowing for the synthesis of propargylic amines from tertiary amides, by addition of terminal alkyne, and CuBr (5 mol%) to the hemiaminal.[49] They extended the scope of this reaction to lactam substrates in 2020, applying it to the synthesis of several small alkaloids (**Scheme 12**, **B**).[50]

In 2017 and 2018, the Dixon group reported the use of three different carbon-based nucleophiles to intercept the iminium ion generated from the silylhemiaminal species: TMSCN,[51] Grignard reagents,[52] and isonitriles (**Scheme 12**, respectively **C**, **D**, and **E**).[53] The cyanide ion masked as TMSCN is able to

produce α-amino nitriles in a reductive Strecker reaction, while Grignard reagents deliver α-branched tertiary amines, and isonitriles, through nitrilium ions, grant access to α-amino amides, thiomaides, and tetrazoles. Several drugs and natural products could be functionalised as application of these methodologies.

Finally, in 2018, Huang used isocyanoacetateester pronucleophiles to intercept the iminium ion through similar nitrilium intermediates, and intramolecular participation of the ester, followed by final aromatisation (**Scheme 12, F**).[54]

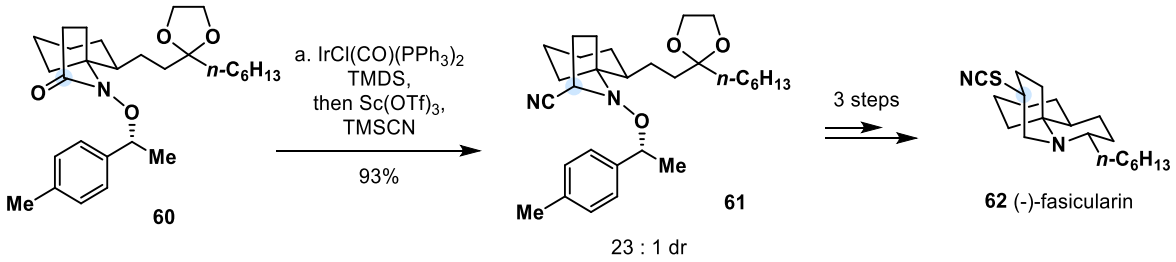


Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1-5 mol%), TMDS, PhMe or CH_2Cl_2, rt, 30 min, ; (b) PPTS or TBAF, rt, 5 min; (c) CuBr (5 mol%), alkyne, rt 12 h; (d) TMSCN, rt, 30 min or 15 h; (e) R_4MgBr, –78 °C to rt, 4 h; (f/g) R_5NC, AcOH/AcSH/$TMSN_3$, rt, 15 h; (h) DABCO, isocyanoacetate ester rt, 30 min.

Scheme 12. C–C bond forming methodologies using Vaska's complex .

In addition to enabling the development of new C–C bond forming methodologies, Vaska's complex has also been used as a tactical functionalisation tool in several total syntheses of alkaloids.

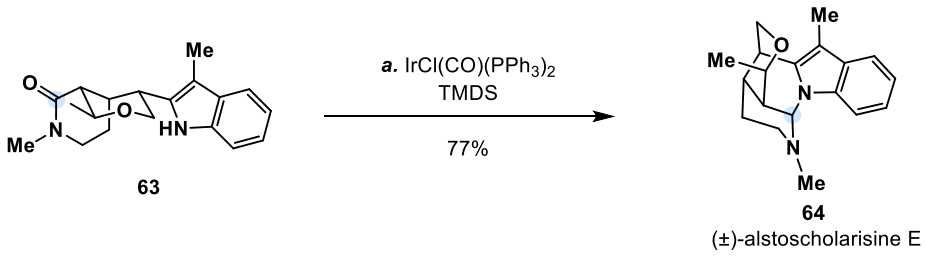
The Strecker reaction shown above was, for instance, applied in 2019 to the synthesis of fasicularin **62** by Chida and Sato,[55] with $Sc(OTf)_3$ as a Lewis acid additive.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (10 mol%), TMDS, toluene, rt, 1 h, then $Sc(OTf)_3$ (10 mol%), TMSCN, −78 °C, 12 h, 93%.

Scheme 13. Reductive Strecker reaction towards fasicularin

Other nucleophiles have also been shown to intercept the iminium ion. In 2020, Martin *et al* published a short and high yielding total synthesis of (±)-alstoscholarisine E **64**.[56] This alkaloid displays a rare aminal functional group fusing two piperidine ring together. The authors accessed a highly advanced synthetic intermediate **63**, missing a critical C–N bond. After several attempts based on known reductive conditions, such as DIBAL-H, Schwartz's reagent, and other tin and titanium-based reagents, Vaska's complex, alongside TMDS emerged as the most competent reductive system in this transformation, allowing iminium ion formation and subsequent trapping by the indole nitrogen, delivering the natural product in 77% yield.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (2 mol%), TMDS, CH_2Cl_2, rt, 2.5 h, 77%.

Scheme 14. Vaska's complex in the final step of Martin's (±)-alstoscholarisine E total synthesis.

1.3.5 Partial reduction of amides to enamines

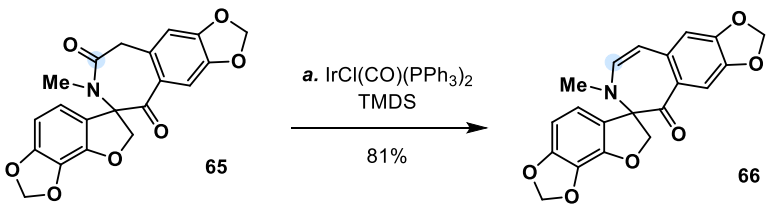
Enamines are generally unstable, and are thus rarely the desired product in organic synthesis, but rather an intermediate for further reaction. This instability can be however mitigated by conjugating the π-electrons with a suitable functional group, such as an arene in Nagashima's initial report of Vaska's complex and TMDS as a powerful reductive system for tertiary amides.[29, 30] In 2019, Huang *et al* also demonstrated that β-amido esters could be smoothly converted to vinylogous carbamates under mild reaction conditions (**Scheme 15**).[57]



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt, 1 h

Scheme 15. Synthesis of β enamino esters catalysed by Vaska's complex.

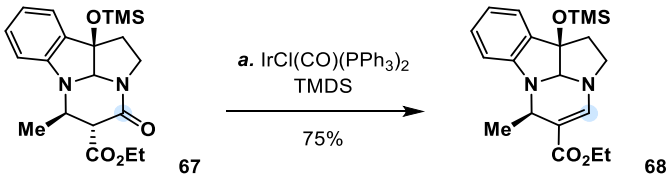
Provided they have sufficient stabilisation, conjugated enamines also occur within natural products. To this end, the iridium-based catalytic system found use in the total synthesis of the proposed structure of turkiyenine by the Iwabuchi group in 2015.[58] Having assembled the carbon skeleton of the natural product, lactam **65** was chemoselectively reduced by Vaska's complex and TMDS to give amine **66** (structure confirmed by single crystal X-ray analysis). The authors reported that the use of traditional reductants, such as DIBAL-H, was unselective and reduced the ketone carbonyl. The physical data of the synthetic and natural material was however inconsistent,[59] and the structural identity of the alkaloid remains uncertain to this day.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt, 2 h, 81%.

Scheme 16. Synthesis of β enamino esters catalysed by Vaska's complex.

In 2018, the Huang group reported a total synthesis of (–)-verrupyrroloindoline, a natural product displaying a β-enaminoester. Using reaction conditions that would become standard in their report on methodology development (see **Scheme 15**), the aza-lactam in **67** could be reduced to the silyl-protected natural product **68**.[60]

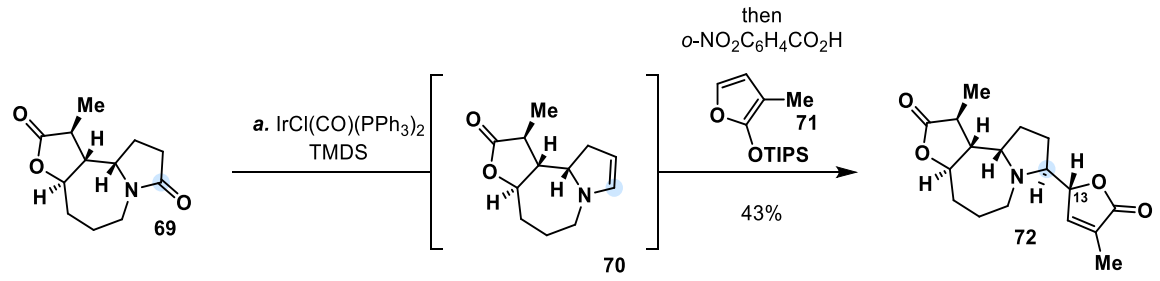


Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (20 mol%), TMDS, PhMe, rt, 12 h, 75%.

Scheme 17. Synthesis of a cyclic β-enamino esters catalysed by Vaska's complex in Huang's total synthesis of (–)-verrupyrroloindoline.

The true value of enamines lies in their ability to take part in spectacular cascade sequences. Being nucleophilic, they can react with electrophilic acceptors, generating an iminium ion which is itself a strongly electrophilic species. Vaska's catalyst and TMDS can be used to generate the iminium ion, which can lose a proton to become the more stable enamine form. With the simplest electrophile, a proton, the reactive iminium ion can be reformed in reaction conditions favourable for an external nucleophile to perform a 1,2 addition.

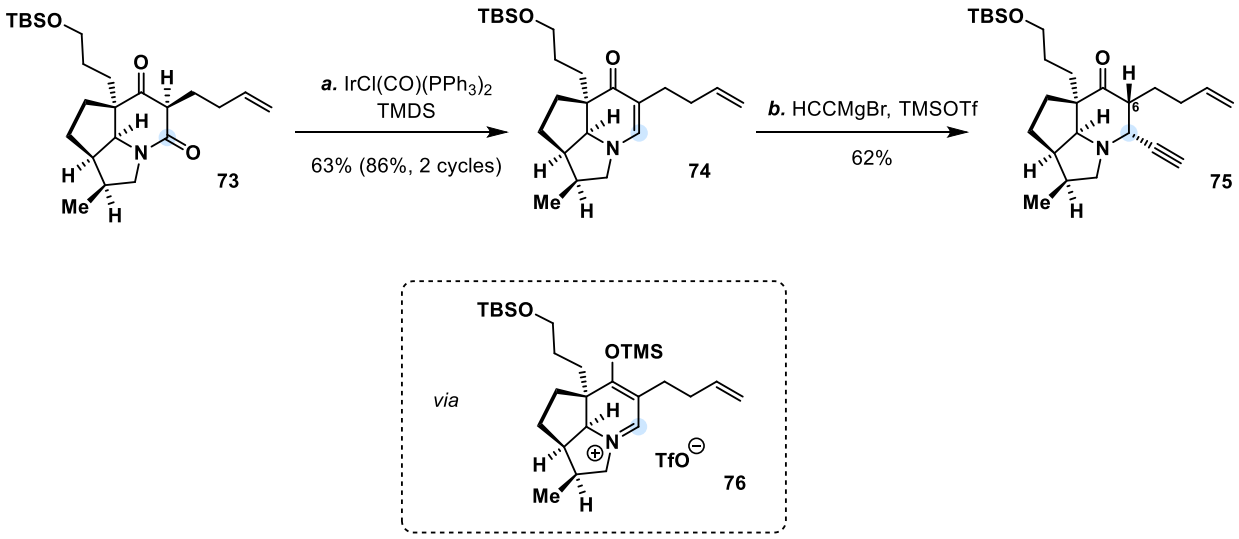
This was the approach taken by Chida and Sato in their total synthesis of stemonine in 2017.[61] Chemoselective reduction of the lactam over the lactone in stemoamide **69** gave the enamine **70**, which upon protonation with ortho-nitrobenzoic acid gave the iminium ion. Siloxyfuran **71** was then introduced, and a vinylogous Mukaiyama-Mannich reaction could take place to deliver α-functionalized amine **72**, one reduction away from the natural product.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt, 1 h, then **71**, 2-$NO_2C_6H_4CO_2H$, MeCN, rt, 24 h, 43% (+30% C^{13} epimer).

Scheme 18. Transient enamine as iminium ion precursor in the total synthesis of stemonine.

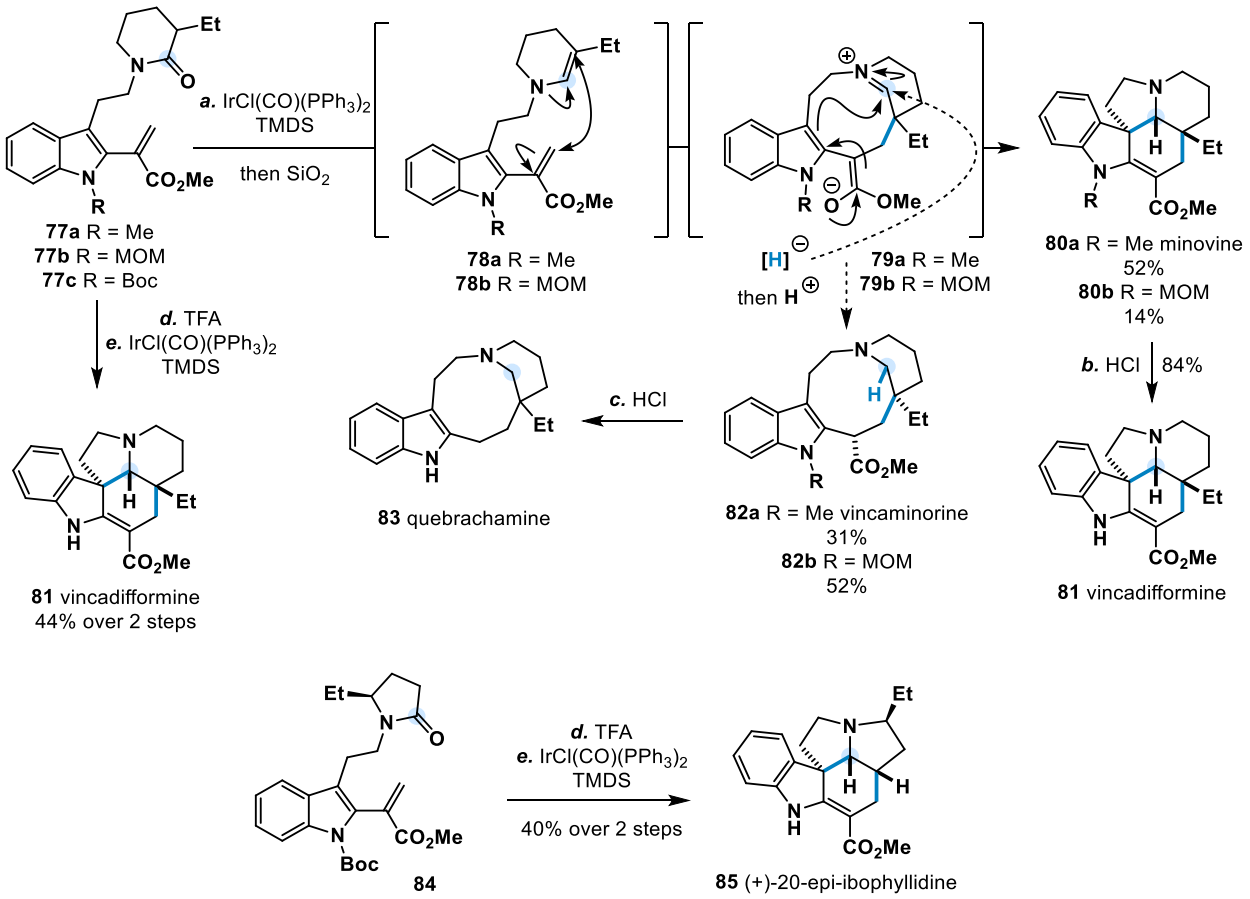
In 2019, Sarpong *et al* disclosed an elegant total synthesis of daphlongamine H and isodaphlongamine H.[62] One of the key steps was the formation of vinylogous lactam **74** from β-ketoamide **73**. The authors surveyed "various reduction methods" and found that the combination of Vaska's complex and TMDS to be "uniquely effective ... highlight[ing] [its] remarkable chemoselectivity". The β-enamino ketone **74** was used in the next step as an electrophile, *via* prior activation with TMSOTf, presumably to generate intermediate **76**. This approach again exploits the enamine (here β-enamino ketone) as a stable precursor to a reactive iminium ion electrophile.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (2.5 mol%), TMDS, PhMe, rt, 50 min, 63%, 86% after 2 cycles; (b) TMSOTf, −78 °C, 10 min, then HCCMgBr, 5 min, −78 °C to rt, 62% (+17% C^6 epimer).

Scheme 19. Transient β-enamino ketone in the total synthesis of daphlongamine H and isodaphlongamine H.

Last, but not least, more complex cascade sequences can be designed from enamines generated by the iridium catalytic system. In 2016, the Dixon group disclosed a divergent synthesis of five aspidosperma and iboga alkaloids using a common strategy.[63] Lactams **77a** and **77b** were submitted to the reductive conditions, generating (protected) secodine intermediate **78a** and **78b**, respectively, the biosynthetic precursor to several indole alkaloids. Upon Michael addition of the enamine to the acrylate moiety, cyclic iminium ions **79a** and **79b** were generated, respectively. Direct reduction of this electrophile by hydridic species generated by the catalytic system delivered 9-membered ring vincaminorine **82a** (R=Me) and **82b** (R = MOM) respectively, which was further decarboxylated and MOM-deprotected to produce quebrachamine **83**. Alternatively, the cyclic iminium species were also found to undergo a vinylogous Mannich reaction to produce the pentacyclic minovine **80a** (R=Me) or **80b** (R=MOM) respectively, which afforded vincadifformine **81** after MOM-deprotection. The use of no protecting group exclusively produced vincadifformine **81** in 44% yield (**Scheme 20**, conditions ***d.*** and ***e.***).



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt, 10 min, then SiO_2, –78 °C to rt, 1 - 2 h, 31% **82a**, 52% **82b**, 52% **80a**, 14% **80b** (b) 3 N HCl, MeOH, 55 °C, 48 h, 71%; (c) 6 N HCl, 90 °C, 2 h, 61%; (d) TFA, Me_2S, CH_2Cl_2, rt, 1 h; (e) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt 1 h, 44% over 2 steps **81**, 40% over 2 steps **85**.

Scheme 20. Cascade sequences from a common enamine species in Dixon's divergent synthesis of five indole alkaloids.

1.4 Conclusion and thesis aims

The remarkable interest of the synthetic community for the use of Vaska's complex as a catalytic system for the chemoselective reduction of amides, sparked in 2009 by Nagashima, has led to the publication of numerous C–C bond methodologies in the second half of the 2010's. There is synthetic utility both in the chemoselective and exhaustive reduction of amides (mostly lactams) to (cyclic) amines, as well as for the partial reduction of the amide carbonyl, as it allows access to silylhemiaminals, which can be functionalized downstream in various C–C bond forming methodology. The fate of the developed catalytic system appears bound to its applications in the synthesis of densely functionalised amines, in particular naturally occurring alkaloids, or highly advanced amine structures, precursors to the natural product.

We felt that, at the time when this work started, and still to this day, Vaska's complex – in conjunction with TMDS – could find further use in triggering the transformation of available and simple amides and lactams into complex polycyclic amines architectures. Several cyclisation types can be designed: Chapter 2 of this work describes a spirocyclisation from indole-tethered amides, while Chapter 3 introduces a cycloaddition methodology based on the generation and reaction of stabilized azomethine ylides.

Furthermore, we believe the potential of the iridium-based catalytic system to set off elegant cascade sequences for the total synthesis of alkaloids is currently underexploited. Chapter 4 is dedicated to the research towards the design and application of a synthetic sequence leading to the total synthesis of a pentacyclic alkaloid, catharanthine.

Finally, Chapter 5 will demonstrate the scalability of the developed methodologies, and outline preliminary results for future work.

1.5 References for Chapter 1

(1) Meynet, G.; Maeder, A. The origin of primary nitrogen in galaxies. *Astronomy & Astrophysics* **2002**, *381*, L25–L28.

(2) Schiff Jr, P. L. Opium and Its Alkaloids, *Am. J. Pharm. Educ.*, **2002**, *66*, 186–194.

(3) Amirkia, V.; Heinrich, M. Alkaloids as drug leads – A predictive structural and biodiversity-based analysis. Phytochemistry letters, **2014**, *10*, xlvii–liii.

(4) Hajos, Z. G.; Parrisch, D. R. Asymmetric synthesis of bicyclic intermediates of natural product chemistry, *J. Org. Chem.* **1974**, *39*, 12, 1615–1620.

(5) Zuo, W.; Tauer, Sebastian; Prokopchuk, E. D.; Morris, R. H. Iron Catalysts Containing Amine(imine)diphosphine P-NH-N-P Ligands Catalyze both the Asymmetric Hydrogenation and Asymmetric Transfer Hydrogenation of Ketones. *Organometallics* **2014**, *33*, 20, 5791–5801.

(6) For a review, see Surry, D. S.; Buchwald, S. L. Diamine ligands in copper-catalysed reactions *Chem. Sci.*, **2010**, *1*, 13–31.

(7) Delépine, M. unknown title, *Bull. Soc. Chim. Fr.* **1895**, *13*, 352–361.

(8) For a review, see Gibson, M. S.; Bradshaw, R. W. The Gabriel Synthesis of Primary Amines. *Angew. Chem. Int. Ed.*, **1968**, *7*, 919–930.

(9) For a review, see Gololobov, Y. G. Sixty years of Staudinger Reaction. *Tetrahedron*, **1981**, *37*, 3, 437–472.

(10) For a review, see Ruiz-Castillo, P., Buchwald, S. L. Applications of Palladium-Catalysed C-N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564–12649.

(11) For a review, see West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019**, *119*, 12491–12523.

(12) For a recent review, see Leitch, J. A.; Rossolini, T.; Rogova, T.; Maitland, J. A. P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal.* **2020**, *10*, 2009–2025.

(13) Brunner, H.; Miehling, W. Enantioselektive Hydrosilylierung van Ketonen Mit CuI-Katalysatoren. *J. Organomet. Chem.* **1984**, *275*, C17-C21.

(14) Apple, D. C.; Brady, K. A.; Chance, J. M.; Heard, N. E.; Nile, T. A. Iridium Complexes as Hydrosilylation Catalysts. *J. Mol. Catal.* **1985**, *29*, 55-64.

(15) Schmidt, T. Molybdenum Oxadiene Catalysts for the Chemoselective Hydrosylilation of α,β-unsaturated Ketones and Aldehydes. *Tetrahedron Lett.* **1994**, *35*, 3513-3516.

(16) Ojima, I.; Nihonyan, M.; Nagai, Y. Rhodium Complex Catalysed Hydrosilylation of Carbonyl Compounds. *J. Chem. Soc., Chem. Commun.* **1972**, 938.

(17) Eaborn, C.; Odell, K.; Pidcock, A. Hydrosylilation of Carbonyl Compounds Catalyzed by Ruthenium Complexes. *J. Organomet. Chem.* **1973**, *63*, 93-97

(18) Nakano, T.; Nagai, Y. Bis(η^5-cyclopentadienyl)diphenyltitanium-catalyzed Hydrosilylation of Ketones. *Chem. Lett.* **1988**, 481-484

(19) Ohkuma, T.; Hashiguchi, S.; Noyori, R. A Practical Method for Activation of Commercial Lithium Hydride: Reductive Silylation of Carbonyl Compounds with Lithium Hydride and Chlorotrimethylsilane. *J. Org. Chem.* **1994**, *59*, 217-221

(20) Dombray, T., Helleu, C., Darcel, C.; Sortais, J.-B. Cobalt Carbonyl-Based Catalyst for Hydrosilylation of Carboxamides. *Adv. Synth. Catal.* **2013**, *355*, 3358-3362

(21) Das, S.; Join, B.; Junge, K.; Beller, M. A General and Selective Copper-catalyzed Reduction of Secondary Amides. *Chem. Commun.* **2012**, *48*, 2683-2685

(22) (a) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. A Convenient and General Iron-Catalyzed Reduction of Amides to Amines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510; (b) Sunada, Y.; Kawakami, H.; Imaoka, T.; Motoyama, Y.; Nagashima, H. Hydrosilane Reduction of Tertiary Carboxamides by Iron Carbonyl Catalysts. *Angew. Chem. Int. Ed.* **2009**, *48*, 9511-9514; (c) Das, S.; Wendt, B.; Möller, K.; Junge, K.; Beller, M. Two Iron Catalysts are Better than One: A General and Convenient Reduction of Aromatic and Aliphatic Primary Amides. *Angew. Chem. Int. Ed.* **2012**, *51*, 1662-1666

(23) Volkov, A.; Tinnis, F.; Slagbrand, T.; Pershagen, I.; Adolfsson, H. $Mo(CO)_6$ Catalysed Chemoselective Hydrosilylation of α,β-Unsaturated Amides for the Formation of Allylamines. *Chem. Commun.* **2014**, *50*, 14508-14511

(24) Kuwano, R.; Takahashi, M.; Ito, Y. Reduction of Antides to Amines via Catalytic Hydrosilylation by a Rhodium Complex *Tetrahedron Lett.* **1998**, *39*, 1017-1020

(25) Li, B.; Sortais, J.-B.; Darcel, C. Unexpected Selectivity in Ruthenium-Catalyzed Hydrosilylation of Primary Amides: Synthesis of Secondary Amines. *Chem. Commun.* **2013**, *49*, 3691-3693

(26) (a) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. Zinc-Catalyzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance. *J. Am. Chem. Soc.* **2010**, *132*, 6, 1770-1771; (b) Das, S.; Addis, D.; Junge, K.; Beller, M. Zinc-Catalyzed Chemoselective Reduction of Tertiary and Secondary Amides to Amines. *Chemistry*, **2011**, *17*, 12186-1219.

(27) Hanada, S.; Motoyama, Y.; Nagashima, H. Dual Si−H effects in platinum-catalyzed silane reduction of carboxamides leading to a practical synthetic process of tertiary-amines involving self-encapsulation of the catalyst species into the insoluble silicone resin formed. *Tetrahedron Lett.* **2006**, *47*, 6173-6177.

(28) Pesti, J.; Larson, G. L. Tetramethyldisiloxane: A Practical Organosilane Reducing Agent. *Org. Process Res. Dev.* **2016**, *20*, 1164-1181.

(29) Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. Highly efficient synthesis of aldenamines from carboxamides by iridium-catalyzed silane-reduction/dehydration under mild conditions. *Chem. Commun.* **2009**, 1574−1576.

(30) (a) Tahara, A.; Miyamoto, Y.; Aoto, R.; Shigeta, K.; Une, Y.; Sunada, Y.; Motoyama, Y.; Nagashima, H. Catalyst Design of Vaska-Type Iridium Complexes for Highly Efficient Synthesis of π-Conjugated Enamines. *Organometallics* **2015**, *34*, 4895-4907; (b) Tahara, A.; Kitahara, I.; Sakata, D.; Kuninobu, Y.; Nagashima, H. Donor–Acceptor π-Conjugated Enamines: Functional Group-Compatible Synthesis from Amides and Their Photoabsorption and Photoluminescence Properties. *J. Org. Chem.* **2019**, *84*, 15236-15254; (c) A, Tahara.; H, Nagashima. Recent topics of iridium-catalyzed hydrosilylation of tertiary amides to silylhemiaminals. *Tetrahedron. Lett.* **2020**, *61*, 151423; (d) Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. Iridium-PPh_3 Catalysts for Conversion of Amides to Enamines. Organometallics, **2019**, *38*, 852-862.

(31) Vaska, L Hydrido complexes of iridium. *J. Am. Chem. Soc.* **1961**, *83*, 3, 756.

(32) Vaska, L.; DiLuzio, J. W. Carbonyl and Hydrido-Carbonyl Complexes of Irdium by Reaction with Alcohols. Hydrido Complexes by Reaction with Acid. *J. Am. Chem. Soc.* **1961**, *83*, 12, 2784-2785.

(33) Vaska, L. Oxygen-Carrying Properties of a Simple Synthetic System. *Science*, **1963**, *140*, 809−810.

(34) Vaska, L.; DiLuzio, J. W. Activation of hydrogen by a transition metal complex at normal conditions leading to a stable molecular dihydride. *J. Am; Chem. Soc.* **1962**, *84*, 679−680.

(35) Vaska, L.; Rhodes, R. E. Homogeneous Catalytic Hydrogenation of Ethylene and Acetylene with Four-Coordinated Iridium and Rhodium Complexes. Reversible Catalyst-Substrate Adducts. *J. Am. Chem. Soc.* **1965**, *87*, 21, 4970−4971.

(36) Osborn, J. A., Wilkinson, G.; Young, J. F. Mild Hydroformylation of Olefins using Rhodium Catalysts. *Chem. Commun.* **1965**, 17.

(37) Jakubec, P.; Hawkins, A.; Felzmann W.; Dixon, D. J. Total Synthesis of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **2012**, *134*, 42, 17482–17485.

(38) Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. Iridium-Catalyzed Reductive Nitro-Mannich Cyclization. *Chem. Eur. J.* **2015,** *21*, 111–114.

(39) Nakajima, M.; Sato, T.; Chida, N. Iridium-Catalyzed Chemoselective Reductive Nucleophilic Addition to N-Methoxyamides. *Org. Lett.* **2015**, *17*, 1696-1699.

(40) Nakayama, Y.; Maeda, Y.; Kotatsu, M.; Sekiya, R.; Ichiki, M.; Sato, T.; Chida, N. Enantioselective Total Synthesis of (+)-Neostenine. Chem. - A Eur. J. **2016**, *22*, 3300–3303.

(41) Gammack Yamagata, A. D.; Dixon, D. J. Enantioselective Construction of the ABCDE Pentacyclic Core of the *Strychnos* Alkaloids. *Org. Lett.* **2017**, *19*, 1894-1897.

(42) Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J. Total Synthesis of (–)-Himalensine A. *J. Am. Chem. Soc.* **2017**, *139*, 17755-17758.

(43) Chen, Y.; Hu, J.; Guo, L.-D.; Zhong, W.; Ning, C.; Xu, J. A Concise Total Synthesis of (–)-Himalensine A. *Angew. Chem. Int. Ed.* **2019**, *58*, 7390-7394.

(44) Zhong, J.; Chen, K.; Qiu, Y.; He, H.; Gao, S. A Unified Strategy to Construct the Tetracyclic Ring of Calyciphylline A Alkaloids: Total Synthesis of Himalensine A. *Org. Lett.* **2019**, *21*, 3741-3745.

(45) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. Total Syntheses of Daphenylline, Daphnipaxianine A, and Himalenine D. *Angew. Chem. Int. Ed.* **2018**, *57*, 952-956.

(46) Sugai, T.; Okuyama, Y.; Shin, J.; Usui, S.; Hisada, S.; Osanai, R.; Oishi, T.; Sato, T.; Chida, N. Synthesis of Kaitocephalin Facilitated by Three Stereoselective Allylic Transposition Reactions. Chem. Lett. **2018**, *47*, 454–457.

(47) Zhang, J.; Yan, Y.; Hu, R.; Li, T.; Bai, W.-J.; Yang, Y. Enantioselective Total Syntheses of Lyconadins A–E through a Palladium-Catalyzed Heck-Type Reaction. *Angew. Chem. Int. Ed.* **2020**, *59*, 2860-2866.

(48) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from N-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138*, 5246-5249.

(49) Huang, P.-Q.; Ou, W.; Han, F. Chemoselective reductive alkynylation of tertiary amides by Ir and Cu(I) bis-metal sequential catalysis. *Chem. Commun.* **2016**, *52*, 11967–11970.

(50) Ou, W.; Lu, G. S.; An, D.; Han, F.; Huang, P. Q. Two-Step Catalytic Transformation of N-Benzyllactams to Alkaloids (±)-Solenopsin, (±)-Solenopsin A, and (+)-Julifloridine. *Eur. J. Org. Chem.* **2020**, *2020*, 52–56.

(51) Fuentes de Arriba, Á. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation. *Angew. Chem. Int. Ed.* **2017,** *56*, 3655-3659.

(52) Xie, L.-G.; Dixon, D. J. Tertiary amine synthesis via reductive coupling of amides with Grignard reagents. *Chem. Sci.* **2017,** *8*, 7492-7497.

(53)) Xie, L. G.; Dixon, D. J. Iridium-catalyzed reductive Ugi-type reactions of tertiary amides. *Nat. Commun.* **2018**, *9*, 2841.

(54) Hu, X.-N.; Shen, T.-L.; Cai, D.-C.; Zheng, J.-F.; Huang, P.-Q. The iridium-catalysed reductive coupling reaction of tertiary lactams/amides with isocyanoacetates. *Org. Chem. Front.* **2018**, *5*, 2051-2056.

(55) Yamamoto, S.; Komiya, Y.; Kobayashi, A.; Minamikawa, R.; Oishi, T.; Sato, T.; Chida, N. Asymmetric Total Synthesis of Fasicularin by Chiral N-Alkoxyamide Strategy. *Org. Lett.* **2019**, *21*, 1868–1871.

(56) Wood, M. D.; Klosowski, D. W.; Martin, S. F. Stereoselective Total Synthesis of (±)-Alstoscholarisine E. *Org. Lett.* **2020**, *22*, 786–790.

(57) Yang, Z.-P.; Lu, G.-S.; Ye, J.-L.; Huang, P.-Q. Ir-catalyzed chemoselective reduction of β-amido esters: A versatile approach to β-enamino esters. *Tetrahedron.* **2019**, *75*, 1624-1631.

(58) Kobayashi, H.; Sasano, Y.; Kanoh, N.; Kwon, E.; Iwabuchi, Y. Total Synthesis of the Proposed Structure of Turkiyenine. *Eur. J. Org. Chem.* **2016**, *2016*, 270-273.

(59) Weiss, I.; Freyer, A. J.; Shamma, M. (+)-Turkiyenine: An Unusual Extension of the Biogenetic Sequence for the Isoquinoline Alkaloids. *J. Am. Chem. Soc.* **1984**, *106*, 6101-6102.

(60) Yang, Z.-P.; He, Q.; Ye, J.-L.; Huang, P.-Q. Asymmetric Total Synthesis and Absolute Configuration Determination of (–)-Verrupyrroloindoline. *Org. Lett.* **2018**, *20*, 4200-4203.

(61) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. Unified Total Synthesis of Stemoamide-Type Alkaloids by Chemoselective Assembly of Five-Membered Building Blocks. *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391.

(62) Hugelshofer, C. L.; Palani, V.; Sarpong, R. Calyciphylline B-Type Alkaloids: Total Syntheses of (–)-Daphlongamine H and (–)-Isodaphlongamine H. *J. Am. Chem. Soc.* **2019**, *141*, 8431-8435.

(63) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates. *Angew. Chem. Int. Ed.* **2016**, *55*, 13436–13440.

Chapter 2 : Spirocyclisation of indole-tethered amides

2.1 Introduction

2.1.1 The Pictet-Spengler reaction

The Pictet-Spengler reaction is an intramolecular variant of a Friedel-Crafts reaction, with an electron-rich aromatic nucleophile (often an indole), and a tethered iminium ion as the electrophile.[1] The iminium ion is often accessed via the condensation between a tryptamine derivative and an aldehyde, and constitutes a very straightforward way to access tetrahydro-β-carbolines. In Nature, the reaction between tryptamine **86** and secologanin **87** produces strictosidine **88**, a biosynthetic precursor to one of the largest natural product family: the monoterpene indole alkaloids (MIAs), comprising several thousand natural products isolated to date, with remarkably diverse structures arising from various skeletal rearrangements.[2]

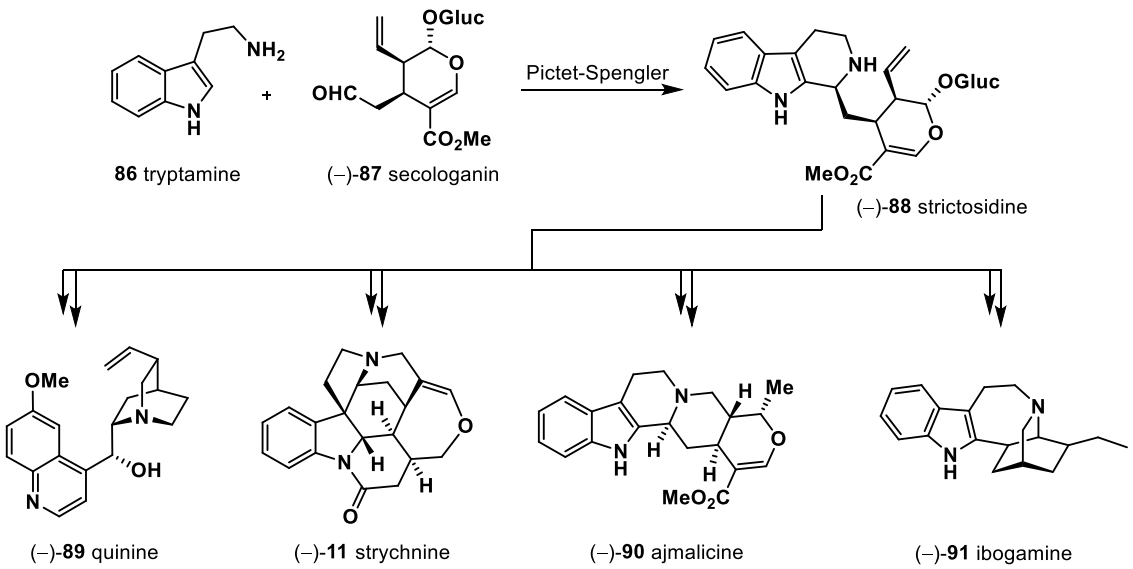


Figure 4. The Pictet-Spengler reaction at the biosynthetic origin of the monoterpene indole alkaloids (MIAs), and a sample of the structural diversity exhibited by alkaloids of this family.

The mechanism that was largely accepted during the 20th century was a nucleophilic addition from the C^3 position of the indole to give a spirocyclic intermediate **94**, which would then undergo a migration to the C^2-position (**95**). A final deprotonation would then result in rearomatization and formation of the product **96** (blue path, **Figure 5**). Guided by computational studies, the recent work of O'Connor *et al* (enzymatic Pictet-Spengler) and Zheng *et al* (Pictet-Spengler in solution) showed that both additions at C^2 and C^3 are possible, but that the migration requires a relatively high activation energy, thus suggesting that the equilibrium between intermediate **94** and **95** could occur *via* reverting to the iminium ion **93** rather than through migration.[3] The authors conclude than rather than one mechanism being prevalent over the other, the reality is most likely intermediate between these two extreme scenarios.

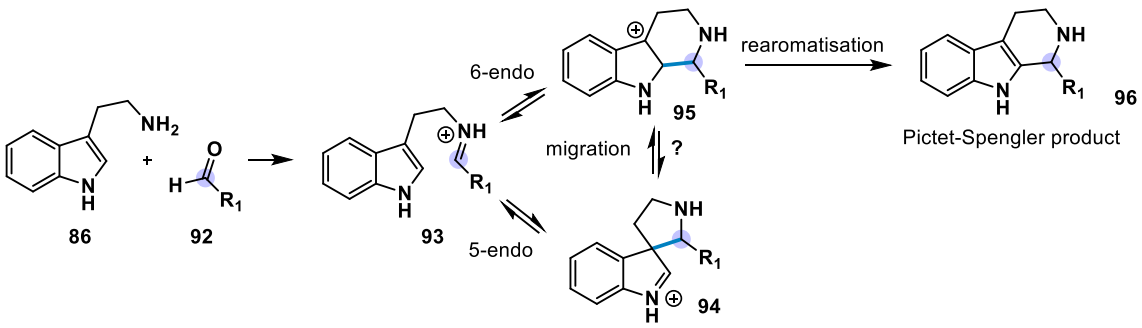


Figure 5. The Pictet-Spengler reaction mechanism (with an indole nucleophile).

2.1.2 Aim of the project

We imagined that instead of using condensation between an aldehyde and tryptamine, the catalytic system based on Vaska's catalyst for the reduction of amides (**97**) could give access to the dynamic interplay between the cationic species **98**, **99** and **100** (**Figure 6**).[4] In addition to accessing trisubstituted iminium ions (resulting in tertiary amine products), we reasoned that since the catalytic system provided reduction potential, it could divert the mechanism of the Pictet-Spengler reaction before the irreversible rearomatization delivers the tetrahydrocarboline product. This reduction of the spirocyclic indolenium

99 would result in the production of spiroindoline **102**, the interrupted Pictet-Spengler product, whose skeleton is also found in nature, often with interesting biological properties.[i]

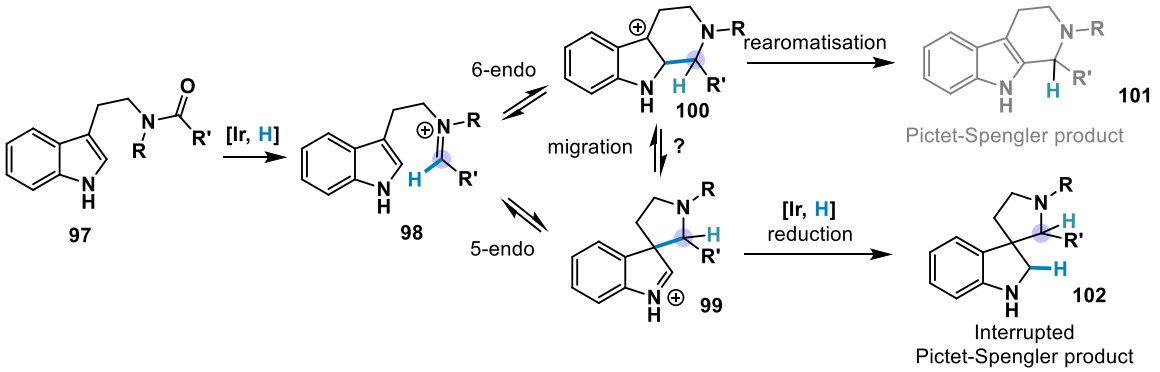


Figure 6. Interrupting the Pictet-Spengler reaction towards spirocyclic indolines.

2.1.3 Spirocycles

Spirocycles – or spiro compounds – (from the latin spira – twist) are organic molecules containing a bicyclic moiety where the two rings are connected *via* a single atom. They can be carbocyclic or heterocyclic depending on whether they contain a heteroatom as part of the bicyclic portion. They occur in nature (see **103–106**, **Figure 7**),[5] but also in man-made chemicals (**107**, **108**).[6] Due to their sp^3-rich nature whilst maintaining structural rigidity, spirocycles have emerged in the last few decades as useful scaffolds, particularly for drug-development.[6b]

[i] See for instance section 2.5 of this Chapter.

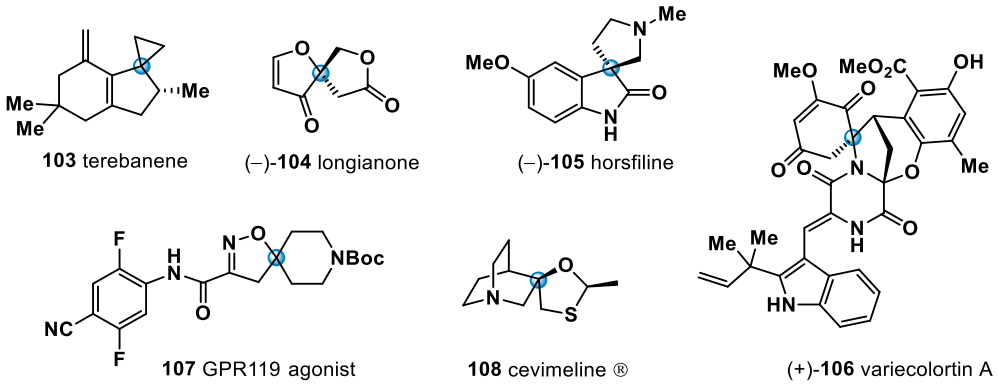
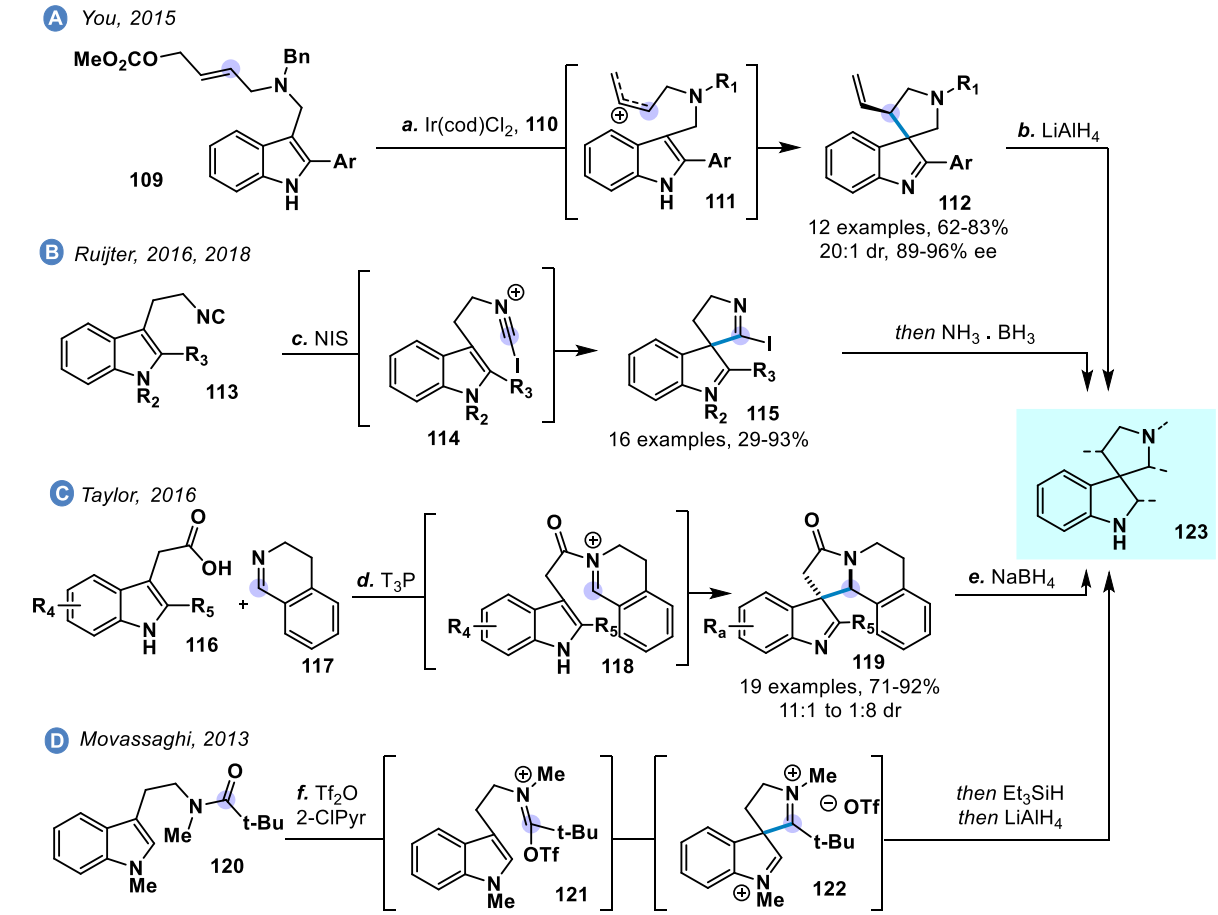
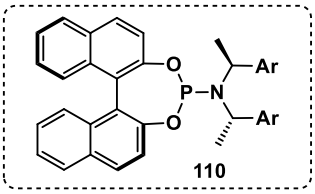


Figure 7. Spirocyclic architectures in nature and active principle ingredients.

2.1.4 Previous spirocyclisation methodologies towards spiroindoline structures

Spiroindolines have been accessed through similar approaches in the literature. Methods usually require the synthesis of very reactive cationic species, such as π-allyl cations,[7] nitrilium ions,[8] *N*-acyl iminium ions,[9] or imidoyl triflates (**Scheme 21**, respectively **A** to **D**),[10] to generate spiroindolenine species **112**, **115**, **119**, and **122**, which are subsequently reduced with a source of hydride.[11]





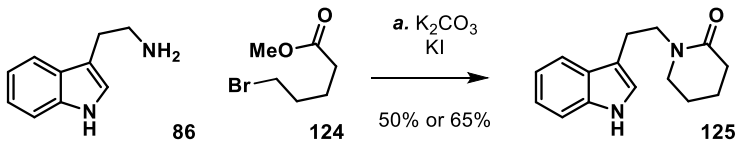
Reagents and conditions: (a) $Ir(cod)Cl_2$ (2 mol%), **110** (4 mol%), *n*-propylamine, THF, 50 °C, 30 min, evaporation, then **109**, K_3PO_4, THF, 50 °C, 27–44 h; (b) $LiAlH_4$, THF, 66 °C, 14–24 h; (c) NIS, MeCN, rt, 30 min, then $NH_3{\cdot}BH_3$, rt, 2 h (d) DIPEA, T_3P, THF, rt, 16 h (e) $NaBH_4$, MeOH, 65 °C, 3.5 h; (f) Tf_2O, 2-ClPyr, MeCN, 0 °C to rt, 30 min then Et_3SiH, rt, 8 h, then $LiAlH_4$, 0 °C, 10 min.

Scheme 21. Previous methods accessing spirocyclic indoline structures from various cationic species.

Though these methods give access to a range of substituted spiroindolines, because of the reactive intermediates and reagents required, functional group tolerance is generally limited to alkyl, aryl and ether substituents. Moreover, the spiroindolenines generated need to be reduced in a separate step, often under harsh conditions (with reactive $LiAlH_4$, $NaBH_4$, $NH_3{\cdot}BH_3$, or Et_3SiH). To date, no reaction conditions have been reported that directly produce the saturated spiroindoline.

2.2 Reaction development: discovery and optimisation

We selected indole-tethered lactam **125** as the model substrate for reaction discovery. This structure was easily accessible from tryptamine **86** and bromo-ester **124**. Originally, the alkylation/lactamisation reaction was done in *n*-BuOH as solvent following a literature procedure,[12] but EtOH was later found to be a superior solvent for the transformation.

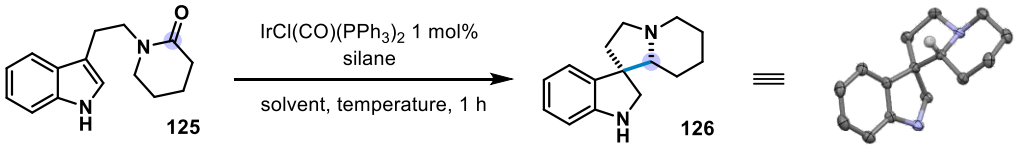


Reagents and conditions: (a) K_2CO_3, KI, *n*-BuOH, 118 °C, 16 h, 50%, or K_2CO_3, KI, EtOH, 78 °C, 16 h, 65%

Scheme 22. Synthesis of the model substrate.

In line with previous conditions used for the partial reduction of lactams and amides,[13] a toluene solution of the starting material was reacted with 1 mol% of the iridium catalyst $[Ir(CO)(PPh_3)_2Cl)]$, and 2 equivalents of TMDS as the silane. Pleasingly, the desired aza-spirondoline product was formed in 55% yield, and with a promising 80 : 20 dr (**Scheme 23**, **entry 1**). Since gas evolution was observed at the start of the reaction, we hypothesised that the N-H of the indole was silylated initially, consuming an equivalent of the silane.[14] Accordingly, an extra equivalent of TMDS was added, which pleasingly raised the NMR yield to 77% (**entry 2**). Other silanes were studied, with no success (**entries 3–5**). A solvent screen revealed that both yield and diastereoselectivity were increased in CH_2Cl_2 (**entries 6–8**), and lowering the temperature of the reaction to −15 °C allowed isolation of the product in an excellent 96 : 4 dr (**entry 10**).[ii]

[ii] The aspects of diastereoselectivity will be discussed in section 2.4 of this chapter.



Entry	Solvent	Silane (equiv.)	Temperature	Yield[a] (%)	dr[b]
1	PhMe	TMDS (2)	rt	55	80 : 20
2	PhMe	TMDS (3)	rt	77	80 : 20
3	PhMe	$PhSiH_3$ (3)	rt	0	-
4	PhMe	Ph_2SiH_2 (3)	rt	0	-
5	PhMe	Et_3SiH (3)	rt	0	-
6	THF	TMDS (3)	rt	32	86 : 14
7	$CHCl_3$	TMDS (3)	rt	74	66 : 34
8	CH_2Cl_2	TMDS (3)	rt	93	90 : 10
9	CH_2Cl_2	TMDS (3)	0 °C	90	91 : 9
10	CH_2Cl_2	TMDS (3)	-15 °C	91	96 : 4

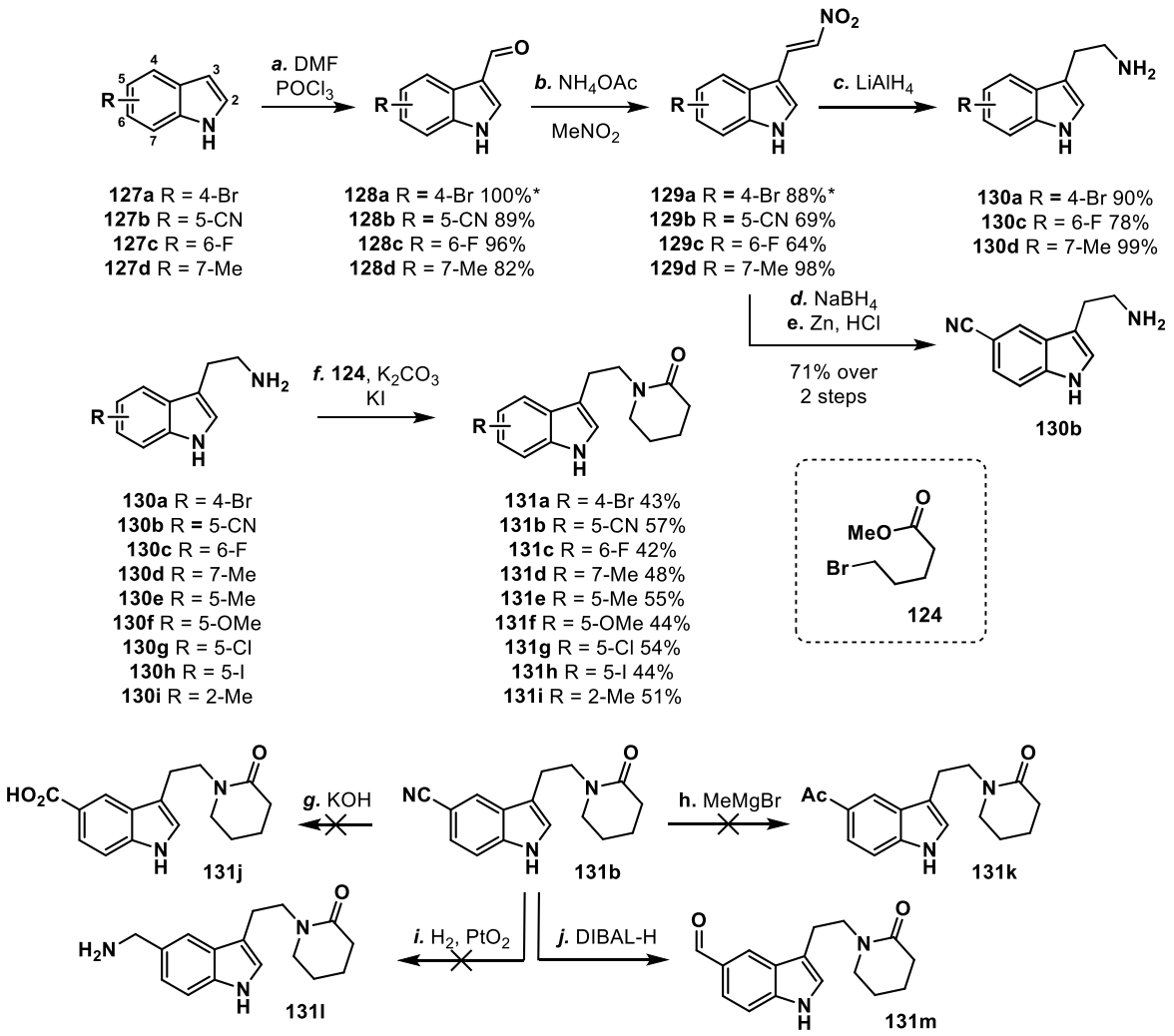
[a] ^{1}H NMR yield determined against *m*-nitro dimethylaniline as an internal standard.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Scheme 23. Optimisation of the reaction conditions.

2.3 Scope of the reaction

2.3.1 Variation of the indole

In order to assess the reaction on a range of substrates, variations on the indole moiety of the substrate was investigated. A library of tryptamines with various electron-withdrawing and electron-donating groups at all positions of the indole was synthesized. When the substituted tryptamine was not commercially available, C^3-formylation of the appropriately substituted indole, followed by Henry reaction with nitromethane, and reduction of the alkene and nitro group to the saturated amine delivered the desired tryptamine (**Scheme 24**, **129a**, **129c** and **129d**).[15] For the nitrile containing **129b**, the nitro group and alkene reductions were done in two separate steps to avoid reduction of the C≡N triple bond. Following lactamisation conditions developed for the model substrate, these substituted tryptamines were elaborated into the desired indole-tethered lactam substrates (**131a–131i**) for the spirocyclisation. A divergent synthesis of several derivatives of **131b** was attempted, but neither hydrolysis, carbonyl reaction with methyl magnesium bromide, or hydrogenation could deliver the desired carboxylic acid **131j**, methyl ketone **131k** or amine **131l**, respectively. Aldehyde **131m** could however be obtained although in 80% purity *via* DIBAL-H mediated reduction of **131b**. It should be noted that DIBAL-H needed to be used as the CH_2Cl_2 solution (1 M) rather than the THF solution (1 M) to avoid reduction of the amide carbonyl.



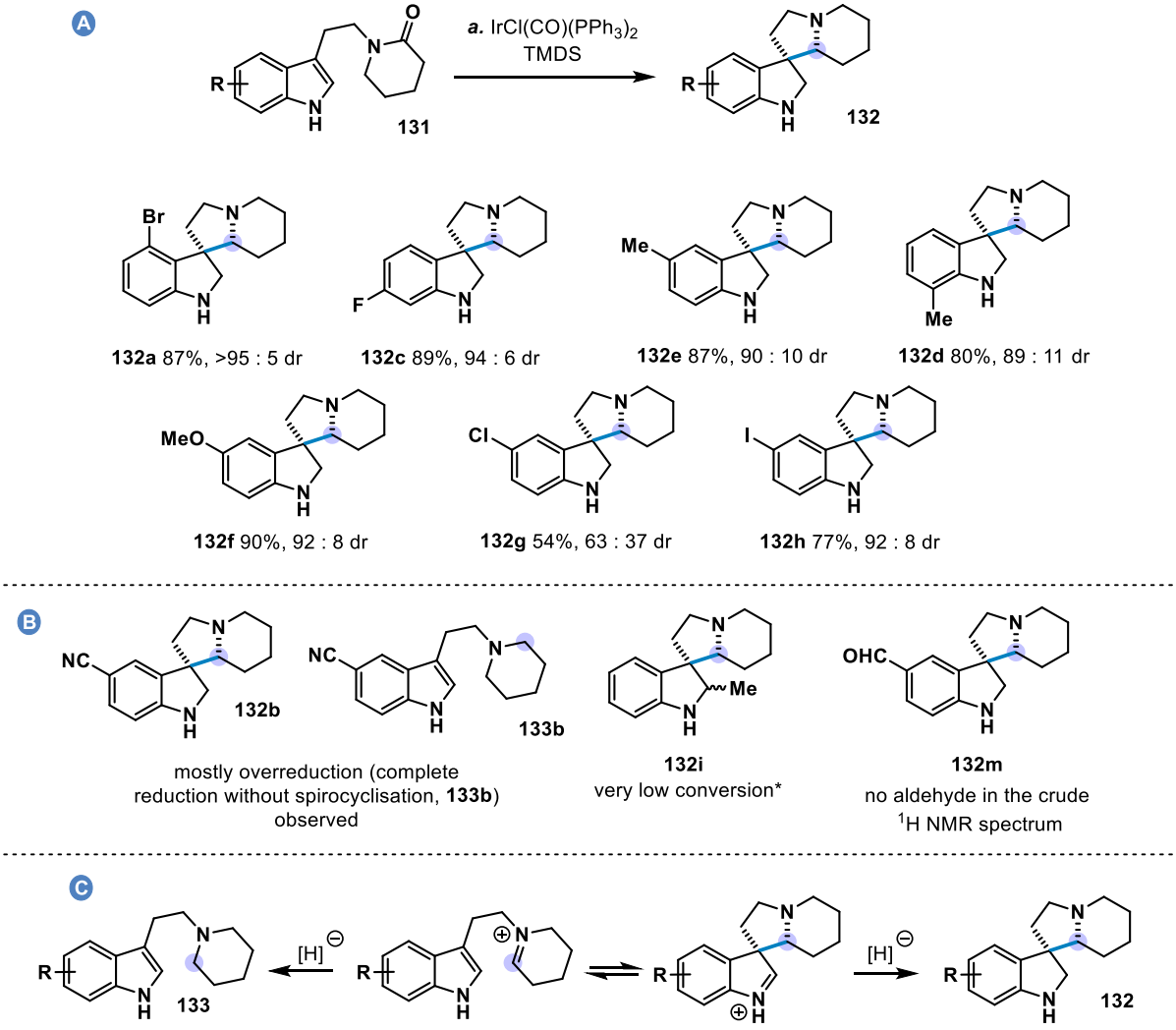
* Made by Dr M. Muratore, previous member of the group.

Reagents and conditions: (a) $POCl_3$, DMF, rt, 3 h; (b) NH_4OAc, $MeNO_2$, 100 °C, 1 h; (c) $LiAlH_4$, THF, rt, 36 h; (d) $NaBH_4$, 1:1 DMF/MeOH rt, 75 min, 72%; (e) Zn, 1 : 1 MeOH/HCl (2M), 98%; (f) **124**, K_2CO_3, KI, EtOH, 78 °C, 16 h; (g) KOH, 9 : 1 EtOH/H_2O, 80 °C, 16 h (h) MeMgBr, THF, 66 °C, 16 h (i) H_2, PtO_2 (20%$_w$), $CHCl_3$ (cat), EtOH, rt, 16 h; (j) DIBAL-H, CH_2Cl_2, rt, 2 h, 21%, impure.

Scheme 24. Synthesis of 10 substrates with variations on the aromatic indole moiety.

These substrates were all submitted to the spirocyclisation reaction. Pleasingly, 4-Br, 6-F, 5-Me, 7-Me, 5-OMe, 5-Cl, 5-I were all tolerated and gave the desired spirocycles in generally very good yield and around 90 : 10 dr. Surprisingly, 5-Cl substrate exhibited a much lower level of diastereocontrol and yield.[iii]

[iii] The diastereoselectivity will be discussed in section **2.4** of this Chapter.



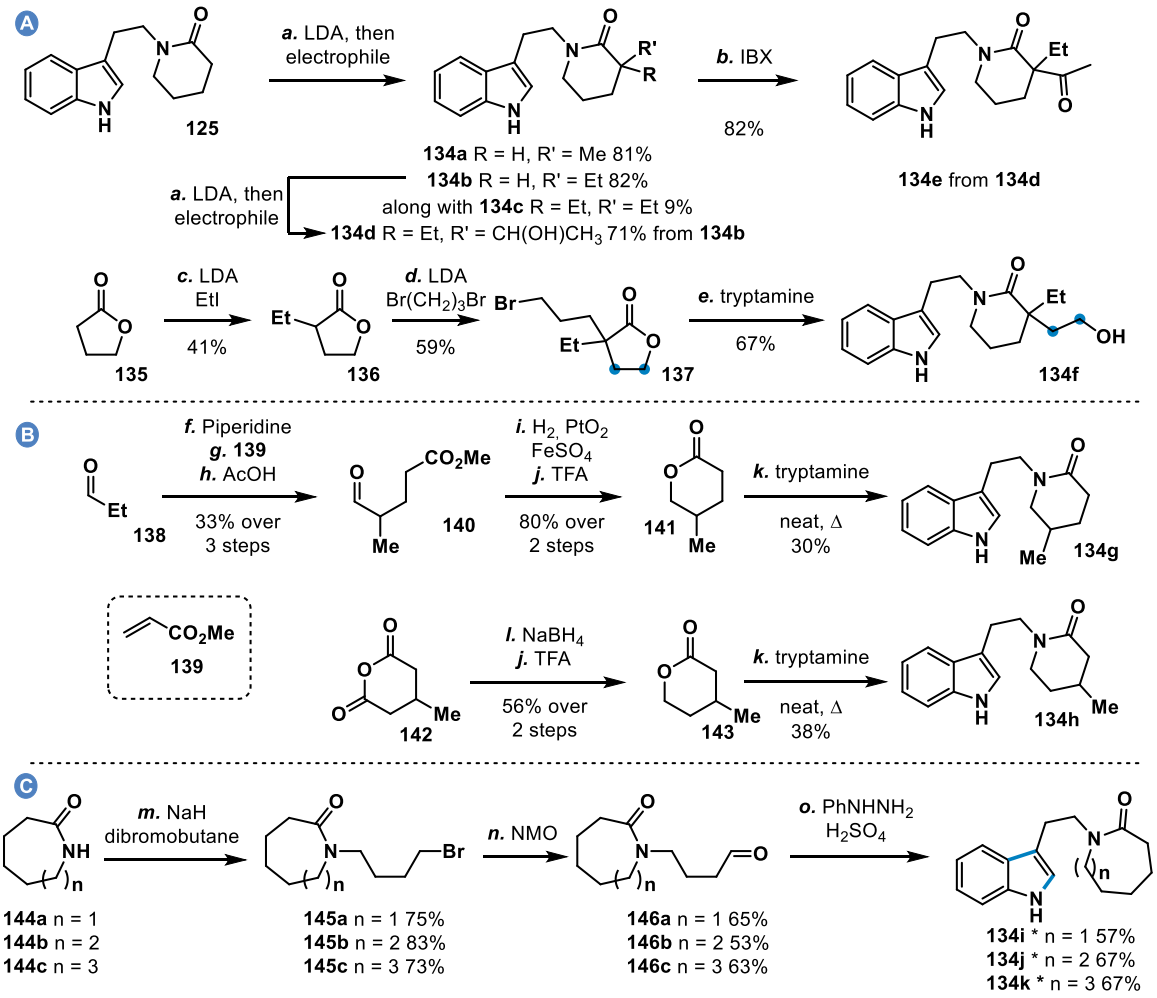
Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, CH_2Cl_2, –15 °C, 1 h. * attempts were made at rt and at 80 °C over 16 h but with no improvement.

Scheme 25. Scope on the indole moiety: **A**. successful examples, **B**. unsuccessful examples, **C**. mechanism for "over-reduction" by-product.

Unfortunately, 5-CN **131b** did not produce the desired spirocyclic product **132b** in isolable quantities. The strong electron-withdrawing character of the nitrile substituent most likely reduces the nucleophilicity of the indole ring, and further reduction of the iminium ion give rise to the fully reduced non-cyclised product **133b** (herein referred to as the "over-reduced product" see **Scheme 25**, **C**). Disappointingly, C^2-substituted **131i** only yielded trace quantity of **132i**. Finally, the aldehyde functional group of **131m** did not survive the reductive conditions of the reaction, likely due to a partial N-formyl character, being in the para-position to the indole Nitrogen.

2.3.2 Variation of the lactam moiety

In order to investigate the scope of the reaction with respect to the lactam moiety, a range of substrates containing various patterns of substitution on the δ-lactam, as well as derivatives of capro-, enantho-, and caprylolactams were synthesized, following several synthetic plans.



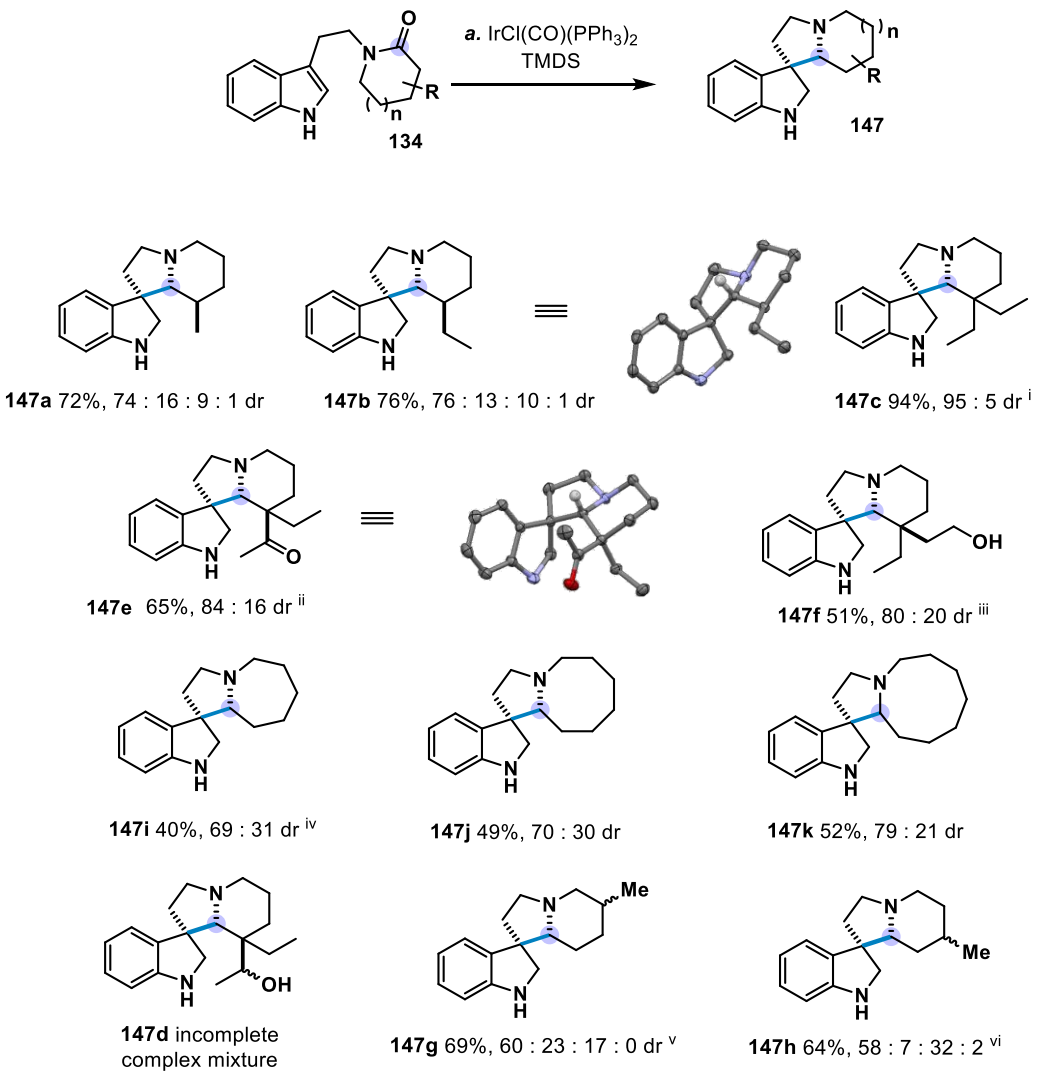
Reagents and conditions: (a) LDA (2 equiv.), then MeI, THF, −78 °C, 3 h, 62% (**134a**), or LDA (2 equiv.), then EtI, THF, −78 °C, 3 h, 82% (**134b**), along with 9% (**134c**) or LDA (2 equiv.), then acetaldehyde, THF, −78 °C, 3 h, 71%, inconsequetial 3 : 1dr (**134d**); (b) IBX, DMSO, 77 °C, 3 h, 82% (c) LDA then EtI, 9 : 1 THF/HMPA, −78 °C, 3 h, 41%; (d) LDA, then EtI, 9 : 1 THF/HMPA, −78 °C, 3 h, 59%; (e) tryptamine, EtOH, 78 °C, 16 h, 67%; (f) Piperidine, K_2CO_3, neat, rt, 18 h; (g) **139**, MeCN, 82 °C, 24 h, then (h) AcOH, H_2O, 82 °C, 48 h; 33% over 3 steps; (i) H_2, PtO_2, $FeSO_4 \cdot 7H_2O$ EtOH, rt, 16 h, 80%; (j) TFA, CH_2Cl_2, rt, 15 h, quant. (**141** and **143**); (k) tryptamine, neat, 200 °C, 30% (**134g**), 38% (**134h**), (l) $NaBH_4$, THF, rt, 72 h (m) NaH, $Br(CH_2)_4Br$, 4 : 1 THF/DMF, rt, 18 h, 75% (**145a**), 83% (**145b**), 73% (**145c**) ; (e) NMO, DMSO, rt, 16 h, 65% (**146a**), 53% (**146b**), 63% (**146c**) (f) $PhNHNH_2$, 25 : 1 THF/H_2SO_4, , 66 °C, 57% (**134i**), 67% (**134j**), 67% (**134k**).

* substrates in part C already prepared by Dr A. W. Gregory, a previous member of the group.

Scheme 26. Synthesis of substrates with variations on the lactam moiety (substrates **134i-k** prepared by Dr A. W. Gregory).

Using the natural reactivity of our previously synthesized model substrate **125**, alkylation could be performed in α position of the lactam carbonyl. Pleasingly, the indole N-H did not require a protecting group as it could be deprotonated and did not interfere with the alkylation reaction. Alkylation with MeI gave **134a**, while the use of EtI led to isolation of both the mono- and bis alkylated **134b** and **134c**. Subjecting **125** to aldol conditions with acetaldehyde as the acceptor could also be undertaken, and subsequent IBX-mediated oxidation delivered α-quaternary ketone **134e**.

Starting from γ-butyrolactone **135**, another α-quaternary lactone **137** could be obtained,[16] and after *N*-alkylation with concomitant lactone opening, lactam **134f** could be accessed. γ-methyl and β-methyl substituted **134g** and **134h** could be synthesized by a one-pot *N*-alkylation lactamisation procedure from the lactone in harsh conditions (neat, 200 °C), in moderate yields.[17] Finally, in order to access the 7-, 8-, and 9-membered ring lactams derivatives, an *N*-alkylation with 1,4 dibromobutane, followed by a Ganem oxidation, and a Fischer indole synthesis delivered **134i–134k**.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, CH_2Cl_2, –15 °C, 1 h. [i] rt, 6 h; [ii] catalyst loading: 5 mol% 6 h; [iii] catalyst loading: 5 mol%, rt, 24 h; [iv] performed by Dr A. W. Gregory; [v] 90% purity, isolated as the mixture of 2 isomers [vi] NMR yield, an inseparable mixture of the overreduced product and the 4 diastereoisomers was obtained

In this scheme, the dr are obtained from ^1H NMR analysis of the crude reaction. When four number are give, the first two numbers represent the isomers with an exo-S*, R* configuration.

Scheme 27. Scope on the lactam moiety.

The presence of a new stereocentre results in another set of diastereoisomer being produced for **147a** and **147b**. The diastereoselectivity on the 5-membered spiro pyrrolidine was thus 90 : 10, while the α-stereocentre induced a 82 : 18 control (where the methyl induced addition on the least hindered face,

resulting in the pictured isomer being predominant). Ethyl-substituted **147b** followed the same trend, and single crystal X-ray diffraction analysis confirmed the relative configuration of the major isomer.[iv]

Pleasingly, α-quaternary **134c** underwent cyclisation under the same reaction conditions, although due to the high steric demand – the 5-endo cyclisation being on a neopentylic iminium ion – higher catalyst loading, longer reaction time, and higher reaction temperature were required.

The functional group tolerance was tested with ketone-containing **134e** and primary alcohol containing **134f**. Pleasingly, these two substrates not only produced the desired aza-spiroindoline products, but the presence of the oxygen atom induced in both cases complete stereocontrol over the α-stereocenter, and only two isomers of the product were observed in the crude reaction mixture. It should be noted that the ketone carbonyl was not affected by the reductive conditions of the spirocyclisation, highlighting the chemoselectivity of the reductive system.

Capro-, enanthro- and caprylolactams derivatives **134i–134k** all underwent spirocyclisation to give **147i-147k**, although in moderate yields which largely reflects the propensity for over-reduction in these systems. This most likely arises from ring strain in these 7-, 8-, and 9-membered cyclic iminium ions which places the electrophilic carbon in a position less prone to undergo the 5-endo spirocyclisation.

Lastly, alcohol **134d** could not be completely converted, and isolation of the product was not possible, while **134g** and **134h** produced a very complex mixture of diastereomers and overreduction product (see a discussion on stereoselectivity section 2.4 of this chapter).

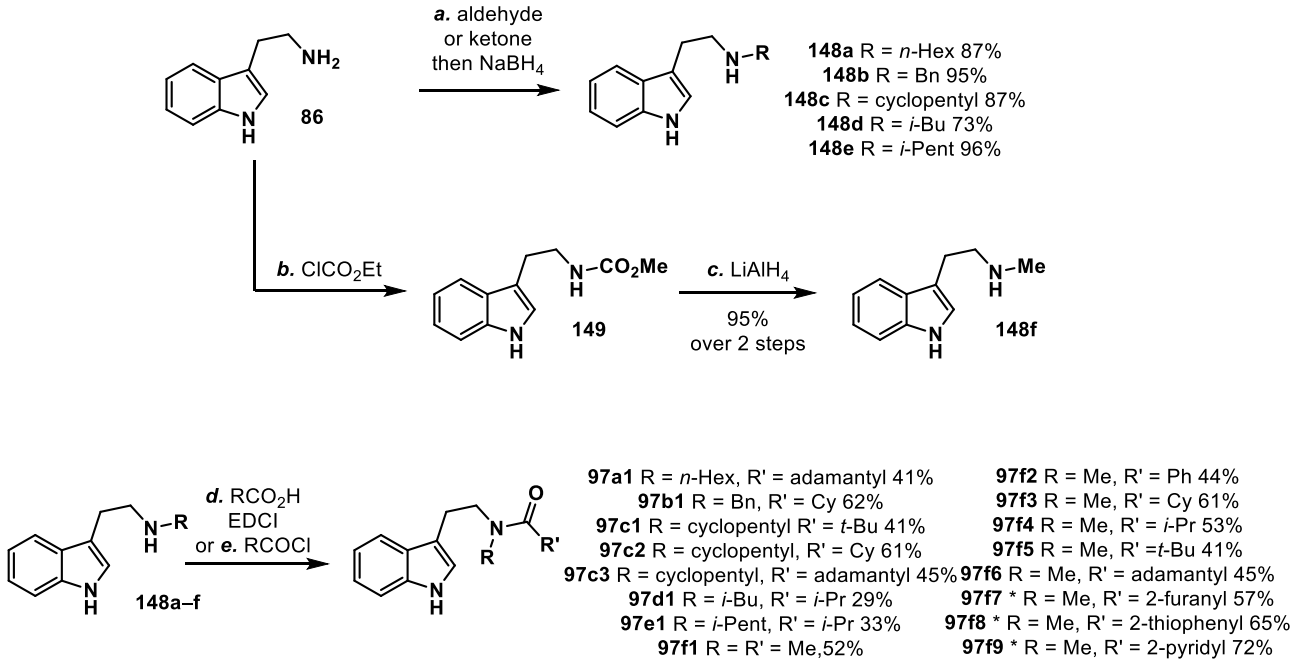
2.3.3 Introduction of acyclic amides

To access a wider range of spirocyclic indoline structures, we chose to synthesize substrates containing acyclic amides in place of the lactam. Though less abundant in nature, the tricyclic products could

[iv] It should be noted that only two isomers could be isolated in pure form (the most and third most abundant compounds in this mixture), the rest being isolated as a mixture of isomers.

incorporate aromatic rings and non-polar side chains, with two points of variations on the nitrogen atom of the amide, thus making this class attractive from a library generation point of view.

Using again tryptamine **86** as a branch point, a range of *N*-alkyl tryptamines **148a–148f** was made using either reductive amination or reduction of a carbamate. Simple amide coupling with either a carboxylic acid or the activated acyl chlorides gave substrates **97a1–97f9**. It should be noted that when moderate yields were obtained, they are often a consequence of using trituration or recrystallisation as operationally simple purification methods.



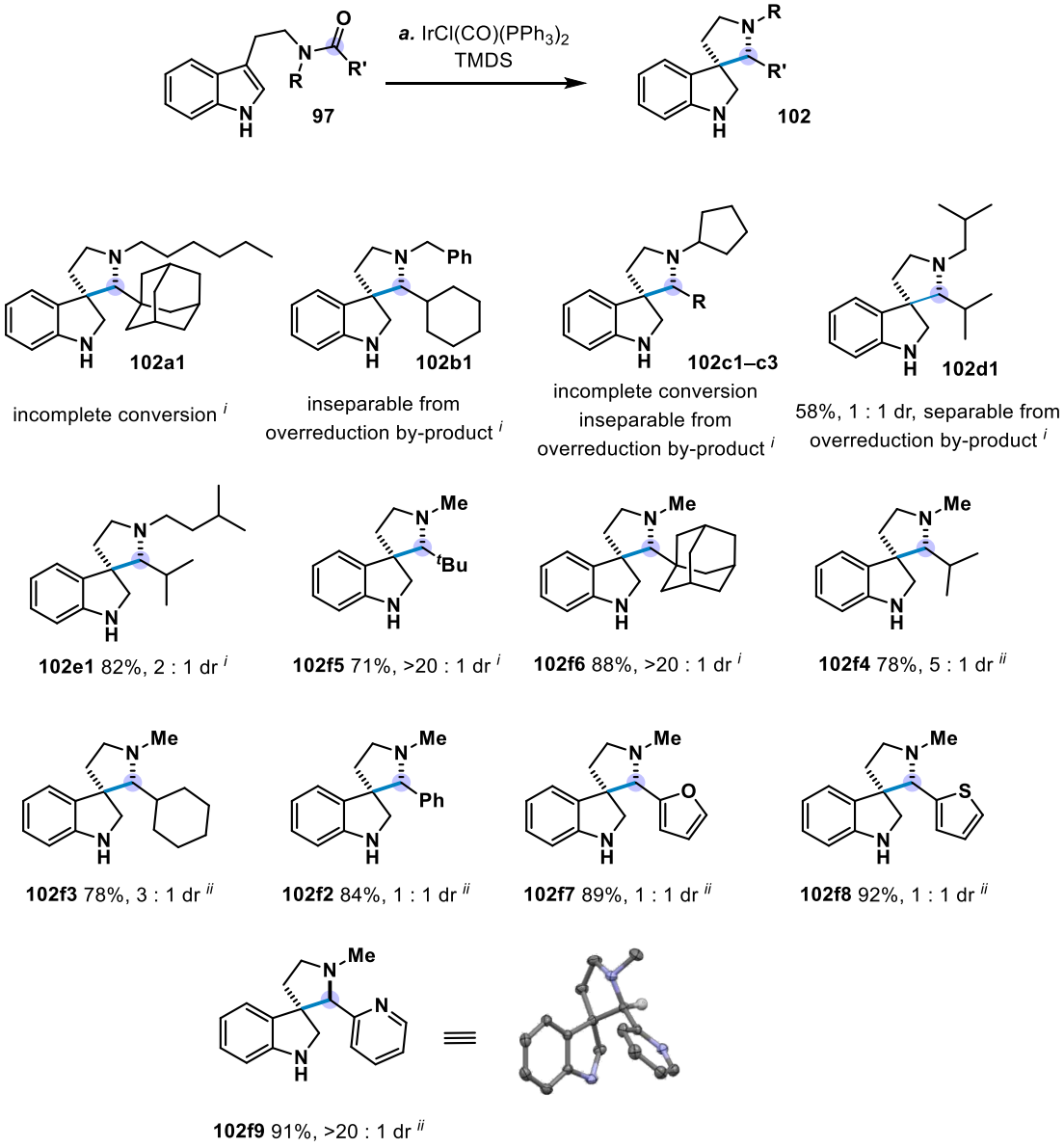
Reagents and conditions: (a) hexanal (**148a**, 87%), or benzaldehyde (**148b**, 95%), or cyclopentanone (**148c**, 87%), or isobutanal (**148d**, 73%), or isovaleraldehyde (**148e**, 96%), MeOH, rt, 36 h, then $NaBH_4$, rt, 30 min; (b) ethyl chloroformate, NaOH (4 M), $CHCl_3$, rt, 3 h; (c) $LiAlH_4$, THF, 0 °C to 66 °C, 1 h, (**148f**, 95% over 2 steps); (d) 2-furanoic acid (**97f7**, 57%), or 2-thiophene carboxylic acid (**97f8**, 65%)) or 2-pyridine carboxylic acid (**97f9**, 72%), EDCI, DMAP (10 mol%), CH_2Cl_2, rt, 16 h; (e) AcCl (**97a1**, 52%) or PhCOCl (**97f2**, 44%), or CyCOCl (**97f3**, **97b1**, **97c2**, 61%, 62%, 61% respectively) or iPrCOCl (**97f4**, **97d1**, **97e1**, 53%, 29%, 33% respectively) or tBuCOCl (**97f5**, **97c1**, 41%, 41% respectively) or 1-adamantyl carbonylchloride (**97f6**, **97a1**, **97c3**, 45%, 41%, 45% respectively), NEt_3, CH_2Cl_2, rt, 3 h.

* subtrates prepared by Dr A. W. Gregory, a previous member of the group.

Scheme 28. Synthesis of acyclic amides containing substrates.

This library of sixteen indole-tethered amides was subjected to the spirocyclisation conditions with various degrees of success (**Scheme 29**). From substrates **97a1**, **97b1**, **97c1–c3**, it was clearly demonstrated that the steric bulk of the side-chain originating from the nitrogen atom is crucial both for

conversion of the amide to the silylated hemiaminal, and for the 5-endo cyclisation to prevail over the hydride reduction giving rise to the over-reduced by-product. As a result, complex inseparable mixtures were obtained with α-branched *N*-cyclopentyl **97c1–c3** and *N*-benzyl **97b1**. Moderate yield of the desired spirocyclic product **102d1** was obtained (the major by-product observed in the crude reaction mixture being the overreduced acyclic amine), while a good yield of 82% was observed for **102e1**, showing that branching on the nitrogen side-chain was possible if at a remote enough position so as to not hinder the approach of the iminium ion to the C^3 position of the indole. Pleasingly, with *N*-Me examples, most substrates generated the spiroindolines, even with extreme steric bulk on the amide carbonyl side (**97f5** and **97f6**), as well as in the presence of acidic protons (**97f3** and **97f4**) or (hetero)aromatic amides (**97f2**, **97f7**–**f9**). These last examples are of particular importance for potential applications in medicinal chemistry, due to the usual difficulty to develop methodologies compatible with such heterocycles (in particular pyridine). It is worth noting the general loss of diastereocontrol in the spirocyclisation compared to lactam-based substrates, with the exception of the pyridyl example, interestingly showing opposite selectivity: this will be discussed in the next section of this chapter.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, CH_2Cl_2, rt, 1 h. [i] catalyst loading: 5 mol%, rt, 24 h; [ii] catalyst loading: 1 mol%, rt, 6 h

Scheme 29. Scope with acyclic amides.

2.4 Diastereocontrol in the spirocyclisation reaction

2.4.1 Determination of relative stereoconfiguration

The determination of the relative configuration of the spiroindoline products was mostly achieved through NMR analysis. Single crystal X-ray analysis of the cyclized model substrate gave unambiguous

stereochemical assignment, which was in accordance with NOESY experiments. A remarkable splitting of the ^{1}H NMR signal of the indoline CH_2 group in the case of the major (exo-S*,R*) isomer - also called « syn isomer » in this chapter for simplicity - was visible, and this phenomenon - consequence of the diasterotopic nature of the two protons - was observed for all examples with a sterically demanding group. The following figures illustrates this phenomenon.

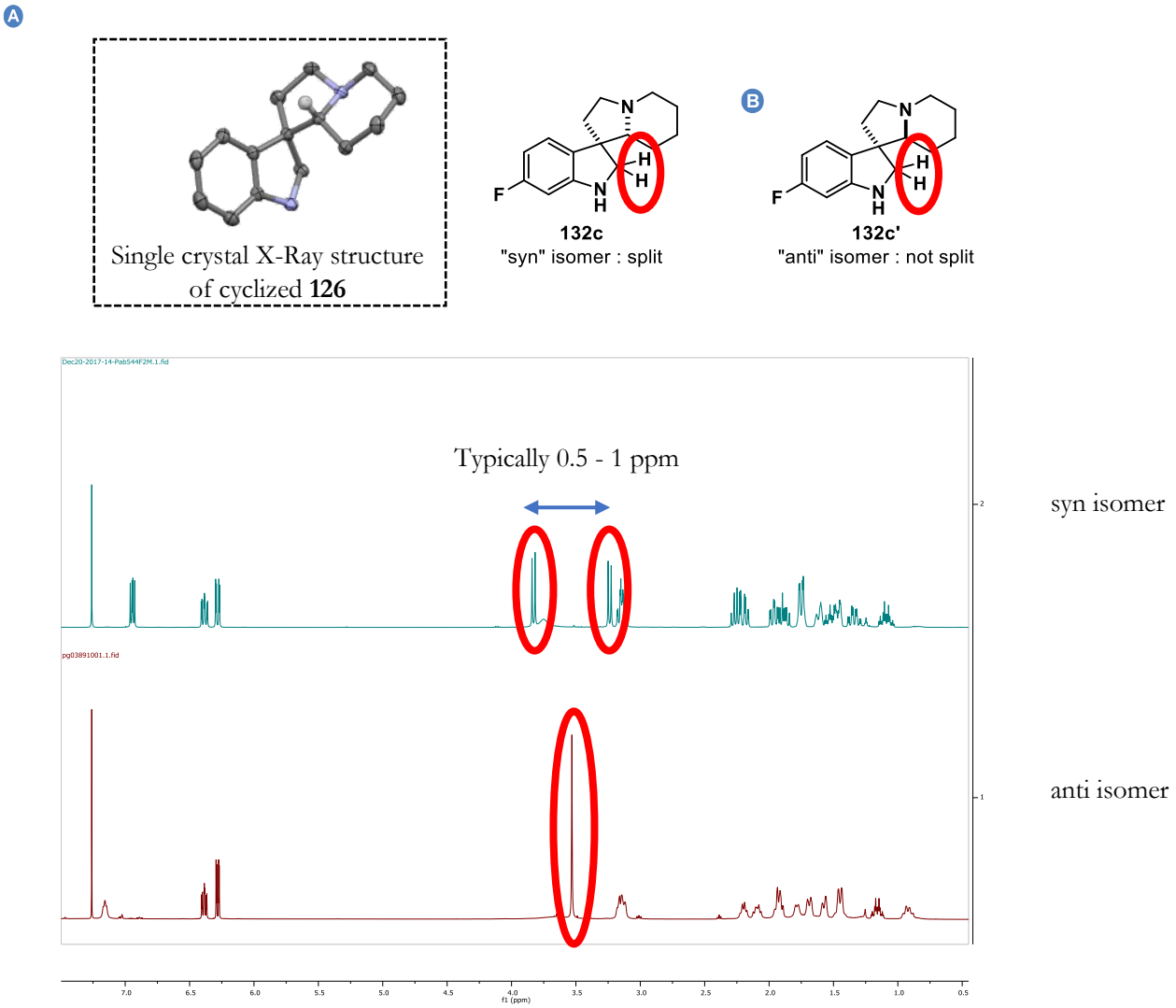


Figure 8. Comparison of the splitting of the diastereotopic protons of syn and anti cyclized isomers.

For examples containing three stereocentres, single crystal X-ray analysis confirmed the relative configuration of the major isomer. Methyl-substituted **137a** was assigned by analogy with **137b**.

Finally, for aromatic and heteroaromatic examples **102f2, 102f7–102f9**, NOESY analysis confirmed the relative stereoconfiguration. A single crystal could also be grown for pyridyl example **102f9**, which stands out as it was produced as a single diastereomer (see section **2.4.5** for a discussion).

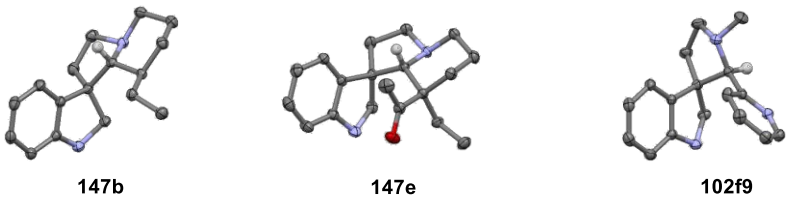


Figure 9. X-ray structures of three of the spiroindolines. All protons atoms but the one at the newly-formed tertiary stereocentre are omitted for clarity.

2.4.2 Origin of the diastereoselectivity: cyclic examples

For this spirocyclisation reaction to be diastereoselective, there most likely has to be a facial recognition between the indole and the iminium moiety during the C-C bond forming step.[v] If the *si* face of the indole is indeed to react with the *re* face of the iminium ion, the major *syn* isomer is ultimately produced while the *si* face of the indole reacting with the *si* face of the iminium species generates the minor *anti* isomer. As the reaction has no chiral component, the *re* face of the indole also reacts with the *si* face of the iminium ion in a transition state of equal energy, producing the enantiomer of the major isomer. The product is thus obtained in a racemic fashion.

Our hypothesis is that the endo transition state is disfavoured due to steric clash between the indole and the aliphatic part of the cyclic iminium ion (**Figure 10**, **A** vs **B**). The structure of the transition state should follow a Bürgi-Dunitz-type trajectory for the approach of the indole, with an envelope shape for

[v] The other possibility would be production of the two diastereoisomers of the 5-endo cyclisation, and the final reduction being faster on the isomer giving rise to the syn isomer of the product. The cyclisation event being most likely reversible, an effect similar to a dynamic kinetic resolution could be observed. Although this hypothesis cannot be ruled out, the experimental data as well as preliminary computational data fits best the explanation that follows.

the forming pyrrolidine ring forming. This places the cyclic iminium ion in an endo position relative to the indole which causes steric clash and thus an increase in the $\Delta\Delta G^{\neq}$.

This hypothesis is corroborated by the perfect diastereoselectivity observed in the case of 4-Br substituted **132a**: in the disfavoured proposed transition state the bromine atom would be pointing directly towards the cyclic iminium ion (**Figure 10**, **C**).

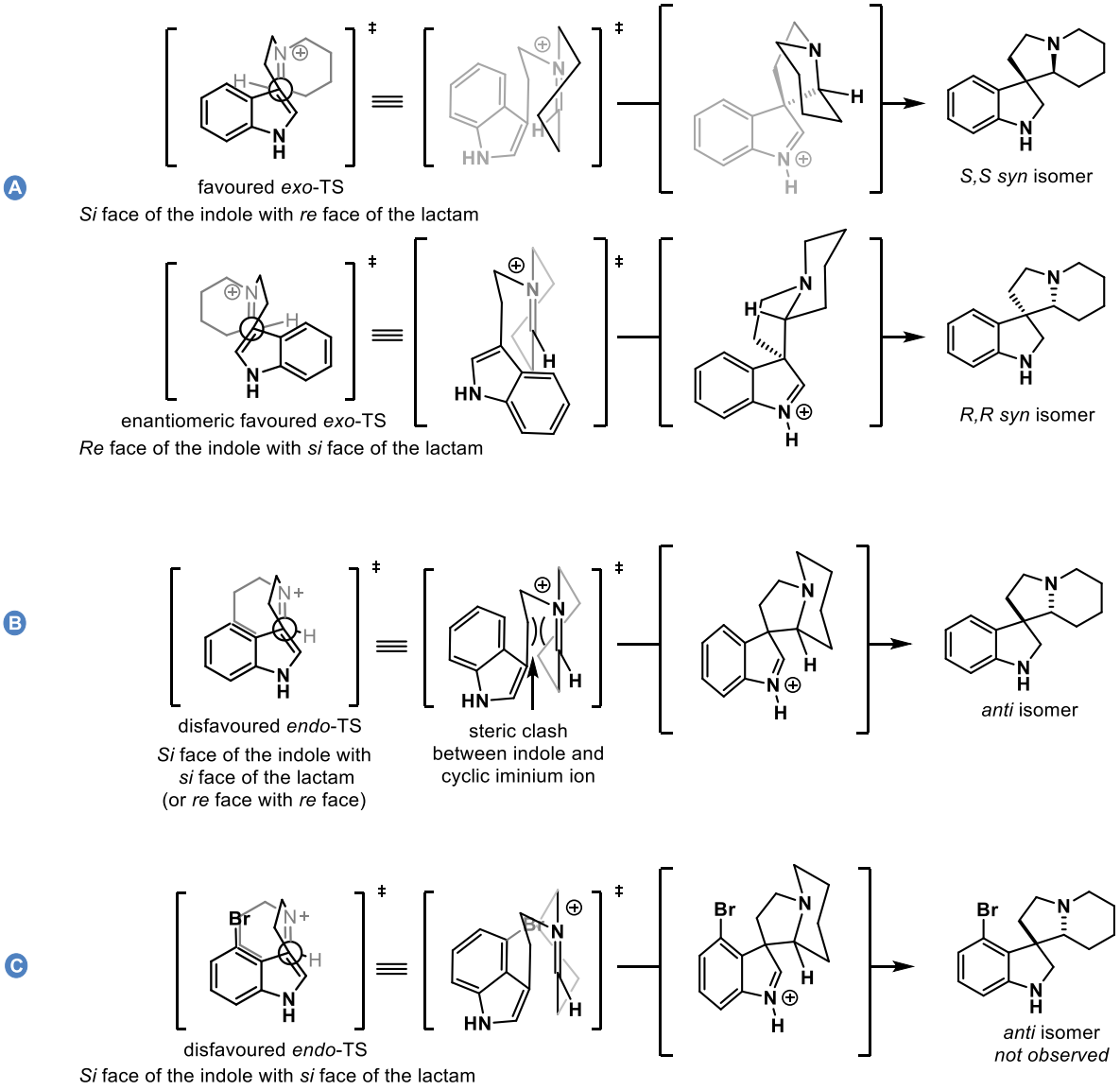


Figure 10. Proposed transition state structure for cyclic examples.

2.4.3 Origin of the diastereoselectivity: substituted cyclic examples

In the cases where the cyclic iminium ion is substituted, up to three stereocentres are present in the product, and thus four diastereomers can be produced. The two stereocentres of the pyrrolidine ring follow the principles discussed in the previous section, where selectivity originating from the existing stereocentre - independent from the *syn* to *anti* ratio - should also be observed.

The α-alkylated examples show a selectivity of 73 : 16 : 9 : 1 (90 : 10 *syn* to *anti* at the pyrrolidine stereocentres, 82 : 18 *anti* to *syn* at the α-position), and 76 : 13 : 10 : 1 (89 : 11 *syn* to *anti* at the pyrrolidine stereocentres, 86 : 14 *anti* to *syn* at the α-position) for methyl substituted **147a**, and ethyl substituted **147b** respectively. The relatively good (>5 : 1) dr obtained at the α-position simply arises from preferred addition onto the least hindered face of the iminium electrophile (**Figure 11**, **A1** vs **A2**). It is worth noting that in order to follow the Furst-Plattner rule, the α-substituent must be in a pseudo-axial position (**Figure 11**, **A1** vs **A1'**).[18]

The case of β-methyl substituted **147g** is interesting, though complex. In the crude reaction mixture as analysed by ^{1}H NMR, the four diastereomers are observed as a 59 : 7 : 32 : 2 mixture (66 : 34 *syn* to *anti* at the pyrrolidine stereocentres, 90 : 10 *anti* to *syn* at the β-position). In this case, the substituent is in the β-position of the iminium ion, and the effect deriving from the Furst Plattner is thus stronger (explaining a 90 : 10 *anti* to *syn* selectivity that is higher than the 82 : 18 observed for **147a**). As for the endo/exo selectivity, the presence of the β-substituent seems to unexplainably reduce the energy gap between the endo and exo transition state (**Figure 11**, **B1** and **B1'**, closer in energy than the other pairs of transition states, see A vs B in **Figure 10**).

Finally, γ-methyl substituted **147h** displays a selectivity of 60 : 23 : 17 : 0 (83 : 17 *syn* to *anti* at the pyrrolidine stereocentres, the steric bulk being held further away from the bond forming site than in the case of **147a**, a poorer selectivity was observed (**Figure 11**, **C1** vs **C2**). Analysis of the ^{1}H NMR of the reaction did not allow stereochemical assignments to be determined unambiguously at the γ-position.

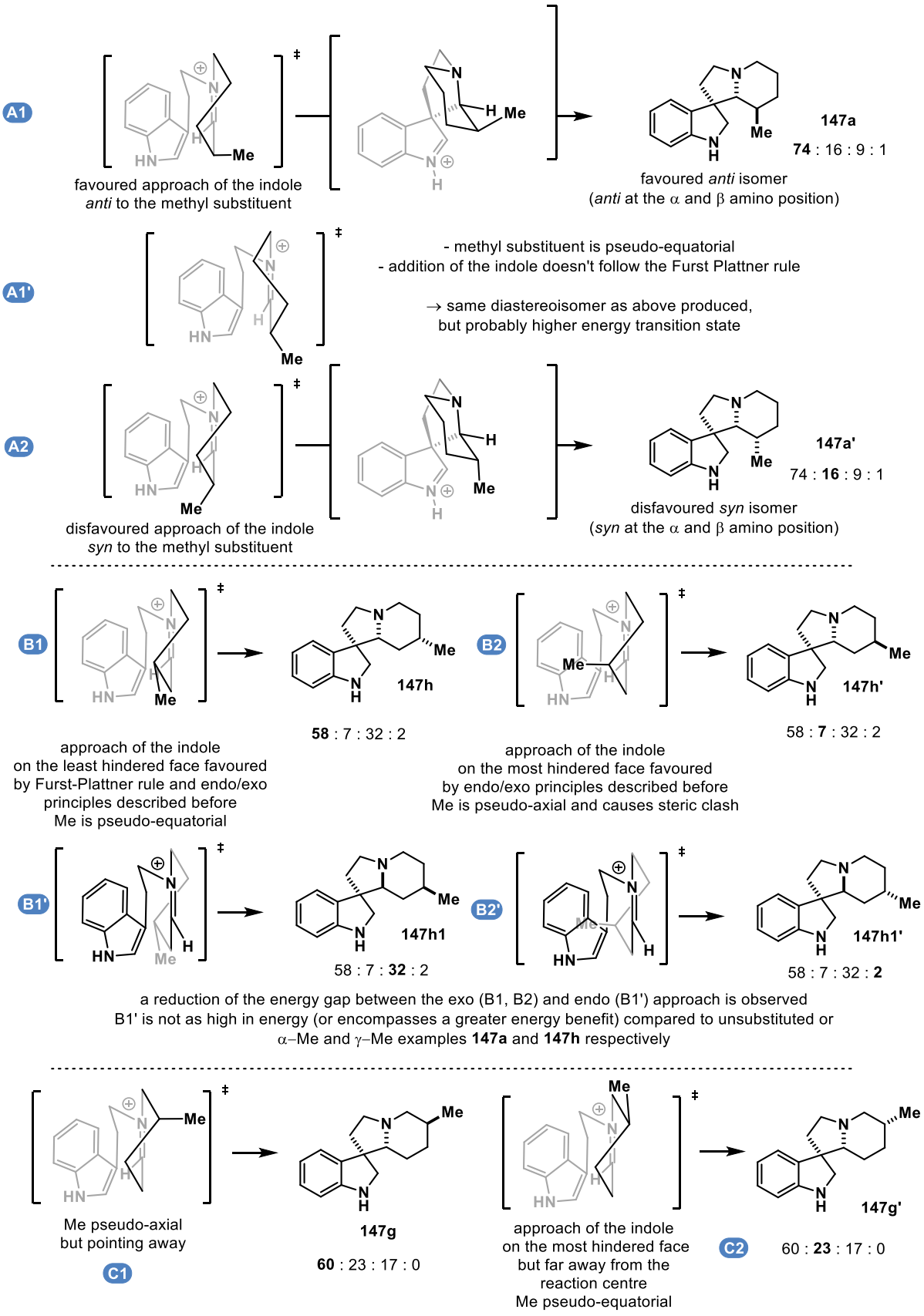


Figure 11. Proposed transition states for substituted cyclic examples with one stereocentre in the lactam substrate.

The last case studies was with α-quaternary oxygen-containing substrates. Surprisingly for **147e** and **147f**, the stereocontrol from the quaternary stereocentre is complete (>20 : 1 as opposed to <5 : 1 for alkyl-substituted examples). This could be attributed to an orbital stabilisation between the Lewis basic lone pairs of the oxygen atom and the empty iminium orbital, leading to an approach of the indole exclusively *anti* to the oxygen-containing group.

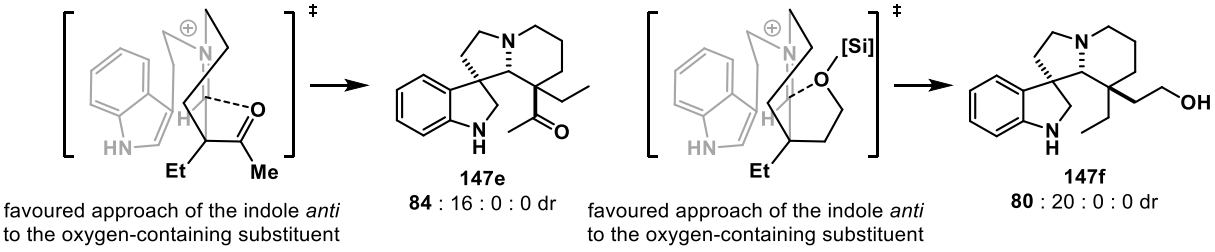


Figure 12. Oxygen-containing substrates lead to the exclusive formation of two stereoisomers.

2.4.5 Origin of the diastereoselectivity: acyclic examples

Two trends exist for the spiroindoline products obtained from acyclic amides : the (hetero)-aromatic containing substrate, where no (or very close to no) diastereoselectivity is observed, and the amides with an sp^3-rich framework on the carbonyl side, following the selectivity trend established by cyclic lactam substrates.

Again, these results are (bar the 2-pyridyl substituted example **102f9**) in line with our prior hypothesis (see **Figure 13**). The substrates with an aromatic amide have a flat substituent which, as opposed to the cyclic or sp^3-rich iminium ion, will cause reduced steric clash with the indole in the endo transition state. One could even imagine that a π-stacking interaction could reduce the energy level of this transition state, particularly with pyridyl **102f9** (π-stacking is indeed notoriously stronger between electron-rich (indole) and electron-poor (pyridine) aromatic rings).[19] Other than this, it would be unclear why this substrate shows complete diastereoselectivity, particularly considering it gives rise to the *anti* diastereoisomer, the minor isomer for all of the other substrates.

For furyl-, thiophenyl- and phenyl- substituted, **102f7**, **102f8** and **102f2**, this lack of steric clash in the endo transitions state results in a 1 : 1 observed dr.

Finally, the situation is more complex with the branched amine **102d1** and **102e1**. Interestingly, for the *N*-*i*-butyl **102d1**, a dr of 1 : 1 can be observed, in contrast with the *N*-Me **102f4** (dr of 5 : 1). It is unclear why a bulkier side-chain reduces the diastereoselectivity, especially considering *N*- *i*-pentyl **102e1** does show a selectivity, albeit reduced compared to **102f4**, of 2 : 1 dr. One could speculate about the steric effects caused by syn-pentane interactions for **102d1**, and its potential impact on the geometry of the iminium ion, but the full explanation remains unclear.

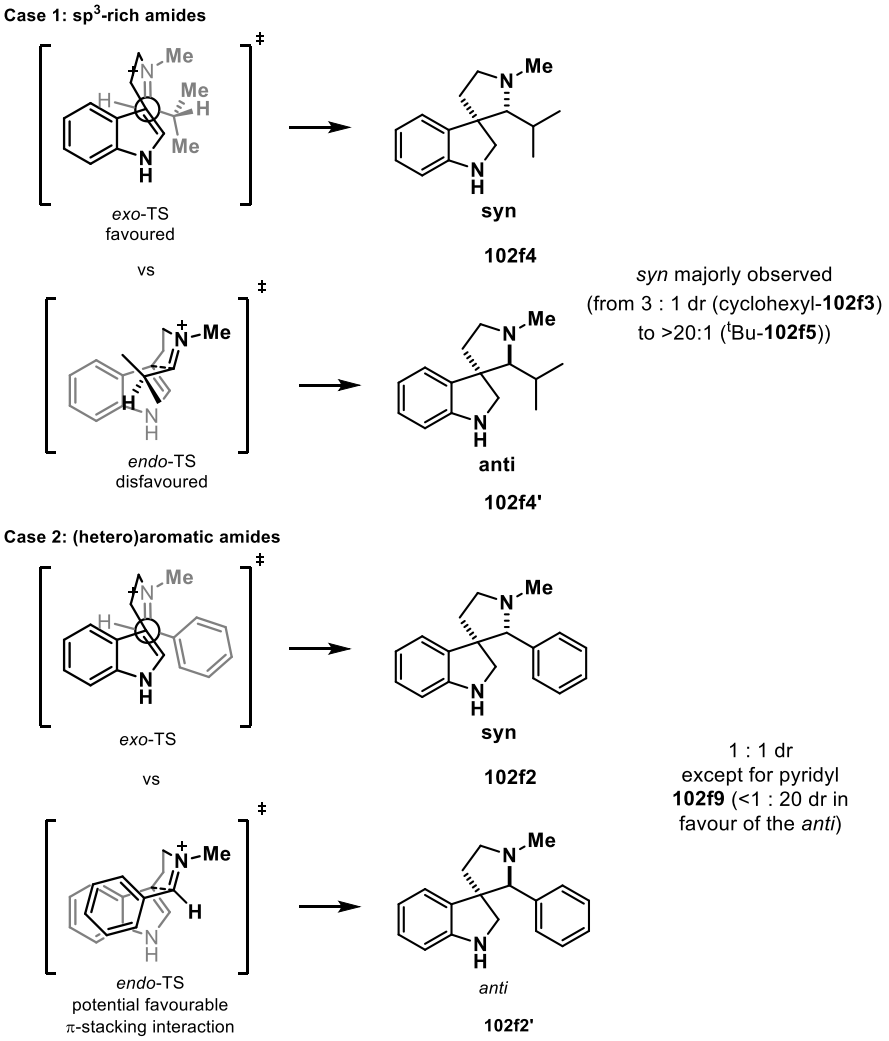


Figure 13. Proposed transition states model for acyclic examples.

2.5 Efforts towards C^2-substituted indolines

2.5.1 Aspidospermidine and limaspermidine

On close examination of the scope, it appeared that two of the spirocyclic indoline products (**147p** and **147f**) had a structure resembling that of two natural products, aspidospermidine **150** and limaspermidine **151** respectively.

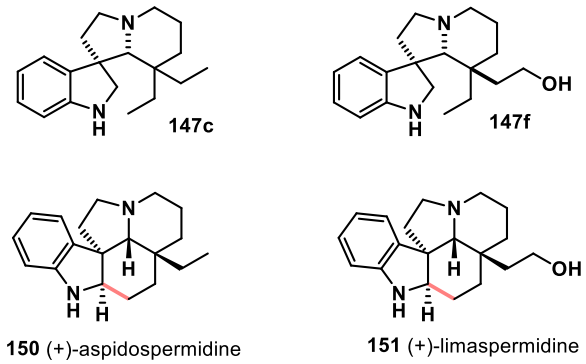


Figure 14. Two products obtained via the developed methodology, and two natural products with a very similar structure.

A simple C–C bond between the C^2 position of the indole and the terminal carbon of an ethyl group separates the cyclised substrates from the natural products. If the formation of such a C-C bond was not possible with the current knowledge in organic chemistry, efforts could be made to design substrates allowing the production of spirocyclic indoline structures that could be elaborated into the natural products. Since C^2 substituted indoles were shown to be poor substrates for the spirocyclisation (see **Scheme 25, B, 131i**), we looked into forming the desired bond either during or after the cascade sequence leading to the formation of the spirocyclic indoline products.

2.5.2 Interrupting an interrupted Pictet-Spengler ?

The putative mechanism of the spirocyclisation methodology discussed previously includes a spirocyclic indolenium intermediate, which is then reduced by the catalytic system. However, we conceived that with a suitably placed competitive carbon-centred nucleophile, one could hope to interrupt the sequence to create a C^2-substituted indoline.

In order to outcompete the hydride reduction, we chose to construct a substrate with an intramolecular nucleophile at C^{16}, which in turn could produce the desired 6-membered ring.

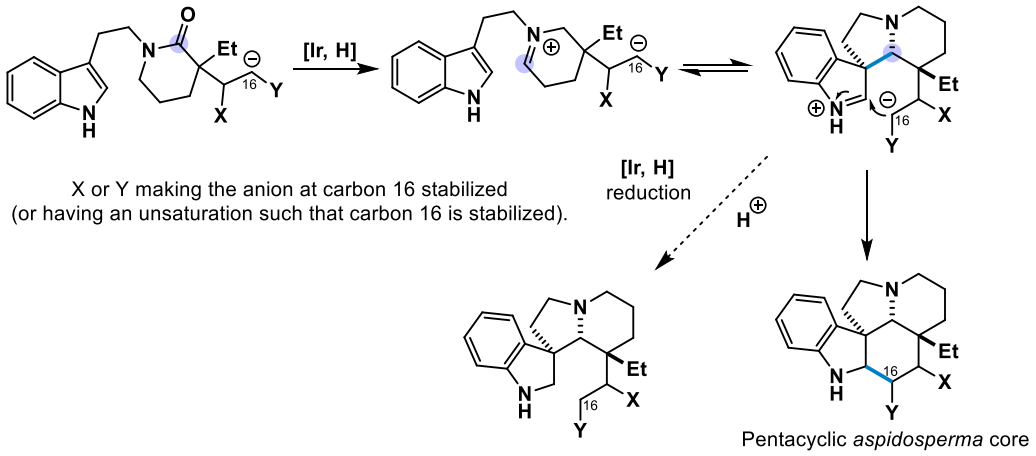


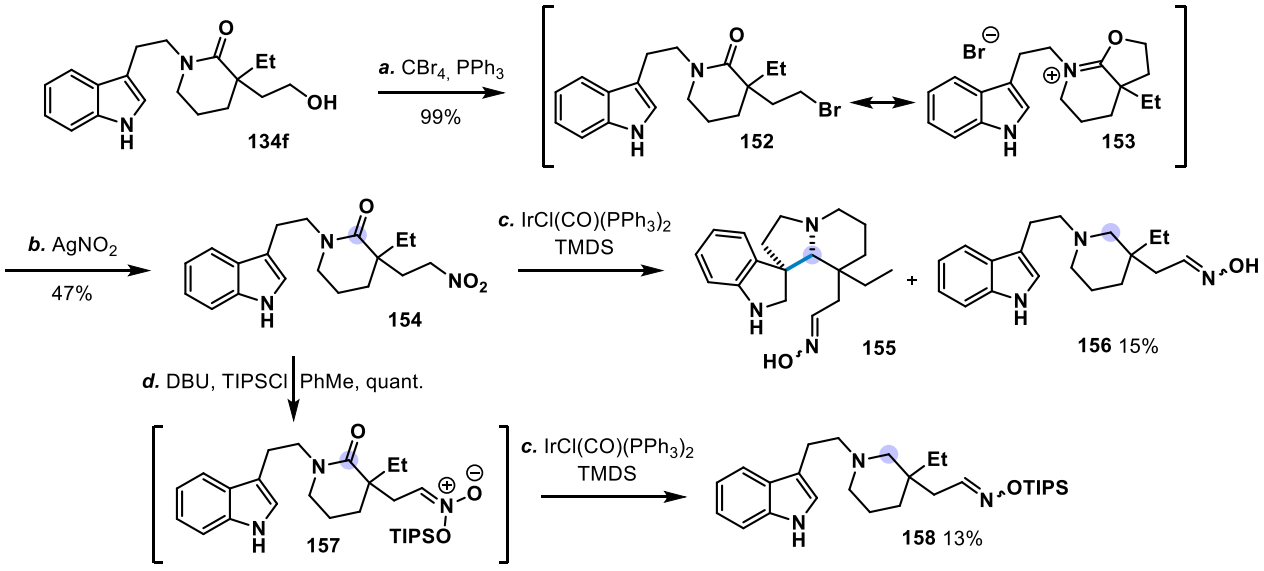
Figure 15. Proposed interruption of the final reduction by C^{16} attack on transient indolenium to complete a one pot-two cyclisation strategy.

2.5.3 Nitro and nitronates

With some precedent existing for iridium-catalysed nitro-Mannich reaction,[13c] we chose to start our investigations by introducing a nitro group at the C^{16} position. The synthesis started with primary alcohol **134f**, previously prepared during the exploration of the scope. To render the carbon bearing the alcohol functional group potentially nucleophilic, we chose to convert the alcohol into a nitro group. This was achieved through an Appel reaction, followed by nitration with silver nitrite to give **154**. Interestingly the intermediate bromide could be isolated as a mixture of two forms **152** and **153**. The amide was in this

case nucleophilic enough to intramolecularly displace the bromide, to form an imidate salt. This was fortunately inconsequential, as the nitrite ion was able to react to produce the desired substrate **154**.

When submitted to the reaction conditions, interestingly, no conversion was observed. Switching solvent to toluene uncovered reactivity, however no desired C-C bond was formed. ^{1}H NMR analysis of the crude reaction mixture showed peaks corresponding to a cyclised product with a methylene indoline signal, tentatively assigned as **155**, along with over-reduced product **156**, which was the sole product of the reaction isolable after flash column chromatography. In both cases interestingly, the nitro group was reduced to an oxime, which is a remarkable feature of the catalytic system, not precedented to the best of our knowledge.



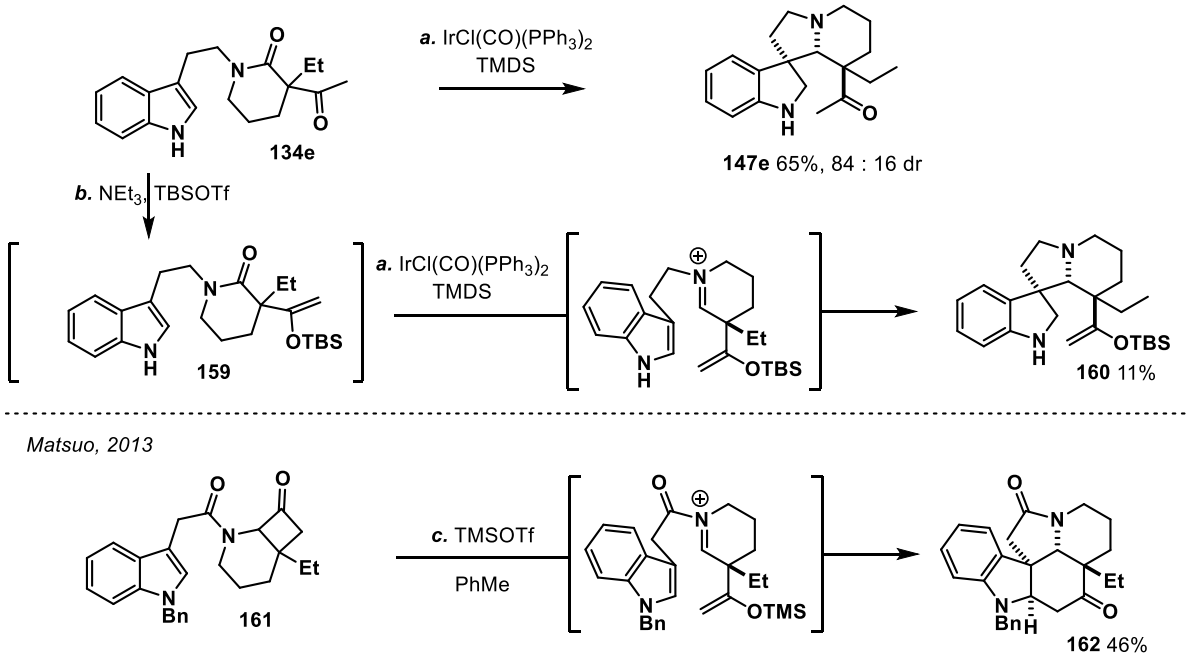
Reagents and conditions: (a) CBr_4, PPh_3, CH_2Cl_2, rt, 1 h, 99%; (b) $AgNO_2$, CH_2Cl_2, rt, 1 h, 47%; (c) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, rt, 16 h, traces **155** , 15% **156** (d) DBU, TIPSCl, PhMe-d_8, rt, 1 h.

Scheme 30. Nitro-Mannich strategy fails to deliver the desired cyclisation at C^2.

In an attempt to render the carbon bearing the nitro group more nucleophilic, pre-activation to the silyl nitronate was also carried out *in situ*. When complete conversion to the nitronate **157** was observed, standard spirocyclisation conditions were applied. This time, the crude reaction mixture did not show any indoline signal at all, and the only recoverable material was the over-reduced non-cyclised silyl oxime **158**.

2.5.4 Ketone and enol ether

Faced with a clear incompatibility of the nitro group with our developed reaction, we turned our attention towards making the C^{16} nucleophilic by introducing a carbonyl in the adjacent position. We had already shown that substrate **147e** could undergo spirocyclisation, but unsurprisingly, in the absence of a suitable base, the α-position of the carbonyl was insufficiently nucleophilic to intercept the spirocyclic indolenium. Again, pre-activation via the formation of a silyl enol ether was attempted, but when submitted to the reaction condition, only a low yield of **160** could be obtained, with no desired C–C bond formation (similar results were observed with less sterically hindered TES enol ether).



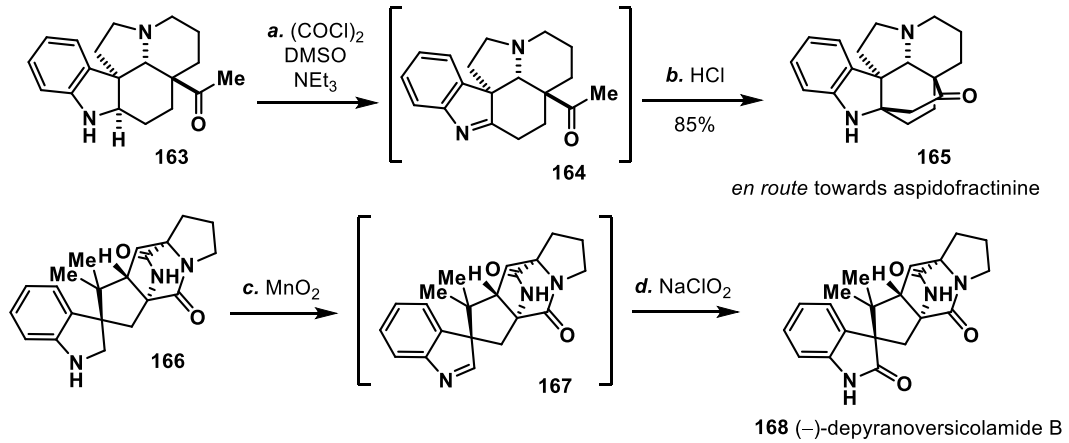
Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, CH_2Cl_2, rt, 16 h, 65%, 84 : 16 dr
(b) DBU, TIPSCl, PhMe-d_8, rt, 1 h; (c) TMSOTf, PhMe, 111 °C, 10 min, 46% **162**, 32 % of the epimer at the quaternary α position.

Scheme 31. No cyclisation at C^2 with a silyl enol ether **159** despite a precedented approach.

This was surprising considering a similar – but subtly different – approach had previously been used by Matsuo *et al* in their synthesis of (±)-aspidospermidine.[20] We can only infer that in our case, the hydride reduction outcompetes an intramolecular carbon-based nucleophile. Consequently, this concluded our efforts towards constructing the missing C–C bond during the spirocyclisation step.

2.5.5 Functionalisation at C^2 post-spirocyclisation

Having been unsuccessful to make the crucial C-C bond in the key step - most likely because of the impossibility to compete with the final hydride reduction in the mechanism of the spirocyclisation - we directed our efforts towards regenerating an electrophile at C^2 after the spiroindoline formation. Some precedent exists for the oxidation of indolines to 3-H indoles,[21] even with a quaternary carbon at the C^3 position,[22] but the desired imine product **164** and **167** appeared to be rather unstable.[23] Nevertheless, such a transformation was utilised in a formal synthesis of aspidofractinine in 1989,[22b] using a Swern oxidation followed by a Mannich reaction to give **165**, and in a total synthesis of (-)-depyranoversicolamide B **168** more recently in 2015,[22c] where an unsubstituted-at-C^2 indoline was oxidized to an unstable imine **167**, and subsequently further oxidized to the spiroxindole natural product.



Reagents and conditions: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −60 °C to rt, 1 h; (b) HCl, MeOH, 65 °C, unknown reaction time, 85% over 2 steps; (c) MnO_2, CH_2Cl_2, rt, 2 h; (d) $NaClO_2$, NaH_2PO_4, MeCN, rt, 3 h.

Scheme 32. Precedent for oxidation of an indoline with subsequent use of the imine as an electrophile.

Due to its structural similarity with indoline **163**, spirocyclised product **147e** was used as a model substrate for these transformations. If the configuration at the quaternary carbon would give rise to a precursor of an epimer of aspidospermidine, the connectivity should still give an indication of the reactivity of the spiroindoline.

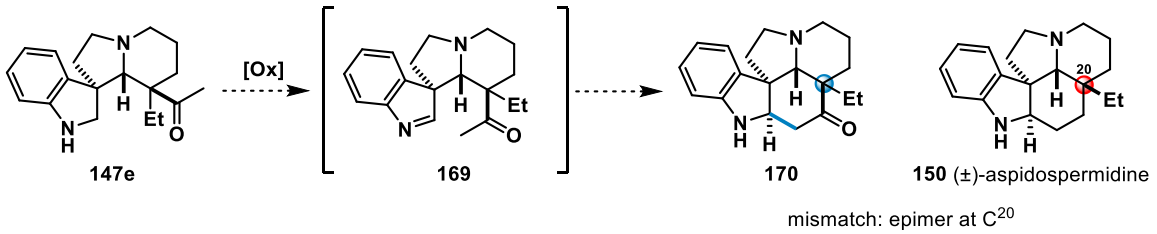
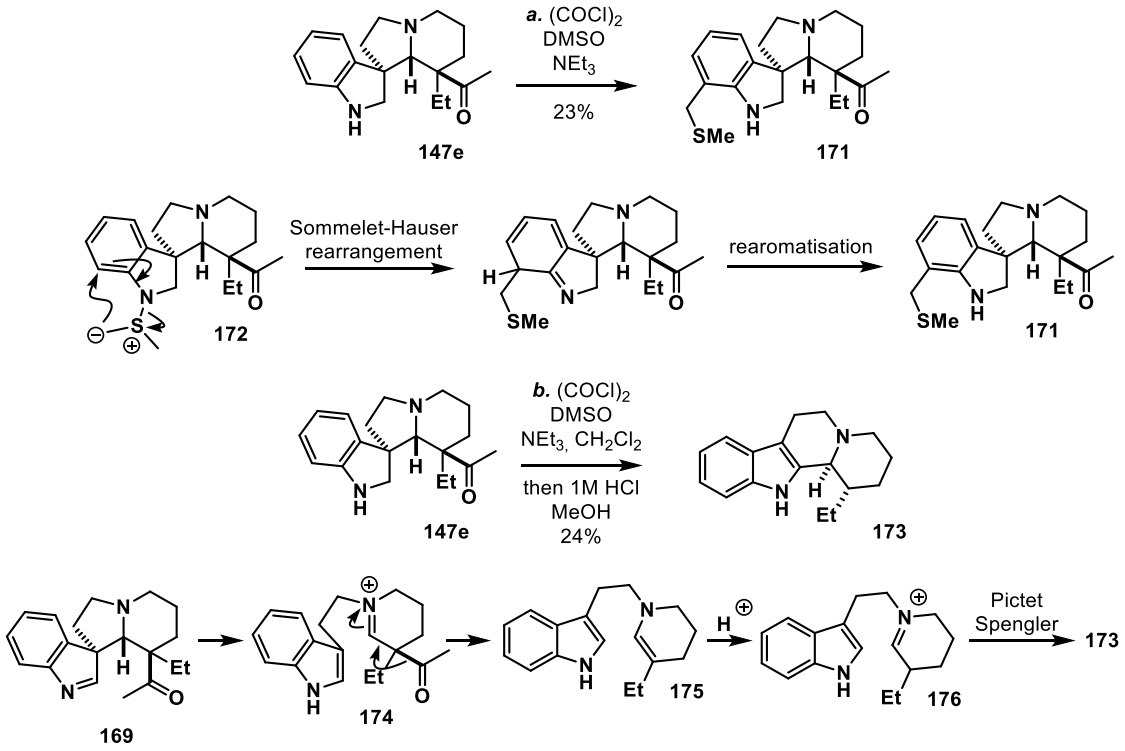


Figure 16. **147e**: precursor to an epimer of aspidospermidine?

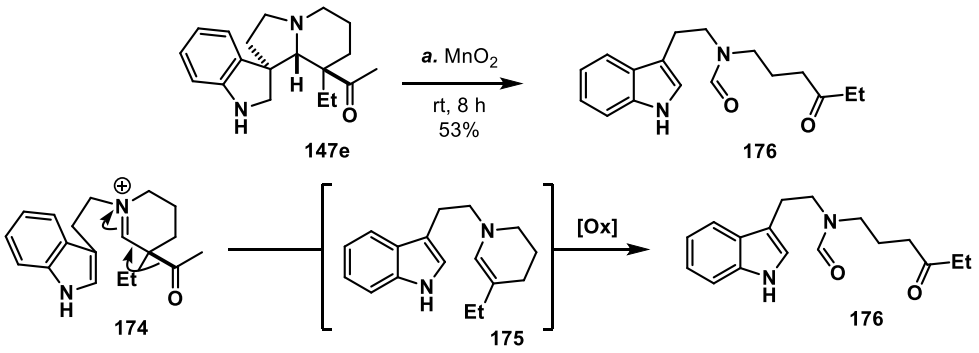
When typical reaction conditions for a Swern reaction were applied, we were surprised to isolate, albeit in low yield, C^7-thiomethoxyether functionalised indole **171**. If the Sommelet-Hauser-type rearrangement taking place from the azasulfonium intermediate **172** is to some extent known,[24] this is to the best of our knowledge the first time such intermediates are accessed in a one-pot process in a Swern-like oxidation approach. This product still shows that the Swern oxidation process is being initiated, and we decided to attempt to submit the crude of the reaction to the Mannich conditions employed during the formal synthesis of aspidofractinine. To our surprise, we isolated rearomatised tetrahydro-β-carboline **173**, matching the literature.[25] We believe the desired imine **169** is produced, but collapses back to the iminium ion **174** that was an intermediate of our developed spirocyclisation. A deacetylation then occurs, and enamine-iminium tautomerization give rise to cyclic iminium ion **176**. In the acidic reaction conditions, typical of a Pictet Spengler reaction, the fate of the iminium species follows a 6-endo cyclisation to give the observed rearranged product **173**.



Reagents and conditions: (a) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 1 h, 23%; (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C to rt, 10 min then 1 M HCl, MeOH, 80 °C, 16 h, 24%.

Scheme 33. Attempted Swern oxidation leads to undesired C7-functionlisation or skeletal rearrangement.

In order to avoid the use of acidic conditions, and due to the existence of some precedent for C2-unsubstituted indoline (see **Scheme 34**),[22c] we attempted the Manganese-mediated oxidation. If the desired imine (**169**, **Scheme 33**) was probably an intermediate in this reaction, complete skeletal rearrangement was observed, and *N*-formyl-substituted **176** was isolated. We believe the same undesired iminium species (**174**, **Scheme 34**) is generated from the imine (**169**, **Scheme 33**) but that somehow elimination of the acyl group produces a cyclic enamine **177**, and that a manganese-based oxidant promotes an unprecedented oxidative cleavage to *N*-formyl ketone **176**.



Reagents and conditions: (a) MnO_2, CH_2Cl_2, rt, 8 h, 53%.

Scheme 34. Manganese-mediated oxidation results in skeletal simplification.

In light of these results, we can safely conclude that the propensity for the putative imine to undergo preferential skeletal rearrangement does not allow functionalisation at C^2 after the spirocyclisation.

2.5.6 Conclusion

Combined with the unsuccesful attempts at having a substituted C^2 position in the starting material (section **3.3.1**) or to form a bond at this strategic position during the spirocyclisation (section **3.5.2**), we concluded that our developed methodology was, unfortunately, not suitable for the generation of useful intermediates towards some of the monoterpene indole alkaloids.

It however remains of value for the rapid generation of a library of spirocyclic indolines, and is a demonstration of the ability of Vaska's complex to trigger intramolecular cyclisation (here spirocyclisation).

2.6 References for Chapter 2

(1) For an extensive review, see Cox, E. D.; Cook, J. M. The Pictet-Spengler condensation: a new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 6, 1797−1842.

(2) For a review, see Szabó, L. F. Rigorous Biogenetic Network for a Group of Indole Alkaloids Derived from Strictosidine. *Molecules* **2008***, 13,* 1875−1896.

(3) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stockigt, J.; Peters, B.; O'Connor, S. Strictosidine Synthase: Mechanism of a Pictet-Spengler Catalyzing Enzyme. *J. Am. Chem. Soc.* **2008**, *130*, 710−723.

(4) Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. Iridium-Catalyzed Reductive Nitro-Mannich Cyclization. *Chem. - Eur. J.* **2015**, *21*, 111−114.

(5) Chupakhin, E.; Babich, O.; Prosekov, A.; Asyakina, L.; Krasavin, M. Spirocyclic Motifs in Natural Products. Molecules **2019**, *24*, 4165−4201.

(6) For a review of spirocycles in drugs, see: (a) Chupakhin, E.; Tice, C. M.; Singh, S. B. The use of spirocyclic scaffolds in drug discovery. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682; for a review of spirocycles for fragment collection, see: (b) Sveiczer, A.; North, A. J. P.; Kidd, S. L.; Sore, H. F.; Spring D. R. Spirocycles as Rigidified sp^3-Rich Scaffolds for a Fragment Collection. *Org. Lett.* **2019** *21*, 4600−4604.

(7) (a) Zhuo, C.-X.; Zhou, Y.; Cheng, Q.; Huang, L.; You, S.-L. Enantioselective Construction of Spiroindolines with Three Contiguous Stereogenic Centers and Chiral Tryptamine Derivatives via Reactive Spiroindolenine Intermediates. *Angew. Chem., Int. Ed.* **2015**, *54*, 14146−14149. For a method to rearomatize aza-spiroindolines into Pictet−Spengler-like products, see: (b) Wu, Q.-F.; Zheng, C.; Zhuo, C.- X.; You, S.-L. Highly efficient synthesis and stereoselective migration reactions of chiral five-membered azaspiroindolenines: scope and mechanistic understanding. *Chem. Sci.* **2016**, *7*, 4453−4459.

(8) (a) Saya, J. M.; Roose, T. R.; Peek, J. J.; Weijers, B.; de Waal, T. J. S.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. Iodospirocyclization of Tryptamine-Derived Isocyanides: Formal Total Synthesis of Aspidofractinine. *Angew. Chem., Int. Ed.* **2018**, *57*, 15232−15236; (b) Saya, J. M.; Oppelaar, B.; Cioc, R. C.; van der Heijden, G.; Vande Velde, C. M. L.; Orru, R. V. A.; Ruijter, E. Synthesis of polycyclic spiroindolines by highly diastereoselective interrupted Ugi cascade reactions of 3-(2-isocyanoethyl)indoles. *Chem. Commun.* **2016**, *52*, 12482−12485.

(9) Chambers, S. J.; Coulthard, G.; Unsworth, W. P.; O'Brien, P.; Taylor, R. J. K. From Heteroaromatic Acids and Imines to Azaspirocycles: Stereoselective Synthesis and 3D Shape Analysis. *Chem. - Eur. J.* **2016**, *22*, 6496−6500.

(10) (a) Medley, J. W.; Movassaghi, M. Synthesis of Spirocyclic Indolines by Interruption of the Bischler Napieralski Reaction. *Org. Lett.* **2013**, *15*, 3614−3617. (b) White, K. L.; Mewald, M.; Movassaghi, M. Direct Observation of Intermediates Involved in the Interruption oft he Bischler-Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403−7411. (c) Antropow, A. H.; Garcia, N. R.; White, K. L.; Movassaghi, M. Enantioselective Synthesis of (−)-Vallesine: Late-Stage C17-

Oxidation via Complex Indole Boronation. *Org. Lett.* **2018**, *20*, 3647−3650. (d) Medley, J. W.; Movassaghi, M. A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Arylative Dimerization of Aspidosperma Alkaloids. *Angew. Chem., Int. Ed.* **2012**, *51*, 4572−4576.

(11) For methods based on other reactive electrophilic species, see (a) Li, Y.; Zhang, Q.; Du, Q.; Zhai, H. Rh-Catalyzed [3 + 2] Cycloaddition of 1-Sulfonyl-1,2,3-triazoles: Access to the Framework of Aspidosperma and Kopsia Indole Alkaloids. *Org. Lett.* **2016**, *18*, 4076− 4079; (b) Delgado, R.; Blakey, S. B. Cascade Annulation Reactions To Access the Structural Cores of Stereochemically Unusual Strychnos Alkaloids. *Eur. J. Org. Chem.* **2009**, 1506−1510.

(12) Hoefgen,B.; Decker, M.; Mohr, P.; Schramm, A. M.; Rostom, S. A. F.; El-Subbagh, H.; Schweikert, P. M.; Rudolf, D. R.; Kassack, M. U.; Lehmann J. Dopamine/Serotonin Receptor Ligands. 10:1 SAR Studies on Azecine-type Dopamine Receptor Ligands by Functional Screening at Human Cloned D1, D2L, and D5 Receptors with a Microplate Reader Based Calcium Assay Lead to a Novel Potent D1/D5 Selective Antagonist. *J. Med. Chem.* **2006**, *49*, 760-769.

(13) (a) Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. Highly efficient synthesis of aldenamines from carboxamides by iridium-catalyzed silane-reduction/dehydration under mild conditions. *Chem. Commun.* **2009**, *12*, 1574−1576; (b) Nakajima, M.; Sato, T.; Chida, N. Iridium-Catalyzed Chemoselective Reductive Nucleophilic Addition to N-Methoxyamides. *Org. Lett.* **2015**, *17*, 1696−1699; (c) Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D. J. Iridium-Catalyzed Reductive Nitro-Mannich Cyclization. *Chem. - Eur. J.* **2015**, *21*, 111−114; (d) Nakayama, Y.; Maeda, Y.; Kotatsu, M.; Sekiya, R.; Ichiki, M.; Sato, T.; Chida, N. Enantioselective Total Synthesis of (+)-Neostenine. *Chem. - Eur. J.* **2016**, *22*, 3300−3303; (e) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalysed Generation of Reactive Enamine Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436− 13440; (f) Fuentes de Arriba, A. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation. *Angew. Chem., Int. Ed.* **2017**, *56*, 3655−3659; (g) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. Unified Total Synthesis of Stemoamide-Type Alkaloids by Chemoselective Assembly of Five-Membered Building Blocks. *J. Am. Chem. Soc.* **2017**, *139*, 18386−18391; (h) Yamamoto, S.; Komiya, Y.; Kobayashi, A.; Minamikawa, R.; Oishi, T.; Sato, T.; Chida, N. Asymmetric Total Synthesis of Fasicularin by Chiral N-Alkoxyamide Strategy. *Org. Lett.* **2019**, *21*, 1868−1871; (i) Gammack Yamagata, A. D.; Dixon, D. J. Enantioselective Construction of the ABCDE Pentacyclic Core of the Strychnos Alkaloids. *Org. Lett.* **2017**, *19*, 1894−1897; (j) Huang, P.-Q.; Ou, W.; Han, F. Chemoselective reductive alkynylation of tertiary amides by Ir and Cu(I) bis-metal sequential catalysis. *Chem. Commun.* **2016**, *52*, 11967−11970; (k) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from N-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138* (16), 5246−5249; (l) Yang, Z.-P.; Lu, G.-S.; Ye, J.-L.; Huang, P.-Q. Ir-catalyzed chemoselective reduction of β-amido esters: A versatile approach to β-enamino esters. *Tetrahedron* **2019**, *75* (12), 1624−1631; (m) Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. Iridium-PPh3 Catalysts for Conversion of Amides to Enamines. *Organometallics* **2019**, *38*, 852−862; (n) Hu, X.-N.; Shen, T.-L.; Cai, D.-C.; Zheng, J.-F.; Huang, P.-Q. Iridium-Catalysed Reductive Coupling Reaction of Tertiary Lactams/Amides with Isocyanoacetates. *Org. Chem. Front.* **2018**, *5*, 2051−2056.

(14) For a discussion on the mechanism of the silylation of alcohols, see: Blackburn, S.N.; Haszeldine, R.N.; Parish, R.V.; Setchfield, J.H. Organosilicon chemistry: XXX. Homogeneous

catalysis by iridium(I) complexes of the reaction between silanes and alcohols or dideuterium. *J. Organomet. Chem.* **1980**, *192*, 329-338.

(15) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon D. J. Direct Enantioselective Brønsted Acid Catalyzed N-Acyliminium Cyclization Cascades of Tryptamines and Ketoacids. *Org. Lett.* **2010**, *12*, 4720−4723.

(16) Herrmann, J. L.; Schlessinger, R. H. Method for Alkylating Lactones *J. Chem. Soc. Chem. Commun.* **1973**, 711−712.

(17) Kalaus, G.; Galambos, J.; Kajtár-Peredy, M.; Tamás, J.; Szabó, L.; Sápi, J.; Szántay, C. A Simple Synthesis of Some D-Noreburnamenine Derivatives, *Lieibigs Ann. Chem.* **1987**, 745−749.

(18) Fürst, A.; Plattner, P. A. 12th International Congress on Pure & Applied Chemistry, New York, **1951**, 409

(19) Martinez, C. R.; Iverson, B. L. Rethinking the term "π-stacking". *Chem. Sci.* **2012**, *3*, 2191−2201.

(20) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J.; Ishibashi, H. Regioselective Inter- and Intramolecular Formal [4+2] Cycloaddition of Cyclobutanones with Indoles and Total Synthesis of (−)-Aspidospermidine. *Angew. Chem., Int. Ed.* **2013**, *52*, 906 –910.

(21) Keirs, D.; Overton, K. Conversion of Amines into Imines by Swern Oxidation. *J. Chem. Soc., Chem. Commun.*, **1987**, 1660−1661.

(22) (a) Baird, K. J.; Grundon, M. F.; Harrison, D. M.; Magee, M. G. The Preparation and Rearrangement of 1-Prenylindoles and 3-Prenylindolenines. *Heterocycles* **1981**, *15*, 713-717; (b) Dufour, M.; Gramain, J.-C.; Husson, H.-P.; Sinibaldi, M.-E.; Troin, Y. Total Synthesis of (±)-Aspidofractinine, *Tetrahedron Lett.* **1989**, *30*, 3429-3432; (c) Qin, W.-F.; Xiao, T.; Zhang, D.; Deng, L.-F.; Wang, Y.; Qin, Y. Total synthesis of (−)-depyranoversicolamide B. *Chem. Commun.,* **2015**, *51*, 16143−16146.

(23) Herlem, D.; Khuong-Huu, F. Oxydation Photochimique d'Amines Tertiaires et d'Alcaloïdes X. *Tetrahedron* **1978**, *35*, 633−639.

(24) Gassman, P. G.; Gruetzmacher, G. D. Azasulfonium Salts. Intermediates in a General Procedure for the Alkylation of Aromatic Amines. *J. Am. Chem. Soc.* **1974**, *96*, 5487−5495.

(25) Lounasmaa, M.; Jokela, R.; Tamminem, T. Conformational Studies of 1-and 3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo2,3-aquinolizines. *Heterocycles*, **1985**, *23*, 1367-1371.

Chapter 3 : [3 + 2] cycloadditions : synthesis and reactivity of azomethine ylides

3.1 Introduction

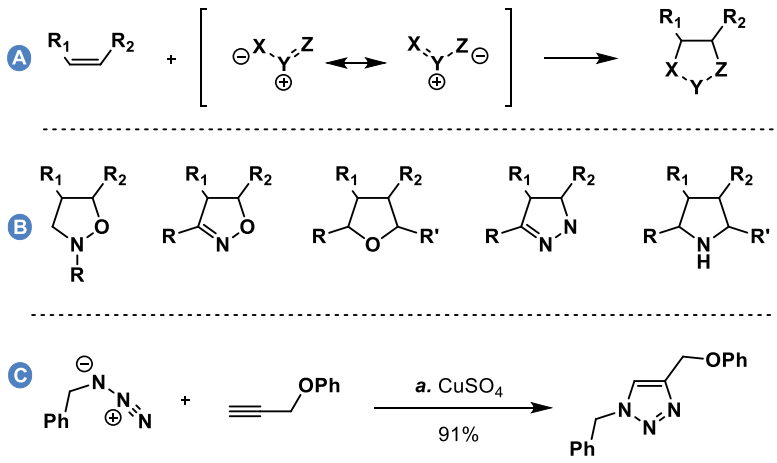
3.1.1 [3 + 2] cycloadditions

From the turn of the 20th century, organic chemistry has evolved from an emerging field of science demonstrating that important compounds could be man-made with sufficient labour and material input, to a refined technology, manufacturing products that are now surrounding us in our everyday life, from active pharmaceutical ingredients to monomers for materials, fragrances and cosmetics. This evolution was influenced by guiding principles of improving yield, atom economy, regio-, diastereo-, and enantio-control, convergent synthesis and rapid generation of complex molecular architectures from simple and inexpensive starting materials.

In this regard, cycloaddition reactions are considered by many as the pinnacle embodiment of all these principles: in one chemical step, two unsaturated molecules are combined to form a cyclic adduct, generating a complex product with the tremendous stereocontrol only displayed by pericyclic reactions.

Although [4 + 2] cycloadditions have been described as early as 1928 by Otto Diels and Kurt Alder,[1] work for which they were awarded the Nobel Prize for chemistry in 1950, 1,3-dipolar cycloaddition reactions were only identified and systematically organized with the work of Huisgen in the 1960's[2] (despite first descriptions at the end of the 19th century).[3] Often called [3 + 2] cycloadditions, as a consequence of the number of atoms involved in the transformation, these reactions facilitate the synthesis of a wide range of 5-membered ring systems, given the possibility to introduce almost any combination of carbon, nitrogen, or oxygen atoms in the dipole. The copper-catalysed azide-alkyne cycloaddition (CuAAC, commonly referred to as the click reaction), independently discovered by

Sharpless and Meldal,[4, 5] is arguably the most famous of these processes, generating a 1,4-triazole heterocycle from an azide and an alkyne.



Reagents and conditions: (a) $CuSO_4{\cdot}5H_2O$ (1 mol%), sodium ascorbate (5 mol%), 2 : 1 H_2O/*t*-BuOH, rt, 8 h

Scheme 35. **A** Generalised [3+2] cycloadditions; **B** Possible heterocyclic products; **C** The "click" reaction (CuAAC).

3.1.2 Azomethine ylides in [3 + 2] cycloadditions

Azomethine ylides contain a carbanion adjacent to an iminium ion. They have extensively been used as 1,3-dipoles since Huisgen described them in 1963,[6] thanks to their accessibility, inherent reactivity (they are said to be one of the few dipoles with a reactivity similar to ozone),[7] and the widespread occurrence of the resulting pyrrolidine heterocycle in numerous desirable targets – alkaloids and small molecules drugs alike.[8, 9]

They have most often been accessed from electrocyclic ring opening of strained aziridines,[10] but a range of primary and secondary amines containing a precursor to a carbon-centred anion can also be condensed with aldehydes to produce the iminium moiety.[11] Alternatively, an imine (or possibly a C=N embedded in an aromatic system) can also be directly activated with a suitable precursor.[12] Finally, less traditional approaches have been developed, requiring the construction of finely-tuned precursors, such as α-metallated amines or imines.[13]

These different strategies will be described separately in the following section.

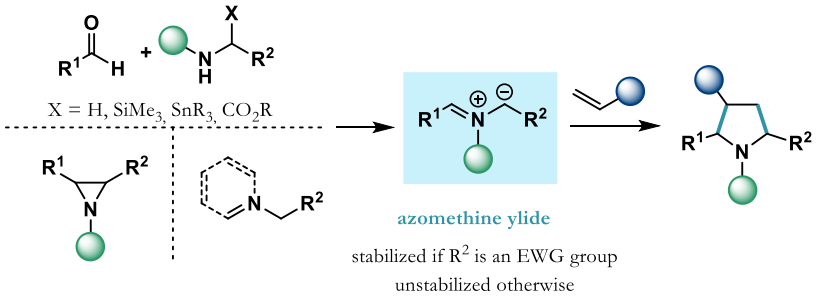
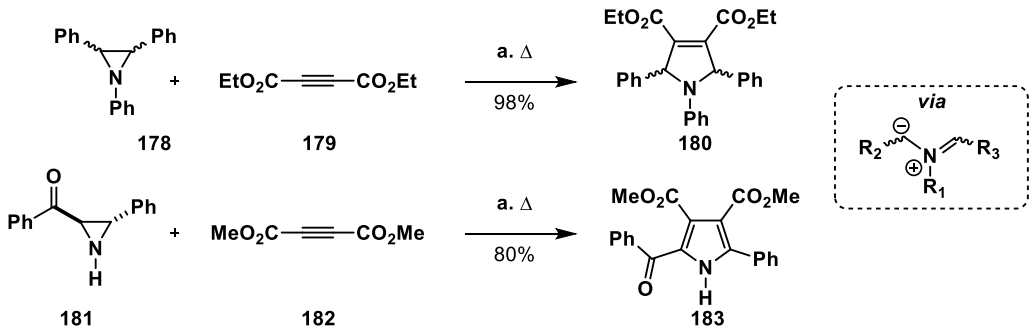


Figure 17. Different approaches for azomethine ylides and their application to pyrrolidine synthesis.

In all of these methodologies, the azomethine ylide can be stabilized if an electron-withdrawing group is installed at the β-position relative to the nitrogen atom, thereby stabilizing the adjacent carbanion.

3.1.3 Precedent for the synthesis and reaction of azomethine ylides

In 1965, Padwa and Heine independently observed the formation of pyrroline or pyrrole products in a thermal reaction between an aziridine species and dialkylacetylene dicarboxylate.[10a, 10b] Since then, several methodologies based on a similar approach have been developed (**Scheme 36**).



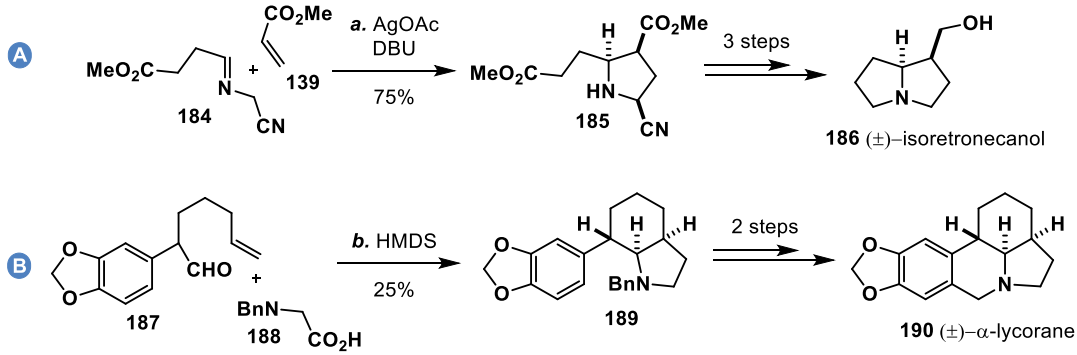
Reagents and conditions: (a) PhMe, 111 °C, 11 h, 98%; (b) xylene, 144 °C, 18 h, 80%

Scheme 36. 1,3-dipoles reacting in [3+2] cycloadditions to generate 5-membered ring heterocycles.

Imines have become one of the mainstream access points to azomethine ylides,[11,12] and often require a Brønsted or Lewis acid, or a metal complex to form the reactive dipole. For example, a silver-based

promoter was deployed in the recent 5-step total synthesis of isoretronecanol **186** by Zhang *et al* (**Scheme 37, A**).[12a]

The imine precursor can also be generated *in situ* by aldehyde and amine condensation, but this approach is rarer. A decarboxylative Strecker reaction can notably afford the dipole, and it has been used in several total syntheses, such as Wang's synthesis of α-Lycorane **190** in 1984: a bicyclic structure is assembled in one step from **187** and **188** with complete relative stereocontrol of all of the newly formed stereocentres (**Scheme 37, B**).[14]



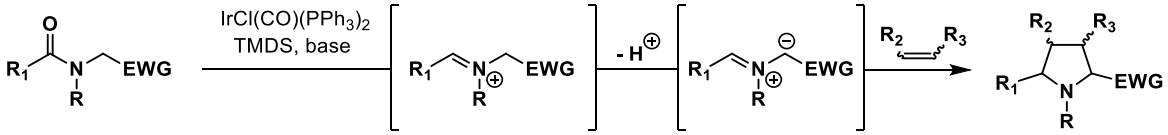
Reagents and conditions: (a) AgOAc (10 mol%), DBU (10 mol%), PhMe, 0 °C, 18 h, 75%; (b) HMDS, PhMe, 111 °C, reaction time not indicated, 25%.

Scheme 37. **A** Imine activation or **B** decarboxylative Strecker reaction towards [3+2] cycloaddition for the total synthesis of natural products.

Often, these methods are based on reacting a primary or secondary amine, or an imine, which results in the formation of pyrrolidine ring products with no substitution on the nitrogen atom.

Remarkably, to this day, tertiary amides have never been used to access pyrrolidine structures through the azomethine ylide dipole.

We imagined that there would be great synthetic value in developing such a reaction. Easily accessible tertiary amides could indeed be elaborated into iminium ions through our iridium-based catalytic system. Further deprotonation of this intermediate could produce the reactive 1,3-dipole if an electron-withdrawing group is acidifying the α-position of the nitrogen. The dipole could in turn be reacted downstream with a range of dipolarophiles to produce cycloadducts.

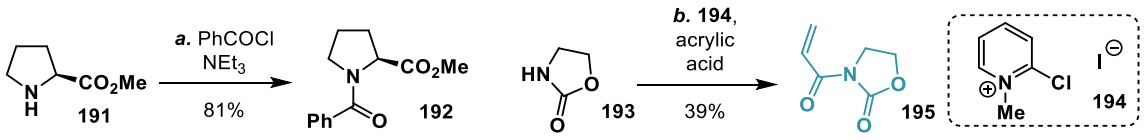


Scheme 38. Concept: an iridium-triggered azomethine ylide formation.

3.2 Reaction development

3.2.1 Reaction discovery and optimisation

Due to its availability, we chose a proline-derived structure for our model substrate; the ester should indeed facilitate the formation of a stabilized azomethine ylide.[i] Simple *N*-benzoylation of proline methyl ester **188** gave **189**, our model substrate for reactivity studies. For the coupling partner, oxazolidinone **192** has previously been reported in such type of reactions,[12h, 15] and was made in one step from acrylic acid and **190** in an amide coupling reaction.[16]



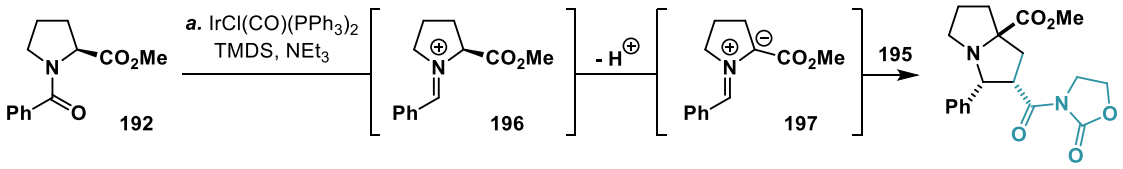
Reagents and conditions: (a) PhCOCl, NEt_3, CH_2Cl_2, rt, 3 h, 81%; (b) **194**, acrylic acid, 39%

Scheme 39. Preparation of the model substrate.

Following our well-established conditions for the Vaska's catalysed amide reduction, we additionally introduced triethylamine as a Brønsted base to deprotonate at the α-position of the iminium ion to generate the dipole **197**. Very pleasingly, subsequent introduction of oxazolidinone **195** resulted in the

[i] The work in this chapter describes the development of a methodology towards the generation and trapping of stabilized azomethine ylides. A joint project, by two PhD students (Ken Yamazaki and Graziano Di Carmine) established, in parallel with this work, the possibility of generating unstabilized dipoles from TMS-methylene amines.

formation of the desired adduct **198** in 50% isolated yield. The reaction produced a single isomer out of the possible eight configurational isomers, showing perfect regio- and stereocontrol, typical of cycloaddition reactions (see next section for a discussion on the selectivity in the case of our model substrate). The bicyclic cycloadduct **198**, with a bridgehead tertiary amine, contains a quaternary centre, and three new stereocentres, all part of the newly formed pyrrolidine ring.

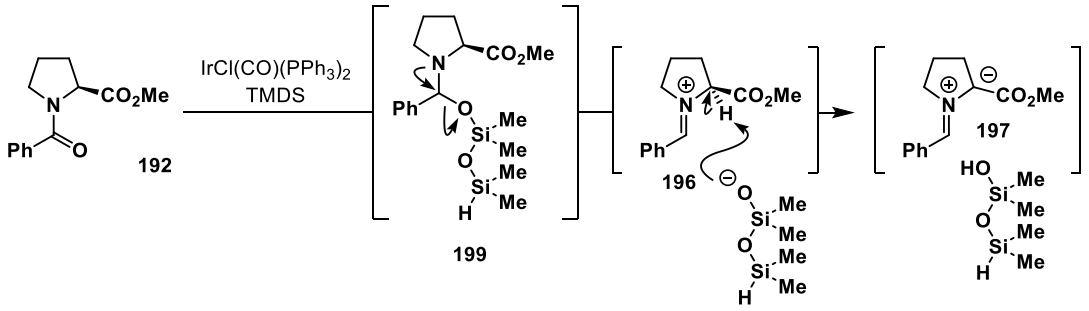


Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, NEt_3, **192**, PhMe, 50%

Entry	Base	TMDS (equiv.)	Temperature	Yield[a] (%)	dr[b]
1	NEt_3	2	rt	50	>20 : 1
2	-	2	rt	88 (86)	>20 : 1
3	-	1.2	rt	65	>20 : 1
4	-	2	80 °C	74	>20 : 1

Scheme 40. Successful [3 + 2] cycloaddition on the model substrate and brief optimisation of the reaction conditions.

Having established that azomethine ylides could indeed be accessed from amides by reductive generation of the iminium ion, and subsequent deprotonation, we began the optimisation of our reaction conditions. Surprisingly, it was observed that in the absence of triethylamine, the product was isolated in an increased yield of 86% (**entry 2**, **scheme 40**). We believe that after ionisation of the silylated hemiaminal **199** (**Scheme 41**) to the iminium species **196**, the proton at the α-position to both the iminium ion and the ester is highly acidic, most likely comparable in pK_a value to a malonate or a β-keto ester. Under the reaction conditions, the silanolate resulting from the iminium ion formation acts as a Brønsted base, and the azomethine ylide **197** can be accessed without the use of an external base.



Scheme 41. Proposed reaction mechanism for the formation of azomethine ylide **197** without external base.

Further control experiment established that 2 equivalents of TMDS were required: using 1.2 equivalents resulted in a reduced yield, representative of the conversion (**entry 3**, **Scheme 40**).[ii]

Finally, increasing the temperature (as this type of cycloadditions are often done at moderate to high temperature) did not improve the outcome of the reaction (**entry 4**, **Scheme 40**).

3.2.2 Selectivity for the model substrate

There are several factors influencing the stereochemical outcome of the model [3+2] cycloaddition.

The configuration of the dipole itself has a major influence. Azomethine ylides can adopt three geometries, outlined by the relative position of the two substituents of the ends of the 1,3 dipole : the U-shaped, the W-shaped, and the S-shaped (see **Figure 18**, **A**).[11a] While the former two lead to a *syn*-relationship between these substituents in the cycloadduct, the latter gives rise to the *anti*-cycloadduct. In our case, the W-shaped dipole cannot exist because of the restriction caused by the pyrrolidine ring. The stereochemical configuration of the isolated adduct suggests, in line with what was observed in previous uses of proline precursors to azomethine ylides, that the S-shape dipole is predominant here over the U-shaped.

[ii] This appears to be in contrast with results obtained for the formation of unstabilised azomethine ylides by other members of the Dixon group.

The azomethine ylide is here a nucleophilic dipole, and reacts through its HOMO. Orbital coefficients, as well as potentially favourable or unfavourable interactions with the dipole will dictate the regioselectivity of the cycloaddition (see **Figure 18**, **B**). In the case of our model substrate, in conjunction with an oxazolidinone dipolarophile, the more "natural" regioselectivity (with the nucleophilic moiety of the dipole being placed at the carbon α to the ester) is observed.

Finally, the configuration of the oxazolidinone relative to the other pair of substituents results from two diastereoisomeric *endo* and *exo* transition states (see **Figure 18**, **C**). Contrary to [4+2] cycloaddition, secondary orbital interactions do not always favour an *endo*-cycloadduct in 1,3-dipolar cycloadditions. Steric, and potential electrostatic and π-interaction, between the pyrrolidine ring, the ester, the positively charged iminium, the polar and Lewis-basic carbamate group all can play a role in stabilizing one transition state over another. In our case, the *endo* product is largely favoured (>20 : 1).

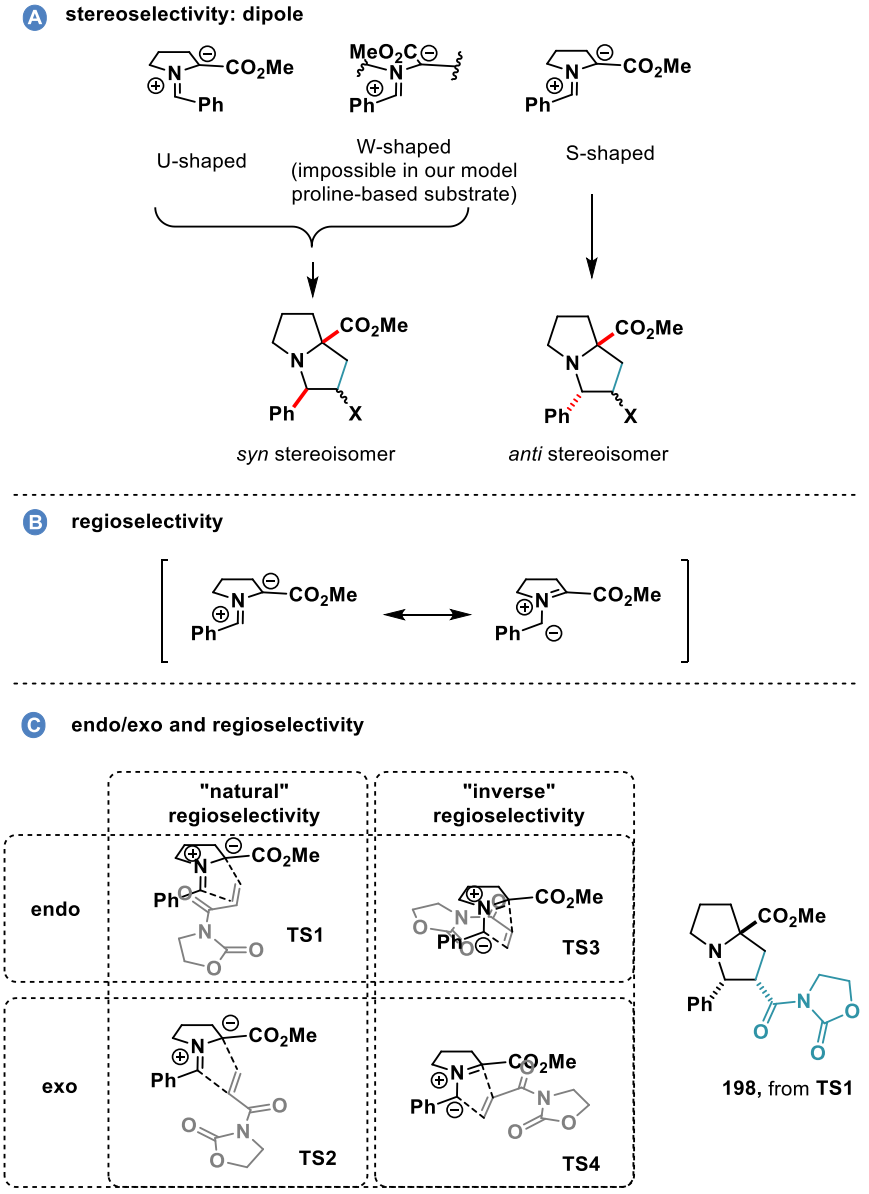
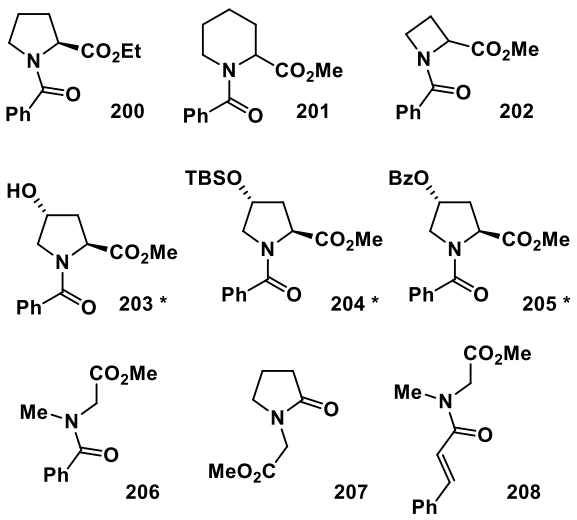


Figure 18. **A**. S-shaped dipole, **B**. Nucleophilic carbon α to the ester, and **C**. endo approach, leading to the production of a single isomer.

3.3 Scope of the reaction

3.3.1 Design and synthesis of the substrates

In order to demonstrate that the reaction was suitable for both cyclic and non-cyclic amide substrates, a range of substrates **200**–**208** were synthesised, *via* a simple benzoylation of available secondary amides (**200**, **206**), pipecolic acid (**201**) and azetidine-2-carboxylic acid derivative (**202**), as well as protected hydroxyprolines (**203**–**205**). A suitably substituted γ-lactam **207**, as well as cinnamic acid derivative **208** were also prepared.



* The prolinol substrates were prepared by Mirxan Farizyan, Master student. **206** and **207** are commercially available.

Figure 19. Amide and lactam starting materials prepared for scope investigation.

3.3.2 Scope of the reaction with regards to the amide

Investigation of the scope began with the successful cycloaddition of **200** giving ethyl ester substituted **209** in 67% yield, which is a slight decrease from the obtained 86% yield observed with the model substrate **192**. The reaction appeared to be sensitive to the steric bulk of the ester. Pleasingly, the four-membered azetidine **202** afforded the bicyclic amine **210** in 69% yield. Very importantly, lactam **207** was

also amenable under the developed reaction conditions, and pyrrolizidine **211** with a different substitution pattern could be obtained. Interestingly in this case, the regiocontrol was not total, and a 5 : 1 regioisomeric mixture of **211a** and **211b** respectively, was obtained. Cinnamyl **208** reacted to give 1,2,3,5-tetrasubstituted pyrrolidine **212** in good yield with complete stereocontrol (**Figure 20**, **A**).

We were, however, surprised to observe that in contrast with proline-derived model substrate **192**, neither pipecolic acid derivative **201** nor hydroxy-proline **203** and its derivatives gave the desired cycloadduct. No azomethine ylide has been formed on a piperidine ring structure, likely due to allylic strain. However, examples of cycloadditions from hydroxyprolines are precedented in the literature,[17] and therefore it is not clear why the formation or reaction of azomethine ylide is disrupted by the 4-hydroxy substituent. In the case of TBS-protected **204**, the staring material was debenzylated (most likely *via* iminium ion formation and hydrolysis) and reacted with the oxazolidinone in a Michael addition fashion, to give **213** in 53% yield. Simple acyclic amide **206** also surprisingly did not give rise to the desired cycloadduct, in contrast with cinnamyl-derived **208** (**Figure 20**, **B**).

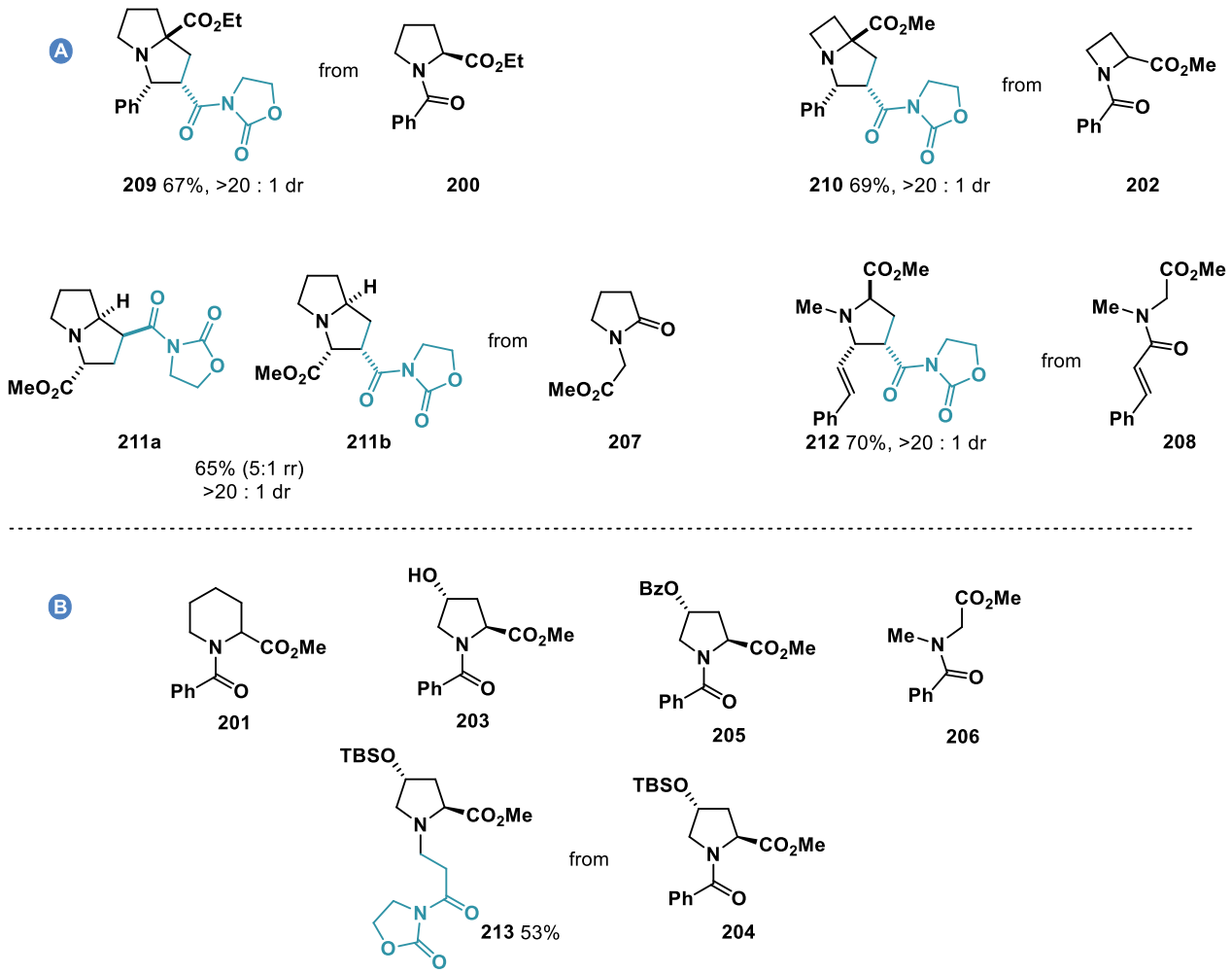


Figure 20. Scope of the amide/lactam: **A**. successful and **B**. unsuccessful examples.

3.3.3 Scope of the reaction with regards to the dipolarophile

Following the success of cycloadditions of azomethine ylides with standard oxazolidinone dipolarophile, we explored the reactivity of more substituted olefins: methacryloyl-, crotonyl-, and cinnamyl-substituted oxazolidinones gave good to excellent yield, with complete stereoselectivity (see **214**–**216**, **Figure 21**). Pleasingly, other types of electron-poor olefins were also well tolerated: *t*-butyl acrylate and α-β unsaturated γ-lactone gave rise to cycloadducts **217** and **220** in 82% and 40% yield respectively, as single isomers. Interestingly, using nitrostyrene or vinyl sulfone resulted in the isolation of two regioisomers, each formed as single stereoisomers (**218a**/**218b** and **219a**/**219b** respectively). This observation is in line with previously reported cycloadditions targeting this exact compound (**218a**/**218b**).[18] It is unclear why

the two isomers are produced, especially in a 1 : 1 ratio. Even more surprisingly, using methyl cinnamate led to the exclusive production of **221** in 64% yield, and as a single isomer, with a regioselectivity opposed to the one observed with the model substrate. On the other hand, when the same dipolarophile was used in conjunction with lactam substrates **207**, the cycloadduct was isolated as a 1 : 1 mixture of regioisomer in 33% yield.

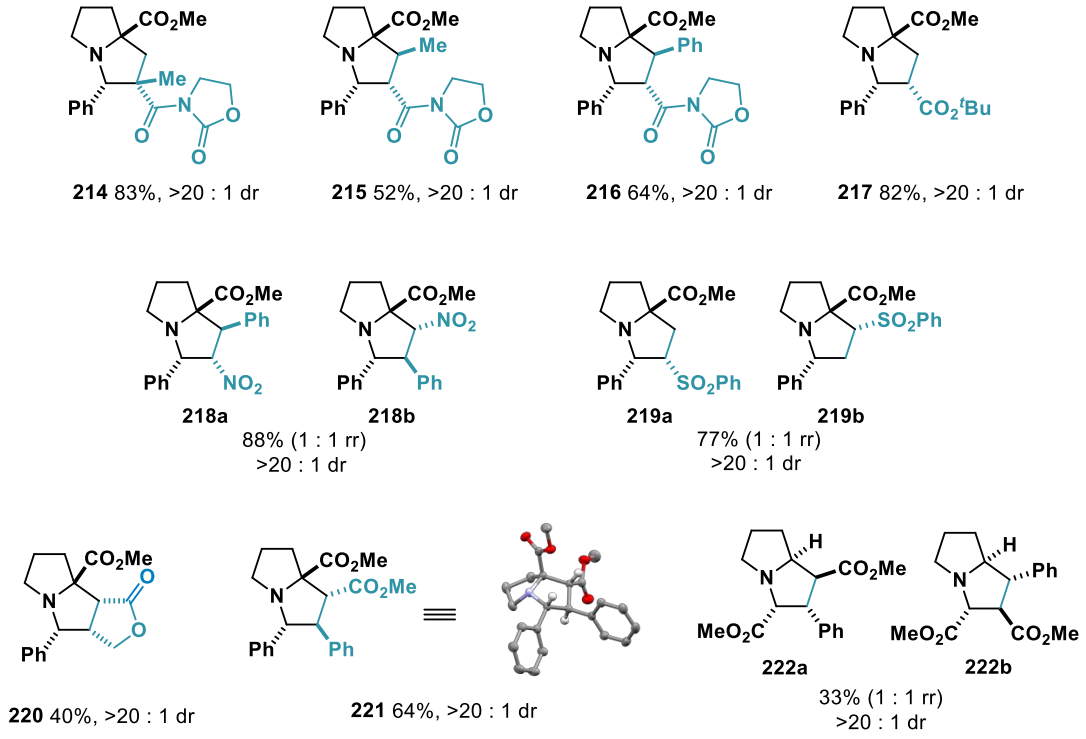


Figure 21. Scope with respect to the dipolarophile.

Despite the intriguing regioselectivity, every single type of olefin used produced the desired cycloadduct in modest to excellent yield, regardless of the nature of the substitution pattern or the nature of the electron-withdrawing group, indicating a broad substrate scope.

3.4 Application to an intra-molecular example

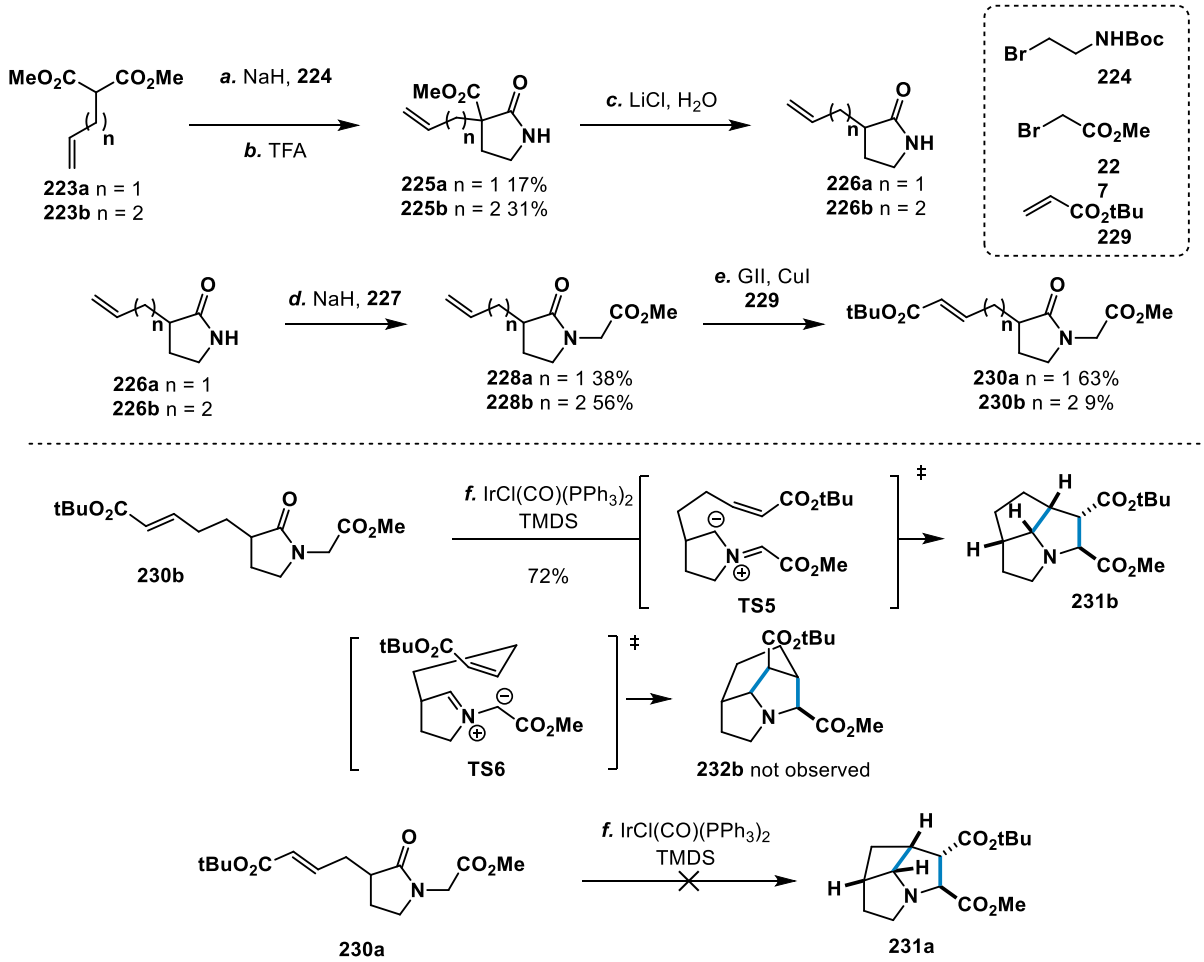
After having demonstrated that the scope of the cycloaddition allowed coupling of simple building blocks, we wanted to showcase the utility of the reaction with a late-stage approach and in settings where iminium ion formation by condensation of an aldehyde and secondary amine was not feasible.

Given that the reaction was previously shown to be successful with γ-lactams, we chose to synthesize a starting material with the five-membered ring lactam, and a tethered intramolecular dipolarophile.

From allyl or homoallyl-substituted malonates **223a/223b**, the lactam was assembled by alkylation with **224**, followed by TFA-mediated Boc deprotection, with concomitant ring-closure to afford **225a** and **225b** respectively. Krapcho decarboxylation gave the α-substituted lactam **226a** and **226b**,[iii] and alkylation with methyl bromoacetate **227**, followed by cross metathesis with *t*-butyl acrylate **229** produced the desired substrates **230a** and **230b**.[iv, 20] Pleasingly, submitting the latter to the [3+2] cycloaddition resulted in the formation of the intricate tricyclic 1-azatricyclo[3.3.0.$2^{4,6}$]decane core **231b** in 72% yield, and as a single isomer (with relative stereochemical configuration established via NOE experiment). It is interesting to note that for this substrate, the regioselectivity is dictated by the geometry of the starting material, and gives the opposite to what was observed with lactam substrate **207**. This result is not surprising given that the alternative conformation places the acrylate moiety in a position that is most likely too far away from the dipole (see **TS 6**, **Scheme 42**).

As expected, the highly strained structure of **231a**, which fuses a cyclobutane ring onto an azabicyclo[3.3.0]octane core, was not observed. When the reaction was performed in an NMR tube set-up, the hemiaminal could be observed, but that intermediate subsequently decomposed to an unassignable ^{1}H NMR spectrum.

[iii] Direct α-alkylation of γ-butyrolactam was also attempted, but even with double deprotonation and in the presence of HMPA, no alkylation was observed.
[iv] The difference in yield can be explained by chelation of the Lewis basic amide carbonyl to the Ru carbenoid species in the case where n=2. This could be overcome by the use of $Ti(OiPr)_4$ to counter the Lewis basicity of the amide.[19]



Reagents and conditions: (a) NaH, **224**, DMF, 50 °C, 42 h, 17% (**225a**), 31% (**225b**); (b) TFA, CH_2Cl_2, rt, 30 min, quant.; (c) LiCl, H_2O, DMSO, 189 °C 3 h, quant. (**226a** and **226b**); (d) NaH, **227**, DMF, 0 to 50 °C, 2 h, 38% (**228a**), 56% (**228b**); (e) Grubs-II, CuI, **229**, CH_2Cl_2, 40 °C, 3 h, 63% (**230a**), 9% (**230b**) (f) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS, PhMe, 72% (**231b**), 0% (**231a**).

Scheme 42. Synthesis and reactivity of examples containing an intramolecular dipolarophile.

This application demonstrated the potential of our developed methodology for the formation and reaction of stabilized azomethine ylides from available amides, both with a building block and a late-stage functionalization approach.

3.5 References for Chapter 3

(1) Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe, I. *Justus Liebigs Annalen der Chemie*. **1928**, *460*, 98−122.

(2) Huisgen, R. 1,3-Dipolar Cycloadditions. Past and Future. *Angew. Chem. Int. Ed. Engl.*, **1963**, *2*, 565−598.

(3) See for instance Buchner, E.; Einwirkung von Diazoessigäther auf die Aether ungesättigter Säuren. *Ber. dtsch. chem. Ges* **1888**, *21*, 2637−2647.

(4) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective Ligation of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(5) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002,** *67,* 3057−3064.

(6) Huisgen, R.; Grashey, R.; Steingruber, E. Azomethin-Ylide und Ihre 1.3-Dipolaren Cycloaddition. *Tetrahedron Lett.* **1963**, *22*, 1441−1445.

(7) Huigens, R.; Scheer, W. Dipolarophilic Activity of Aromatic Bonds towards an Azomethine Ylide. *Tetrahedron Lett.* **1971**, *6*, 481−484.

(8) For reviews of pyrrolidine in natural products, see: (a) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine, azepine and tropane alkaloids. *Nat. Prod. Rep.* **1997**, *14*, 637−651; (b) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine, azepine and tropane alkaloids. *Nat. Prod. Rep.* **2000**, *17*, 435−446.

(9) For a review showing the pyrrolidine ring is amongst the 10 most common heterocycles in small molecule drugs, see: (a) Taylor, R. D.; MacCoss, M.; Lawson, A. D. Rings in Drugs *J. Med. Chem.* **2014**, *24*, 5845−5859; (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals *J. Med. Chem.* **2014**, *57*, 10257−10274.

(10) For methods based on aziridines ring-opening, see (a) Heine, H. W.; Peavy, R. Reaction of 1,2,3-triphenylaziridne with diethylacetylene dicarboxylate and maleic anhydride. *Tetrahedron. Lett.* **1965**, *35*, 3123−3126; (b) Padwa, A.; Hamilton, L. Reactions of aziridines with dimethylacetylene dicarboxylate. *Tetrahedron. Lett.* **1965**, *48*, 4363−4367; (c) Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. 1.3-cycloadditionen von azomethine-yliden aus aziridine-carbonestern. *Tetrahedron Lett.* **1965**, *4*, 397−404; (d) Huisgen, R.; Scheer, W.; Huber, H. J. Am. Chem. Soc. **1967**, *89*, 1753−1755; for other 3+2 cycloaddition where the aziridine generate a different 1,3 zwitterionic dipole, see (e) Ishii, K.; Shimada, Y.; Sugiyama, S.; Noji, M. Photoreactions of β-aziridinyalacrylonitrile. 1,3-Dipolar cycloadditions of photoinduced azomethine ylide *J. Chem. Soc., Perkin Trans. 1* **2000**, 3022-3024; (f) Coldham, I.; Collis, A. J.; Mould, R. J.; Robinson D. E. Pyrrolidines by 1,3- Dipolar Cycloaddition of Conjugated Azomethine Ylides. *Synthesis* **1995**, 1147−1150; (g) Bergmeier, S. C.; Fundy, S. L.; Seth, P. P. *Tetrahedron* **1999**, *55*, 8025−8038; (h) Madushaw, R. J.; Hu, C.-C.; Liu R.-S. *Org. Lett.* **2002**, *4*, 4151−4153; (i) Dauban, P.; Malik, G. A Masked 1,3-Dipole revealed from Aziridines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9026−9029.

(11) For methods where an aldehyde meets a primary or secondary amine, see extensive reviews: (a) Coldham, I.; Hufton R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005**, *105*, 2765−2809; (b) Nájera, C.; Sansano, J. M. Azomethine Ylides in Organic Synthesis. *Curr. Org. chem.* **2003**, *7*, 1105−1150; (c) Hashimoto, T.; Maruoka K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2015**, *115*, 5366-5412; (d) Singh, M. S.; Chowdhury, S.; Koley, S. Progress in 1,3-dipolar cycloadditions in the recent decade: an update to strategic development towards the arsenal of organic synthesis. *Tetrahedron*, **2016**, *72*, 1603−1644.

(12) For various recent methods, see: (a) Li, J.; Zhao, H.; Jiang, X.; Wang, X.; Hu, H.; Yu, L.; Zhang, Y. The Cyano Group as a Traceless Activation Group for the Intra-molecular [3+2] Cycloaddition of Azomethine ylides: A Five-Step Synthesis of (±)Isoretronecanol. *Angew. Chem. Int. Ed.* **2015**, *54*, 6306−6310; (b) Walton, M. C.; Yang Y.-F.; Hong, X.; Houk, K. N.; Overman, L. E. Ligand-controlled Diastereoselective 1,3-Dipolar Cycloadditions of Azomethine Ylides with Methacrylonitrile. *Org. Lett.* **2015**, *17*, 6166−6169; (c) Lauridsen, V. H.; Ibsen, L.; Blom, J.; Jørgensen, K. A. Asymmetric Brønsted Base Catalyzed and Di-rected [3+2] Cycloaddition of 2-Acyl Cycloheptatrienes with Azo-methine Ylides. *Chem. Eur. J.* **2016**, *22*, 3259−3263; (d) Jia, P.; Zhang, Q.; Ou, Q.; Huang, Y. Sequential [1+4]- and [2+3]-Annulation of Prop-2-ynylsulfonium Salts: Access to Hexahydro-pyrrolo[3,2-b]indoles. *Org. Lett.* **2017**, *19*, 4664−4667; (e) Corpas, J.; Ponce, A.; Adrio, J.; Carretero, J. C. Cu^{I}-Catalyzed Asymmetric [3+2] Cycloaddition of Azomethine Ylides with Cyclobutenones. *Org. Lett.* **2018**, *20*, 3179−3182; (f) Yang, X.-C.; Liu, J.-Y.; Liu, Z.; Hu, X.-Q.; Xu, P.-F. Quaternary Carbon Center Forming [3+2] Cyclization Reaction by Adjusting the Substituents of Substrates. *J. Org. Chem.* **2019**, *84*, 13871−13880; (g) Xiong, Y.; Du, Z.; Chen, H.; Yang, Z.; Tan, Q.; Zhang, C.; Zhu, L.; Lan, Y.; Zhang, M. Well-Designed Phosphine-Urea Ligand for Highly Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Methacrylonitrile: A Combined Experimental and Theoritical Study. *J. Am. Chem. Soc.* **2019**, *141*, 961−971; (h) Selva, E.; Soto, J. J.; Nájera, C.; Foubelo, F.; Sansano, J. M. Proline derivatives incorporating hydrophobic long-chain derived from natural and synthetic fatty acids. *Tetrahedron* **2019**, *75*, 10, 1378−1386.

(13) (a) Padwa, A.; Gingrich, H. L.; Lim, R. Regiochemistry of Intramolecular Munchnone Cycloadditions: Preparative and Mechanistic Implications. *J. Org. Chem.* **1982**, *47*, 2447−2456; (b) Smith, R.; Livinghouse, T. An Expedient Synthetic Approach to the Physostigmine Alkaloids via Intramolecular Formamidine Ylide Cycloadditions. *J. Org. Chem.* **1983**, *48*, 1554−1555; (c) Cat-toën, X.; Solé, S.; Pradel, C.; Gornitzka, H.; Miqueu, K.; Bourissou, D.; Bertrand, G. Transient Azomethine-ylides from a Stable Amino-carbene and an Aldiminium Salt. *J. Org. Chem.* **2003**, *68*, 911−914; (d) Wolan, A.; Kowalska-Six, J. A.; Rajerison, H.; Césario, M.; Cordier, M.; Six, Y. 1,3-Dipolar cycloadditions with azome-thine ylides species generated from aminocyclopropanes. *Tetrahedron* **2018**, *74*, 5248−5257; (e) For one example of methyl triflate activation, see Cuevas, J.-C.; Patil, P.; Snieckus, V. α-α'-Disilylated Tertiary Benzamides as Dual Ortho- and α'-Carbanion Synthons. Amide Peterson Olefination Routes to N-Benzoyl Enamines, Iso-quinolines, and Dibenzazocines. *Tetrahedron Lett.* **1989**, *30*, 5841−5844; (f) For a method for secondary amides, see Huang, P.-Q.; Lang, Q.-W.; Hu, X.-N. One-Pot Reductive 1,3-Dipolar Cycloaddition of Secondary Amides: A Two-Step Transformation of Primary Amides. *J. Org. Chem.* **2016**, *81*, 10227−10235.

(14) Wang, C.-L. J.; Ripka, W. C.; Confalone, P. L. A short and stereospecific synthesis of (±)-α-lycorane. *Tetrahedron Lett.* **1984**, *25*, 41, 4613−4616.

(15) Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. Stereoselective Synthesis of Functionalized Pyrrolidines by Ruthenium Porphyrin-Catalyzed Decomposition of α-Diazo Esters and Cascade Azomethine Ylide Formation/1,3-Dipolar Cycloaddition Reactions. *Org. Lett.* **2003**, *5*, 12, 2153−2156.

(16) Knol, J.; Feringa, B. L. Direct Coupling Procedure for the Synthesis of *N*-Acyl-2-oxazolidinones Derived from α,β-Unsaturated Carboxylic Acids. *Synth. Commun.* **2006**, *26*, 2, 261−268.

(17) Mancebo-Aracil J.; Nájera, C.; Sansano, J. M. Multicomponent synthesis of unnatural pyrrolizidines using 1,3-dipolar cycloaddition of proline esters. *Chem. Commun.*, **2013**, *49*, 11218−11220.

(18) Felluga, F.; Pitacco, G.; Visintin, C.; Valentin, E. Synthesis of Polysubstituted Pyrrolizidines from Proline Derivatives and Conjugated Nitroolefins. *Helv. Chim. Acta* **1997**, *80*, 1457−1472.

(19) Fürstner, A.; Langemann, K. Total Syntheses of (+)-Ricinelaidic Acid Lactone and of (-)-Gloeosporone Based on Transition-Metal-Catalyzed C-C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119,* 9130−9136.

(20) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. Enhanced Olefin Cross Metathesis Reactions: The Copper Iodide Effect. J. Org. Chem. **2011**, *76*, 4697−4702.

Chapter 4: Synthesis and cycloadditions of dienamines: total synthesis of (±)–catharanthine

4.1 Catharanthine: biosynthesis and previous syntheses

4.1.1 Catharanthus Roseus, natural source of Vinblastine and Vincristine

Catharanthus roseus, also known as Madagascar periwinkle, is a plant native to Madagascar belonging to the dogbane family *Apocynaceae*. It has been found to be a source of over a hundred alkaloids, named the Vinca alkaloids after the original name of the plant, *Vinca rosea* .[1] Of major importance, vinblastine **233a** and vincristine **233b** are two powerful anticancer drugs that have been used extensively (the second-most-used class of anticancer drugs) over the last 50 years for the treatment of various cancers, such as Hodgkin's disease, non-Hodgkins lymphomas, testicarcinomas, breast cancer, chloro-carcinomas, rhabdomyosarcomas, and Wilm's tumors in children to cite but a few.[2] Despite a very low natural abundance (around 1 g of vinblastine **233a** per 500 kg of dried periwinkle leaves),[3] and some efforts towards their chemical semi-synthesis as early as 1975,[5] the most financially viable source of these compounds is still natural extraction from the plant.[i, 4] In particular, the two indole terpenoid units can be joined in an iron-catalyzed coupling of catharanthine **234** and vindoline **235**, two other major alkaloids extracted from the same plant (**Figure 22**). The C^{16}–C^{21} bond of catharanthine **234** can indeed be broken, and the C_{20} position oxidized, leading to the formation of vinblastine **233a** in a single synthetic step.[4] As such, catharanthine **234** and vindoline **235** are highly attractive targets for total synthesis and, unsurprisingly, have received a lot of interest from the synthetic organic community.

[i] Fortunately, the potency of these compounds allows for doses to be very small (around 10 mg for a month of treatment in testicular cancers for example).

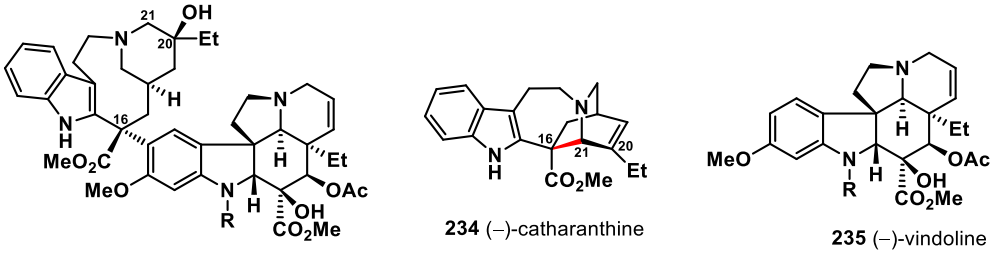
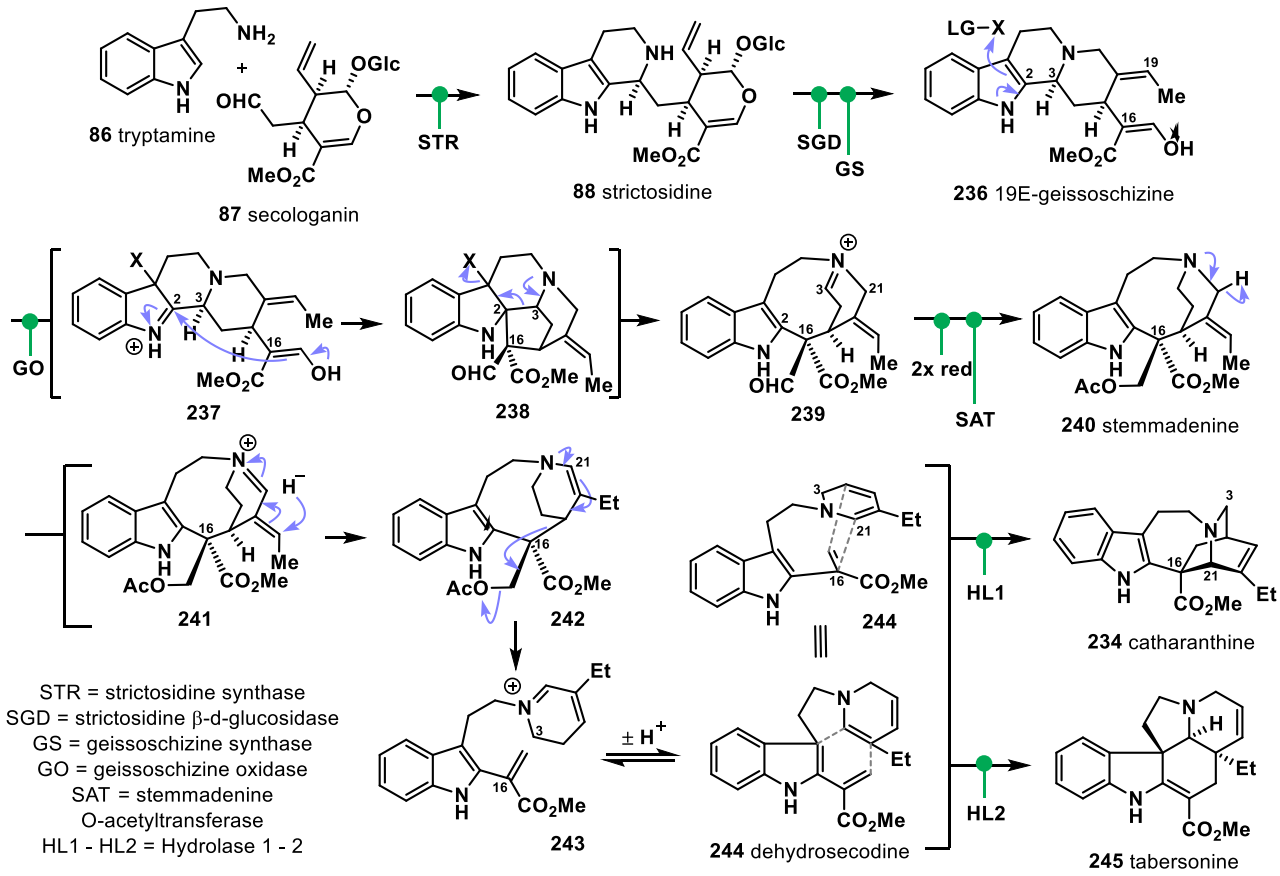


Figure 22. Vinblastine **233a**, and vincristine **233b**, and two of their precursors, catharanthine **234** and vindoline **235**.

4.1.2 Biosynthesis of Catharanthine

Catharanthine belongs to the monoterpene indole alkaloids family (MIA), one of the most abundant and diverse class of specialized plant metabolites.[6] Like almost all of the MIAs, catharanthine is derived from strictosidine **88**, itself the product of a Pictet-Spengler-type reaction between tryptamine **86** and secologanin **87**, catalysed by strictosidine synthase (STR, **Scheme 43**).[ii] A series of rearrangements from the tetrahydro-β carboline then takes place to allow formation of the C^{16}–C^{2} bond (**237** to **238**), followed by C^{2}–C^{3} bond cleavage, allowing for the ring expansion to form the 9-membered ring of stemmadenine **240**. After reduction and acetylation, a 1,3-hydride shift takes place to deliver enamine **242**, which undergoes ring-opening of the strained 9-membered ring to generate the conjugated iminium ion **243**. Proton loss can occur to give **244**, commonly known as dehydrosecodine. This well-studied intermediate can react in two different intramolecular [4+2] cycloaddition modes, to generate either catharanthine **234** or tabersonine **245**, two isomeric pentacyclic natural products.[7]

[ii] Tryptamine and secologanin themselves are derived from tryptophan and geranyl pyrophosphate respectively. For clarity, these pathways are not described here.



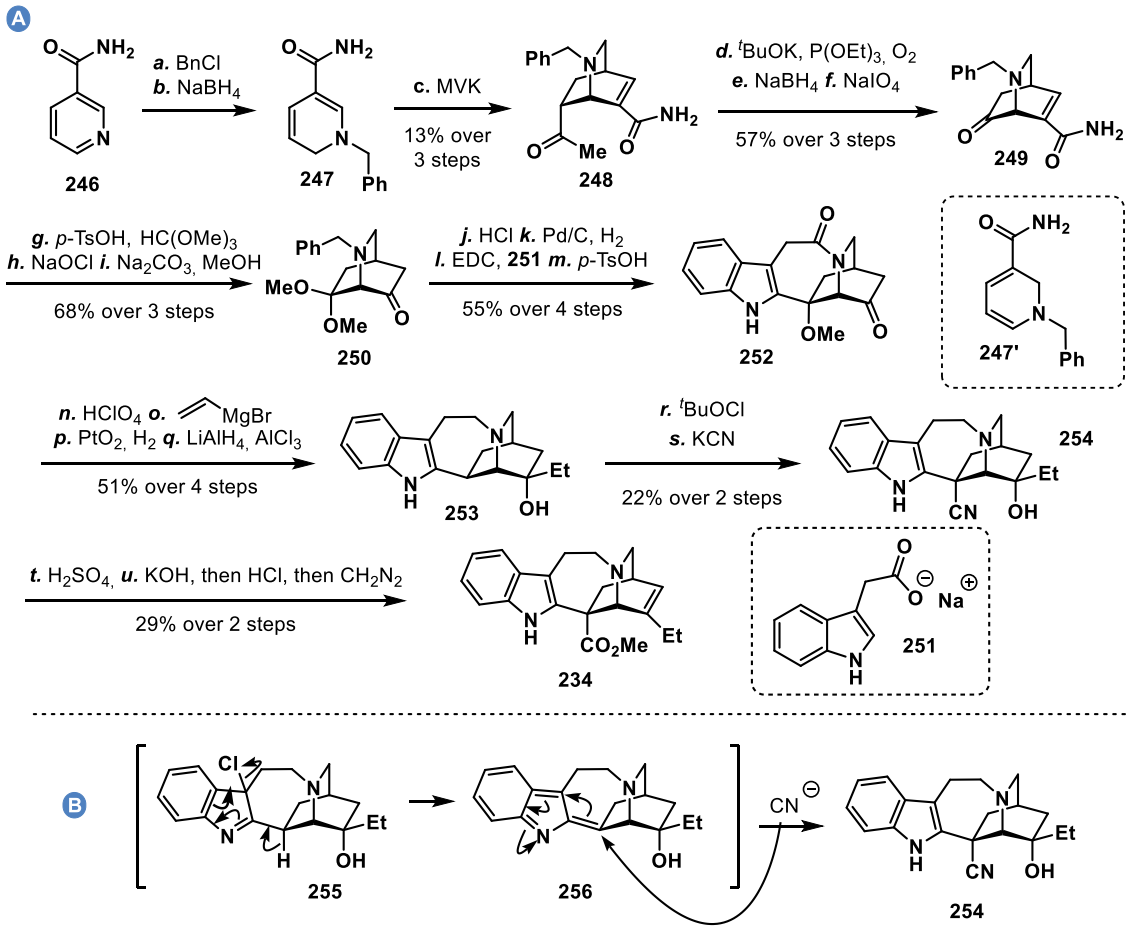
Scheme 43. Biosynthesis of catharanthine.

4.1.3 Büchi's synthesis of catharanthine

First isolated in 1959,[8] the structure of catharanthine was only elucidated two years later through degradation studies by Neuss *et al.*[9] The isoquinuclidine core (2-azabicyclo[2.2.2]octane) was already known in the related Iboga alkaloids: ibogamine, iboluteine, and kisantine.[10] Due to this structural resemblance, catharanthine is sometimes referred as an Iboga alkaloid, though it is technically a Vinca alkaloid wih an Iboga skeleton. In 1970, Büchi *et al* published a pioneering first synthesis,[11] with a strategy that has since been used in 7 formal syntheses.

Starting from nicotinamide **246** (**Scheme 44**, **A**),[11b] benzylation followed by reduction of the resulting pyridinium gave a mixture of 1,2- and 1,6-dihydropyridines **247** and **247'**, which was taken on without further purification in a Diels-Alder reaction with methyl vinyl ketone. A modest amount of the

cycloadduct **248** could be obtained by crystallisation. Oxygenation of the α-position with potassium *t*-butoxide in the presence of oxygen and triethylphosphite gave the hydroxyketone (step ***d.***) which was reduced to the vicinal diol (step ***e.***) before oxidative cleavage afforded ketone **249**. The ketone was protected as the acetal (step ***g.***) before an Hofmann rearrangement afforded **250**. Protonation of the tertiary amine, followed by debenzylation gave the secondary amine, which was coupled with sodium indole 3-acetate **251** (step ***l.***), before the 7-membered ring was formed in a Friedel Crafts-type reaction to give **252**. The ether was hydrolysed (step ***n.***), and 1,2 addition of vinyl magnesium bromide followed by hydrogenation and reduction of the benzylic tertiary alcohol and the amide gave alcohol **253**. Utilising the vicinal indole reactivity, chlorination with *t*-butyl hypochlorite gave the chloroindolenine (**255**, **Scheme 44**, **B**), which was eliminated to render the benzylic position electrophilic (see **256**). Addition of cyanide gave **254**, followed by elimination of the tertiary alcohol (step ***t.***), hydrolysis of the nitrile to the acid, and diazomethane-mediated methyl ester formation completed the first total synthesis of catharanthine **234**.



Reagents and conditions: (a) BnCl, MeOH, 56 °C, 16 h, quant.; (b) $NaBH_4$, Na_2CO_3, 0 °C, 5 min; (c) hydroquinone, MVK, $CHCl_3$, 61 °C, 18 h, 13.4% over 2 steps; (d) ^{t}BuOK in ^{t}BuOH, $P(OEt)_3$, AcOH, CH_2Cl_2, O_2, –20 °C, 2.5 h, 96%; (e) $NaBH_4$, MeOH, 0 °C, 1 h, 100%; (f) $NaIO_4$ in H_2O, MeOH, 0 °C, 20 min, 59%; (g) *p*-TsOH·H_2O, $CH(OMe)_3$, MeOH, 56 °C, 24 h, 86%; (h) NaOCl in H_2O, NaOH in H_2O, MeOH, –19 °C to rt, then rt to 60 °C, 70 min total; (i) Na_2CO_3 in H_2O, MeOH, 100 °C, 79%; (j) HCl in MeOAc (k) MeOH, Pd/C 10%$_w$, H_2, 25 °C, 20 min; (l) **251**, EDCI, H_2O, 24 °C, 1 h, 83% over 3 steps; (m) *p*-TsOH, PhH, 80 °C, 7 min, 66%; (n) $HClO_4$ in H_2O, AcOH, 25 °C, 24 h, 62%; (o) $CH_2CHMgBr$, THF, 0 °C, 30 min, 92%; (p) PtO_2, H_2, THF, 20 min, 99%; (q) $LiAlH_4$, $AlCl_3$, THF, rt, 1 h, 90%; (r) ^{t}BuOCl, NEt_3, –20 °C, 1 h; (s) KCN, DMA, 70 °C, 24 h, 22% over 2 steps; (t) conc. H_2SO_4, rt, 30 min; (u) KOH in diethylene glycol, 150 °C, 16 h, then HCl in MeOH, MeOH, then CH_2N_2 in Et_2O, 0 °C to rt, 75 min total, 29% over 2 steps.

Scheme44. **A** Büchi's 1970 synthesis of catharanthine, **B** with a late-stage quaternary center construction.

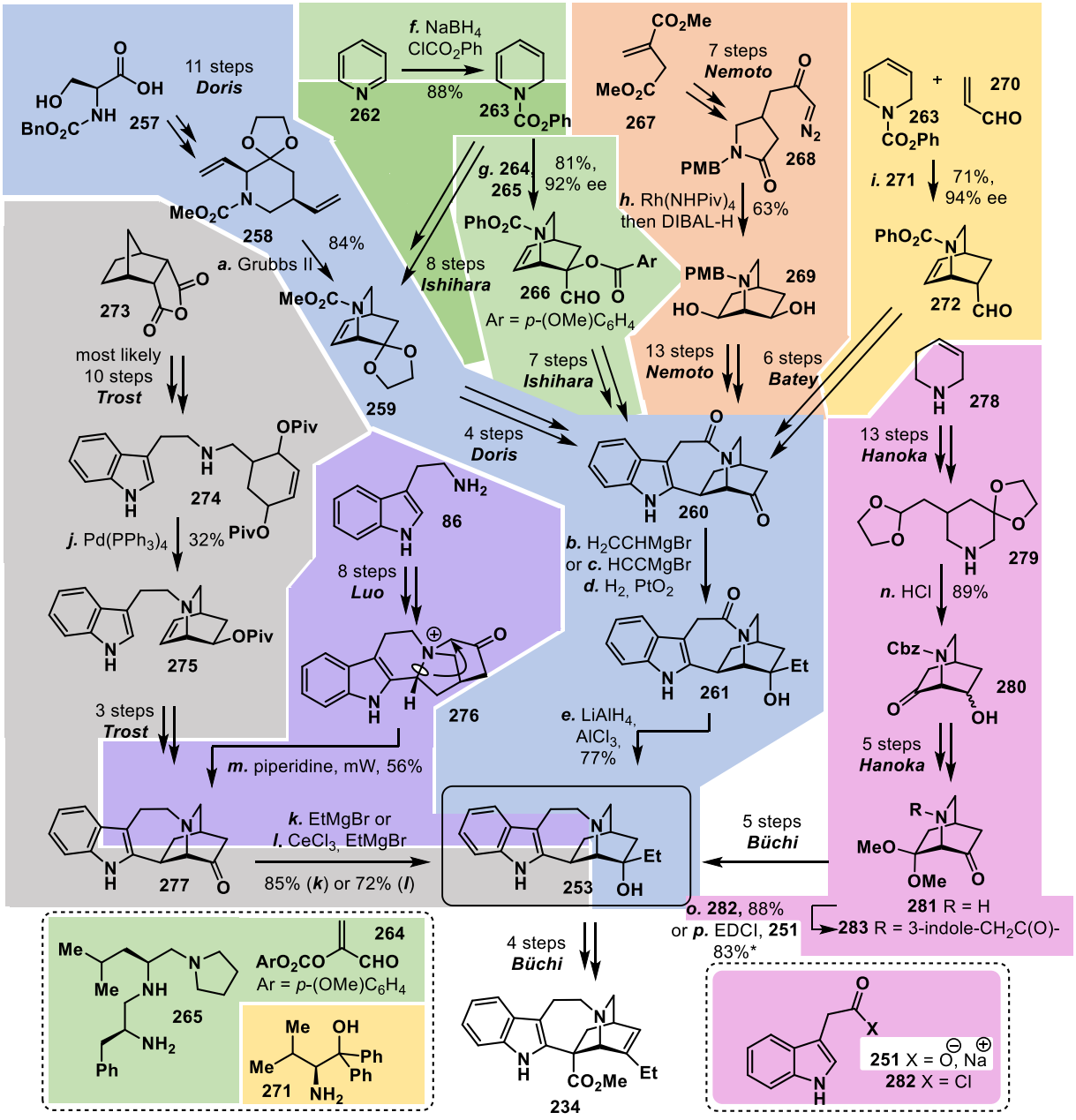
This elegant first total synthesis marked the start of a widespread interest in catharanthine within the synthetic community. The tertiary alcohol **253**, a key strategic intermediate, has been intercepted by many subsequent formal syntheses as it allowed the synthetic focus to shift from the benzylic quaternary center to the isoquinuclidine core. It should however be noted that despite the achievement of this landmark synthesis, there are still many areas where improvement can be achieved. The late-stage installation of the methyl-ester group occurs in a very modest yield (6.4% over 4 steps), and many functional group

manipulations were required to remove the ketone in intermediate **248** the electron-withdrawing properties of which were needed for the key cycloaddition reaction. One potential method to significantly streamline the synthesis is to substitute this electron withdrawing group with the ester functionality required in the final molecule.

4.1.4 Formal syntheses intercepting Büchi's route

By using the indole-fused isoquinuclidine alcohol **253** as a precursor to the ester-bearing quaternary center-containing **234**, Büchi *et al* made the natural product accessible to many methodologies which focused on the 2-azabicyclo[2.2.2]octane core. This resulted in a series of interconnected formal syntheses targeting the bicyclic core in often creative ways. It should be noted that the overall yield of the natural product remains low, due to the low yielding installation of the ester at the quaternary center position. Some of these syntheses also cleverly introduced enantioselectivity in a key step. **Scheme 45** accounts for these interconnections, and highlights the method chosen for the construction of the bicyclic core.

The formal synthesis from chiral pool, by Doris *et al* (light blue path, **Scheme 45**),[12] was of particular importance since it was intercepted by 4 other routes. The key step in this synthesis was a RCM allowing the construction of enantiopure **259** in 12 steps from protected L-serine **257**. This was then elaborated into amide **260**, which was a key intermediate intercepted by Ishihara *et al* (light green path),[13] Batey *et al* yellow path),[14] and Nemoto *et al* (salmon path).[15] The first two syntheses relied on an enantioselective protected dienamine Diels Alder reaction - see **266** and **272** - while the latter was based on an interesting metal carbene amide insertion, resulting in a 28 step synthesis of catharanthine). Ishihara also intercepted the earlier core **259** in another formal synthesis based on a nearly identical enantioselective Diels-Alder reaction (dark green path).[16]



Reagents and conditions: (a) GII, CH_2Cl_2, 40 °C, 20 h, 84%; (b) $CH_2CHMgBr$, THF, 0 °C, 1 h, 48% over two steps; (c) HCCMgBr, THF, 0 °C, 3 h; (d) H_2, PtO_2 (4 mol%), THF, rt, 2 h, 70% (Doris) or H_2, PtO_2 (3 mol%), MeOH, rt, 16 h, 80% over 2 steps (Batey); (e) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 2 h, 77%; (f) PhOCOCl, MeOH, –78°C to –55 °C, 3 h, then rt, 1 h, 88%; (g) **265**, $C_6F_5CO_3H$, $EtNO_2$, –20 °C, 5 min, then **264**, 0 °C, 60 h, 88%, >20:1 dr, 91% ee; (h) $Rh_2(NHPiv)_4$ (0.4 mol%), CH_2Cl_2, rt, 3 min, then DIBAL-H, –78°C, 1 h, 74%; (i) **271**, 19:1 MeCN/H_2O, 1-2 °C, 28 h, 71%, >49:1 dr, 94% ee; (j) $Pd(PPh_3)_4$, NEt_3, MeCN, 75 °C, unknown reaction time, 32%; (k) EtMgBr, THF/Et_2O, –78 °C to –10 °C, unknown reaction time, 85%; (l) $CeCl_3$, EtMgBr, 0 °C, 30 min, 72%; (m) piperidine, HFIP, 150 °C (mW), 3 h, 56%; (n) 10 : 3 THF/10% HCl, 66 °C, 89%; (o) **282**, CH_2Cl_2, 0 °C, 2 min, 88%; (p) **251**, EDCI, H_2O, 24 °C, 1 h, 83% combined with a previous step, see previous scheme.

Scheme 45. Eight interconnected formal synthesis intercepting Büchi's intermediate **253**.

Trost *et al* (grey path) had another approach where the unsaturated isoquinuclidine core was obtained *via* a Tsuji-Trost reaction.[iii, 17] Cyclisation onto the C^2 position of the indole with functional group manipulation gave **277**, and Grignard addition delivered Büchi's intermediate **253**. Interestingly, Luo's synthesis also intercepted the same intermediate **277**,[18] but through an uncommon Stevens rearrangement (a 1,2 shift) as one of the key steps (purple path). They used an organocerium prepared from ethylmagnesium bromide to obtain Büchi's alcohol **253**.

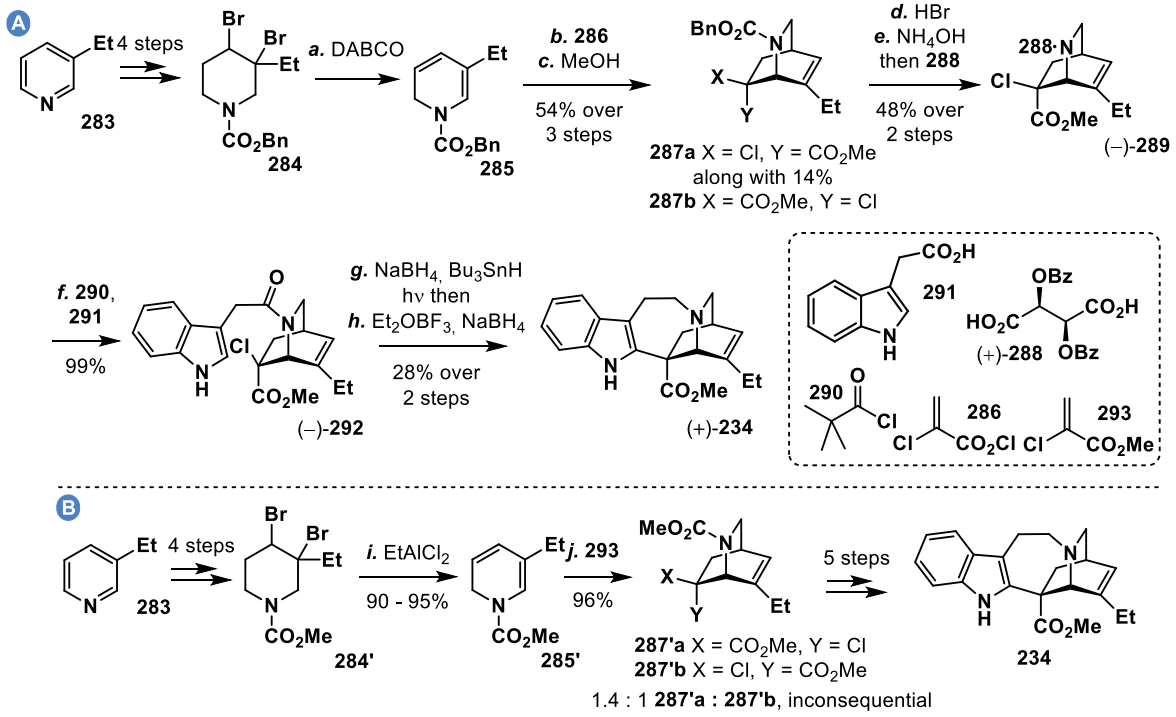
Finally, Hanoka *et al* (pink path) used an acid-catalysed tandem deprotection-aldol reaction to build the bicyclic core **280**.[19] This is to date the longest catharanthine synthesis, with 30 steps from unsaturated piperidine **278**.

4.1.5 Other total syntheses of catharanthine based on a Diels-Alder approach

Catharanthine has also been the subject of other synthetic studies in which the isoquinucleidine core was disconnected *via* a Diels-Alder type reaction.

In the 1980s, Szántay *et al* utilised a carbamate-protected dieneamine (**285**, **Scheme 46**),[20] obtained in 5 steps from ethylpyridine **283** (direct reduction of **283** was not possible due to the preference for the undesired regioisomer of **285**). Diels Alder reaction with 2-chloroacryloyl chloride **286** and methanolysis resulted in stereoselective formation of cycloadduct **287a** (along with the diastereomer **287b**, 3.8 : 1, separable). The major diastereoisomer was taken forward, deprotected, and resolved with a tartaric salt derivative (+)-**288,** to give enantiopure (−)-**289**. Coupling to the indole moiety installed all carbon atoms contained within the final molecule, and photoinduced-cyclisation followed by reduction of the amide gave enantiopure (+)-catharanthine **234**, completing the first enantioselective synthesis of the alkaloid.

[iii] It should be noted that the synthesis is not fully disclosed, and the step count is deduced based on available information. The key diene dicarbonate is indeed only described as the bis acetate – not the bis pivalate required for the synthesis.



Reagents and conditions: (a) DABCO, MeCN, 82 °C, 5 h; (b) **285**, MeCN, rt, 24 h; (c) MeOH, 65 °C, 5 h, 68% over two steps, 3.8 : 1 dr, separable; (d) 2 - 3 N HBr in AcOH, rt, 30 min, 100%; (e) NH_4OH, 1 : 1 $CHCl_3/H_2O$, rt, then **287**, EtOAc, rt, 1 h, 48%; (f) **290**, NEt_3, **291**, DMF −10 °C, 20 min, then **289**, rt, 24 h, 99%; (g) $NaBH_4$, Bu_3SnH (10 mol%), MeOH, low pressure Hg lamp, rt, 2-3 h, 29%; (h) $NaBH_4$, Et_2OBF_3 98%; (i) $EtAlCl_2$, HMPA, 60 °C, 1.5 h, 90-95%; (j) **293**, hydroquinone (5 mol%), 90 °C, 22 h, PhMe, 96%, inconsequential 1.4 : 1 dr.

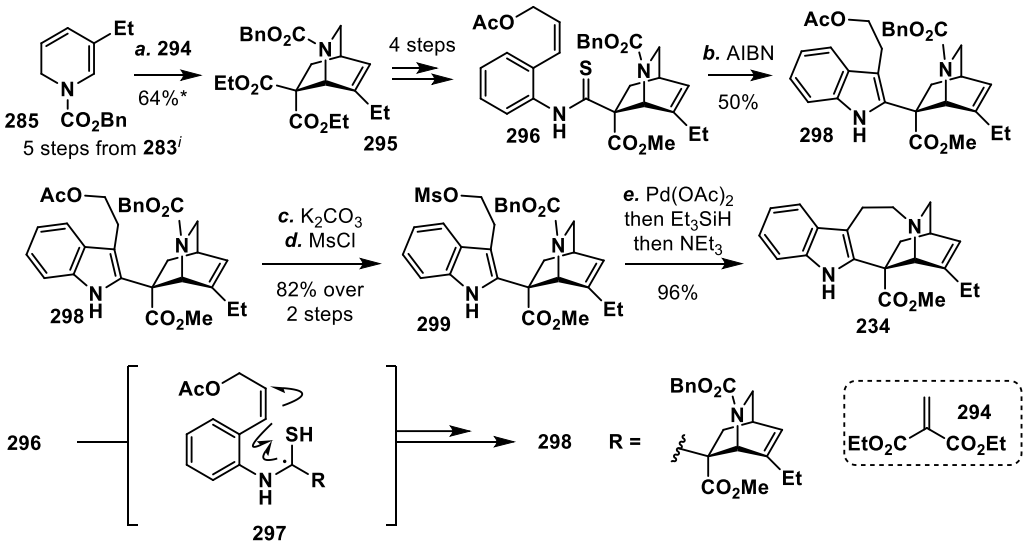
Scheme 46. Two similar approaches toward the total synthesis of catharanthine by Szántay and Raucher respectively.

Using the same strategy disclosed in an early publication from Szántay,[20] Raucher *et al* were first to complete their synthesis (Scheme **46**).[iv, 21] A better yield was obtained by mild elimination of dibromide **284'** to dienamine **285'**, and cycloaddition with methyl α-chloro-acrylate **293** afforded an inconsequential 1.4 : 1 mixture of isomers **287a'** and **287b'** (the undesired diastereoisomer **287a'** was epimerised in a subsequent step). They completed a synthesis of racemic catharanthine **234** in a total of 11 steps. The overall yield was improved to 12% in a subsequent publication.[22]

With the same approach, Fukuyama *et al* used diethylmethylenemalonate **295** as a dienophile with the dieneamine **294** (used by Raucher) to give bicyclic core **295**.[23] The core was coupled to a left-hand side

[iv] Szantay published first the strategy in a synthesis of catharanthine's core, which Raucher allegedly used without citing Szantay's first paper (see reference 20) in his total synthesis of catharanthine. Szantay later completed the total synthesis, and published an improvement on Raucher's route, and called him out on not acknowledging his work. [20]

fragment to produce a thio-anilide **296**, which could undergo a radical-mediated indole formation to afford **298**. Mesylation, followed by a one-step deprotection-hydrogenation-alkylation gave the racemic natural product in 8% overall yield.

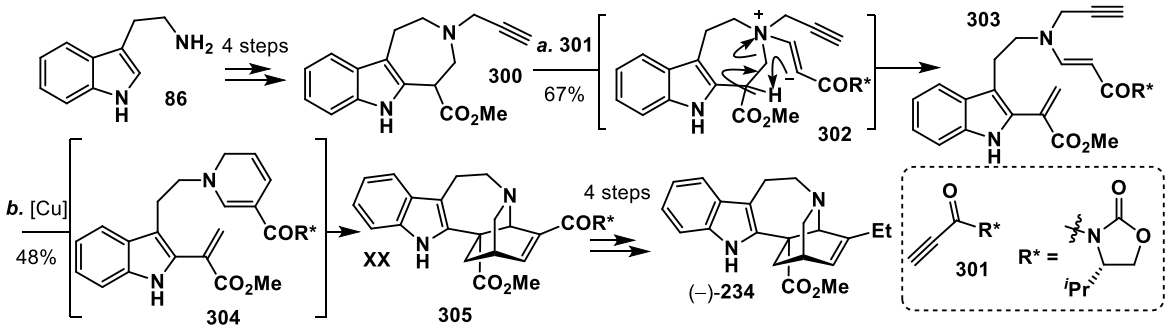


Reagents and conditions: (a) **294**, MeCN, 82 °C, 2 h, * 64% in a 4-step sequence from dibromide similar **284** (see previous scheme) to a lactone obtained by saponification and iodolactonisation of **295**; (b) AIBN, H_3PO_2, NEt_3 *n*-BuOH, 97 °C, 45 min, 50%; (c) K_2CO_3, MeOH, rt, 30 min; (d) MsCl, CH_2Cl_2, 20 min, rt, 82% over 2 steps; (e) $Pd(OAc)_2$, EtOH/EtOAc, rt, 3 min then Et_3SiH, then NEt_3, rt, 15 min. [i] Same step sequence as previous scheme.

Scheme 47. Fukuyama's approach with an uncommon radical-mediated indole formation.

One of the most impressive and recently completed synthesis of *ent*-(−)-catharanthine is the work by Oguri *et al*,[24] featuring a collective approach to several alkaloid families. Starting from tryptamine **86**, an azepine ring fused to an indole **300** was formed and subsequently elegantly transformed into a C^2-acrylate indole **303**. A propargyl-enamine moiety **302**, arising from 1,4-addition of the tertiary amine **300** with **301** followed by ammonium elimination, resulted in the ring-opening of the azepine to give **303**. With the help of Cu(I) catalysis, a cyclic electron-poor dienamine **304** was formed from tertiary amine **303**, and cyclized in a diastereoselective [4+2] cycloaddition to give **305** as a single enantiomer. This two-step sequence spectacularly constructed the isoquinuclidine core from very simple propargyl-substituted **300**. However, the last carbon of the framework had to be introduced in a rather inelegant four-step sequence (methanolysis of the auxiliary, reduction, introduction of a phosphate leaving group followed by

displacement with a methyl Grignard reagent). Nevertheless, this completed the first, and to date only, enantioselective synthesis of the unnatural enantiomer of catharanthine.

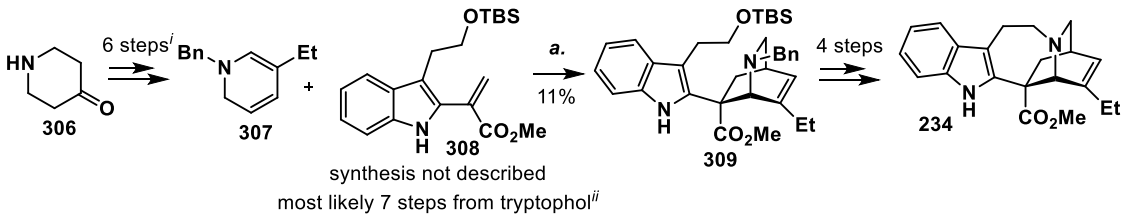


Reagents and conditions: (a) **301**, AcOH, DCE, rt, 4 h, 67%; (b) [Cu(dppf)(MeCN)]PF_6, DCE, 45 °C, 5.5 h, 48%.

Scheme 48. Total synthesis of *ent*-(–)-catharanthine by Oguri *et al.*

Finally, in 1981, Marazano *et al* published a convergent synthesis of the alkaloid.[25] Starting from piperidin-4-one **306**, an ethyl-substituted 1,2-dihydropyridine **307** was made in 6 steps *via* a Shapiro-type reaction, while the indole fragment **308** was made most likely in 7 steps from tryptophol. [v, 26-28] Diels-Alder reaction between **307** and **308** proceded to give **309** in very low yield due to the reductive properties of **307** towards the acrylate moiety of **308**.[25] However, the cycloadduct could be hydrolysed, mesylated, and subsequently intramolecular cyclisation and debenzylation of the quaternary ammonium salt afforded catharanthine.

[v] The synthesis of **308** is not explicitly detailed. We can thus only infer that it was made in 7 steps from tryptophol (TBS protection, indoline-2-thione formation in 2 steps (dithiane formation from the indole, and $NaBH_4$-mediated reduction), 4-step installation of the acrylate (irradiation with methyl acrylate, *S*-alkylation with MeI, oxidation and subsequent elimination).



Reagents and conditions: (a) Et_2O, 20 °C, 15 h.
[i] The first step (benzylation of piperidin-4-one) was not described in the original paper, but the product is not commercially available to the best of our knowledge.
[ii] The authors did not detail the synthesis of **308**, see main text.

Scheme 49. Convergent synthesis of catharanthine by Marazano *et al.*

These five total syntheses,[20, 21, 23-25] as well as Büchi's seminal synthesis,[11] and the eight formal syntheses intercepting Büchi's,[12-19] all used the intuitive [4+2] disconnection of the isoquinuclidine core, with separate coupling or synthesis of the indole moiety.

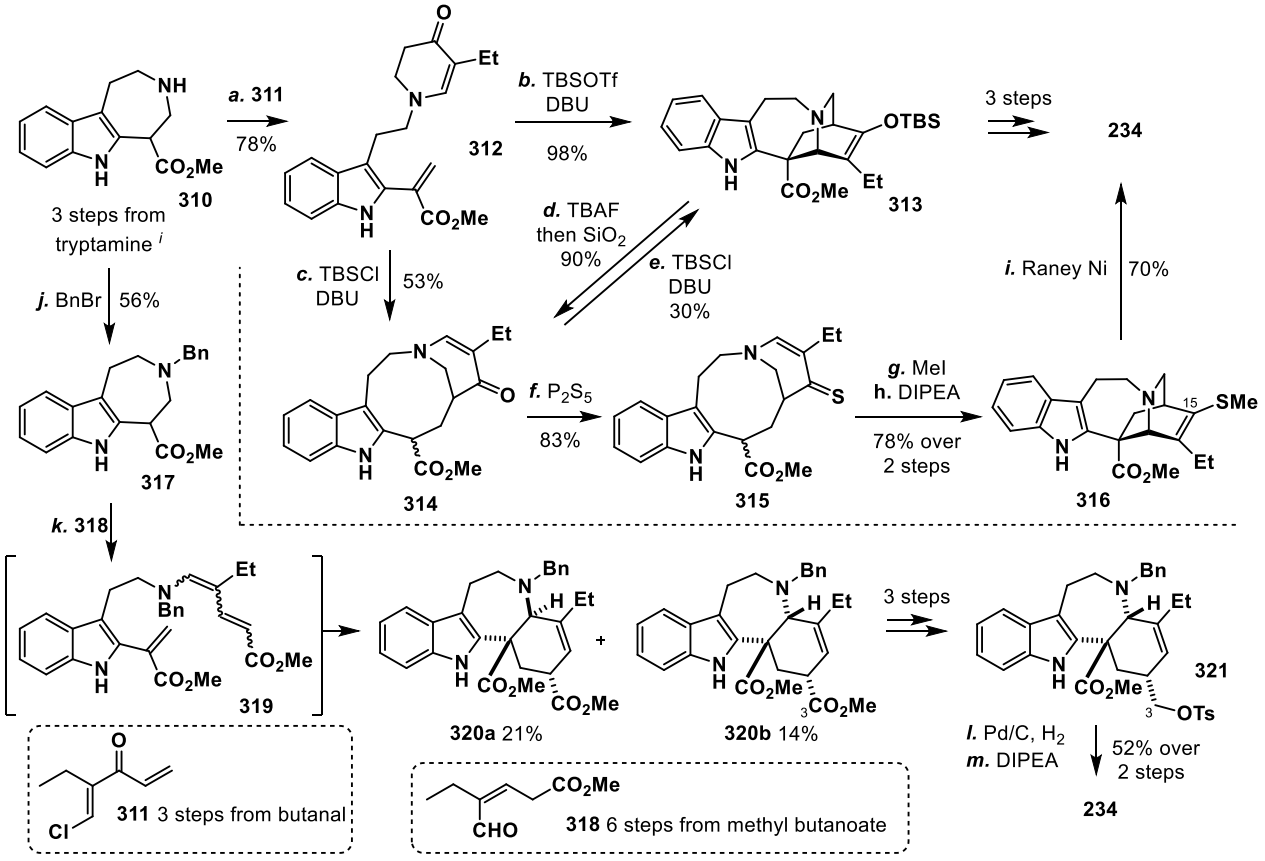
4.1.6 Other total syntheses of catharanthine.

To date, a single group has reported a total synthesis of catharanthine without having recourse to a Diels-Alder strategy. Kuehne *et al* published two syntheses where several σ-bond disconnections were used towards the 2-azabicyclo[2.2.2]octane core.

In his first study published in 1986,[29] Kuehne reported two concise routes to catharanthine. Using a similar azepine-fused indole **310** to Oguri's synthesis as a starting point, and combining it in a convergent approach with **311**, vinylogous lactam **312** was made. Upon enol ether formation, an electron rich dienamine, equivalent to an oxygenated dehydrosecodine, is formed. With a slight change of reaction conditions, both the Diels-Alder adduct **313** and the Mukaiyama Michael product **314** could be accessed. However, difficulties were encountered upon attempted defunctionalization of the cycloadduct **313**. An answer was found *via* a fluorine-mediated silyl deprotection, followed by thio-enol ether formation and Raney-Nickel desulfurization. Alternatively, the carbonyl of cleavamine **314** could be transformed into a C=S double bond, and further activation with methyl iodide followed by base-triggered enolate

formation, and Michael addition formed 15-*S*-methyl catharanthine **316**. Similar Raney Nickel-mediated desulfurisation gave the natural product.

More than two decades later, a different strategy was used in a second synthesis by Kuehne *et al.*[30] A dienamine was again generated from the N-benzylated substrate **310** and an enal **318** obtained in six steps from methyl butanoate. A key IMDA reaction furnished the cyclohexene ring-containing **320** albeit in an 1.5 : 1 dr favouring the undesired diastereomer **320a**. The minor isomer **320b**, isolated in a 14% yield was taken forward, and debenzylation, selective reduction of the C^3 ester, followed by tosylation and nucleophilic substitution gave catharanthine in 11 steps overall.



Reagents and conditions: (a) **311**, MeOH, rt, 30 min, 78% (0.4 mmol scale); (b) DBU, TBSOTf, CH_2Cl_2, 0 °C to rt, reaction time not reported; (c) TBSCl, DBU CH_2Cl_2, 0 °C to rt, reaction time not reported; **314** obtained in 53% yield along with 47% yield of **313** on 6 mmol scale, when the reaction was done on 0.6 mmol scale, a 71% yield of **313** was obtained; (d) TBAF, 2 : 1 THF/H_2O, then SiO_2, 22 °C, "several hours" (as reported); 90%; (e) TBSCl, DBU, CH_2Cl_2, rt to 40 °C, 48 h, 30%; (f) P_2S_5, PhH, 80 °C, 30 min, 83%; (g) MeI, 1:1 CH_2Cl_2/PhH, 20 °C, 2 h, 95%; (h) DIPEA, MeOH, 80 °C, 90 min; 82%; (i) Raney Nickel, MeOH, rt, 1 h, then 65 °C, 15 min, 70%; (j) BnBr, CH_2Cl_2, 20 °C, 10 h, 56%; (k) **318**, $PhCO_2H$ PhMe, 111 °C, 21% **320a**, 14% **320b**, separable; (l) Pd/C, H_2, AcOH, rt, 5 h, 69%; (m) DIPEA, THF, rt, 3 h, 76%.

Scheme 50. Kuehne's two syntheses of catharanthine.

4.1.7 Summary: comparative data in previous syntheses of catharanthine

The following table accounts for all sixteen syntheses of catharanthine, detailing their type (total/formal, synthesis of the racemic/enantiopure natural product), as well as the number of steps in the longest linear sequence (in brackets the total number of steps if different) and the overall yield.

Year	Author	Type of synthesis	Racemic or enantiopure	Origin of chirality	Number of steps in longest linear sequence (total when different)[i, ii]	Overall yield[ii, iii]
1970	Büchi	Total	Racemic	-	20	0.089%
1979	Trost	Formal (Büchi)	Racemic	-	20[iv]	0.036 – 0.040%[iv]
1981	Marazano	Total	Racemic	-	13 (19)[v]	< 0.25%[v]
1982	Hanoka	Formal (Büchi)	Racemic	-	29	0.094%
1985	Raucher	Total	Racemic	-	11	9% / 12%[vi]
1986	Kuehne	Total	Racemic	-	8	< 14%[vii]
1990	Szantay	Total	Enantiopure	resolution with a tartrate derivative	12	< 5.2%[viii]
1999	Fukuyama	Total	Racemic	-	17 (21)	8.3%[ix]
2006	Doris	Formal (Büchi)	Enantiopure	from chiral pool (amino acid)	24	0.071%
2008	Kuehne	Total	Racemic	-	11 (15)	2.8 – 4.9%
2013	Oguri	Total	Enantiopure	chiral auxilary	10 (11)[x]	2.2%
2014	Ishihara	Formal (Doris)	Enantiopure	asymmetric catalysis	17 (19)	0.45% / 0.60%[xi]
2015	Ishihara	Formal (Doris)	Enantiopure	asymmetric catalysis	19	0.49%
2016	Luo	Formal (Büchi)	Enantiopure	asymmetric catalysis	13	0.54%
2018	Batey	Formal (Doris)	Enantiopure	asymmetric catalysis	15	0.62%[xii]
2019	Nemoto	Formal (Doris)	Enantiopure	catalytic desymmetrisation	29	0.049%

i For the purpose of this table, a step is defined via the following statement: "a single reaction step is one in which a substrate is converted to a product in a single reaction flask (irrespective of the number of transformations) without intermediate workup, purification [or solvent swap]", see http://openflask.blogspot.com/2016/12/11-step-synthesis-of-thapsigargin.html
ii In the case of formal syntheses, the number of steps and overall yield is calculated in the shortest linear sequence that would allow obtention of the natural product from the formal synthesis' most advanced material.
iii Yield given is the one of the longest linear sequence. A range is given where some of the step yields were given as a range.
iv Steps and yields are assumed from the similar synthesis of the pivalate dienedicarbamate, see **Scheme 45** and reference 17 for details.
v Yields cannot be obtained or assumed for the synthesis of the indole moiety, see **Scheme 49** and references 25-28 for details.
vi Yield was 9% in a first publication, but was claimed to have been improved to 12% in a subsequent publication.
vii No yield is given for the first step of the synthesis (chloromethylenation of butanal).
viii No procedure or yield was given for the formation of 1-benzyl-3-ethylpyridinium chloride. Inconsistent yields are seen between the experimental section and the discussion of the paper.
ix Minor inconsistencies between the experimental section and the discussion of the paper.
x The authors do not describe the synthesis of the chiral auxilary. It can be made in one step from a chiral oxazolidinone that might have been commercially available then, but isn't today. If not, the total number of steps is 13, not 11.
xi Two reported routes are depicted in the same publication, both of an equal number of steps.
xii The first step of the synthesis is not reported in the publication. This step was present in the synthesis from Ishihara, an equal yield was assumed.

Table 1. An exhaustive summary of the catharanthine syntheses to date.

Several observations can be made from the analysis of these previous syntheses:

- The formal syntheses intercepting Büchi's all result in a low overall yield (<1%)
- By modern standards, the number of steps to access the alkaloid is generally high considering its architectural complexity: 16.7 steps on average.[vi]
- Despite the biosynthesis being known for some time, no biomimetic approach targeting dehydrosecodine **244** (see **Scheme 43**) – the direct precursor of catharanthine – has been undertaken.

In light of these considerations, we set out on a journey to a concise, biomimetic total synthesis of catharanthine, enabled by the iridium-based catalytic system described in previous chapters of this thesis.

4.2 Retrosynthetic plan

We based our retrosynthesis on several key observations:

- The main isoquinuclidine core can be intuitively disconnected by an electronically-favoured IMDA reaction. The forward reaction is biomimetic and taking this approach would consequently imply a synthesis of the elusive dehydrosecodine intermediate **244**.
- The dienamine is a very fragile moiety that will have to be accessed at the latest stage of the synthesis. At the outset, our plan was to generate it *in situ* from an unsaturated δ-lactam, with a chemoselective reduction of the lactam carbonyl in presence of the α,β-unsaturated ester.

[vi] This number is not decreasing with time: the average number of steps (LLS) for the total syntheses of this last decade stays approximately the same (17.2), though arguably some of these steps are dedicated to the production of the natural product as a single enantiomer.

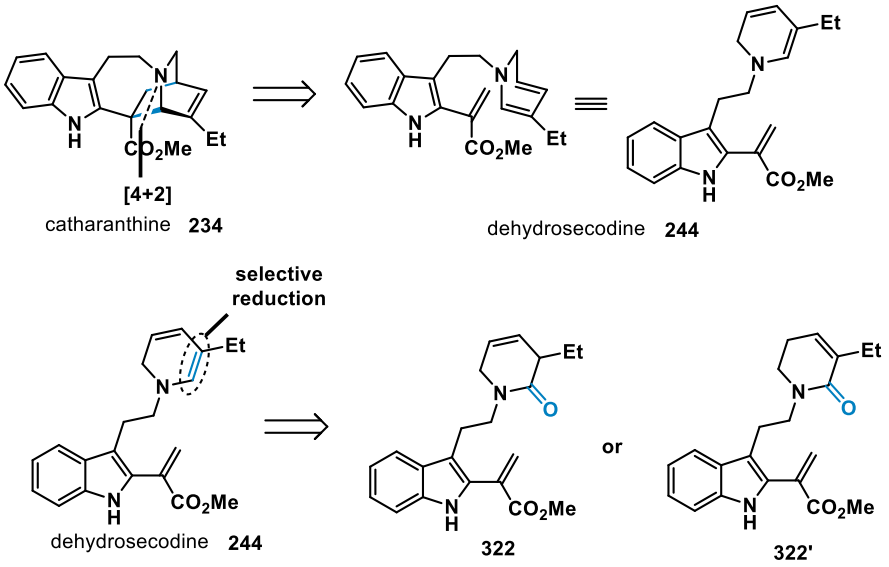


Figure 23. Retrosynthetic analysis of catharanthine: endgame.

This will be the focus of parts **4.3** (studies on model substrate) and **4.5.2** (real system) of this chapter.

- The α,β-unsaturated ester itself at the C^2 position of the indole in **322**/**322'** appears to induce ready dimerisation in previous syntheses. Therefore, it should be installed as late as possible in the synthesis, and thus appear next in our retrosynthesis. Furthermore, only one precedent in the literature exist for the instalment of the α,β-unsaturated ester at the C^2 position using reaction conditions that likely would not be tolerated in this synthesis.[vii, 31] Some new chemistry must be developed for this transformation, possibly a photoredox-enabled Minisci-type addition, followed by a Horner-Wadsworth-Emmons reaction.

[vii] Selective hydrolysis of a benzyl ester necessitated the use of Pd/C (see reference **31**), which would also in our case hydrogenate the desired unsaturation. See section 4.3.5.

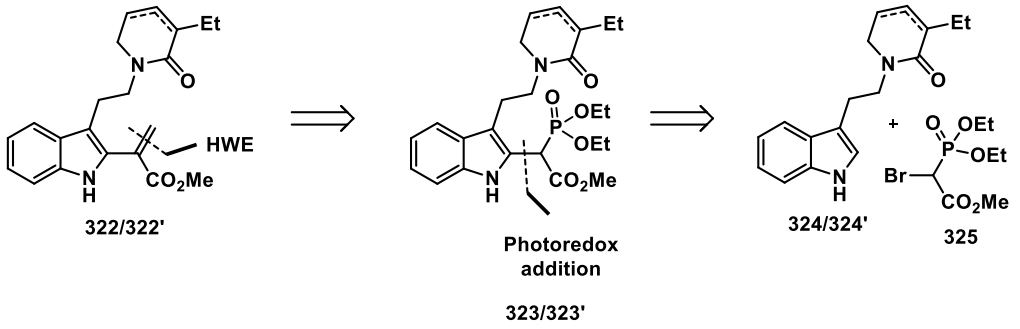


Figure 24. Retrosynthetic analysis of catharanthine: C^2 functionalisation

This will be the focus of section **4.4** of this chapter.

Finally,

- The introduction of the lactam carbonyl would not only allow access to the dehydrosecodine intermediate, it would also simplify the construction of the α-ethyl unsaturated δ-lactam moiety.
- The lactam itself can efficiently be put together at the beginning of the synthesis, allowing the nitrogen to be introduced in the first stage and be carried through without the need to use a protecting group.

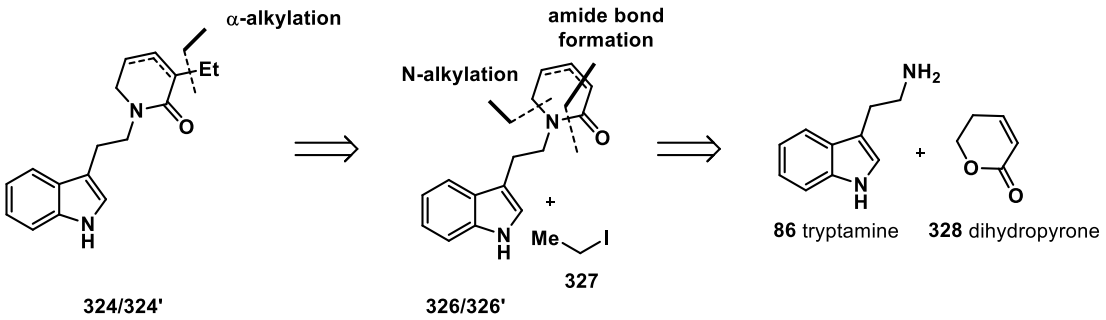


Figure 25. Retrosynthetic analysis of catharanthine: starting material synthesis.

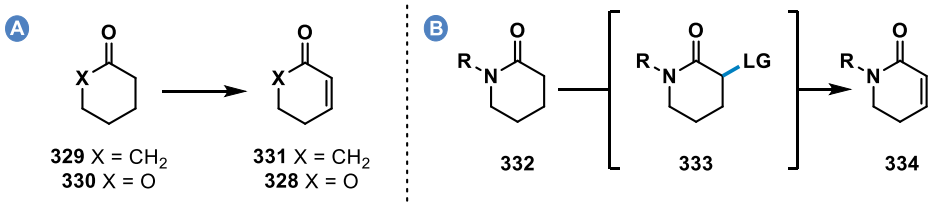
Consequently, we chose to articulate our synthetic studies in four phases:

- Phase I: studies of model substrates to verify that the unsaturated δ-lactam can be reduced by the Vaska's complex/silane catalytic system to dienamines, and that these dienamines can react *in situ* with dienophiles.
- Phase II: introduction of the indole moiety in model studies for the key step, and synthesis of the real substrate.
- Phase III: indole C^2-functionalisation for the installation of the acrylate moiety
- Phase IV: investigations of the key IMDA step.

4.3 Model studies

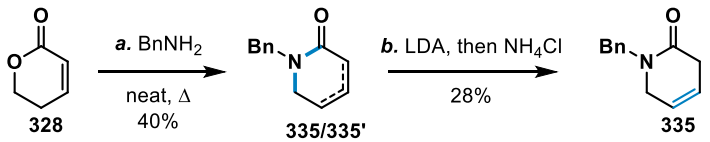
4.3.1 Substrate synthesis and initial [4+2] cycloaddition studies.

Inspection of the literature revealed that α,β-unsaturated δ-lactams are not so easily accessible. Contrary to the chemistry of ketones or esters/lactones,[32] the catalytic dehydrogenation of saturated lactams is not known, though very recently methods requiring protecting groups are paving the way for an amide dehydrogenation.[33] A reliable, though protracted, way to access these compounds is through deprotonation followed by α-selenation or α-sulfenation, oxidation, and then elimination. α-Halogenation followed by elimination is also an alternative.



Scheme 51. **A**. Desaturation of cyclohexanone/δ-valerolactone, **B**. Current strategy towards unsaturated δ-valerolactams.

One report from Nakagawa *et al* demonstrates the possibility to form unsaturated δ-lactams from the high-temperature reaction between a non-volatile primary amine and dihydropyrone **328**.[34] Following this precedent, *N*-benzyl lactam was formed in 40% yield, as a mixture of conjugated and deconjugated unsaturated lactams **335** and **335'**. Deconjugation of the double bond was carried out by stoichiometric deprotonation – reprotonation, in a modest 28% yield.[viii]

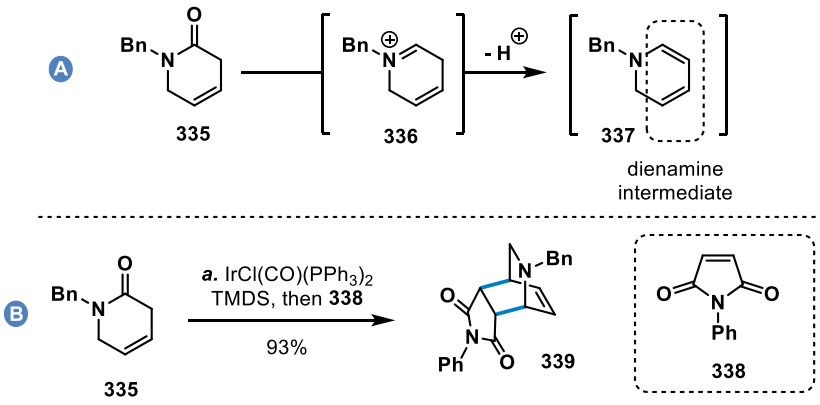


Reagents and conditions: (a) $BnNH_2$, neat, 200 °C, 3 h, 40%; (b) LDA, then NH_4Cl, THF, −78 °C, 1 h, 28%.

Scheme 52. Synthesis of model substrate **335**

With gram-quantities of the β,γ-unsaturated δ-lactam **335** in hand, the desired transformation could be investigated. Our aim in this cascade sequence is to access, *via* the iridium-based catalytic system, the cyclic iminium ion intermediate **336**, in conditions similar to previous work in this thesis. We hypothesised that due to the double bond present in the 6-membered ring, facile deprotonation to the dienamine **337** would occur (see **Scheme 53**, **A**). This will be an electron-rich dienamine, able to participate in Diels-Alder cycloaddition with suitable partners. *N*-Phenyl maleimide **338** was chosen as dienophile, for its high reactivity, and its propensity to produce crystalline adducts.

[viii] Submitting the mixture of isomers in the next step resulted in lower yields, and the base-catalysed conjugation of the double bond did not proceed with good conversion. Therefore, we chose to deconjugate the unsaturation to obtain β-γ unsaturated δ-lactam **335**.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ 0.1 mol% TMDS, 5 min, then N-Ph-maleimide **338**, PhMe, rt, 1 h, 93%.

Scheme 53. **A**. Aiming for the dienamine, **B**. [4+2] cycloaddition

Very pleasingly, under standard reaction conditions for the silylated hemiaminal formation, and after the introduction of *N*-phenyl maleimide **338** once the initial reduction was complete, isoquinuclidine **339** could be isolated in near-quantitative yield as a single diastereoisomer. As expected for this type of cycloaddition, the *endo*-product was obtained, as confirmed by ^{1}H NMR NOESY analysis.

4.3.2 NMR studies: observation and characterization of the dienamine intermediate

In order to confirm the intermediacy of dienamine **337** in this reaction sequence, an experiment was performed in an NMR tube with deuterated toluene as a solvent. ^{1}H NMR spectra of the reaction mixture were measured a) with starting material lactam **335**, b) 20 minutes after introduction of Vaska's complex and TMDS, and c) 90 minutes after the introduction of one equivalent of *N*-phenyl maleimide **338**. Inspection of the ^{1}H NMR of the reaction mixture before any dienophile was added (Figure **26**, b) showed a spectrum perfectly assignable to dienamine **337**.[ix] The reaction profile is also very clean, and

[ix] See Experimental details for 13C NMR, COSY and HSQC.

an internal standard [x] was used to measure a 94% NMR yield of the dienamine **337**, and a 93% NMR yield of isoquinuclidine **339** after reaction with *N*-phenyl maleimide **338**.

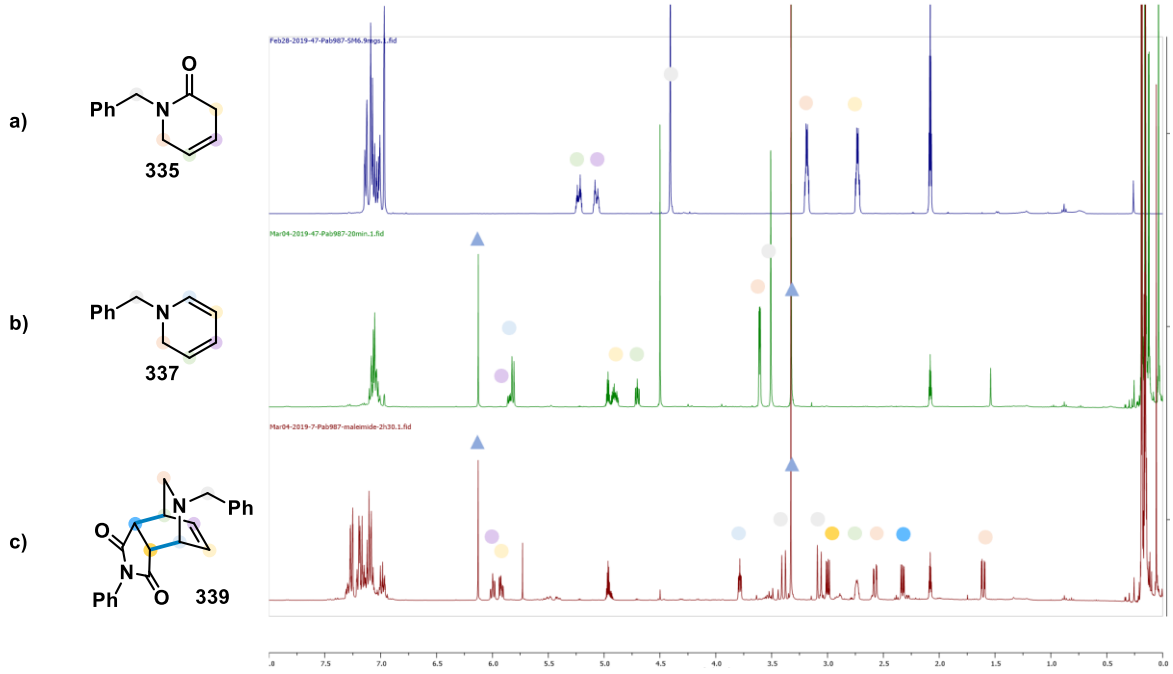
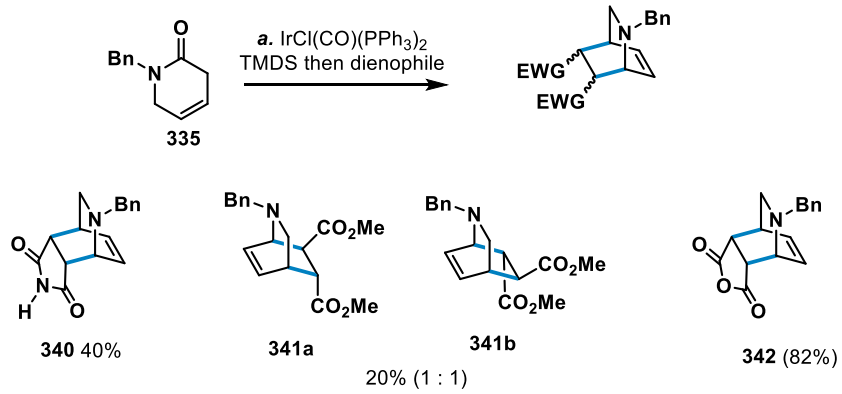


Figure **26**. ^{1}H NMR experiments showing the transient dienamine.

4.3.3 Brief survey of reactivity for the formation of 2-azabicyclo[2.2.2]octane derivatives

In order to confirm that this new reaction could be used in the synthesis of catharanthine, we decided to screen less reactive dienophiles to ensure that the acrylate moiety of dehydrosecodine **244** could be a suitable acceptor in the intramolecular variant of the developed reaction.

[x] Trimethoxybenzene was used, see triangle signals in Figure **26**.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ 0.1 mol% TMDS, 5 min, then dienophile, PhMe, rt (100 °C for **341a/341b**), 16 h, yield as indicated.

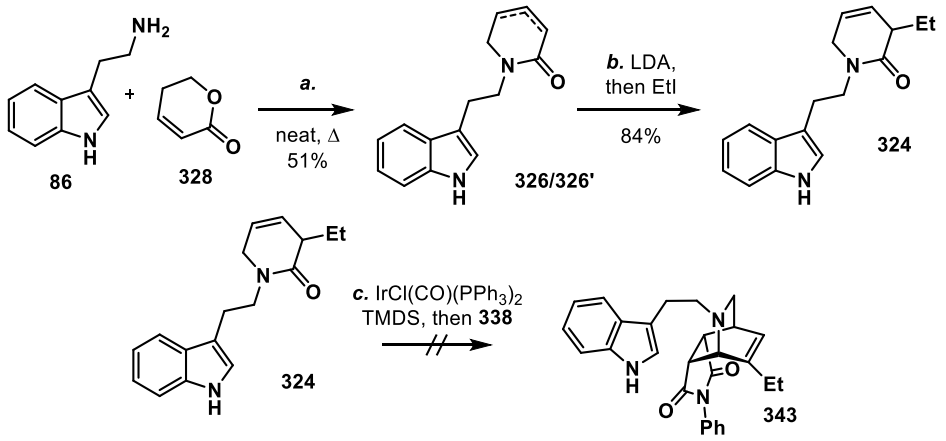
Scheme **54**. Scope of the dienophile.

The use of maleimide as the dienophile led to isolation of **340** in a moderate 40% yield, as a single diastereomer, while dimethyl fumarate led to the production of 2 diastereoisomers **341a** and **341b** in 20% yield, in a 1 : 1 ratio (requiring heat in the cycloaddition step). Maleic anhydride did undergo the desired cyclisation at rt in a good NMR yield, but the product **342** was not stable to FCC. The anhydride moiety within **342** is most likely susceptible to hydrolysis, and the resulting zwitterion could not be purified. Other less reactive dienophiles, such as *t*-Butyl acrylate, did not react with the dienamine, even at elevated temperatures. We hoped that in the case of catharanthine, the reaction would be facilitated – being intramolecular – and that reactivity of the C^2 acrylate would be increased compared to *t*-Butyl acrylate.

4.3.4 Indole-containing model substrate

After having successfully established proof of concept on the desired transformation, we turned our attention to a tryptamine-derived model substrate containing the indole aromatic ring. Following conditions previously described, indole-tethered unsaturated δ-lactam was obtained as a mixture of isomers **326** and **326'**. Pleasingly, the α-alkyation could be carried out in tandem with the deconjugation; an additional equivalent of base was used to remove the unprotected indole N-H proton. The desired

indole-tethered α-ethyl β,γ-unsaturated δ-lactam **343** could thus be obtained using a one-pot sequence in 84% yield.



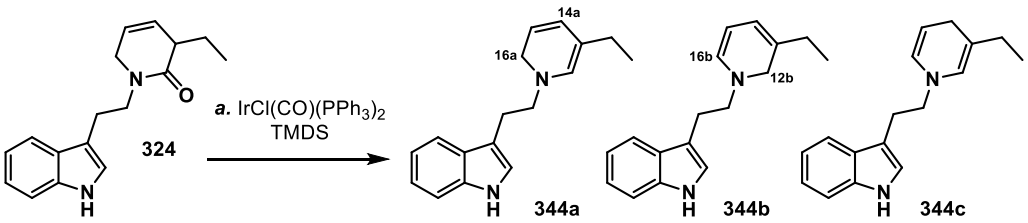
Reagents and conditions: (a) neat, 200 °C, 3 h, 51%; (b) LDA, then EtI, then NH_4Cl, THF, −78 °C, 3 h, 84%; (c) $IrCl(CO)(PPh_3)_2$ 0.1 mol% TMDS, 5 min, then **338**, PhMe, rt, 24 h.

Scheme 55. Synthesis of **324** and unsuccessful IMDA reaction.

Attempts to use **324** as a precursor to isoquinuclidine **343** were surprisingly unsuccessful, and no material could be recovered from thereaction mixture. To investigate the origin of the problem, formation of the dienamine was monitored in deuterated solvent as described previously.

^{1}H NMR taken 5 and 10 minutes after the TMDS was introduced showed a mixture of several alkene species, with rapidly changing ratios. The experiment was repeated with regular ^{1}H NMR measurement.[xi] It appeared clear that the complex alkene region of the NMR could be attributed and assigned to three different isomeric dienamine species: the target 1,6-dihydropyridine **344a** was quickly converting to 1,2-dihydropyridine **344b** and over time to 1,4-dihydropyridine **344c**.

[xi] In order to observe the desired dienamine **344a**, an NMR sample of the starting material was pre-locked and pre-shimmed to get data before the 5-minute mark.



Entry	Time	Crude NMR yield*		
1	3 min	67%	32%	1%
2	4 min	56%	41%	3%
3	5 min	48%	48%	4%
4	6 min	40%	55%	5%
5	7 min	37%	56%	7%
6	30 min	18%	72%	10%
7	240 min	5%	68%	27%
8	960 min	-	5%	95%

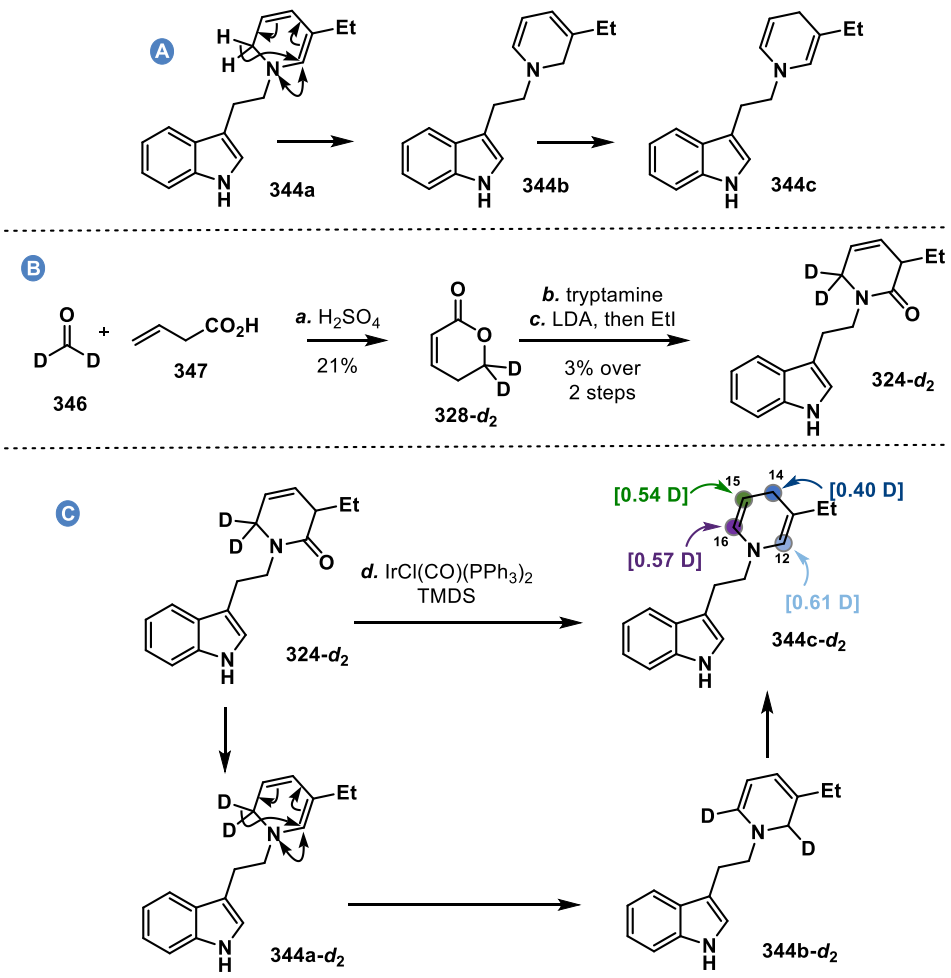
Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ 0.5 mol%, TMDS, rt, toluene-d_8.
* NMR yield was obtained from the ratio of the three dienamines.
344a was identified by an apparent doublet of quartets (most likely a doublet of doublet of doublets) at 5.85 ppm (9.5, 1.5 Hz), assigned to $C_{14a}H$, and a doublet of doublets at 3.72 ppm (4.1, 1.5 Hz), assigned to $C_{16a}H_2$.
344b was identified by a doublet at 5.75 ppm (7.1 Hz), assigned to $C_{16b}H$, and a broad singlet at 3.77 assigned to $C_{12b}H_2$
344c could be completely characterized (see Experimental details, Chapter 6).

Scheme 56. Conversion of model substrate **324** to a mixture of three isomeric dienamines.

It was thus shown that the desired dienamine was unstable under the reaction conditions. Since the intermediate dienamine **344b** could arise from a 1,5-hydride shift (see **Scheme 57**, **A**), we decided to conduct deuteration studies. TMDS-d^2 was made adapting a very recent procedure,[36] but when it was used in the reaction conditions, all signals attributed to the dihydropyridines decreased, showing rapid H-D exchange on most of the protons of the dihydropyridine. We thus chose to synthesize deuterated substrate **325-d_2**, which could be made in 3 steps from commercially available labelled formaldehyde **346**, in comparatively very low yields compared to the non-labelled substrates. When reacted with TMDS and Vaska's complex in an NMR experiment, the desired d²-dienamine **344a-d_2** was quickly converted to the undesired rearranged dienamine **344b-d_2**, confirming the occurrence of the 1,5-deuteride shift[xii].

[xii] Whether this shift is concerted remains unclear. **344a-d_2** can be observed as the major species after *ca.* 10 min reaction time, confirming that the first hydride (here deuteride) shift occurs between position C^{12} and C^{16}.

Overnight, this in turn further rearranged to **344c-d_2**. Most likely, the deuterium atom can be relayed from C^{16} to C^{14} and C^{15}, or C^{12} to C^{14}, and the C^{12} position is consequently depleted in deuterium.



Reagents and conditions: (a) H_2SO_4, then AcONa, AcOH, 120 °C, 6 h, 21% (b) neat, 200 °C, 3 h, 21%; (c) LDA, then EtI, then NH_4Cl, THF, –78 °C, 3 h, 8%, (d) $IrCl(CO)(PPh_3)_2$ 0.5 mol%, TMDS, toluene-d_8, rt, 24 h.

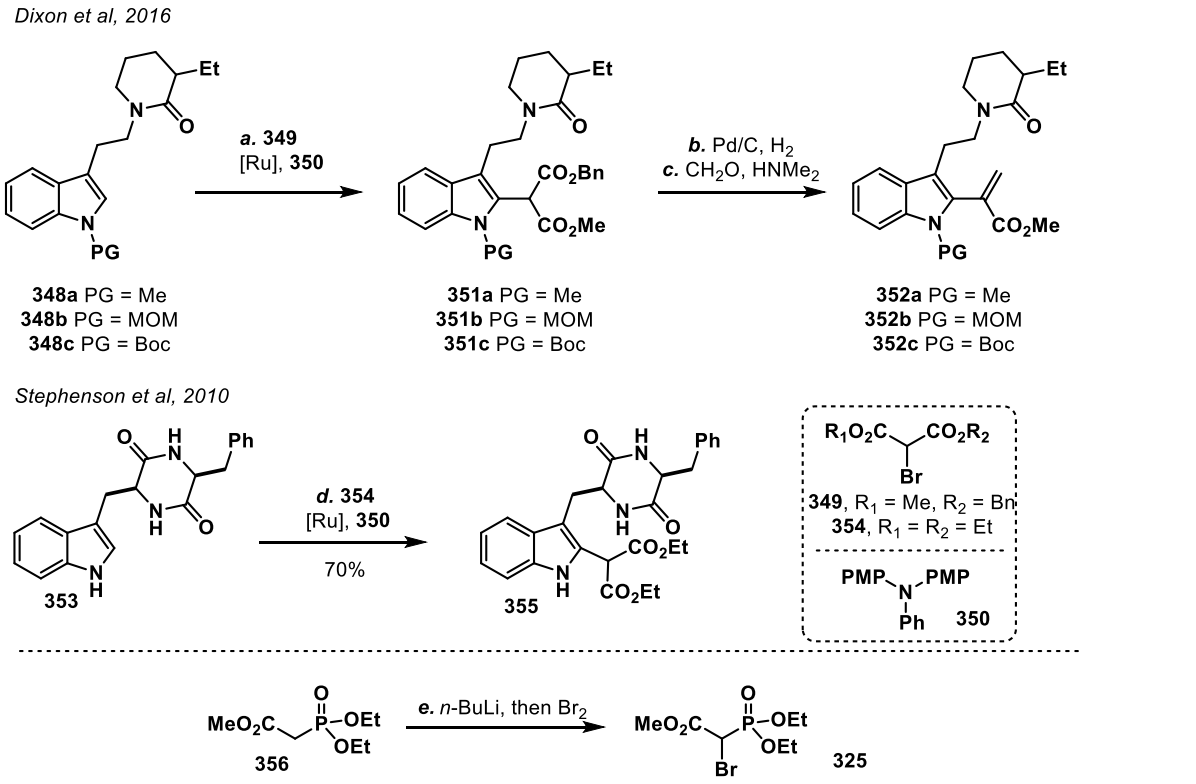
Scheme 57. **A**. Potential hydride shift, **B**. synthesis of deutero-labelled **325-d_2** and **C**. NMR experiment.

In the context of catharanthine, we hoped that the presence of the intramolecular dienophile would accelerate the cycloaddition, hopefully outcompeting any such isomerisation.

4.4 C^2-functionalisation

4.4.1 Proof of concept on C^2-alkylation

To the best of our knowledge, only one precedent for a 3-step alkenylation of the C^2 position of the indole exists,[31] and employs conditions incompatible with our substrate (hydrogenation of a benzyl ester would in our case lead to the saturation of the deconjugated alkene). This strategy was based on a report from Stephenson *et al*, [37] who demonstrated that bromomalonates could be added at the C^2 position of protected and unprotected indoles using photoredox catalysis. We postulated that the second ester group in the malonate coupling partners was only required to make the resulting radical electrophilic, and that therefore, a phosphonate ester would have a similar electronic effect, allowing the desired transformation to take place.

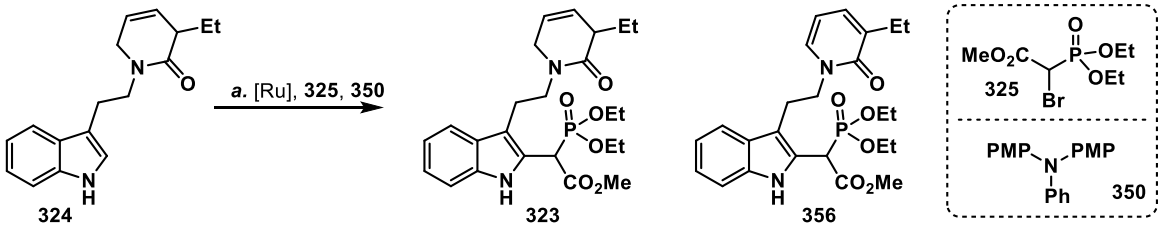


Reagents and conditions: (a) $[Ru(bpy)_3]Cl_2$, 1 mol%, **349**, **350**, blue LEDs, DMF, rt, 12 h, 82% (**351a**), 66% (**351b**), 89% (**351c**); (b) Pd/C, H_2, EtOH, rt, 1 h; (c) CH_2O, $HNMe_2$·HCl, NaOAc, AcOH, rt, 4 h, 55% over 2 steps (**352a**), 55% over 2 steps (**352b**), 82% over 2 steps (**352c**); (d) $[Ru(bpy)_3]Cl_2$, 1 mol%, **350**, **354**, blue LEDs, DMF, rt, 18 h, 70%; (e) *n*-BuLi, DME, 0 °C, 30 min, then Br_2, rt, 2 h, 60%.

Scheme **58**. Precedent for indole-C^2 alkenylation and synthesis of coupling partner **325**.

The coupling partner was prepared in just one step from commercially available phosphono-ester **325**.

Pleasingly, using a bespoke "loop" LED set-up[xiii], desired addition product **323** was observed in the crude reaction mixture, but it could not be isolated after flash column chromatography. Indeed, oxidized pyridone **356** was formed as a side-product and co-eluted with desired C^2-functionalised adduct **323** (see proposed mechanism **Figure 27**). No chromatographic conditions could be found to separate the two compounds. Lowering the equivalents of coupling partner **325** improved the crude ratio of **323** to **356** (Entry **2** – **4**), but not to an extent where the desired **323** could be isolated. Changing the atmosphere of the reaction from nitrogen to argon did not have an impact on the selectivity (Entry **5**), nor did the use of thoroughly degassed solvents (Entry **6**). These observations suggest that the pyridone **356** arises from the over-oxidation of the desired product **323** not because of trace amounts of dissolved molecular oxygen, but rather through a formal dehydrogenation.



Entry	Equivalents 325	Atmosphere	adduct 323	pyridone 356	ratio 323 : 356 [ii]
1	2	N_2	14%	10%	1.4 : 1
2	5	N_2	trace	54%	-
3	1.5	N_2	39%	17%	2.3 : 1
4	1	N_2	38%	13%	3.0 : 1
5	2	Argon	22%	18%	1.2 : 1
6[i]	2	N_2	19%	14%	1.4 : 1

Reagents and conditions: (a) $[Ru(bpy)_3]Cl_2$, 1 mol%, **325**, **350**, blue LEDs, DMF, rt, 14 h.
[i] The DMF was thoroughly degassed by 3 Freeze-Pump-Thaw cycles.
[ii] Ratios obtained by NMR analysis of the isolated mixture of **323** and **356**.

Scheme 59. Optimization for the C^2-alkylation of **324** with **325**.

[xiii] See Supporting information, Chapter 6.

What was likely at play here is an alternative quenching pathway of the photocatalyst, that can oxidise the deprotonated product to a very stable radical. This could be relayed to the unsaturated lactam through several intramolecular HAT events, and further oxidation and aromatisation would produce the undesired pyridone byproduct **356**.[xiv]

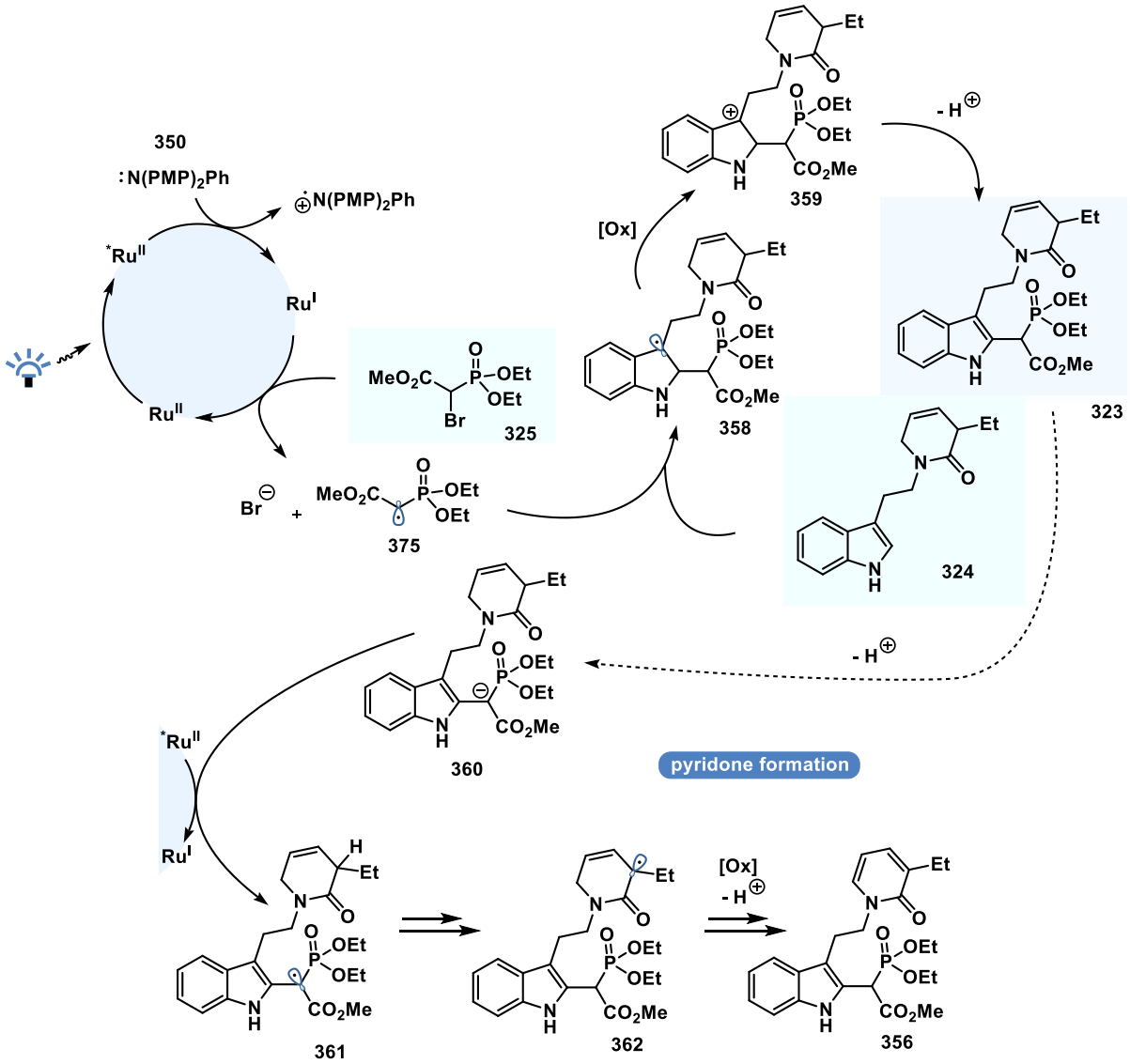


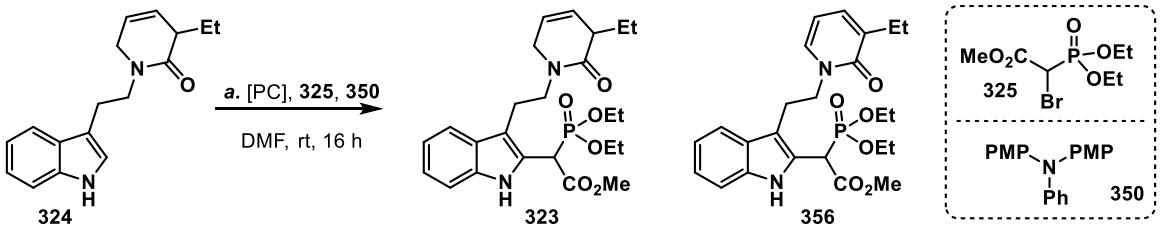
Figure 27. Proposed mechanism for the formation of **323** and undesired pyridone **356**.

[xiv] This hypothesis is in accordance with the fact that more bromophosphonoacetate **325** can generate a build-up of the oxidising Ru^{II} species, as well as the fact that some amine additive **350** is beneficial as it can act as a sacrificial reductant (see optimisation tables in **Scheme 60** and **61**).

All attempts to use flash column chromatography to separate the two reaction products were unsuccessful, as the polarity of these compounds is dictated principally by the phosphono-ester moiety and is hence the same for both compounds. Use of $AgNO_3$-doped silica gel preparative TLC allowed a partial separation, but only enrichment could be achieved, and no pure **323** could be obtained. Reverse-phase preparative HPLC was the only separation technique that afforded pure samples of **323** and **356** for characterization, but no significant amount of material could be obtained from this time-consuming – and limited in scale - method.

4.4.2 Optimisation of the C^2-alkylation

From these preliminary results, it appeared that the reaction conditions needed to be optimised not only for chemical yield, but also for the selectivity between the inseparable desired product **323** and undesired pyridone **356**.



Entry	Photocatalyst	Equivalents phosphonate 325	Equivalents amine 350	Concentration	Conversion [i]	Selectivity [i] (ratio 323 : 356)
1	$Ru(bpy)_3Cl_2$	1.0	2.0	0.1 M	75%	4.8 : 1
2	*fac*-$Ir(ppy)_3$	1.0	2.0	0.1 M	76%	6.5 : 1
3	$[Ir(ppy)_2(dtbbpy)]PF_6$	1.0	2.0	0.1 M	79%	5.1 : 1
4	Eosin Y	1.0	2.0	0.1 M	0%	-
5	$[Ir((dFCF_3)ppy)_2(dtbbpy)]PF_6$	1.0	2.0	0.1 M	79%	4.6 : 1
6	*fac*-$Ir(ppy)_3$	0.9	2.0	0.1 M	73%	8.1 : 1
2	*fac*-$Ir(ppy)_3$	1.0	2.0	0.1 M	76%	6.5 : 1
7	*fac*-$Ir(ppy)_3$	1.1	2.0	0.1 M	81%	4.8 : 1
9	*fac*-$Ir(ppy)_3$	1.5	2.0	0.1 M	92%	2.3 : 1
10	*fac*-$Ir(ppy)_3$	1.0	2.0	0.0125 M	40%	9.0 : 1
11	*fac*-$Ir(ppy)_3$	1.0	2.0	0.02 M	71%	10.8 : 1
12	*fac*-$Ir(ppy)_3$	1.0	2.0	0.05 M	74%	5.7 : 1
2	*fac*-$Ir(ppy)_3$	1.0	2.0	0.1 M	76%	6.5 : 1
13	*fac*-$Ir(ppy)_3$	1.0	2.0	0.2 M	81%	5.2 : 1
6	*fac*-$Ir(ppy)_3$	0.9	2.0	0.1 M	73%	8.1 : 1
14	*fac*-$Ir(ppy)_3$	0.9	1.0	0.2 M	74%	6.8 : 1
15	*fac*-$Ir(ppy)_3$	0.9	1.0 (DIPEA)	0.2 M	3%	-
16	*fac*-$Ir(ppy)_3$	1.0	0.2	0.2 M	86%	13.3 : 1
17	*fac*-$Ir(ppy)_3$	0.9	-	0.2 M	93%	3.4 : 1

Reagents and conditions: (a) Photocatalyst, 1 mol%, **324**, **325**, **350** or DIPEA blue LEDs, DMF, rt, 14 h.
[i] Based on crude NMR ratios between **324**, **323**, and **356**.

Scheme 60. Further optimisation of the C²-alkylation of **324** (some entries (light gray) repeated for clarity).

For the optimisation, a photoredox box was used.[xv] A screen of photocatalysts quickly revealed that all were compatible with the transformation (**entry 1 – 5, Scheme 60**), apart from Eosin Y which is known

[xv] See Experimental details, Chapter 6.

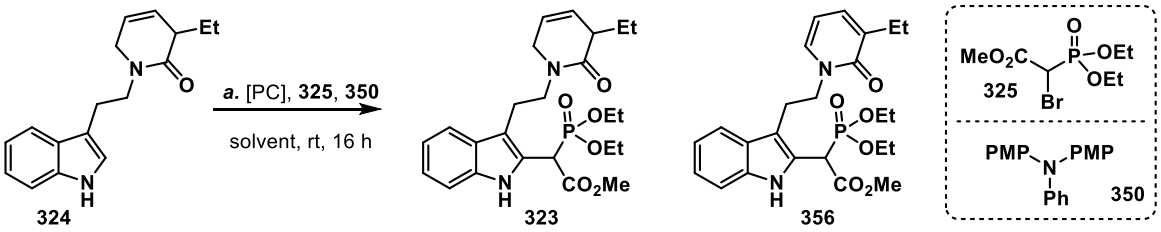
to generally be activated with green light. Selectivity was slightly better with *fac*-Ir(ppy)$_3$, and it was thus decided to continue optimisation with this photocatalyst.

Screening the equivalents of coupling partner **325** confirmed our previous observations: conversion increases with the relative amount of phosphono-ester **325**, but selectivity is reduced (**entry 6 - 9**).

Diluting the reaction seemed to reduce slightly the formation of undesired **356**, at the expense of conversion. Because of the limited scale and material, concentrations of more than 0.2 M could not be screened (**entry 10 - 13**).

Finally, and most interestingly from an outcome point of view, the equivalents and nature of the amine was investigated. Using diisopropylamine resulted in only traces of product (**entry 15**). Keeping **350** as the amine additive, equivalents could be reduced to 1 without any change in the outcome (entry 14). Surprisingly, without any amine, the reaction did proceed, though it proved to be poorly selective (**entry 17**), while catalytic amounts gave increased selectivity (**entry 16**). It is likely that the amine is responsible for reducing the photocatalyst and thus avoiding oxidation of the unsaturated lactam to the undesired pyridone (see mechanism **Figure 27**).

This final result was however not scalable, and the good selectivity could only be observed on small scale (**entry 1, Scheme 61**). A screen of solvents was thus undertaken. Although toluene gave a low conversion, and DMSO produced significant amount of the inseparable pyridone **356** (**entry 2 - 6)**, MeCN, EtOH, and DCE gave a clean crude ^{1}H NMR with an excellent selectivity for the desired product **323** (in the case of EtOH and DCE, no pyridone could be observed to the limit of detection of ^{1}H NMR). The isolated yield was higher in the case of DCE, though it did not match the conversion, and further optimisation was done in this solvent. *fac*-Ir(ppy)$_3$ was still the best catalyst compared with Ru(bpy)$_3$Cl$_2$ (originally used by Stephenson) and the more soluble Ru(bpy)$_3$(PF$_6$)$_2$ (**entry 8 - 10**). Pleasingly, the equivalents of phosphono-ester **325** could be raised to 1 and above without an impact on the selectivity. Surprisingly, in DCE the amine seems to be crucial for the reaction, as opposed to in DMF (**entry 16**), indicating a reaction proceeding either *via* a different mechanism, or that the change in redox potentials between DCE and DMF could be enough to explain this difference in reactivity.



Entry	Solvent	Photocatalyst	Equivalents phosphonate 325	Equivalents amine 350	Conversion [i]	Selectivity [i] (ratio 323 : 356)	Isolated yield
1 [ii]	DMF	*fac*-Ir(ppy)$_3$	0.9	0.2	75%	5.0 : 1	51%
2	PhMe	*fac*-Ir(ppy)$_3$	0.9	0.2	20%	6.5 : 1	-
3	EtOH	*fac*-Ir(ppy)$_3$	0.9	0.2	84%	>20 : 1	39%
4	MeCN	*fac*-Ir(ppy)$_3$	0.9	0.2	78%	31 : 1	-
5	DMSO	*fac*-Ir(ppy)$_3$	0.9	0.2	>90%	2.0 : 1	-
6	DCE	*fac*-Ir(ppy)$_3$	0.9	0.2	>90%	>20 : 1	51%
7	1:1 DMF/DCE	*fac*-Ir(ppy)$_3$	0.9	0.2	71%	7.1 : 1	-
8	DCE	*fac*-Ir(ppy)$_3$	0.9	0.2	>90%	>20 : 1	51%
9	DCE	Ru(bpy)$_3$Cl$_2$	0.9	0.2	47%	3.0 : 1	-
10	DCE	Ru(bpy)$_3$(PF$_6$)$_2$	0.9	0.2	- [iii]	>20 : 1	-
11	DCE	*fac*-Ir(ppy)$_3$	1.05	0.2	>90%	>20 : 1	53%
12	DCE	*fac*-Ir(ppy)$_3$	1.2	0.2	>90%	>20 : 1	53%
13	DCE	*fac*-Ir(ppy)$_3$	1.05	-	0%	-	-
14 [iv]	DCE	*fac*-Ir(ppy)$_3$	1.05	0.2	>90%	>20 : 1	53%

Reagents and conditions: (a) Photocatalyst, 1 mol%, **325**, **350**, blue LEDs, DMF, rt, 14 h, 0.1 mmol scale.
[i] Based on crude NMR ratios between **324**, **323**, and **356**.
ii On 1 mmol scale.
[iii] Although presence of the indole SM could not be confirmed, about 40% coupling partner **325** was present in the crude.
[iv] On 0.3 mmol scale.

Scheme **61**. Final optimisation for desired **323**.

Very pleasingly, the optimized reaction in DCE could be smoothly scaled-up to provide hundreds of milligrams of **323**, of high purity, unlocking access to the final stage of the total synthesis.

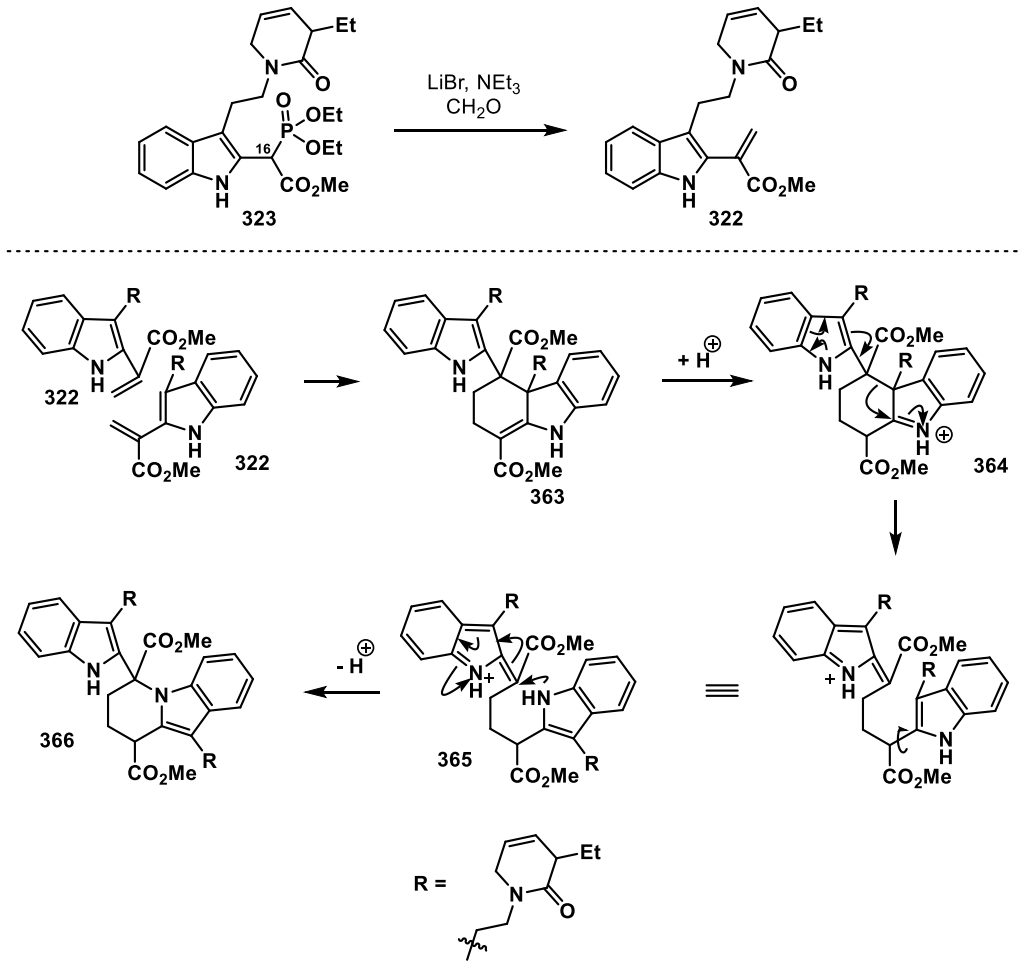
4.5 Endgame: access to and reactivity of dehydrosecodine

4.5.1 HWE reaction and stability of C^2 acrylate-substituted unprotected indoles

With a 3-step route to intermediate **323** now established, we turned our attention to the conversion of the phosphono-ester moiety to the desired α,β-unsaturated ester via a one-carbon homologation.

The proton attached to C^{16}, being benzylic, α to an ester group, and α to a phosphonate group, is very acidic as can be seen by its high chemical shift in ^{1}H NMR (4.72 ppm). Therefore, we decided first to investigate a modification of the Horner-Wadsworth-Emmons (HWE) using a low pKa base. The Rathke modification of the HWE reaction takes advantage of the highly acidic properties of phosphono-esters to use the mildest reaction conditions possible for the transformation.[38] With sufficiently acidic substrates (such as **323**), strong bases such as *n*-BuLi, *t*-BuOK and NaH (for the HWE reaction), and DBU (an already milder variant, the Masamune-Roush modification),[39] are unnecessary for the deprotonation towards the metal salt required for the olefination.

323 was submitted to standard conditions for the Rathke modification, with LiBr as a promoter and source of metal ions for the formation of the lithium enolate, NEt_3 as a base, and formaldehyde as a one-carbon building block. TLC monitoring of the reaction showed quick and clean conversion to a new, less polar spot, but low yields and purity of the desired product **322** were obtained after flash column chromatography. On interrogating the literature, it appeared that C^2-acrylate substituted unprotected indole are unstable and have a propensity to dimerise following the mechanism depicted in **Scheme 62**.[24, 40] An intermolecular cycloaddition can indeed take place, followed by a fragmentation at the newly-formed cyclohexene ring, and an aza-Michael-type reaction, causing rearomatisation, in an overall dimerization reaction.



Reagents and conditions: (a) LiBr, NEt_3, paraformaldehyde, THF, rt, 30 min, then FCC, 13%, or 81% when cold FCC and evaporation.

Scheme 62. Synthesis of dehydrosecodine precursor **322** and its documented decomposition pathway.

In order to avoid leaving **322** undiluted for more than a few minutes, the reaction procedure was modified with an evaporation at 0 °C after the complete conversion was observed by TLC analysis. Additionally, a chilled FCC was performed using pre-cooled (0 °C) toluene and ethyl acetate as the eluent and an ice-jacket cooled chromatography column. The product could be obtained neat and the yield measured, before immediate dilution in toluene. Using this modified approach, a much more satisfactory yield of 81% could be obtained. Even in solution in d_8-toluene, samples of **322** decomposed within hours at room temperature.[xvi] For direct use in the next step, the collected fractions were evaporated at 0 °C to obtain a solution of **322** in the eluting toluene.

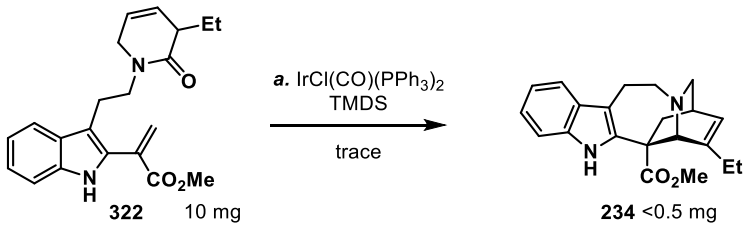
[xvi] Over 80% of the material decomposed overnight in toluene at rt, as measured by ^{1}H NMR.

By using these stringent precautions, we were able to complete the synthesis of the highly sensitive α-substituted acrylate moiety, and introduce all the carbon atoms required for the final catharanthine natural product. All that was left to investigate was the key reduction-triggered intramolecular Diels-Alder reaction.

4.5.2 Initial investigations of IMDA and completion of the synthesis

To access dehydrosecodine **244**, the putative final intermediate in the biosynthesis of catharanthine **234** and tabersonine **245**, the β,γ-unsaturated δ-lactam needed to be reduced to a dienamine as per the method developed in the preliminary studies (see part **4.3** of this chapter).

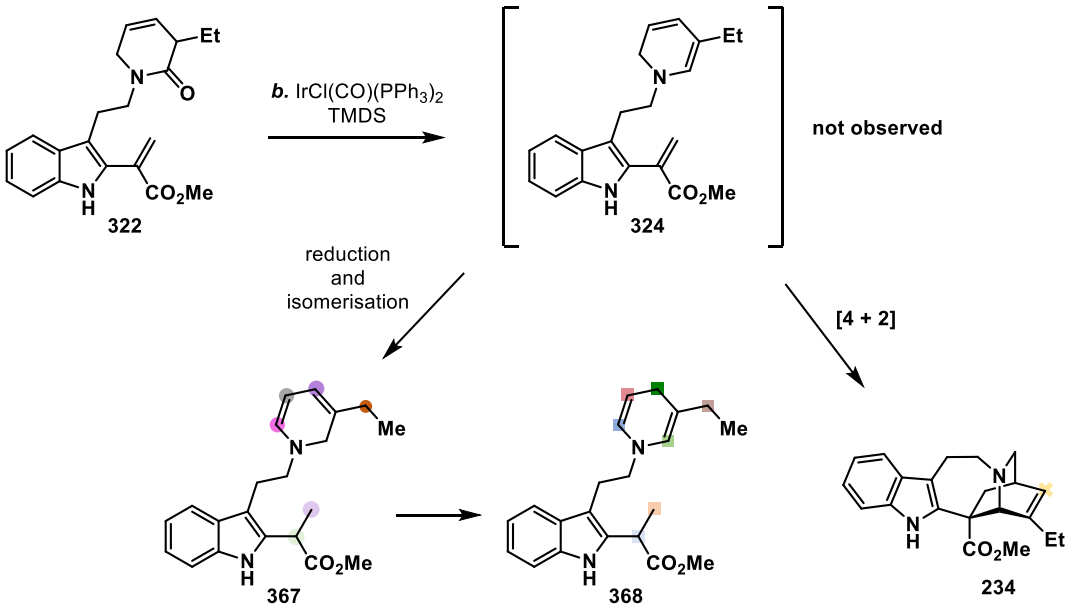
When submitted to these conditions, a complex mixure of reaction products was obtained. Pleasingly, preparative TLC afforded traces of catharanthine **234**, the data of which matched with the literature values. A yield could however not be measured as <0.5 mg of the natural product was obtained. The presence of the natural product could not be confirmed in the crude ^{1}H NMR, as it was a very minor component of the crude mixture. Disappointingly, no other byproduct could be isolated to gather information about why the reaction was so inefficient. A screen of additives was undertaken in a series of repeat reactions, but no significant improvement was obtained.



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$, 1 mol%, TMDS, PhMe, rt, 2 to 16 h. Additives tried: DMSO, NEt_3, $PhCO_2H$, SiO_2, TMSCl, PhCHO, MeOH, H_2O, AcOH, 3 Å and 4 Å MS. Reaction also attempted at 0 °C and −15 °C, and in large headspace vessels.

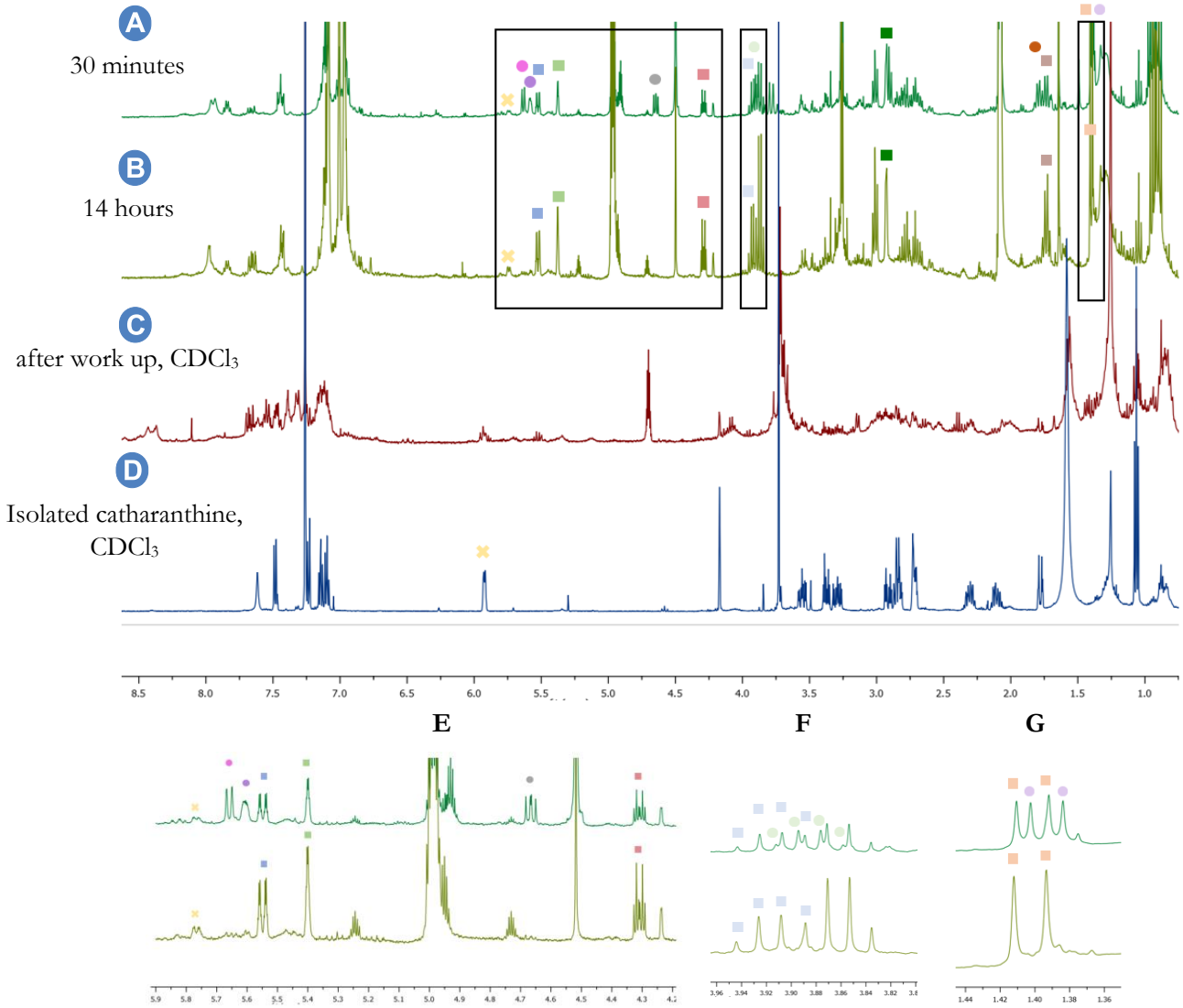
Scheme **63**. First synthesis and isolation of catharanthine.

Consequently, a solution of the starting material in toluene-d_8 was submitted to the standard reduction conditions, and ^{1}H NMR spectra were regularly measured in the hope that transient intermediates could be observed. A complex mixture that could not be deconvoluted was obtained. A reverse addition (catalyst added last) did not give any improvement. However, when the TMDS was diluted in toluene-d_8 and added over 30 minutes as a solution, characteristic signals in the ^{1}H NMR could be attributed to the desired catharanthine **234**, but also to side-products **367** and **368**. These most likely arose from reduction of the acrylate moiety before the IMDA reaction could take place. The isomerisation from **367** to **368** is expected considering the reactivity of the model substrate explored earlier in this chapter. Measuring another ^{1}H NMR after 14 hours showed nearly complete conversion of **367** to **368**, whose structure was definitively assigned on the basis of 2D NMR experiments.



Time			
30 min	45%*	40%*	15%*
14 h	4%*	80%*	16%*
isolated	-	-	11%

Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$, 1 mol%, TMDS added over 30 minutes as a solution in toluene-d_8, toluene-d_8, rt, 16 h.
* NMR yield obtained by ratio of **367**, **368**, and **234**.



Scheme **64**. Reaction in an NMR tube to observe transient dienamine intermediates.

To assess the stability of by-product **368**, a stream of O_2 was passed through the reaction mixture for one minute, before concentration and measurement of the resulting spectrum in $CDCl_3$. The ^1H NMR obtained in this way showed that no **368** was present after this treatment, and the only assignable component of the crude reaction mixture is catharanthine **234** (**Scheme 64**, **D**).

4.5.3 Investigations to suppress the presence of the reducing hydride

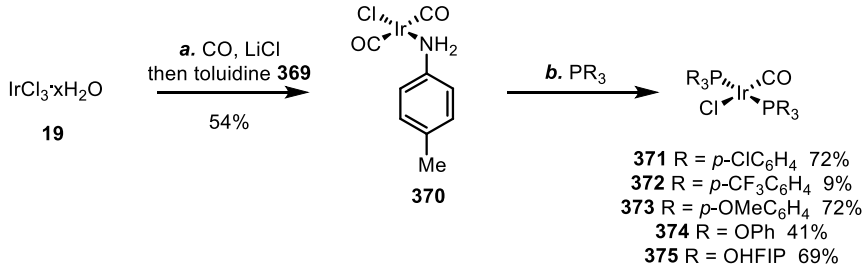
The data acquired clearly indicated that the low yield of catharanthine obtained in these experiments was due to undesired competitive reduction of the dienophile, before the IMDA reactionwas able to take place. Partial reduction of amides and lactams have been conducted in the presence of acrylate previously,[xvii] proving that the amide carbonyl is, in this reaction, more reactive towards the generated hydridic species than the Michael acceptor. In order to quench any over-active hydride species responsible for this reduction, hydride scavengers such as 4-bromobenzaldehyde, or norbornadiene were introduced as additives, but unfortunately did not change the outcome of the reaction. The use of methyl acrylate – to mimic the stereo-electronic effects of the C^2-substituted indole - as an additive only significantly decreased the rate of reaction, without changing the outcome.

Accordingly, we decided to pursue a different approach, in the hope to attenuate directly the nucleophilicity of the hydride in the Ir-H active catalyst species, the putative reducing intermediate in the iridium catalyst cycle. To do so, phosphines with different electronic properties – but of similar structure to the triphenylphosphine moiety of Vaska's catalyst – would be introduced and their performance assessed in the key reaction.

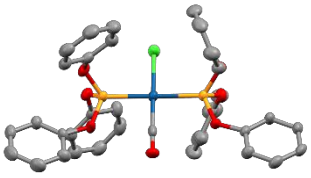
To this end, a versatile iridium complex **370** was made in one step from commercially available $IrCl_3$ hydrate **19**, CO (gas), and toluidine **369**. This complex has been reported in the 1980's as an access point to Vaska-type complexes, and allows easy and efficient generation of a library of catalysts by introduction of the phosphines with simple stirring at rt in the presence of two equivalents of the desired phosphine. Gas evolution was immediately seen, and in under a minute, the desired catalyst precipitates from the toluene reaction mixture, or can be forced to precipitate out of solution by addition of pentane. Filtering and drying the solids results in the isolation of essentially pure complexes. Their electron-density at the iridium centre can be measured by simple IR measurements, by observing the C-O bond stretching frequency, which is linked to the amount of back-bonding it receives.

[xvii] See Chapter 3 of this thesis for instance, intramolecular example **229b**.

It should be noted that phosphines more electron-rich than PPh_3 (such as P(*p*-MeO-Ph)$_3$) resulted in the complex being observed as the oxygen adduct as well, even in the solid phase.[xviii] Vaska's complex in solution itself is known to very quickly bind molecular oxygen. However, with weaker σ donor phosphines, other complexes were much more stable toward this oxidation as the electron density at the iridium centre was reduced. Pleasingly, a crystal could be grown for complex **374**, confirming its structure.



R	C-O stretching frequency (cm^{-1})*
Ph	1949
p-ClC_6H_4	1964
p-$CF_3C_6H_4$	1964
p-$OMeC_6H_4$	1965 and 2000 (oxygen adduct)
OPh	1999
OHFIP	2055



374

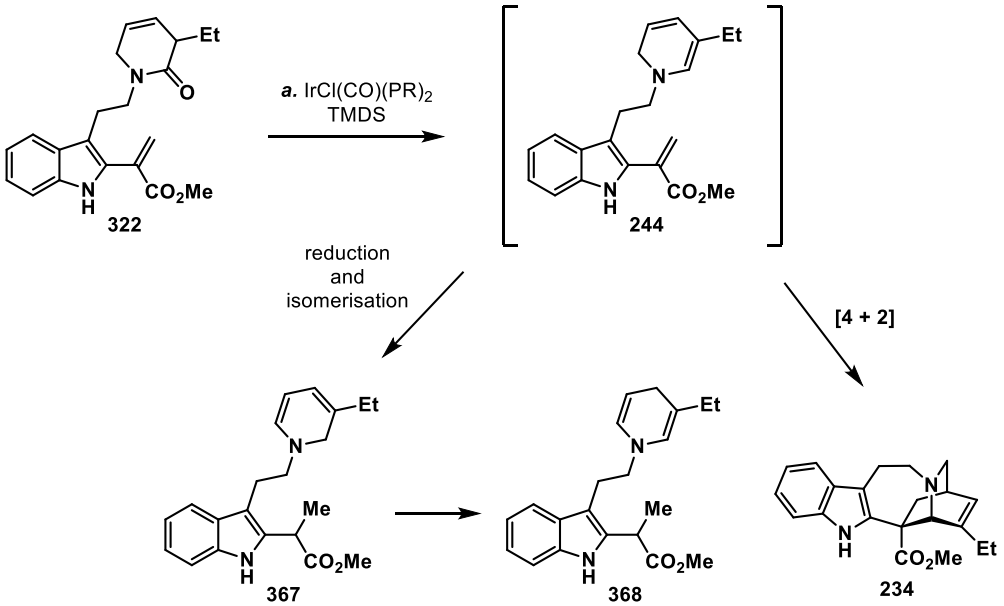
Reagents and conditions: (a) CO (g), LiCl, 2-methoxyethanol, 124 °C, 9 h, 54%; (b) PR_3, PhMe, rt, 1 min, 72 % (**371**), 9% (**372**), 72% (**373**), 41% (**374**), 69% (**375**).
* measured in the solid state.

Scheme 65. Synthesis and CO stretching frequency data of new Vaska-type complexes.

Having established a reliable method for the generation of a library of Vaska-type iridium complexes, we investigated their properties in the key step of the synthesis.

[xviii] We could not determine if the oxygen-bound complex is formed during its isolation, or when handled for characterisation.

Unfortunately, no improvement was observed compared to the traditional Vaska's catalyst. The isolated yield of catharanthine on this final step could not be improved past 13%. The ratios between the reduced species (**367** and **368**), and the natural product **234** were consistently between 5 : 1 and 10 : 1,[xix] indicating that the hydridic species responsible for the reduction of the acrylate was most likely not linked to the iridium complex.



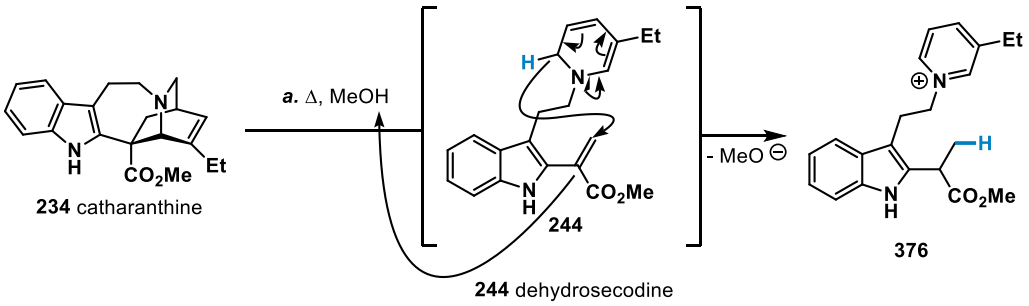
R	NMR yield	NMR yield	NMR yield	Ratio (367+368) : 234
Ph	21%	28%	10%	4.9 : 1
p-$CF_3C_6H_4$	20%	44%	13%	4.9 : 1
p-$OMeC_6H_4$ *	-	-	-	-
OPh	20%	53%	13%	5.6 : 1
OHFIP	11%	39%	5%	10 : 1

Reagents and conditions: (a) $IrCl(CO)(PR_3)_2$, 1 mol%, TMDS added over 30 minutes as a solution in toluene-d_8, toluene-d_8, rt, 30 min. NMR yield obtained after *ca.* 30 min against internal standard (TMB).
* No conversion observed

Scheme **66**. Studies on the key reductive cycloaddition step with new Vaska-type complexes.

[xix] The small variations here are due to inaccuracies in the NMR integration, in weighing the catalyst amount (0.1 mg), and slight time difference between the addition and the ^{1}H NMR measurement. This would particularly impact the ratio of rearranged dienamine **368** over original dienamine **367** since the conversion between those two species was very fast in model substrate of section **4.3.4**.

The problem that we could not solve is in essence the same as the one faced by Marazano *et al* in their synthesis of catharanthine (see Scheme **49** of this chapter), and suggest the dihydropyridine itself might be reducing the acrylate appendage. More indicative perhaps is the work of Cherry and Scott:[42] when trying to access dehydrosecodine **244** from catharanthine **234** *via* a thermal retro-[4+2] cycloaddition – essentially the opposite reaction to what we conceptualized as our key step – the authors also oserved this hydride transfer.



Reagents and conditions: (a) MeOH, 140 °C, 2 h, 50%.

Scheme **67**. Cherry and Scott's retro-cycloaddition of catharanthine, in attempts to identify dehydrosecodine, leads to intramolecular hydride transfer.

Although the reaction conditions they employed to access dehydrosecodine **244** (a sealed methanolic solution of catharanthine is heated at 140 °C for 2 hours) are conceivably harsher than our room temperature/toluene procedure, we did observe a similar propensity of dehydrosecodine **244** to undergo the undesired rearrangement. This data, in line with our investigations of the stability and reactivity of model substrate **324** (see NMR experiment section **4.3.4** of this chapter)[xx] led us to the conclusion that, in the absence of the enzymatic chaperone, a biomimetic approach of catharanthine **234** *via* dehydrosecodine **244** will inevitably favour the unproductive hydride transfer pathway.

[xx] In our case, the resulting pyridinium is reduced back to the dihydropyridine by the catalytic system.

4.5.4 Conclusion

Our efforts towards the natural product resulted in an unprecedentedly short 5-step biomimetic synthesis of racemic catharanthine, with an overall yield of 2% (18% in the four first steps of the synthesis). Despite the disappointment of being unable to overcome the competitive hydride transfer in the final key step, the chemistry developed along the way, as well as the new understanding of dienamine reactivity, in particular of dehydrosecodine, should be of interest to the synthetic community.

4.6 References for Chapter 4

(1) van Der Heijden, R.; Jacobs, D. I.; Snoeijer, W.; Hallard, D.; Verpoorte, R. The Catharanthus alkaloids: Pharmacognosy and biotechnology. *Curr. Med. Chem.* **2004**, *11*, 5, 607–628.

(2) Moudi, M.; Go, R.; Yien, C. Y.; Nazre, M. Vinca alkaloids. *Int. J. Prev. Med.* **2013**, *4*, 11, 1231–1235.

(3) Noble, R. L. The discovery of the vinca alkaloids-chemotherapeutic agents against cancer. *Biochem. Cell Biol.* **1990**, *68*, 1344–1351.

(4) (a) Ishikawa, H.; Colby, D. A.; Boger, D. L. Direct Coupling of Catharanthine and Vindoline to Provide Vinblastine: Total Synthesis of (+)- and *ent*-(−)-Vinblastine. *J. Am. Chem. Soc.* **2008**, *130*, 2, 420−421 (b) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues. *J. Am. Chem. Soc.* **2009**, *131*, 13, 4904–4916.

(5) For the seminal work of Potier *et al*, see: (a) Potier, P.; Langlois, N.; Langlois, Y.; Guéritte, F. Partial synthesis of vinblastine-type alkaloids. *J. Chem. Soc., Chem. Commun.* **1975**, 670−671; (b) Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. Application of a modification of the Polonovski reaction to the synthesis of vinblastine-tye alkaloids, *J. Am. Chem. Soc.* **1976**, *98*, 7017−7024; for the work of Kutney *et al*, see: (c) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. Studies on the Synthesis of Bisindole Alkaloids. II. The Synthesis of 3',4'-Dehydrovinblastine, 4'-Deoxovinblastine and Related Analogues. The Biogenetic Approach. *Heterocycles* **1975**, *3*, 639−649; (d) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. Total Synthesis of Indole and Dihydroindole Alkaloids. IX Studies on the synthesis of bisindole alkaloids in the vinblastine- vincristine series. The biogenetic approach. *Helv. Chim. Acta* **1976**, *59*, 2858−2882.

(6) Szabó, L. F. Rigorous Biogenetic Network for a Group of Indole Alkaloids Derived from Strictosidine. *Molecules* **2008**, *13,* 1875−1896.

(7) Qu, Y.; Easson, M. E. A. M.; Simionescu, R.; Hajicek, J.; Thamm, A. M. K.; Salim, V.; De Luca, V. Solution of the multistep pathway for assembly of corynanthean, strychnos, iboga, and aspidosperma monoterpenoid indole alkaloids from 19*E*-geissoschizine. *Proc. Natl. Acad. Sci.* **2018**, *115,* 12, 3180−3185.

(8) Gorman, M.; Neuss, N.; Svoboda, G. H.; Barnes, A. J., Jr.; Cone, N. J. A Note on the Alkaloids of *Vinca rosea* Linn. (*Catharanthus roseus* G. Don.) 11. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, 48, 256.

(9) Neuss. N.; Gorman, M. The Structure of Catharanthine, a Novel Variant of the Iboga Alkaloids. *Tetrahedron Lett.* **1961**, *6*, 206−210.

(10) Bartlett, M. F.; Dickel, D. F.; Taylor, W. I. The Alkaloids of Tabernanthe iboga. Part IV. The Structures of Ibogamine, Ibogaine, Tabernanthine and Voacangine. *J. Am. Chem. Soc.* **1958**, *80*, 1, 126−136.

(11) (a) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. Syntheses of Velbenamine and Catharanthine. *J. Am. Chem. Soc.* **1970**, *92*, 4, 999−1005; for the first steps of the synthesis, see: (b) Büchi, G., Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. The Total Synthesis of Iboga Alkaloids. *J. Am. Chem. Soc.* **1966,** *88*, 13, 3099−3109.

(12) Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. Formal Synthesis of (+)-Catharanthine. *Angew. Chem., Int. Ed.* **2006**, *45*, 5334–5336.

(13) Hatano, M.; Goto, Y.; Izumiseki, A.; Akakura, M.; Ishihara, K. Boron Tribromide-Assisted Chiral Phosphoric Acid Catalyst for a Highly Enantioselective Diels−Alder Reaction of 1,2-Dihydropyridines. *J. Am. Chem. Soc.* **2015**, *137*, 13472−13475.

(14) Kim, S. J.; Batey, R. A. Enantioselective isoquinuclidine synthesis via sequential Diels-Alder/visible-light photoredox C–C bond cleavage: a formal synthesis of the indole alkaloid catharanthine. *Org. Chem. Front.*, **2018**, *5*, 2934–2939.

(15) Kono, M.; Harada, S.; Nozaki, T.; Hashimoto, Y.; Murata, S.-i.; Groger, H.; Kuroda, Y.; Yamada, K.-i.; Takasu, K.; Hamada, Y.; Nemoto, T. Asymmetric Formal Synthesis of (+)-Catharanthine via Desymmetrization of Isoquinuclidine. *Org. Lett.* **2019**, *21*, 3750−3754.

(16) Ishihara, K.; Yamada, H.; Akakura, M. An enantioselective Diels–Alder reaction of 1,2-dihydropyridines with α-acyloxyacroleins catalyzed by a chiral primary ammonium salt. *Chem. Commun.* **2014**, *50*, 6357−6360.

(17) (a) Trost, B. M.; Godleski, S. A.; Belletire, J. L. Synthesis of (±)-Catharanthine via Organopalladium Chemistry. *J. Org. Chem.* **1979**, *44*, 12, 2052–2054; (b) for the synthesis of the starting material, see Paquette, L. A.; Ward, J. S.; Boggs, R. A.; Farnham, W. B. Valence Isomerization of Homocubanes. Reversible Complex Formation and Kinetic Substituents Effects Operating during Silver (I)-Induced Bond Reorganization. *J. Am. Chem. Soc.* **1975**, *97*, 1101−1112.

(18) Zhang, Y.; Xue, Y.; Li, G. ; Yuan, H.; Luo, T. Enantioselective synthesis of Iboga alkaloids and vinblastine via rearrangements of quaternary ammoniums. *Chem. Sci.*, **2016**, *7*, 5530–5536.

(19) Imanishi, T.; Yagi, N.; Shin, H. Hanaoka, M. 1,6-Dihydro-3(2H)-pyridinones. III. A Formal Synthesis of (±)-Catharanthine. *Chem. Pharm. Bull.* **1982**, *30*, 11, 4052−4059.

(20) Szántay, C.; Bolcskei, H.; Gács-Baitz, E. Synthesis of Vinca Alkaloids and Related Compounds XLVIII Synthesis of (+)-Catharanthine and (±)-Allocatharanthine. *Tetrahedron*, **1990**, *46*, 5, 1711−1732.

(21) Raucher, S.; Bray, B. L. Total Synthesis of (±)-Catharanthine. *J. Org. Chem.* **1985**, *50*, 3237−3239.

(22) Raucher, S. Bray, B. L.; Lawrence, R. F. Synthesis of (±)-Catharanthine, (+)-Anhydrovinblastine, and (-)-Anhydrovincovaline. *J. Am. Chem. Soc.* **1987**, *109*, 2, 442−446.

(23) (a) Reding, M. T.; Fukuyama, T. Stereocontrolled Total Synthesis of (±)-Catharanthine via Radical Mediated Indole Formation. *Org. Lett.,* **1999,** *1*, 7, 973−976; (b) Reding, M. T.; Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. Synthesis of 2,3-Disubstituted Indoles by Radical Cyclization with Hypophosphorous Acid and its Application to Total Synthesis of (±)-Catharanthine, *Heterocycles* **2002**, *56*, 313−330.

(24) Mizoguchi, H.; Oikawa, H.; Oguri, H. Biogenetically inspired synthesis and skeletal diversification of indole alkaloids. *Nature Chem.* **2014**, *6*, 57–64.

(25) Marazano, C.; Le Goff, M.-T.; Fourrey, J.-L.; Das, B. C. An Unequivocal Synthesis of 1-Benzyl-3-ethyl-1,6-dihydropyridine and its Use for a Biogenetically Modelled Synthesis of (±)-Catharanthine. *J. Chem. Soc., Chem. Comm.* **1981**, 389–391.

(26) Marazano, C.; Fourrey, J.-L.; Das, B. C. Cycloaddition Reactions of 2-(Indol-2-yl)acrylates and *N*-alkoxycarbonyl-1,2-dihydropyridine; New Synthesis of Desethylcatharanthine. *J. Chem. Soc., Chem. Comm.* **1981**, 37–39.

(27) Marazano, C.; Fourrey, J.-L.; Das, B. C. Novel Access to 2-Substituted Indoles and a Convenient Synthesis of Secodine-type Alkaloids. *J. Chem. Soc. Chem. Comm.* **1977**, 742–743.

(28) Hino, T.; Suzuki, T.; Takeda, S.; Kano, N.; Ishii, Y.; Sasaki, A.; Nakagawa, M. Preparation of 3-Substituted 2-Indolinethiones *via* Diindolyl Disulfides. The Reaction of 3-Substituted Indoles with Sulfur Monochloride. *Chem. Pharm. Bull.* **1973**, *21*, 12, 2739–2748.

(29) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G. Marko, I. Studies in Biomimetic Alkaloid Syntheses. 14. Controlled, Selective Syntheses of Catharanthine and Tabersonine, and Related Desethyl Compounds, through Generation of 15-Oxosecodine Intermediates. *J. Org. Chem.* **1986**, *51*, 2913–2927.

(30) Huang, N.; Jiang, T.; Wang, T.; Soukri, M.; Ganorkar, R.; Deker, B.; Léger, J.-M.; Madalengoitia, J.; Kuehne, M. E. The acyclic dienamine–indoloacrylate addition route to catharanthine. *Tetrahedron* **2008**, *64*, 9850–9856.

(31) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436–13440.

(32) For reviews, see: (a) Muzart, J. One-Pot Syntheses of α,β-Unsaturated Carbonyl Compounds through Palladium-Mediated Dehydrogenation of Ketones, Aldehydes, Esters, Lactones and Amides. *Eur. J. Org. Chem.* **2010**, 3779–3790; (b) Iosub, A. V.; Stahl, S. S. Palladium-Catalyzed Aerobic Dehydrogenation of Cyclic Hydrocarbons for the Synthesis of Substituted Aromatics and Other Unsaturated Products. *ACS Catal.* **2016**, *6*, 8201–8213.

(33) (a) Chen, Y.; Turlik, A.; Newhouse, T. R. Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide. *J. Am. Chem. Soc.* **2016**, *138*, 4, 1166–1169; (b) Teskey, C. J.; Adler, P.; Gonçalves, C. R.; Maulide, N. Chemoselective α,β-Dehydrogenation of Saturated Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 447–451; (c) Wang, M.-M.; Sui, G.-H.; Cui, X.-C.; Wang, H.; Qu, J.-P.; Kang, Y.-B. Radical α,β-Dehydrogenation of Saturated Amides via α-Oxidation with TEMPO under Transition Metal-Free Conditions. *J. Org. Chem.* **2019**, *84*, 12, 8267–8274.

(34) Nakagawa, M.; Kiuchi, M.; Obi, M.; Tonozuka, M.; Kobayashi, K.; Hino, T.; Ban, Y. Reaction of Tryptamine and Aniline with δ-Valerolactone and Its Dehydro Derivatives. A New Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-α]quinolizine. *Chem. Pharm. Bull.* **1975**, *23*, 2, 304–312.

(35) Burchat, A. F.; Chong, J. M.; Nielsen, N. Titration of alkyllithiums with a simple reagent to a blue endpoint. *J. Organomet. Chem.* **1997**, *542*, 281–283.

(36) Prakash, S.; Cook, A.; Zheng, Y.-L.; Newman, S. G. Exhaustive Reduction of Esters Enabled by Nickel Catalysis. *ChemRxiv* **2019**, doi.org/10.26434/chemrxiv.9917150.v1

(37) Furst, L.; Matsuura, S.; Narayanam, J.; Tucker, J. W. Stephenson, C. R. J. Visible Light-Mediated Intermolecular C-H Functionalization of Electron-Rich Heterocycles with Malonates. *Org. Lett.* **2010**, *12*, 13, 3104–3107.

(38) Rathke, M. W.; Nowak, M. The Horner-Wadsworth-Emmons modification of the Wittig reaction using triethylamine and lithium or magnesium salts. *J. Org. Chem.* **1985**, *50*, 15, 2624–2626.

(39) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

(40) Cordell, G. A.; Smith, G. F.; Smith, G. N. The Presecamines, a New Group of Dimeric Inole Alkaloids from Rhazya Species, and Their Thermally Derived Monomers, Secodine and 15,20-Dihydrosecodine. J. *Chem. Soc. D.* **1970**, 191–192.

(41) Klabunde, U.; Forster, D.; Weinreis, W. O. Dicarbonylchloro(p-toluidine)iridium(I). *Inorganic Syntheses* **1974**, *15*, 82–84.

(42) Scott., A. I.; Cherry, P. C. Further Observations on the Biogenetic-Type Chemistry of the Indole Alkaloids. *J. Am. Chem. Soc.* **1969**, *91*, 21, 5872–5873.

Chapter 5 : Larger scale applications and preliminary results for future work

In the previous chapters of this thesis, we have developed methodologies based on Vaska's complex as a chemoselective catalyst for the reduction, functionalisation and cyclisation of amides and lactams, and applied its use to the total synthesis of catharanthine **234**. Due to the ubiquity of amides and lactams in every synthetic laboratory, from pharmaceutical companies to academic groups, and the desirability of the amine products that can be obtained through these methodologies, we are confident that the catalytic system and the newly developed methodologies can find widespread use, and replace in a broad range of cases the metal hydride reagents still traditionally used, despite non-ideal safety profiles and ease of handling. In order to facilitate end user take-up, in particular within an industrial setting, we decided to investigate the scalability of some of the methodologies developed in our group over the last few years.

5.1 Large scale reaction: use of Grignard reagents for the synthesis of α-branched amines

As described in **Scheme 12** of section **1.3.4** of this work, in 2017, the Dixon group published a methodology to reductively couple tertiary amides to Grignard reagents,[1] producing α-branched amines. To demonstrate the utility of this strategy on large scale, we set out to develop and publish a detailed procedure for a reaction on a 100 mmol-scale.

5.1.1 Optimisation on 10 mmol-scale

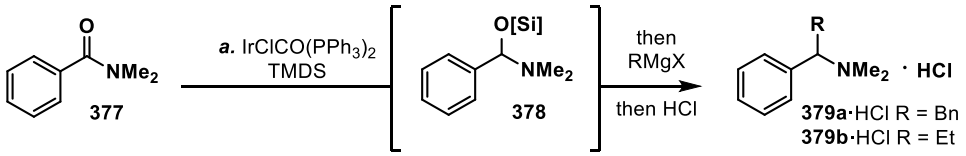
We sought to improve some aspects of the reaction, without straying too far from the published conditions.

Dimethylbenzamide **377** was chosen as the model substrate as it was widely commercially available, and a model substrate in the initial methodology publication.

Very pleasingly, the equivalents of Grignard reagent required could be reduced to 1.1, and the concentration doubled with no significant impact on the yield (**entry 2**, **Scheme 68**).

To facilitate purification of the product upon scale-up, the hydrochloride salt of the amine **379a**·HCl and **379b**·HCl product was made quantitatively at the end of the reaction.

More importantly, the catalyst loading was reduced successively from 1 mol% to 0.2 and 0.1 mol% with no change (**entry 2** and **3**, respectively). At 0.05 mol%, the time for the reduction phase of the reaction had to be increased to 35 min, as checked by TLC. This is however a 20-fold improvement on the original loading, and a TON of 2000 and TOF of 0.95 s^{-1} [(meaning one mole of catalyst converts 0.95 mole of substrate per second), **entry 4**].



Entry	Grignard	Equivalents Grignard	Concentration	Catalyst loading	Reduction time	Yield
1[i]	BnMgCl	2	0.1 M	1 mol%	15 min	89%[ii]
2	BnMgCl	1.1	0.2 M	0.2 mol%	20 min	82%
3	BnMgCl	1.1	0.2 M	0.1 mol%	20 min	83%
4	BnMgCl	1.1	0.2 M	0.05 mol%	35 min	81%
5	EtMgBr	1.1	0.2 M	0.05 mol%	35 min	75%

Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (x mol%), TMDS, rt, xx min, then RMgX, −78 °C to rt, 4 h, then HCl in dioxane (4 M), Et_2O, rt, 1 min.
[i] From the original methodology paper,[1]
[ii] The purity of this material was not thoroughly checked, see footnote i next page.

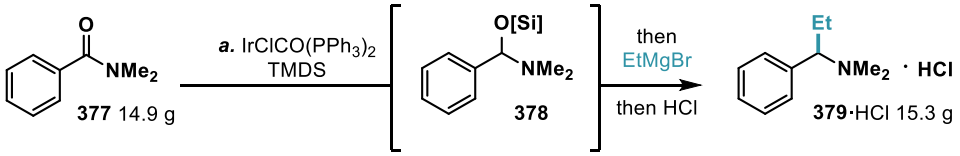
Scheme **68**. Initial optimisation on 10 mmol scale.

The product amine **379a** posesses a phenethylamine moiety, very often associated with psychoanaleptic, hallucinogenic and empathogenic activities on the central nervous system.[2] In fact, **379a** is also known as Lefetamine, a regulated substance that has analgesic properties, and has been abused as an opioid.[3, 4] Consequently, we chose to use EtMgBr as an alternative Grignard reagent, resulting in the formation of **379b**, a more benign amine product, with little change in product yield (**entry 5**, **Scheme 68**).

Having improved the reaction conditions to satisfactory levels on the intermediate 10 mmol scale, it was time to put the methodology to trial on a larger 100 mmol scale.

5.1.2 Scale-up: 100 mmol-scale

The reaction was set up on a 100 mmol, or 14.9 g of dimethylbenzamide **377**. The reaction proceeded well, and upon treatment of the amine product with HCl in dioxane, 15.3 g (75%) of the hydrochloride salt **379b**·HCl could be isolated, with no difference with the 10 mmol scale reaction. On a repeat, a yield of 78% (15.9 g) was obtained. The puritiy was determined to be high (>97%) in both instances by internal standard NMR spectroscopy techniques.[i]



Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (0.05 mol%), TMDS, rt, 40 min, then EtMgBr, −78 °C to rt, 4 h, then HCl in dioxane (4 M), Et_2O, rt, 1 min, 75%, 78% (repeat).

Scheme **69**. Initial optimisation on 10 mmol scale.

[i] A purity of 97.6% was measured with quantitative NMR using 15.2 mg of compound **379b**·HCl and 18.4 mg of standard (trimethoxybenzene). The repeat reaction on identical scale provided 15.6 g (78%) of the desired product **379b**·HCl, whose purity was evaluated to be 97.2%

5.1.3 Financial and safety considerations

A typical drawback of transition-metal catalysis is usually the cost of the metal, particularly with iridium.[5] In order to assess the likelihood that this reaction could be used in an industrial set-up, **Table 2** compares the financial aspects of our reaction to standard reduction methods.[ii], [6-9]

Entry	Reduction conditions	Total Price [i]
1	$IrCl(CO)(PPh_3)_2$ (0.05 mol%) TMDS (2 equiv.)	£ 20
2	$LiAlH_4$ (1 equiv.)	£ 11
3	$PhSiH_3$ (1 equiv.)[ii, 6]	£ 77
4	$Zn(OAc)_2$ (10 mol%) EtO_2SiMeH (3 equiv.) [7]	£ 207
5	$NaBH_4$ (2.5 equiv.) MsOH(3.5 equiv.) [8]	£ 42
6	$Co_2(CO)_8$ (0.5 equiv.) TMDS (2.2 equiv.) [9]	£ 17

[i] Prices taken from Sigma Aldrich, pro rata of the price of the available quantity directly above that needed for a 100 mmol scale reaction.
Solvents not taken into account. Rounded up to the next pound sterling.
[ii] Requires a borane or inorganic base, not taken in consideration due to them being significantly cheaper than the silane.

Table **2**. Financial comparison of different reduction methods.

Due to the very low catalyst loading, the price of Vaska's complex only adds up to £5.46 for the reduction of 100 mmol of substrate. The reductant itself, TMDS (£14.7 for 200 mmol), is considerably cheaper than other silane reagents (**entry 3**, **4**). Only the use of $LiAlH_4$ (**entry 2**) or TMDS and $Co_2(CO)_8$ (**entry 6**) achieves a reduction for a lesser price. This however comes at the expense of safety aspects: both of these reaction conditions use elevated temperatures, and both $LiAlH_4$ and $Co_2(CO)_8$ are pyrophoric solids, with the latter releasing carbon monoxide gas spontaneously.

[ii] These reaction conditions have been employed for the exhaustive reduction of the same substrate **377** to dimethylbenzylamine.

In light of these numbers and considerations, we do believe that our catalytic system is very competitive, especially considering the possibility to use the reduction methodology to make α-branched amine products, more valuable than the fully reduced amine.

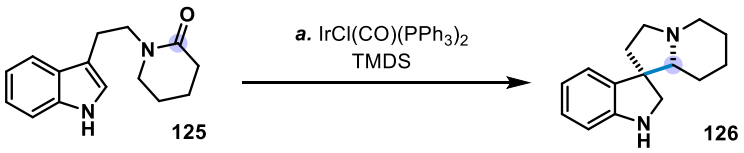
5.2 Further catalyst-loading reduction: intramolecular spirocyclisation

Encouraged by the viability to decrease catalyst loading in the Grignard methodology, we also wanted to investigate the scalability of the spirocyclisation methodology described in Chapter 2 of this work.

When the model substrate was submitted to the optimized conditions, with 0.1 mol% catalyst, full conversion to the spirocyclic amine was observed. Pleasingly, no detrimental change was observed at 0.01 mol%. At 0.001 mol% (or 10 ppm) however, the limit of the catalytic system was reached, and the reaction stopped at 41% conversion. With the final 3 g of our material **125**, a loading of 0.0025 mol% (25 ppm, 240 μg of catalyst[iii]) was trialled, and afforded the desired product **126** in 86% yield and 96 : 4 dr. This translates into a TON of over 40 000, and TOF of 11.1 s^{-1} even at −10 °C.[iv] We infer that this improvement compared to the Grignard methodology originates from the presence of the intramolecular nucleophile. The silyl hemiaminal species is indeed reacted further as it forms (see **Figure 6**, Chapter 2 for the mechanism), and its concentration therefore stays low, making the conversion of **125** fast compared to the Grignard methodology, where all of the amide starting material **377** is converted to the silyl hemiaminal species **378** (**Scheme 69**) before further reaction when the nucleophile (Grignard reagent) is subsequently introduced.

[iii] To have an accurate measurement, successive dilutions from 24 mgs of catalyst were carried out.

[iv] At the time of this work, this was the lowest catalyst loading ever achieved for Vaska' complex in amide reduction. Since then, Nagashima *et al* could achieve a TON of 100 000 using photoirradiation with a high-pressure mercury lamp.[10]



Entry	catalyst loading	conversion	Yield	dr
1	0.1 mol%	complete	89%	96 : 4
2	0.01 mol%	complete	91%	96 : 4
3	0.001 mol%	41%	38%	96 : 4
4	0.0025 mol%	95%	86%	96 : 4

Reagents and conditions: (a) $IrCl(CO)(PPh_3)_2$ (0.0025-0.1 mol%), TMDS, CH_2Cl_2, –10 °C, 1 h.

Scheme **70**. ppm-level catalyst loading on a scale-up of the spirocyclisation methodology.

These TONs and TOFs, and the maintained yield on multi-gram and multi-decagram scale are very attractive for amide reductive functionalisation chemistry and demonstrate, to some extent, the suitability of Vaska's complex for use in industry for this purpose.

5.3 Towards the development of new Vaska-type iridium complexes for the reduction of functional groups other than teriary amides and lactams

The remarkable chemoselectivity of Vaska's complex and TMDS for tertiary amide partial reduction has been showcased throughout the research described in this thesis, as well as in the numerous reports published during the past five years.

One could anticipate that there could also be great value in using a similar approach for secondary amides, or even less Lewis basic carbonyl-containing functional groups.

To this end, we wanted to explore the reactivity of the iridium complexes synthesised originally for our key step in the total synthesis of catharanthine **234** (see section **4.5**).

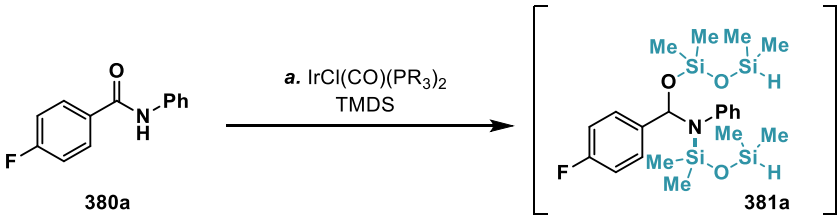
5.3.1 Reduction of secondary amides

The chemoselectivity for tertiary amides most likely originates from the Lewis basic properties of the carbonyl. Based on this postulate, we hypothesised that the comparatively electron-poor iridium complexes that were synthesised as described in section **4.5.3** of this work during the total synthesis of catharanthine could exhibit interesting properties. In fact, Nagashima *et al* described, independently and during the course of this work, the use of electron-poor Vaska-type complexes to increase conversion of poorly reactive tertiary amide substrates.[11]

We consequently set out to assess the reactivity of the newly-synthesised complexes on their reducing potential against new functional groups.

We chose secondary amide **380a** as our model substrate. The fluorine atom acts as a tag to measuring the conversion through ^{19}F NMR techniques.

As expected, the complexes with an electron density on the iridium centre closest to Vaska's complex (**371–373**) did not show any activity. The phosphite-derivative **374** did however cause vigourous bubbling when added to a TMDS and **380a** solution in benzene-d_6, suggesting the reaction of an hydridic species with the secondary amide N–H to generate hydrogen gas. Full conversion to a new species, as monitored by ^{1}H and ^{19}F NMR, was observed after 72 hours, and upon careful evaporation of the volatile TMDS by-products, a bis-silylated species could be observed as the sole non-volatile product of the reaction.



Entry	catalyst	observation
1	**20** R = Ph	no conversion
2	**371** R = *p*-ClC_6H_4	no conversion
3	**372** R = *p*-$CF_3C_6H_4$	no conversion
4	**373** R = *p*-$OMeC_6H_4$	no conversion
5	**374** R = OPh	bubbling immediately ocurrs, conversion to a new species

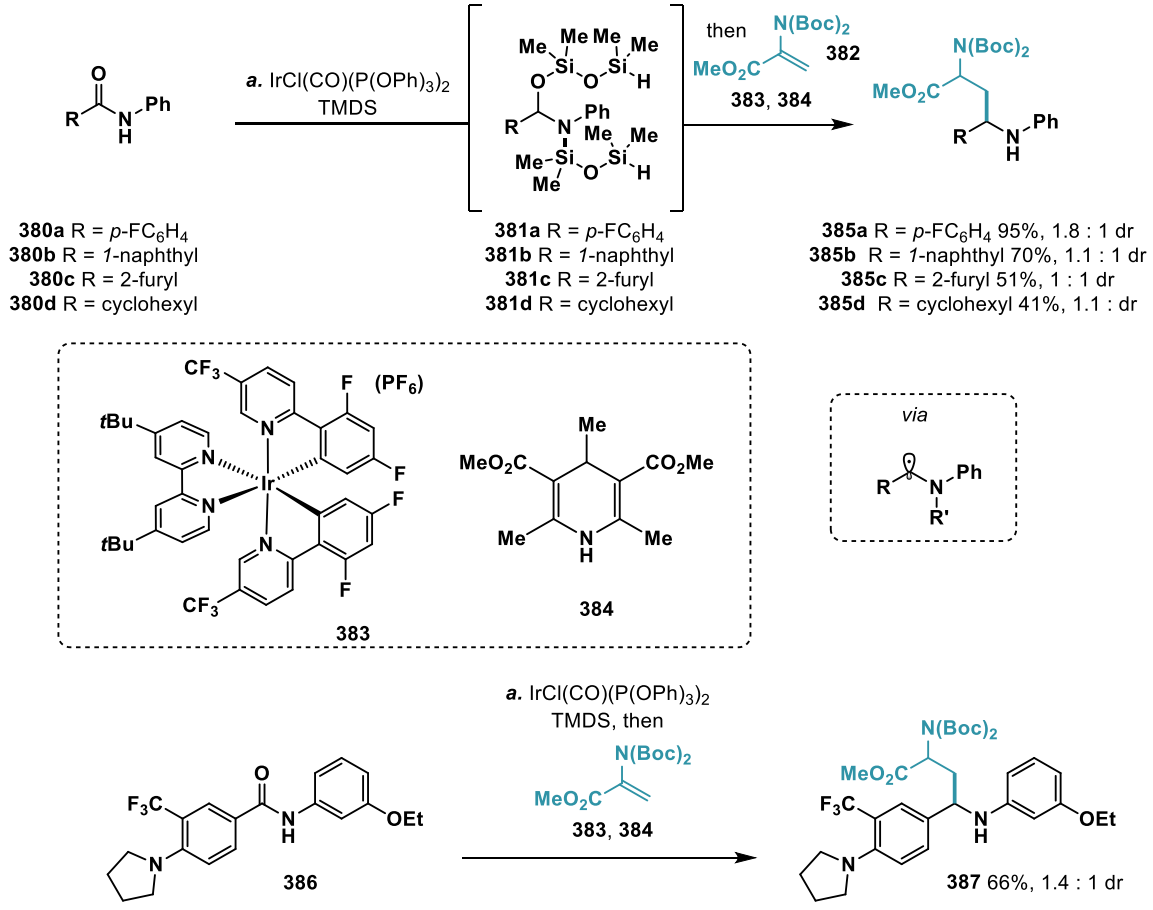
Reagents and conditions: (a) $IrCl(CO)(PR_3)_2$ (1 mol%), TMDS, d_6-benzene, rt, 72 h.

Scheme **71**. Performance of new Vaska-type complexes for the reduction of secondary amides.

This very promising result encouraged us to investigate the possibility to use this intermediate as an imine surrogate. This fitted well within a current programme in our group for the generation of nucleophilic α-amino radicals from imines, and downstream addition to electron-deficient conjugated acceptors.[12]

Therefore, secondary amides **380a–380d** were synthesized and were reduced in the same reaction conditions as established above. This resulted in the quantitative formation of bis-silylated hemiaminals **381a–381d**. These could be submitted to standard conditions established for the formation of nucleophilic α-amino radicals from imines, with photocatalyst **383** and Hantzsch ester **384**.[v] Compound **382** was chosen as the radical acceptor, having been precedently used in this type of methodology.[12b, 12c] Very pleasingly, and in line with the results obtained with imines as starting materials (as opposed to bis-silylated hemiaminal species here),[12c] functionalized amines **385a–385d** could be isolated in moderate to excellent yields, albeit with a low dr.[vi, vii]

[v] The functionalisation part of the reaction was carried out by Tanya Rogova, PhD student.
[vi] The drs are in line with the original imine-based methodology.
[vii] The weak N-Si is most likely hydrolysed during the work-up of the reaction to deliver the functionalised secondary amine.



Reagents and conditions: (a) $IrCl(CO)(P(OPh)_3)_2$ (1 mol%), TMDS, toluene-d_8, rt, 72 h, then **383** (1 mol%), **382**, **384**, 1 : 1 PhMe/DMSO, blue light, rt, 16 h. The functionalisation part of this reaction was carried out by Tanya Rogova, PhD student.

Scheme **72**. Hydrosilylation and *N*-silylation of secondary amides for the synthesis of α-functionalized secondary amines.

Last, but not least, this strategy was applied to the reductive derivatisation of EPPTB **387**. This drug candidate, developed by Hoffman-LaRoche, is one of the first known Trace Amine-Associated Receptor 1 (TAAR1) antagonist.[13] Again, tandem hydrosilylation and *N*-silylation occurred and could eventually lead to the generation of **387**, in 66% yield and 1.4 : 1 dr. This final demonstration of the suitability of the newly-developed catalytic system for functionalised secondary amides, in medicinal chemistry for instance, exemplifies the value of our reductive strategy.

In summary, in order to circumvent the chemoselectivity of Vaska's complex for tertiary amides, we synthesized an iridium complex able to transiently silylate secondary amides, and thus render it susceptible to hydrosilylation. It is remarkable that a simple modification of triphenylphosphine to triphenylphosphite in the complex allowed catalytic activity for both the *N*-Silylation and the reductive hydrosilylation parts of the reaction.

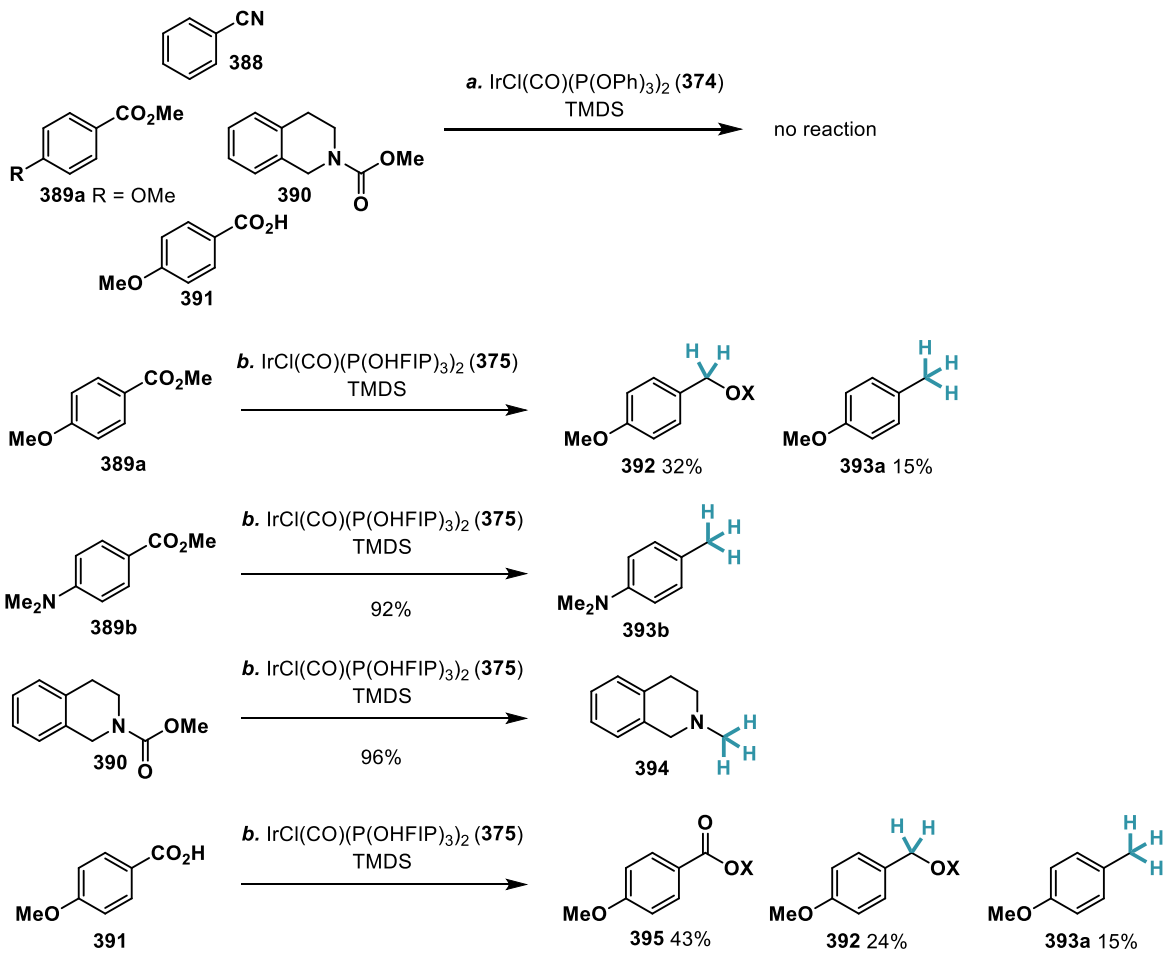
5.3.2 Reduction of esters and carbamates: preliminary results

After the successful application of electron-poor Vaska-type iridium complex **374** to the reduction of secondary amides, we turned our attention to other functional groups. Nitrile **388**, ester **389**, carbamate **390** and acid **391** were chosen as model substrates.

With the phosphite-iridium complex **374** used in the previous section, no reaction was observed at rt.

However, when using our most electron-poor complex **375** at 80 °C, consumption of ester **389a** was observed within 1 h. Reduction products were generated, with a benzylic alcohol being identified (**392**), along with 30% of the exhaustively reduced **393a**.[viii] To investigate whether a more electron-rich carbonyl would show enhanced reactivity, para-dimethylamino **389b** was submitted to the same reaction conditions. Pleasingly, the ester group could be reduced all the way down to tolyl-**393b** in almost quantitative yield. Similarly, carbamate **390** produced the fully reduced *N*-Me **394** in 90% yield. Even draconic acid **391** could produce the exhaustively reduced **393a** albeit in low yields, alongside other silylated species (**392** and **395**).

[viii] It is not clear whether the benzyl alcohol is a free alcohol (OH) or is silylated.



Reagents and conditions: (a) $IrCl(CO)(P(OPh)_3)_2$ (1 mol%), TMDS, toluene-d_8, rt, 24 h; (b) $IrCl(CO)(P(OHFIP)_3)_2$ (**375**) (1 mol%), TMDS, benzene-d_6, 80 °C, 1 h. In this scheme, X represents an unidentified silicon group, that could not be confirmed to be [Si]. Yields are NMR yields, as measured against dodecane as an internal standard.

Scheme **73**. Evaluation of Vaska-type complexes **374** and **375** in the reduction of non-amide functional groups.

These preliminary results were very encouraging, and we believe that with a suitable method to rapidly generate a library of electron-poor Vaska-type iridium complexes (see section **4.5.3** of chapter 4), future work should be focused towards synthesizing these complexes and evaluating their performance as catalysts alongside TMDS for the reduction of various carbonyl-containing functional groups.

5.4 Conclusion

From the development of a reductive spirocyclisation in Chapter 2, and of the design of cascade sequences initiated by the reduction of amides and lactams in Chapter 3, to the total synthesis of catharanthine in Chapter 4, we have demonstrated that by its reactivity and chemoselectivity, Vaska's complex can be used as an efficient catalyst for the reduction of amides. The mild conditions in which the reduction takes place, as well as the scalability of these reactions, demonstrated in Chapter 5, make the complex an ideal tool for the reductive functionalisation of amides. It is able to bring together simple building blocks for the construction of polycyclic structures, but also to act as a delicate late-stage functionalisation tool, or to be the trigger to elegant cascade sequences for alkaloid total synthesis. In all of these approaches, it garners access to complex amine architectures in a remarkably efficient fashion.

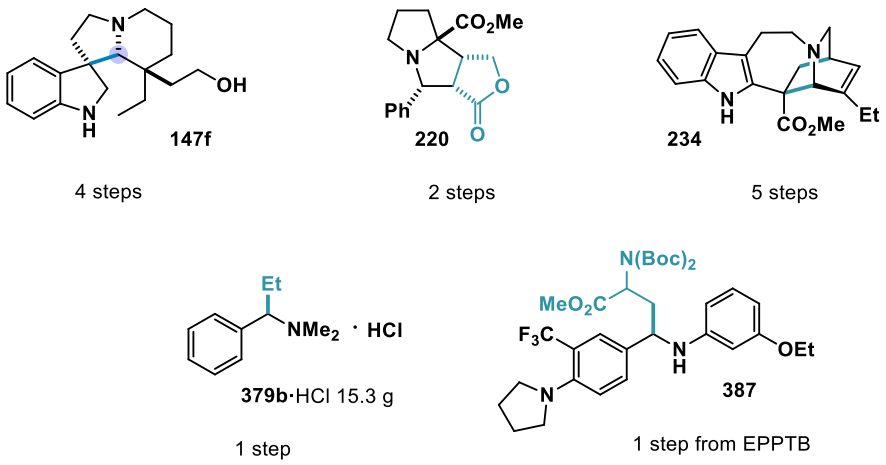


Figure **28**. Diverse complex amine products obtained efficiently throughout this work.

We hope that this work will contribute towards the popularisation of Vaska's complex in the synthetic organic community at large, and that it will inspire the future design of more iridium complexes to allow exploration of new reactivity.

5.5 References for Chapter 5

(1) Xie, L.-G.; Dixon, D. J. Tertiary amine synthesis via reductive coupling of amides with Grignard reagents. *Chem. Sci.* **2017,** *8*, 7492–7497.

(2) King, L. A.; New phenethylamines in Europe. *Drug Test. Analysis* **2014**, *6*, 808–818.

(3) Mannelli, P.; Janiri, L.; De Marinis, M.; Tempesta, E. Lefetamine: new abuse of an old drug – clinical evaluation of opioid activity. *Drug Alcohol Depend.* **1989**, *24*, 95–101.

(4) Wink, C. S.; Meyer, G. M. J.; Zapp, J. Lefetamine, a controlled drug and pharmaceutical lead of new designer drugs: synthesis, metabolism, and detectability in urine and human liver preparations using GC-MS, LC-MSn, and LC-high resolution-MS/MS. *Anal. Bioanal Chem.* **2015**, *407*, 1545–1557.

(5) Ludwig, J. R.; Schindler, C. S. Catayst: Sustainable Catalysis. *Chem.* **2017**, *2*, 313–316.

(6) (a) Yao, W.; Fang, H.; He, Q.; Peng, D.; Liu, G.; Huang, Z. A BEt_3-Base Catalyst for Amide Reduction with Silane. *J. Org. Chem.* **2019**, *84*, 6084−6093; (b) Fernández-Salas, J. A.; Manzini, S.; Nolan, S. P. Facile and efficient KOH-catalysed reduction of esters and tertiary amides. *Chem. Commun.* **2013**, *49*, 9758–9760.

(7) Das, S.; Addis, D.; Junge, K.; Beller, M. Zinc-catalyzed Chemoselective Reduction of Tertiary and Secondary Amides to Amines. *Chem. Eur. J.* **2011**, *17*, 12186–12192.

(8) Wann, S. R.; Thorsen, P. T.; Kreevoy, M. M. Reduction of Carboxylic Acid Derivatives by BH_4^- in Acidic Dimethyl Sulfoxide. *J. Org. Chem.* **1981**, *46*, 2579–2581.

(9) Dombray, T.; Helleu, C.; Darcel, C.; Sortais, J.-B. Cobalt Carbonyl-Based Catalyst for Hydrosilylation of Carboxamides. *Adv. Synth. Catal.* **2013**, *355*, 3358–3362.

(10) Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. Iridium-PPh_3 Catalysts for Conversion of Amides to Enamines. Organometallics, **2019**, *38*, 852–862.

(11) Tahara, A.; Miyamoto, Y.; Aoto, R.; Shigeta, K.; Une, Y.; Sunada, Y.; Motoyama, Y.; Nagashima, H. Catalyst Design of Vaska-Type Iridium Complexes for Highly Efficient Synthesis of π-Conjugated Enamines. *Organometallics* **2015**, *34*, 4895−4907.

(12) (a) Fuentes de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. Umpolung Synthesis of Branched α-Functionalized Amines from Imines via Photocatalytic Three-Component Reductive Coupling Reactions. *Chem. Commun.* **2016**, *52*, 14434−14437; (b) Leitch, J. A.; Fuentes de Arriba, A. L.; Tan, J.; Hoff, O.; Martinez, C. M.; Dixon, D. J. Photocatalytic Reverse Polarity Povarov Reaction. *Chem. Sci.* **2018**, *9*, 6653−6658; (c) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3- Diamines. *Org. Lett.* **2018**, *20*, 6794−6798.

(13) Bradaia, A., Trube, G., Stalder, H., Norcross, R. D., Ozmen, L., Wettstein, J. G.; Pinard, A.; Buchy, D.; Gassmann, M.; Hoener, M. C.; Bettler, B. The selective antagonist EPPTB reveals

TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. *Proc. Natl. Acad. Sci.* **2009**, *106*, 20081–20086.

Chapter 6 : Experimental Details

6.1 General Experimental details

General Techniques: Reactions were carried out under a nitrogen atmosphere unless stated otherwise. Glassware was oven-dried and cooled under vacuum then purged with nitrogen before use. Room temperature refers to 22 ± 2 °C. Inert atmosphere techniques, such as Schlenk technique, were used for the handling of air/moisture sensitive reagents. Reactions carried out at 0 °C were cooled using an ice bath, those at –10/–15 °C were cooled using a mixture of ice and NaCl, and those at –78 °C were carried out using a solid CO_2/acetone bath. Reactions carried out at high temperatures were heated using an oil bath or, preferably, using DrySyn® heating blocks. Reaction temperatures refer to external temperatures, for example of a heating block or oil bath, not of internal reaction temperatures unless stated otherwise.

Nomenclature and Numbering: Compounds are named following IUPAC nomenclature as generated by ACD LABS or ChemDraw. Carbon atoms are numbered in a systematic way where possible to ease comparison between related compounds in a synthetic sequence, not necessarily in accordance with IUPAC conventions, with the exception of natural products (conventional numbering following biosynthesis).

Solvents and Reagents: Ether refers to diethyl ether; petrol refers to the fraction of petroleum ether that boils between 30 and 40 °C. Where solvent dryness was important, CH_2Cl_2, Et_2O, methanol, THF, and toluene were either obtained from dry solvent bottles with septa (Aldrich), an MBRAUN-SPS solvent purification system in which solvent is passed through an activated alumina column under nitrogen, or by standing over 3 Å molecular sieves under an atmosphere of nitrogen. Reagents were used as obtained without further purification unless stated otherwise. Chromatography: Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC60 F254 plates (particle size 0.2 mm). TLC sheets were visualised by UV light, then developed by staining with potassium permanganate, anisaldehyde, cerium ammonium molybdate, vanillin, or iodine on silica. Purification by flash column chromatography[1] was carried out using Merck silicagel 60 F254 (particle size 43–60 μm).

Characterisation: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVF400 (400/101 MHz), Bruker AVB500 (500/126 MHz), Bruker AVC500 (500/126 MHz), and Bruker DPX200 (200 MHz) NMR spectrometers. Spectra are referenced to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16; C_7D_7H: δ_H 2.08, δ_C 20.43; $(CD_3)_2CO$: δ_H 2.05, δ_C 206.26; C_6D_5H: δ_H 7.16; CD_2HOD: 3.31, δ_C 49.00). Chemical shifts (δ) are given in parts per million (ppm, ± 0.01) and coupling constants (*J*) are given in Hertz (Hz, ± 0.1 as measured on Mestrenova, without rounding). The following convention is used to report chemical shifts: δ (multiplicity, number of protons, coupling constant(s), assignment), with chemical shifts reported in descending order. When a large roof effect was observed, it was included after the multiplicity. Peak assignments were made based on chemical shifts, integrations, coupling constants, and two-dimensional techniques such as COSY and HSQC. Where necessary, additional experiments such as HMBC, nOe, and NOESY were also used. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), heptet (h), nonuplet (n), a combination e.g. doublet of doublets (dd), or as a multiplet (m) over a peak range. Additionally, peaks may be described as broad (br), or apparent (app)

Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer. Selected diagnostic absorption maxima (νmax) are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra were acquired using a Micromass LCT Premier spectrometer (ESI). High resolution mass spectra were recorded by Chemistry Research Laboratory staff using a Bruker Daltronics MicroTOF spectrometer (ESI). Mass to charge ratios (m/z) are reported in Daltons. Melting points were recorded using a Leica Galen III hot-stage microscope apparatus and are reported uncorrected in degrees Celcius (°C). Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter at 25 °C. No specific rotations were measured in this work, due to the reactions developed being racemic.

X-Ray Crystallography: Single crystal X-ray diffraction data were collected using an Enraf–Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr Heyao Shi (University of Oxford) with assistance and guidance from Dr Amber L. Thompson and Dr Kirsten E. Christensen (University of Oxford Chemical Crystallography department).

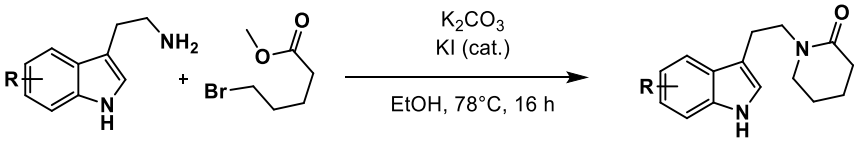
Synthesis of Known Compounds: The synthesis of compounds previously reported in the literature are labelled as such. Two relevant pieces of characterisation are given, unless the compound is used without purification in the next step. References are given for experimental procedures and data.

Compounds not made myself: Data will be included here if an assignment or an additional piece of information was not present in the original report.

Missing data: Due to the recent COVID-19 pandemic, and the CRL closure, some IR and HRMS data could not be measured. The NMR data for some compounds is also missing due to the CRL being unaccessible for 11 weeks (and not having reopened at the time when this statement is written). This data will be compiled and suggested as a correction at the time of the viva if at all possible.

6.2 Experimental Details for Chapter 2

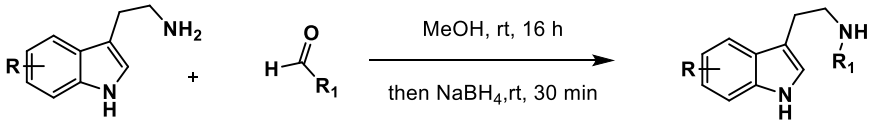
6.2.1 General Procedure A: one-pot alkylation-lactamisation



A suspension of tryptamine (1.00 equiv., either commercially available or synthesized according to literature),[3] methyl 5-bromovalerate (1.00 equiv.), K_2CO_3 (2.20 equiv., or 3.20 equiv. when the tryptamine hydrochloride salt was used), and KI (0.0100 equiv., 1.00 mol%) in EtOH (2 mL/mmol tryptamine) was refluxed for 16 h before being allowed to reach rt. The resulting suspension was concentrated *in vacuo* until most of the solvent was evaporated and then partitioned between H_2O (4 mL/mmol tryptamine) and CH_2Cl_2 (4 mL/mmol tryptamine). The layers were separated and the aqueous layer was extracted with

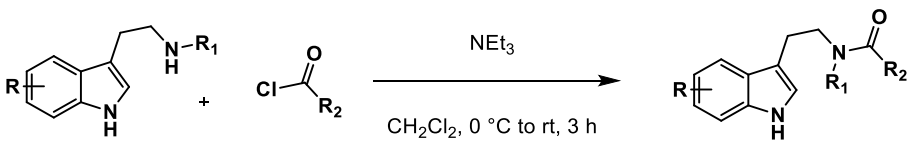
CH_2Cl_2 (3 × 2 mL/mmol tryptamine). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* trituration or FCC afforded the corresponding indole-tethered lactam.

6.2.2 General Procedure B: reductive amination of tryptamines



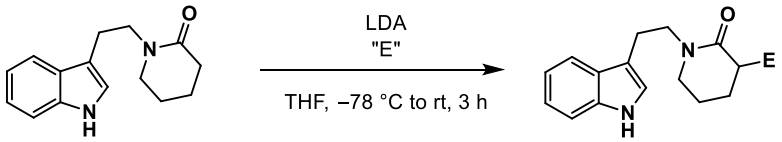
The aldehyde (1.00 equiv.) was added to a solution of the tryptamine in MeOH (4 mL/mmol tryptamine) and stirred for 16 h. $NaBH_4$ (1.66 equiv.) was then added portionwise at rt and the resulting solution was stirred for 30 min before being concentrated *in vacuo* to about a third of its original volume. It was then quenched with saturated $NaHCO_3$ (3 mL/mmol tryptamine) and partitioned between EtOAc (5 ml/mmol tryptamine) and H_2O (5 mL/mmol tryptamine). The layers were separated and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude amine was used in the next step without further purification.

6.2.3 General Procedure C: amide bond formation with acid chlorides



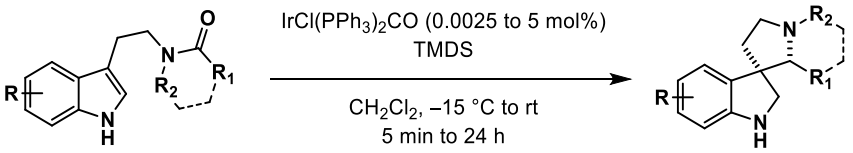
A solution of the tryptamine (1.00 equiv.) and NEt_3 (1.20 equiv., or 2.20 equiv. if when the tryptamine hydrochloride salt was used) in CH_2Cl_2 (7 mL/mmol tryptamine) was added dropwise at 0 °C to a solution of the acid chloride (1.05 equiv.) in CH_2Cl_2 (3 mL/mmol tryptamine). The resulting solution was left to reach rt over 3 h. H_2O (5 mL/ mmol tryptamine) was then added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL/mmol tryptamine) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* trituration or FCC afforded the corresponding indole-tethered amide.

6.2.4 General Procedure D: α-functionalisation



n-BuLi (1.6 or 2.5 M in hexanes, 2.20 equiv.) was added dropwise to a solution of *i*-Pr_2NH (2.20 equiv.) in THF (2.5 mL/mmol lactam) at −78 °C. After 30 min, a solution of lactam (1.00 equiv.) in THF (5.0 mL/mmol lactam, might require heating to dissolve the lactam) was added dropwise. The resultant reaction mixture was stirred for a further 30 min, before the electrophile - small alkyl iodides, aldehydes - (1.05 equiv.) was added dropwise. The reaction was stirred for 3 h, before being quenched with saturated NH_4Cl (1.0 mL/mmol lactam) and allowed to reach rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC afforded the corresponding pure α-functionalised lactam.

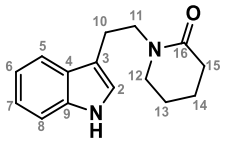
6.2.5 General Procedure E: spirocyclisation



TMDS (3.00 to 4.00 equiv.) was added to a solution of indole-tethered lactam (1.00 equiv.) and Vaska's complex (0.00250 to 5.00 mol%) in CH_2Cl_2 (0.1 M to 0.5 M) at rt, 0 °C or −15 °C. The resulting bubbling solution was stirred at the desired temperature for 5 min, 1 h, 6 h, 16 h, or 24 h, before being concentrated *in vacuo*. Direct purification *via* FCC [CH_2Cl_2/NH_3 in MeOH (2 M)] afforded the corresponding spirocyclic indoline. In general, a large amount of Silica gel was necessary to allow separation of the diastereoisomers. Additional separation was sometimes required, and preparative TLC was generally the best method.

6.2.6 Synthesis of the starting materials with variations on the indole

1-(2-(1H-indol-3-yl)ethyl)piperidin-2-one (125)



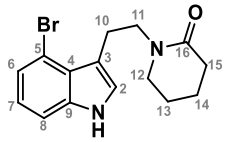
Prepared according to **General Procedure A** from tryptamine **86**. Purification *via* trituration (EtOAc) gave **125** as a white solid (9.10 g, 60%).

mp 150–152 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.45 (br s, 1H, NH), 7.66 (app d, 1H, J = 7.7 Hz, C^5H), 7.36 (ddd, 1H, J = 8.1, 1.0, 1.0 Hz, C^8H), 7.18 (ddd, 1H, J = 8.0, 7.2, 1.3 Hz, C^7H), 7.11 (ddd, 1H, J = 8.1, 7.0, 1.1 Hz, C^6H), 7.02 (d, 1H, J = 2.4 Hz, C^2H), 3.66 (app t, 2H, J = 7.4 Hz, $C^{11}H_2$), 3.17 (app t, 2H, J = 6.4 Hz, $C^{12}H_2$), 3.04 (app t, 2H, J = 7.5 Hz, $C^{10}H_2$), 2.40 (t, 2H, J = 6.4 Hz, $C^{15}H_2$), 1.63–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

All other data in agreement with literature.[1]

1-(2-(4-bromo-1H-indol-3-yl)ethyl)piperidin-2-one (131a)



Prepared according to **General Procedure A** from **130a**. Purification *via* trituration in EtOAc gave **131a** as a white solid (159 mg, 43%).

mp 170–172 °C

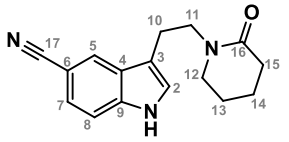
IR 3210 (br, N–H), 2938, 2861 (C–H), 1615 (C=O), 1499.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.98–9.12 (br s, 1H, NH), 7.32 (d, 1H, J = 8.1 Hz, C^8H), 7.25 (d, 1H, J = 7.7 Hz, C^6H), 7.05–7.10 (br s, 1H, C^2H), 6.97 (t, 1H, J = 7.8 Hz, C^7H), 3.67–3.73 (m, 2H, $C^{11}H_2$), 3.29 (t, 2H, J = 5.8 Hz, $C^{12}H_2$), 3.24 (dd, 2H, J = 9.1, 6.4 Hz, $C^{10}H_2$), 2.42 (t, 2H, J = 6.3 Hz, $C^{15}H_2$), 1.70–1.81 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.0 (C^{16}), 137.9 (C^9), 125.5 (C^4), 124.9 (C^2), 123.7 (C^6), 122.6 (C^7), 114.1 (C^3), 113.6 (C^5), 111.0 (C^8), 49.7 (C^{11}), 48.6 (C^{12}), 32.6 (C^{15}), 23.9 (C^{10}), 23.3 (C^{13}), 21.4 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}ON_2Br^+$) requires **m/z** 321.0597, found **m/z** 321.0598.

3-(2-(2-oxopiperidin-1-yl)ethyl)-1H-indole-5-carbonitrile (131b)



Prepared according to **General Procedure A** from **130b**. Purification *via* trituration in EtOAc gave **131b** as a white solid (1.16 g, 57 %).

mp 158–160 °C

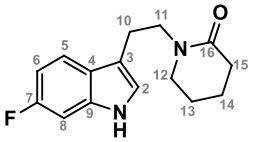
IR 3179 (br, N–H), 2948 (C–H), 2217 (C≡N), 1612 (C=O), 1501, 1471, 1447.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.41–9.02 (br s, 1H, NH), 7.95–8.00 (m, 1H, C^5H), 7.38–7.43 (m, 2H, C^8H, C^7H), 7.14–7.20 (m, 1H, C^2H), 3.65 (app t, 2H, J = 7.8 Hz, $C^{11}H_2$), 3.19–3.26 (m, 2H, $C^{12}H_2$), 2.99–3.06 (m, 2H, $C^{10}H_2$), 2.37–2.42 (m, 2H, $C^{15}H_2$), 1.70–1.78 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.2 (C^{16}), 138.1 (C^9), 127.5 (C^4), 124.8 (C^7), 124.5 (C^2), 124.4 (C^5), 121.0 (C^{17}), 114.0 (C^3), 112.4 (C^8), 102.2 (C^6), 48.6 (C^{12}), 48.2 (C^{11}), 32.5 (C^{15}), 23.3 (C^{13}), 22.7 (C^{10}), 21.3 (C^{14}).

HRMS (ES^+) missing

1-(2-(6-fluoro-1H-indol-3-yl)ethyl)piperidin-2-one (131c)



Prepared according to **General Procedure A** from **130c**. Purification *via* trituration in EtOAc gave **131c** as a white solid (328 mg, 42 %).

mp 152–154 °C

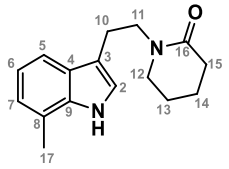
IR 3240 (br, N–H), 2936, 2856 (C–H), 1617 (C=O), 1499.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.41–8.52 (br s, 1H, NH), 7.55 (dd, 1H, J = 8.7, 5.3 Hz, C^5H), 7.03 (dd, 1H, J = 9.7, 2.3 Hz, C^8H), 6.98–7.01 (m, 1H, C^2H), 6.87 (ddd, 1H, J = 9.5, 8.6, 2.3 Hz, C^6H), 3.64 (app t, 2H, J = 7.4 Hz, $C^{11}H_2$), 3.17 (t, 2H, J = 5.5 Hz, $C^{12}H_2$), 3.00 (app t, 2H, J = 7.5 Hz, $C^{10}H_2$), 2.39 (t, 2H, J = 6.3 Hz, $C^{15}H_2$), 1.64–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.0 (C^{16}), 160.1 (d, J = 237.2 Hz, C^7), 136.3 (d, J = 12.7 Hz, C^9), 134.4 (C^4), 122.3 (d, J = 3.6 Hz, C^2), 119.6 (d, J = 10.2 Hz, C^5), 113.5 (C^3), 108.1 (d, J = 24.7 Hz, C^6), 97.6 (d, J = 26.0 Hz, C^8), 48.8 (C^{12}), 48.5 (C^{11}), 32.6 (C^{15}), 23.3 (C^{13}), 23.1 (C^{10}), 21.4 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}ONF^+$) requires **m/z** 261.1398, found **m/z** 261.1398.

1-(2-(7-methyl-1H-indol-3-yl)ethyl)piperidin-2-one (131d)



Prepared according to **General Procedure A** from **130d**. Purification *via* trituration in EtOAc gave **131d** as a white solid (280 mg, 48 %).

mp 148–150 °C

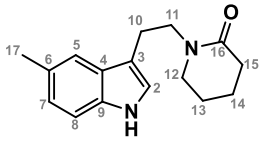
IR 3252 (br, N–H), 2943 (C_{Ar}–H), 1613 (C=O), 1499, 1448, 1417.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.03–8.49 (br s, 1H, NH), 7.51 (d, 1H, J = 7.8 Hz, C^5H), 7.02–7.08 (m, 2H, C^6H, C^2H), 6.99 (d, 1H, J = 7.0 Hz, C^7H), 3.66 (app t, 2H, J = 7.5 Hz, $C^{11}H_2$), 3.18 (t, 2H, J = 5.6 Hz, $C^{12}H_2$), 3.03 (app t, 2H, J = 7.5 Hz, $C^{10}H_2$), 2.49 (s, 3H, $C^{17}H_3$), 2.40 (t, 2H, J = 6.2 Hz, $C^{15}H_2$), 1.65–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 169.9 (C^{16}), 136.0 (C^9), 127.2 (C^4), 122.6 (C^7), 122.0 (C^2), 120.6 (C^8), 119.6 (C^6), 116.6 (C^5), 113.8 (C^3), 48.7 (C^{12}), 48.6 (C^{11}), 32.6 (C^{15}), 23.4 (C^{13}), 23.3 (C^{10}), 21.4 (C^{14}), 16.8 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires **m/z** 257.1648, found **m/z** 257.1649.

1-(2-(5-methyl-1H-indol-3-yl)ethyl)piperidin-2-one (131e)



Prepared according to **General Procedure A** from **130e**. Purification *via* FCC (1:2 pentane/EtOAc) gave **131e** as a white solid (178 mg, 55 %).

mp 106–108 °C

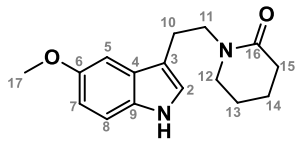
IR 3256 (br, N–H), 2940, 2861 (C–H), 1613 (C=O), 1498.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.22–8.39 (br s, 1H, NH), 7.42–7.44 (m, 1H, C^5H), 7.24 (d, 1H, J = 8.3 Hz, C^8H), 7.01 (dd, 1H, J = 8.3, 1.6 Hz, C^7H), 6.97–6.99 (m, 1H, C^2H), 3.65 (app t, 2H, J = 7.4 Hz, $C^{11}H_2$), 3.16 (t, 2H, J = 5.8 Hz, $C^{12}H_2$), 3.02 (app t, 2H, J = 7.5 Hz, $C^{10}H_2$), 2.46 (s, 3H, $C^{17}H_3$), 2.41 (t, 2H, J = 6.4 Hz, $C^{15}H_2$), 1.63–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 169.9 (C^{16}), 134.8 (C^9), 128.5 (C^4), 127.9 (C^6), 123.6 (C^7), 122.3 (C^2), 118.5 (C^5), 112.8 (C^3), 111.0 (C^8), 48.8 (C^{12}), 48.6 (C^{11}), 32.6 (C^{15}), 23.3 (C^{13}), 23.2 (C^{10}), 21.6 (C^{17}), 21.4 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires **m/z** 257.1648, found **m/z** 257.1650.

1-(2-(5-methoxy-1H-indol-3-yl)ethyl)piperidin-2-one (131f)



Prepared according to **General Procedure A** from commercially available **130f**. Purification *via* FCC (100 % EtOAc) gave **131f** as a white solid (950 mg, 66 %).

mp 135–137 °C

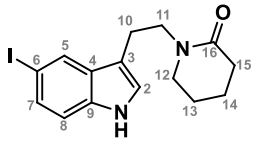
IR 3245 (br, N–H), 2940 (C–H), 1613 (C=O), 1486.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.12–8.25 (br s, 1H, NH), 7.24 (d, 1H, J = 8.8 Hz, C^8H), 7.12 (d, 1H, J = 2.4 Hz, C^5H), 7.00 (br d, 1H, J = 2.4 Hz, C^2H), 6.85 (dd, 1H, J = 8.8, 2.4 Hz, C^7H), 3.87 (s, 3H, $C^{17}H_3$), 3.65 (app t, 2H, J = 8.3 Hz, $C^{11}H_2$), 3.17 (app t, 2H, J = 5.6 Hz, $C^{12}H_2$), 3.00 (app t, 2H, J = 7.6 Hz, $C^{10}H_2$), 2.40 (t, 2H, J = 6.4 Hz, $C^{15}H_2$), 1.65–1.77 (m, 4H, $C^{14}H_2$, $C^{13}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 169.9 (C^{16}), 154.1 (C^6), 131.6 (C^9), 128.1 (C^4), 122.8 (C^2), 113.2 (C^3), 112.3 (C^7), 112.0 (C^8), 100.8 (C^5), 56.1 (C^{17}), 48.8 (C^{12}), 48.4 (C^{11}), 32.6 (C^{15}), 23.4 (C^{13}), 23.2 (C^{10}), 21.5 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}O_2N_2^+$) requires **m/z** 273.1598, found **m/z** 273.1596.

1-(2-(5-iodo-1H-indol-3-yl)ethyl)piperidin-2-one (131h)



Prepared according to **General Procedure E** from **130h** by Dr Alex W. Gregory.

mp 141–143 °C

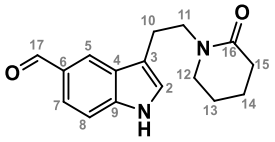
IR 3212 (br, N–H), 2942 (C_{Ar}–H), 1617 (C=O), 1500, 1450.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.22–8.31 (br s, 1H, NH), 7.93–7.95 (m, 1H, C^5H), 7.42 (dd, 1H, J = 8.5, 1.6 Hz, C^7H), 7.14 (dd, 1H, J = 8.5, 0.5 Hz, C^8H), 7.01 (d, 1H, J = 2.3 Hz, C^2H), 3.59–3.65 (m, 2H, $C^{11}H_2$), 3.14 (dd, 2H, J = 6.2, 5.1 Hz, $C^{12}H_2$), 2.98 (ddd, 2H, J = 8.0, 6.8, 0.9 Hz, $C^{10}H_2$), 2.40 (t, 2H, J = 6.4 Hz, $C^{15}H_2$,), 1.61–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.0 (C^{16}), 135.5 (C^9), 130.43 (C^7), 130.42 (C^4), 127.9 (C^5), 123.0 (C^2), 113.3 (C^8), 113.1 (C^3), 82.9 (C^6), 48.9 (C^{12}), 48.5 (C^{11}), 32.6 (C^{15}), 23.4 (C^{13}), 22.9 (C^{10}), 21.4 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}ON_2I^+$) requires **m/z** 369.0458, found **m/z** 369.0462.

3-(2-(2-oxopiperidin-1-yl)ethyl)-1H-indole-5-carbaldehyde (131m)



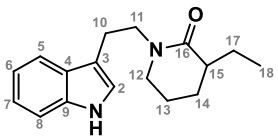
DIBAL-H (1.0 M in CH_2Cl_2, 1.85 mL, 1.85 mmol) was added dropwise to a solution of lactam **131b** (0.25 g, 0.94 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction was warmed to rt and stirred for 16 h before being quenched with saturated NH_4Cl (1.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.0 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (100% EtOAc) followed by a purification *via* prep TLC (100% EtOAc) gave **131m** as a yellow oil (61 mg, 21 %, 80% purity).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 10.00 (s, 1H, $C^{17}H$), 9.38–9.49 (br s, 1H, NH), 8.14–8.16 (m, 1H, C^5H), 7.71 (dd, 1H, J = 8.5, 1.6 Hz, C^7H), 7.42 (app d, 1H, J = 8.4 Hz, C^8H), 7.09 (app d, 1H, J = 2.3 Hz, C^2H), 3.68 (app dd, 2H, J = 8.2, 6.8 Hz, $C^{11}H_2$), 3.20–3.25 (m, 2H, $C^{12}H_2$), 3.06 (ddd, 2H, J = 8.4, 6.5, 0.9 Hz, $C^{10}H_2$), 2.37–2.42 (m, 2H, $C^{15}H_2$), 1.68–1.77 (m, 4H, $C^{13}H_2$, $C^{14}H_2$).

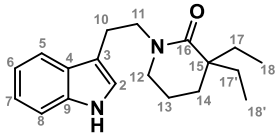
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 192.7 (C^{17}), 170.2 (C^{16}), 140.1 (C^9), 129.2 ($C^{4/6}$), 127.6 ($C^{4/6}$), 124.1 (C^8), 123.9 (C^5), 122.6 (C^7), 115.1 (C^3), 112.0 (C^2), 48.7 (C^{12}), 48.4 (C^{11}), 32.5 (C^{15}), 23.3 (C^{13}), 22.9 (C^{10}), 21.3 (C^{14}).

6.2.7 Synthesis of the starting materials with variations on the lactam

1-(2-(1H-indol-3-yl)ethyl)-3-ethylpiperidin-2-one (134b) and 1-(2-(1H-indol-3-yl)ethyl)-3,3-diethylpiperidin-2-one (134c)



134b



134c

Prepared according to **General Procedure D** from lactam **125** and EtI. Purification *via* FCC (2 : 1 petroleum ether 30–40 °C/EtOAc) gave dialkylated **134c** as a white solid (1.08 g, 9%).

Data for **134c**:

mp 96–98 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.15 (br s, 1H, NH), 7.69 (app d, 1H, J = 7.8 Hz, C^5H), 7.36 (ddd, 1H, J = 8.1, 1.0, 1.0 Hz, C^8H), 7.18 (ddd, 1H, J = 8.2, 7.0, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.04 (d, 1H, J = 2.4 Hz, C^2H), 3.66 (app t, 2H, J = 7.6 Hz, $C^{11}H_2$), 3.22 (t, 2H, J = 5.8 Hz, $C^{12}H_2$), 3.02 (app t, 2H, J = 7.6 Hz, $C^{10}H_2$), 1.62–1.82 (m, 6H, $C^{13}H_2$, $C^{14}H_2$, C^{17}Ha, $C^{17'}$Ha), 1.48 (dq, 2H, J = 13.6, 7.6 Hz, C^{17}Hb, $C^{17'}$Hb), 0.85 (t, 6H, J = 7.4 Hz, $C^{18}H_3$, $C^{18'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 174.9 (C^{16}), 136.4 (C^9), 127.6 (C^4), 122.2 (C^2), 122.0 (C^7), 119.4 (C^6), 119.0 (C^5), 113.5 (C^3), 111.2 (C^8), 49.1 (C^{12}), 48.9 (C^{11}), 45.4 (C^{15}), 31.6 (C^{17}, $C^{17'}$), 28.7 (C^{14}), 23.4 (C^{10}), 20.4 (C^{13}), 9.0 (C^{18}, $C^{18'}$).

All other data in agreement with literature.[4]

Further elution (1 : 2 petroleum ether 30–40 °C/EtOAc) gave mono alkylated **134b** as a white solid (9.17 g, 82%).

Data for **134b**:

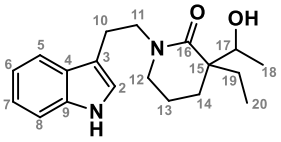
mp 116–118 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.59 (br s, 1H, NH), 7.67 (app d, 1H, J = 7.8 Hz, C^5H), 7.36 (ddd, 1H, J = 8.1, 1.0, 0.9 Hz, C^8H), 7.18 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz, C^7H), 7.11 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.00 (d, 1H, J = 2.3 Hz, C^2H), 3.65 (app t, 2H, J = 7.6 Hz, $C^{11}H_2$), 3.11–3.24 (m, 2H, $C^{12}H_2$), 2.99–3.07 (m, 2H, $C^{10}H_2$), 2.25 (ddt, 1H, J = 9.3, 6.0, 4.1 Hz, $C^{15}H$), 1.94–2.07 (m, 1H, C^{14}Ha), 1.88 (dtdd, 1H, J = 12.8, 6.3, 3.2, 1.1 Hz, C^{17}Ha), 1.67–1.82 (m, 1H, C^{13}Ha), 1.43–1.68 (m, 3H, C^{17}Hb, C^{14}Hb, C^{13}Hb), 0.95 (t, 3H, J = 7.5 Hz, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 172.7 (C^{16}), 136.4 (C^9), 127.6 (C^4), 122.2 (C^2), 121.9 (C^7), 119.2 (C^6), 118.8 (C^5), 113.1 (C^3), 111.3 (C^8), 48.84 (C^{12}), 48.76 (C^{11}), 43.0 (C^{15}), 25.8 (C^{17}), 25.0 (C^{14}), 23.2 (C^{10}), 21.8 (C^{13}), 11.6 (C^{18}).

All other data in agreement with literature.[5]

1-(2-(1H-indol-3-yl)ethyl)-3-ethyl-3-(1-hydroxyethyl)piperidin-2-one (134d)



Prepared according to **General Procedure D** from lactam **134b** and acetaldehyde. Purification *via* FCC (4 : 1 petroleum ether 30–40 °C/EtOAc) gave **134d** as an unconsequential 4 (**A**) : 1 (**B**) mixture of diastereoisomers and as a pale yellow thick oil (582 mg, 71%).

IR 3280 (br, N–H, O–H), 2966 (C–H), 1603 (C=O, amide), 1493, 1457.

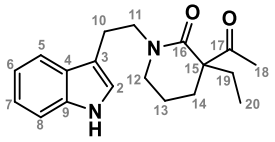
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.34 (br s, 1H, NH), 7.65 (app d, 1H, J = 7.9 Hz, C^5H), 7.36 (ddd, 1H, J = 8.2, 1.0, 0.9 Hz, C^8H), 7.19 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.02 (d, 1H, J = 2.3 Hz, C^2H), 5.02 (br s, 0.8H, OH (**A**)), 4.40 (d, 0.2H, J = 9.1 Hz, OH (**B**)), 3.87 (q, 0.8H, J =6.3 Hz, $C^{17}H$ (**A**)), 3.61–3.72 (m, 2.2H, $C^{11}H_2$, $C^{17}H$ (**B**)), 3.12–3.26 (m, 2H, $C^{12}H_2$), 2.96–3.10 (m, 2H, $C^{10}H_2$), 2.12 (dq, 1H, J = 13.6, 7.6 Hz, C^{19}Ha), 1.61–1.80 (m, 3H, $C^{13}H_2$, C^{14}Ha), 1.49–1.59 (m, 1H, C^{14}Hb), 1.41 (dq, 1H, J = 14.7, 7.4 Hz, C^{19}Hb), 1.16 (d, 0.6H, J = 6.4 Hz, $C^{18}H_3$ (**B**)), 1.12 (d, 2.4H, J = 6.4 Hz, $C^{18}H_3$ (**A**)), 0.91 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 175.7 (C^{16} (**B**)), 175.6 (C^{16}(**A**)), 136.6 (C^9), 127.7 (C^4), 122.4 (C^2), 122.3 (C^7), 119.6 (C^6), 118.9 (C^5), 113.12 (C^3 (**B**)), 113.05 (C^3 (**A**)), 111.6 (C^8), 72.3 (C^{17} (**A**)), 71.8 (C^{17} (**B**)), 49.4 (C^{12}), 49.1 (C^{11}), 48.2 (C^{15}), 29.5 (C^{14}), 25.3 (C^{19}), 23.5 (C^{10}), 20.8 (C^{13}), 19.4 (C^{18} (**B**)), 16.9 (C^{18} (**A**)), 10.3 (C^{20} (**A**)), 8.7 (C^{20} (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}O_2N_2^+$) requires **m/z** 315.2067, found **m/z** 315.2070.

Note: C^{10} to C^{15} and C^{19}couldn't be identified for the minor diastereoisomer (**B**) in the ^{13}C NMR.

1-(2-(1H-indol-3-yl)ethyl)-3-acetyl-3-ethylpiperidin-2-one (134e)



IBX (470 mg, 1.68 mmol) was added to a solution of lactam **134d** (480 mg, 1.53 mmol) in EtOAc (20 mL). The resulting suspension was sealed in a microwave vial and heated at 100 °C for 4 h before being allowed to cool down to rt, and filtered. The solids were washed with EtOAc (3 × 5 mL) and the washing concentrated *in vacuo* to give **134e** as a yellow oil that crystallized upon standing (450 mg, 94%).

mp 100–102 °C

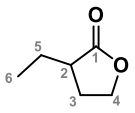
IR 3284 (br, N–H), 2967 (C–H), 1704 (C=O, ketone), 1614 (C=O, amide), 1492, 1458.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.32 (br s, 1H, NH), 7.66 (app d, 1H, J = 7.7 Hz, C^5H), 7.35 (ddd, 1H, J = 8.2, 1.0, 0.9 Hz, C^8H), 7.18 (ddd, 1H, J = 8.2, 7.1, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.02 (d, 1H, J = 2.3 Hz, C^2H), 3.77 (ddd, 1H, J = 13.1, 8.4, 6.6 Hz, $C^{11}Ha$), 3.62 (ddd, 1H, J = 13.1, 8.2, 6.7 Hz, $C^{11}Hb$), 3.13–3.27 (m, 2H, $C^{12}H_2$), 2.97–3.10 (m, 2H, $C^{10}H_2$), 2.23–2.29 (m, 1H, $C^{14}Ha$), 2.22 (s, 3H, $C^{18}H_3$), 1.85–2.02 (m, 2H, $C^{19}H_2$), 1.63–1.75 (m, 2H, $C^{13}H_2$), 1.46–1.56 (m, 1H, $C^{14}Hb$), 0.84 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 208.1 (C^{17}), 169.8 (C^{16}), 136.4 (C^9), 127.5 (C^4), 122.3 (C^2), 122.1 (C^7), 119.4 (C^6), 118.8 (C^5), 112.9 (C^3), 111.3 (C^8), 60.7 (C^{15}), 49.0 (C^{11}), 48.8 (C^{12}), 29.6 (C^{19}), 27.4 (C^{14}), 26.9 (C^{18}), 23.2 (C^{10}), 20.3 (C^{13}), 9.1 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{25}O_2N_2^+$) requires **m/z** 313.1911, found **m/z** 313.1909.

3-ethyldihydrofuran-2(3H)-one (136)

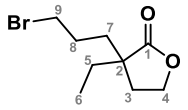


n-BuLi (2.5 M in hexanes, 9.29 mL, 23.2 mmol) was added dropwise to a solution of *i*-Pr_2NH (3.27 mL, 23.2 mmol) in anhydrous THF (23 mL) at –78 °C. After 30 min, freshly distilled γ-butyrolactone **135** (1.79 mL, 23.2 mL) in anhydrous THF (12 mL) was added dropwise over 10 min. The resulting yellow solution was stirred for a further 30 min before EtI (1.87 mL, 23.2 mL) in anhydrous HMPA (4.45 mL) was added dropwise over 10 min. The acetone bath temperature was adjusted to –40 °C and the reaction mixture was stirred for a further 3h, before saturated NH_4Cl (20 mL) was added. The reaction mixture was allowed to reach rt before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude contains HMPA and must be handled with care. Purification *via* FCC (1 : 1 petroleum ether 30–40 °C/Et_2O) afforded **136** as a colourless free-flowing oil (1.09 g, 41%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.34 (td, 1H, J = 8.8, 3.1 Hz, C^4Ha,), 4.19 (td, 1H, J = 9.2, 6.7 Hz, C^4Hb), 2.48 (dtd, 1H, J = 9.5, 8.7, 4.8 Hz, C^3Ha), 2.38 (dddd, 1H, J = 12.1, 8.8, 6.7, 3.0 Hz, C^3Hb), 1.84–2.02 (m, 2H, C^5H_2), 1.51 (ddt, 1H, J = 15.9, 14.4, 7.4 Hz, C^2H), 1.01 (t, 3H, J = 7.5 Hz, C^6H_3).

All other data in agreement with literature.[6]

3-(3-bromopropyl)-3-ethyldihydrofuran-2(3H)-one (137)

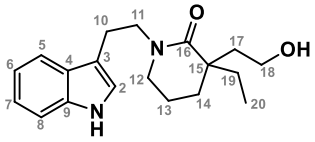


n-BuLi (2.5 M in hexanes, 4.90 mL) was added dropwise to a solution of *i*-Pr_2NH (1.72 mL, 12.3 mmol) in anhydrous THF (10 mL) at –78 °C. After 30 min, α-ethyl-γ-butyrolactone **136** (1.00 g, 8.76 mmol) in anhydrous THF (3.1 mL) was added dropwise over 5 min. The resulting yellow solution was stirred for a further 30 min before 1,3-dibromopropane (1.96 mL, 19.3 mmol) in anhydrous HMPA (3.66 mL, 21.0 mmol) was added dropwise over 10 min. The reaction mixture was stirred for a further 3h, before saturated NH_4Cl (10 mL) was added. The reaction mixture was allowed to reach rt before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with H_2O (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude contains HMPA and must be handled with care. Purification *via* FCC (4 : 1 petroleum ether 30–40 °C/Et_2O) afforded a 3 : 1 mixture of **137** and **136** as a colourless oil (1.44 g, 59%, 74% brsm).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.26 (2 x dd, 2H, J = 6.8, 1.0 Hz, C^4H_2), 3.40 (td, 2H, J = 6.1, 0.8 Hz, C^9H_2), 2.07–2.20 (m, 2H, C^3H_2), 1.92–2.03 (m, 1H, C^8Ha), 1.59–1.90 (m, 5H, C^8Hb, C^5H_2, C^7H_2), 0.95 (t, 3H, J = 7.5 Hz, C^6H_3).

All other data in agreement with literature.[7]

1-(2-(1H-indol-3-yl)ethyl)-3-ethyl-3-(2-hydroxyethyl)piperidin-2-one (134f)



To a 100 mL round-bottom flask was added the 3 : 1 mixture of **137** and **136** (1.44 g, 5.25 mmol **137**), K_2CO_3 (1.45 g, 10.5 mmol), tryptamine (1.26 g, 7.89 mmol) and EtOH (40 mL). The resulting suspension was heated at reflux over 16 h before being allowed to cool down to rt. The reaction mixture was concentrated until most of the EtOH was evaporated, and the resulting mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (gradient from 3 : 1 EtOAc/petroleum ether 30–40 °C to 100% EtOAc) afforded **134f** as an off-white solid (1.11 g, 67%). If needed, further purification can be performed *via* recrystallisation in EtOAc (10 mL/300 mg).

mp 115–117 °C

IR 3263 (br, N–H, O–H), 2939 (C–H), 1606 (C=O), 1493, 1457.

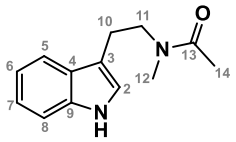
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.22 (br s, 1H, NH), 7.66 (br d, 1H, J = 7.8 Hz, C^5H), 7.36 (ddd, 1H, J = 8.1, 1.0, 1.0 Hz, C^8H), 7.19 (ddd, 1H, J = 8.2, 7.0, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.05 (d, 1H, J = 2.3 Hz, C^2H), 4.18 (dd, 1H, J = 8.2, 3.4 Hz, OH), 3.89 (ddt, 1H, J = 11.5, 8.4, 3.0 Hz, C^{18}Ha), 3.55–3.73 (m, 3H, $C^{11}H_2$, C^{18}Hb), 3.13–3.25 (m, 2H, $C^{12}H_2$), 3.02 (ddt, 1H, J = 8.1, 7.2, 1.0 Hz, $C^{10}H_2$), 1.79–1.90 (m, 2H, C^{19}Ha, C^{17}Ha), 1.60–1.78 (m, 5H, C^{17}Hb, C^{19}Hb, $C^{13}H_2$, C^{14}Ha), 1.47–1.58 (m, 1H, C^{14}Hb), 0.83 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.4 (C^{16}), 136.4 (C^9), 127.6 (C^4), 122.3 (C^2), 122.1 (C^7), 119.4 (C^6), 118.9 (C^5), 113.1 (C^3), 111.3 (C^8), 59.1 (C^{18}), 49.4 (C^{12}), 49.1 (C^{11}), 44.1 (C^{15}), 40.6 (C^{17}), 31.6 (C^{14}), 29.7 (C^{19}), 23.1 (C^{10}), 19.4 (C^{13}), 8.3 (C^{20}).

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{19}H_{27}O_2N_2^+$) requires **m/z** 315.2067, found **m/z** 315.2067.

6.2.8 Synthesis of the starting materials with variations on the amide

N-(2-(1H-indol-3-yl)ethyl)-N-methylacetamide (97fl)



Prepared according to **General Procedure C** from N-Me-tryptamine **148f** and acetyl chloride. Purification *via* trituration in EtOAc afforded **97fl** as a 56 (**A**) : 44 (**B**) mixture of rotamers and as a white solid (129 mg, 52%).

mp 84–86 °C

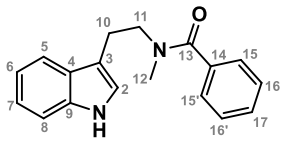
IR 3258 (br, N–H), 2926, 2855, 1624 (C=O), 1491, 1457.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.28–8.30 (br s, 0.56H, NH (**A**)), 8.18–8.27 (br s, 0.44H, NH (**B**)), 7.64–7.68 (m, 0.44H, C^{5}H (**B**)), 7.55–7.59 (m, 0.56H, C^{5}H (**A**)), 7.37 (app tt, 1H, J = 8.1, 1.0H, C^{8}H (**A**), C^{8}H (**B**)), 7.17–7.24 (m, 1H, C^{7}H (**A**), C^{7}H (**B**)), 7.09–7.17 (m, 1H, C^{6}H (**A**), C^{6}H (**B**)), 7.04 (br d, 0.44H, J = 2.5 Hz, C^{2}H (**B**)), 6.97 (br d, 0.56H, J = 2.3 Hz, C^{2}H (**A**)), 3.66–3.72 (m, 0.88H, C^{11}H$_2$ (**B**)), 3.55–3.61 (m, 1.12H, C^{11}H$_2$ (**A**)), 2.99–3.04 (m, 2H, C^{10}H$_2$ (**A**), C^{10}H$_2$ (**B**)), 2.99 (s, 1.68H, C^{12}H$_3$ (**A**)), 2.91 (s, 1.32H, C^{12}H$_3$ (**B**)), 2.09 (s, 1.32H C^{14}H$_3$ (**B**)), 1.85 (s, 1.68H, C^{14}H$_3$ (**A**)).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.0 (C^{13} (**A**)), 170.7 (C^{13} (**B**)), 136.44 (C^9 (**A**)), 136.41 (C^9 (**B**)), 127.6 (C^4 (**B**)), 127.1 (C^4 (**A**)), 122.44 (C^7 (**B**)), 122.35 (C^2 (**A**)), 122.1 (C^2 (**B**), C^7 (**A**)), 119.7 (C^6 (**A**)), 119.4 (C^6 (**B**)), 118.8 (C^5 (**B**)), 118.3 (C^5 (**A**)), 113.3 (C^3 (**B**)), 112.1 (C^3 (**A**)), 111.6 (C^8 (**A**)), 111.3 (C^8 (**B**)), 51.5 (C^{11} (**A**)), 48.8 (C^{11} (**B**)), 36.9 (C^{12} (**B**)), 33.5 (C^{12} (**A**)), 24.3 (C^{10} (**A**)), 23.4 (C^{10} (**B**)), 22.2 (C^{14} (**B**)), 21.2 (C^{14} (**A**)).

All other data in accordance with literature.[8]

_N_-(2-(1H-indol-3-yl)ethyl)-N-methylbenzamide (97f2)



Prepared according to **General Procedure C** from *N*-Me-tryptamine **148f** and benzoyl chloride. Purification via trituration in EtOAc to afforded **97f2** as a 60 (**A**) : 40 (**B**) mixture of rotamers in CD_3OD and as a white solid (360 mg, 44%).

mp 197–199 °C

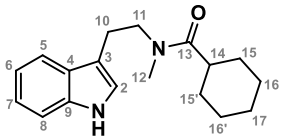
IR 3174 (br, N–H), 1607 (C=O), 1574, 1501, 1476, 1445.

^{1}H NMR (CD_3OD, 500 MHz) δ_H: 7.67 (d, 0.4H, J = 7.9 Hz, C^5H, (**B**)), 7.39–7.44 (m, 1.2H, $C^{16}H$ (**B**), $C^{16'}H$ (**B**), $C^{17}H$ (**B**)), 7.35 (d, 0.4H, J = 8.1 Hz, C^8H (**B**)), 7.27–7.33 (m, 2H, C^8H (**A**), $C^{15}H$ (**B**), $C^{15'}H$ (**B**), $C^{17}H$ (**A**)), 7.14–7.19 (m, 1.6H, $C^{16}H$ (**A**), $C^{16'}H$ (**A**)), C^2H (**B**)), 7.10 (t, 0.4H, J = 7.5 Hz, C^7H (**B**)), 7.01–7.07 (m, 1H, C^6H (**B**), C^7H (**A**)), 6.99 (d, 0.6H, J = 7.9 Hz, C^5H (**A**)), 6.90–6.95 (m, 1.8H, C^2H (**A**), $C^{15}H$ (**A**), $C^{15'}H$ (**A**)), 6.82 (ddd, 0.6H, J = 7.9, 6.9, 1.0 Hz, C^6H (**A**)), 3.84 (t, 0.8H, J = 7.3 Hz, $C^{11}H_2$ (**B**)), 3.57 (t, 1.2H, J = 7.0 Hz, $C^{11}H_2$ (**A**)), 3.13–3.19 (m, 2.6H, $C^{10}H_2$ (**B**), $C^{12}H_3$ (**A**)), 2.96 (t, 1.2H, J = 6.9 Hz, $C^{10}H_2$ (**A**)), 2.83 (s, 1.2H, $C^{12}H_3$ (**B**)).

^{13}C NMR (CD_3OD, 126 MHz) δ_C: 174.7 (C^{13} (**A**)), 173.6 (C^{13} (**B**)), 138.2 (C^9 (**B**)), 138.1 (C^9 (**A**)), 130.8 (C^{17} (**B**)), 137.8 (C^{14} (**B**)), 137.3 (C^{14} (**A**)), 130.2 (C^{17} (**A**)), 129.6 (C^{16}, $C^{16'}$ (**B**)), 129.3 (C^{16}, $C^{16'}$ (**A**)), 128.9 (C^4 (**B**)), 128.6 (C^4 (**A**)), 127.8 (C^{15}, $C^{15'}$ (**B**)), 127.4 (C^{15}, $C^{15'}$ (**A**)), 123.9 (C^2 (**A**)), 123.6 (C^2 (**B**)), 122.4 (C^7 (**B**)), 122.3 (C^7 (**A**)), 119.7 (C^6 (**A**), C^6 (**B**)), 119.4 (C^5 (**B**)), 118.8 (C^5 (**A**)), 113.0 (C^3 (**B**)), 112.3 (C^8 (**B**)), 112.2 (C^8 (**A**)), 111.9 (C^3 (**A**)), 53.4 (C^{11} (**A**)), 50.1 (C^{11} (**B**)), 38.8 (C^{12}(**B**)), 33.3 (C^{12} (**A**)), 24.9 (C^{10} (**A**)), 23.8 (C^{10} (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{19}ON_2^+$) requires **m/z** 279.1492, found **m/z** 279.1487.

N-(2-(1H-indol-3-yl)ethyl)-N-methylbenzamide (97f3)



Prepared according to **General Procedure C** from **148f**. Purification *via* FCC gave **97f3** as a 57(**A**) : 43(**B**) mixture of rotamers and as a light brown solid (260 mg, 46%).

mp 86–88 °C

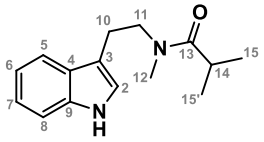
IR 3187 (br, N–H), 2926, 1616 (C=O), 1487, 1446, 1401.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.48–8.58 (br s, 0.57H, NH (**A**)), 8.32–8.40 (br s, 0.43H, NH (**B**)), 7.68 (app d, 0.43, J = 7.9 Hz, C^5H (**B**)), 7.60 (app d, 0.57H, J = 7.8 Hz, C^5H (**A**)), 7.38 (dt, 0.57H, J = 8.4, 1.0 Hz, C^8H (**A**)), 7.36 (dt, 0.43H, J = 8.0, 0.9 Hz, C^8H (**B**)), 7.13–7.23 (m, 1.57H, C^6H (**A**), C^7H (**A**), C^7H (**B**)), 7.11 (ddd, 0.43H, J = 8.0, 7.0 1.1 Hz, C^6H (**B**)), 7.01 (d, 0.43H, J = 2.3 Hz, C^2H (**B**)), 6.94 (d, 0.57H, J = 2.4 Hz, C^2H (**A**)), 3.68 (dd, 0.86H, J = 8.4, 6.7 Hz, $C^{11}H_2$ (**B**)), 3.62 (app t, 1.14H, J = 6.8 Hz, $C^{11}H_2$ (**A**)), 2.93–3.05 (m, 5H, $C^{10}H_2$ (**A**), $C^{10}H_2$ (**B**)), $C^{12}H_3$ (**A**), $C^{12}H_3$ (**B**)), 2.46 (t, 0.43H, J = 11.6, 3.4 Hz, $C^{14}H$ (**B**)), 2.04 (t, 0.57H, J = 11.0, 4.0 Hz, $C^{14}H$ (**A**)), 1.20–1.86 (m, 8H, $C^{15}H_2$ (**A**), $C^{15}H_2$ (**B**), $C^{15'}H_2$ (**A**), $C^{15'}H_2$ (**B**), $C^{16}H_2$ (**A**), $C^{16}H_2$ (**B**), $C^{16'}H_2$ (**A**), $C^{16'}H_2$ (**B**)), 1.07 (qt, 0.86H, J = 13.1, 3.5 Hz, $C^{17}H_2$ (**B**)), 0.77 (qt, 1.14H, J = 12.8, 3.8 Hz, $C^{17}H_2$ (**B**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.1 (C^{13} (**A**)), 176.2 (C^{13} (**B**)), 136.6 (C^9 (**A**)), 136.4 (C^9 (**B**)), 127.6 (C^4 (**A**)), 127.2 (C^4 (**B**)), 122.8 (C^2 (**B**)), 122.3 (C^2 (**A**)), 122.0 (C^7 (**A**)), 122.0 (C^7 (**B**)), 119.7 (C^5 (**A**)), 119.3 (C^5 (**B**)), 118.9 (C^6 (**B**)), 118.2 (C^6 (**A**)), 113.2 (C^3 (**B**)), 111.9 (C^3 (**A**)), 111.7 (C^8 (**A**)), 111.3 (C^8 (**B**)), 50.0 (C^{11} (**A**)), 49.0 (C^{11} (**B**)), 41.1 (C^{14} (**B**)), 40.4 (C^{14} (**A**)), 35.9 (C^{12} (**B**)), 33.6 (C^{12} (**A**)), 29.5 (C^{15}, $C^{15'}$ (**A**)), 29.3 (C^{15}, $C^{15'}$ (**B**)), 26.01 (C^{16}, $C^{16'}$ (**A**)), 25.99 (C^{16}, $C^{16'}$ (**B**)), 25.8 (C^{17} (**B**)), 25.7 (C^{17} (**A**)), 24.7 (C^{10} (**A**)), 24.3 (C^{10} (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}ON_2^+$) requires **m/z** 285.1961, found **m/z** 285.1956.

N-(2-(1H-indol-3-yl)ethyl)-N-methylisobutyramide (97f4)



Prepared according to **General Procedure C** from **148f**. Purification *via* FCC gave **97f4** as a 1 : 1 mixture of rotamers and as a yellow oil (260 mg, 53%).

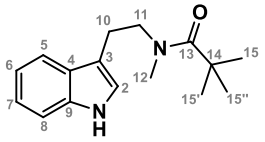
IR 3257 (br, N–H), 2969, 1615 (C=O), 1457.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.39–8.49 (br s, 0.5H, NH (**A**)), 8.24–8.37 (br s, 0.5H, NH (**B**)), 7.69 (d, 0.5H, J = 7.8 Hz, C^5H (**B**)), 7.57 (d, 0.5H, J = 7.8 Hz, C^5H (**A**)), 7.34–7.41 (m, 1H, C^8H (**A**), C^8H (**B**)), 7.09–7.24 (m, 2H, C^6H (**A**), C^6H (**B**), C^7H (**A**), C^7H (**B**)), 7.02 (d, 0.5H, J = 2.3 Hz, C^2H (**B**)), 6.97 (d, 0.5H, J = 2.4 Hz, C^2H (**A**)), 3.66–3.72 (m, 1H, $C^{11}H_2$ (**B**)), 3.63 (app t, 1H, J = 7.2 Hz, $C^{11}H_2$ (**A**)), 2.95–3.06 (m, 5H, $C^{10}H_2$ (**A**), $C^{10}H_2$ (**B**)), $C^{12}H_3$ (**A**), $C^{12}H_3$ (**B**)), 2.79 (sept, 0.5H, J = 6.8 Hz, $C^{14}H$ (**B**)), 2.57 (sept, 0.5H, J = 6.7 Hz, $C^{14}H$ (**A**)), 1.14 (d, 3H, J = 6.7 Hz, $C^{15}H_3$, $C^{15'}H_3$ (**B**)), 0.95 (d, 3H, J = 6.6 Hz, $C^{15}H_3$, $C^{15'}H_3$ (**A**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.7 (C^{13} (**A**)), 177.0 (C^{13} (**B**)), 136.5 (C^9 (**A**)), 136.4 (C^9 (**B**)), 127.6 (C^4 (**A**)), 127.2 (C^4 (**B**)), 122.5 (C^2 (**B**)), 122.3 (C^2 (**A**)), 122.2 (C^7 (**A**)), 122.0 (C^7 (**B**)), 119.7 (C^5 (**A**)), 119.4 (C^5 (**B**)), 118.9 (C^6 (**B**)), 118.3 (C^6 (**A**)), 113.3 (C^3 (**B**)), 112.1 (C^3 (**A**)), 111.6 (C^8 (**A**)), 111.3 (C^8 (**B**)), 50.4 (C^{11} (**A**)), 49.2 (C^{11} (**B**)), 35.9 (C^{12} (**B**)), 33.9 (C^{12} (**A**)), 30.6 (C^{14} (**A**)), 30.0 (C^{14} (**B**)), 24.8 (C^{10} (**A**)), 23.3 (C^{10} (**B**)), 19.6 (C^{15}, $C^{15'}$ (**A**)), 19.3 (C^{15}, $C^{15'}$ (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}ON_2^+$) requires **m/z** 245.1648, found **m/z** 245.1647.

N-(2-(1H-indol-3-yl)ethyl)-N-methylpivalamide (97f5)



Prepared according to **General Procedure C** from **148f**. Purification *via* FCC gave **97f5** as a light brown solid (350 mg, 48%).

mp 132–134 °C

IR 3269 (br, N–H), 2949 (C-H), 1614 (C=O), 1480, 1405.

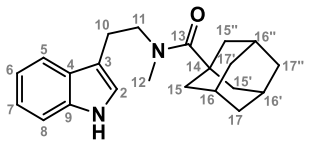
^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ_H: 10.84 (s, 1H, NH), 7.59 (d, 1H, J = 7.8 Hz, C^5H), 7.34 (dt, 1H, J = 8.1, 0.9 Hz, C^8H), 7.15 (d, 1H, J = 2.3 Hz, C^2H), 7.07 (ddd, 1H, J = 8.2, 7.0, 1.3 Hz, C^7H), 6.98 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 3.50–3.58 (m, 2H, $C^{11}H_2$), 3.00 (s, 3H, $C^{12}H_3$), 2.85–2.91 (m, 2H, $C^{10}H_2$), 1.19 (s, 9H, $C^{15}H_3$, $C^{15'}H_3$, $C^{15''}H_3$).

^{13}C NMR ($(CD_3)_2SO$, 400 MHz) δ_C: 175.8 (C^{13}), 136.2 (C^9), 127.2 (C^4), 122.7 (C^2), 121.0 (C^7), 118.34 (C^5), 118.28 (C^6), 111.4 (C^8), 50.6 (C^{11}), 38.2 (C^{12}), 36.3 (C^{14}), 28.1 (C^{15}, $C^{15'}$, $C^{15''}$), 23.0 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}ON_2^+$) requires **m/z** 259.1805, found **m/z** 259.1801.

Note: C^3 was not observed in ^{13}C NMR.

(3r,5r,7r)-N-(2-(1H-indol-3-yl)ethyl)-N-methyladamantane-1-carboxamide (97f6)



Prepared according to **General Procedure C** from **148f**. Purification *via* trituration in EtOAc gave **97f6** as a light orange solid (430 mg, 63%).

mp 152–154 °C

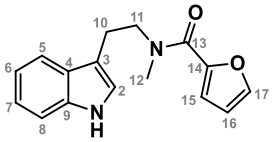
IR 3219 (br, N–H), 2905, 2851 (C–H), 1601 (C=O), 1488, 1456, 1428.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.24–8.33 (br s, 1H, NH), 7.66 (app d, 1H, J = 7.8 Hz, C^5H), 7.37 (dt, 1H, J = 8.2, 1.0 Hz, C^8H), 7.20 (ddd, 1H, J = 8.2, 7.0, 1.3 Hz, C^7H), 7.13 (ddd, 1H, J = 8.1, 7.0, 1.1 Hz, C^6H), 7.01 (d, 1H, J = 2.3 Hz, C^2H), 3.66–3.74 (m, 2H, $C^{11}H_2$), 3.09 (s, 3H, $C^{12}H_3$), 2.99–3.05 (m, 2H, $C^{10}H_2$), 2.04 (s, 9H, $C^{15}H_2$, $C^{15'}H_2$, $C^{15''}H_2$, $C^{16}H$, $C^{16'}H$, $C^{16''}H$), 1.72 (s, 6H, $C^{17}H_2$, $C^{17'}H_2$, $C^{17''}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.9 (C^{13}), 136.4 (C^9), 127.5 (C^4), 122.1 (C^2), 122.0 (C^7), 119.5 (C^6), 118.9 (C^5), 113.2 (C^3), 11.3 (C^8), 51.6 (C^{11}), 42.0 (C^{14}), 39.0 (C^{15}, $C^{15'}$, $C^{15''}$), 37.1 (C^{12}), 36.8 (C^{17}, $C^{17'}$, $C^{17''}$), 28.7 (C^{16}, $C^{16'}$, $C^{16''}$), 23.8 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{29}ON_2^+$) requires **m/z** 337.2274, found **m/z** 337.2269.

N-(2-(1H-indol-3-yl)ethyl)-N-methylfuran-2-carboxamide (97f7)



Prepared according to **General Procedure C** from **148f**. Purification *via* FCC gave **97f7** as an unassignable 1 : 1 mixture of rotamers and as an orange oil (350 mg, 57%).

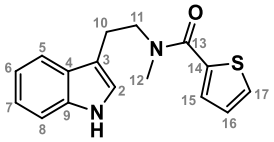
IR 3262 (br, N–H), 1606 (C=O), 1568, 1492, 1456, 1403.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.01–8.12 (br s, 1H, NH), 7.55–7.78 (m, 1H, C^5H), 7.41–7.54 (m, 1H, $C^{17}H$), 7.36 (app d, 1H, J = 8.1 Hz, C^8H), 7.20 (ddd, 1H, J = 8.2, 7.0, 1.2 Hz, C^7H), 7.12 (t, 1H, J = 7.5 Hz, C^6H), 6.90–7.10 (m, 2H, $C^{15}H$, $C^{16}H$), 6.36–6.53 (m, 1H, C^2H), 3.76–3.98 (m, 2H, $C^{11}H_2$), 3.10–3.30 (m, 5H, $C^{10}H_2$, $C^{12}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 160.6, 160.2 (C^{16}), 148.5 (C^{14}), 143.9, 143.6 (C^{17}), 136.4 (C^9), 127.5 (br, C^4), 122.3 (C^7), 122.1 (C^{15}), 119.6 (C^6), 119.0, 118.7 (C^5), 116.2 (C^{13}), 113.3, 112.7 (C^3), 11.3 (C^2, C^8), 51.3, 50.1 (C^{11}), 37.2, 35.0 (C^{12}), 25.1, 23.3 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}O_2N_2^+$) requires **m/z** 269.1285, found **m/z** 269.1280.

N-(2-(1H-indol-3-yl)ethyl)-N-methylthiophene-2-carboxamide (97f8)



Prepared according to **General Procedure D** from **148f**. Purification *via* FCC gave **97f8** as a light brown solid (530 mg, 65%).

mp 124–126 °C

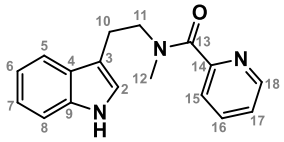
IR 3215 (br, N–H), 1600 (C=O), 1525, 1481, 1451.

^{1}H NMR ($(CD_3)_2SO$, 400 MHz) δ_H: 10.58 (s, 1H, NH), 7.65 (d, 1H, J = 7.0 Hz, $C^{17}H$), 7.50 (d, 1H J = 7.8 Hz, $C^{5}H$), 7.32–7.38 (m, 2H, $C^{8}H$, $C^{15}H$), 7.12 (d, 1H, J = 2.4 Hz, $C^{2}H$), 7.04–7.10 (m, 2H, $C^{7}H$, $C^{16}H$), 6.97 (t, 1H, J = 7.4 Hz, $C^{6}H$), 3.76 (app t, 2H, J = 7.6 Hz, $C^{11}H_2$), 3.12 (s, 3H, $C^{12}H_3$), 3.00-3.07 (m, 2H, $C^{10}H_2$).

^{13}C NMR ($(CD_3)_2SO$, 101 MHz) δ_C: 162.8 (C^{13}), 137.8 (C^{14}), 136.0 (C^{9}), 128.3 (C^{17}), 128.1 (C^{15}), 126.9 (C^{4}), 126.4 (C^{16}), 122.3 (C^{2}), 120.5 (C^{7}), 117.8 (C^{6}), 117.6 (C^{5}), 110.9 (C^{8}), 110.8 (C^{3}), 49.9 (C^{11}), 35.3 (C^{12}), 23.0 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}ON_2S^+$) requires **m/z** 285.1056, found **m/z** 285.1051.

N-(2-(1H-indol-3-yl)ethyl)-N-methylpicolinamide (97f9)



Prepared according to **General Procedure D** from **148**. Purification *via* trituration in EtOAc afforded **97f9** as a 66 (**A**) : 34 (**B**) mixture of rotamers and as a light brown solid (580 mg, 72%).

mp 122–124 °C

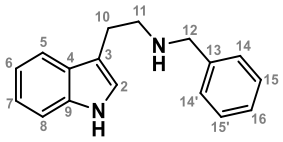
IR 3261 (br, N–H), 1624 (C=O), 1563, 1497, 1459, 1423.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.60 (dq, 0.34H, J = 4.6, 0.9 Hz, $C^{18}H$ (**B**)), 8.46 (ddd, 0.66H, J = 4.9, 1.7, 1.0 Hz, $C^{18}H$ (**A**)), 8.29–8.37 (br s, 1H, NH (**A**,**B**)), 7.78 (td, 0.34H, J = 7.7, 1.8 Hz, $C^{16}H$ (**B**)), 7.73 (app d, 0.34H, J = 7.9 Hz, C^5H (**B**)), 7.60 (dt, 0.34H, J = 7.8, 1.1 Hz, $C^{15}H$ (**B**)), 7.31–7.40 (m, 1.34H, C^8H (**B**), $C^{16}H$ (**A**), $C^{17}H$ (**B**)), 7.27 (dt, 0.66H, J = 8.2, 0.9 Hz, C^8H (**A**)), 7.19 (ddd, 0.34H, J = 8.2, 7.0, 1.1 Hz, C^7H (**B**)), 7.08–7.17 (m, 2.32H, C^5H (**A**), C^6H (**B**), C^7H (**A**), $C^{17}H$ (**A**)), 6.98 (dt, 0.66H, J = 7.8, 1.1 Hz, $C^{15}H$ (**A**)), 6.92 (ddd, 0.66H, J = 8.0, 7.0, 1.0 Hz, C^6H (**A**)), 6.88 (d, 1H, J = 2.4 Hz, C^2H (**A**,**B**)), 3.85–3.90 (m, 0.68H, $C^{11}H_2$ (**B**)), 3.76 (app t, 1.32H, J = 7.2 Hz, $C^{11}H_2$ (**A**)), 3.15–3.21 (m, 2.66H, $C^{10}H_2$ (**B**), $C^{12}H_3$ (**A**)), 3.04 (s, 1.02H, $C^{12}H_3$ (**B**)), 3.02 (t, 1.32H, J = 7.2 Hz, $C^{10}H_2$ (**A**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 169.7 (C^{13} (**A**)), 168.8 (C^{13} (**B**)), 155.0 (C^{14} (**B**)), 154.3 (C^{14} (**A**)), 148.4 (C^{18} (**B**)), 147.8 (C^{18} (**A**)), 137.1 (C^{16} (**B**)), 136.7 (C^{16} (**A**)), 136.41 (C^9 (**B**)), 136.37 (C^9 (**A**)), 127.6 (C^4 (**B**)), 127.3 (C^4 (**A**)), 124.4 (C^{17} (**B**)), 124.0 (C^{17} (**A**)), 123.5 (C^{15} (**B**)), 123.2 (C^{15} (**A**)), 122.5 (C^2 (**A**)), 122.3 (C^2 (**B**)), 122.1 (C^7 (**B**)), 122.0 (C^7 (**A**)), 119.4 (C^5 (**B**)), 119.3 (C^5 (**A**)), 118.9 (C^6 (**B**)), 118.3 (C^6 (**A**)), 113.0 (C^3 (**B**)), 112.1 (C^3 (**A**)), 111.33 (C^8 (**B**)), 111.27 (C^8 (**A**)), 51.4 (C^{11} (**A**)), 49.2 (C^{11} (**B**)), 37.7 (C^{12} (**B**)), 33.7 (C^{12} (**A**)), 24.4 (C^{10} (**A**)), 23.0 (C^{10} (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}ON_3^+$) requires **m/z** 280.1444, found **m/z** 280.1440.

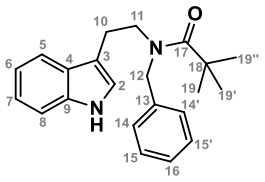
N-benzyl-2-(1H-indol-3-yl)ethan-1-amine (148b)



Prepared according to **General Procedure B** tryptamine **86** and benzaldehyde. **148b** was obtained as an orange oil that was used in the next step without further purification (7.42 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.03–8.15 (br s, 1H, NH), 7.59 (dd, 1H, J = 7.9, 1.1 Hz, C^5H), 7.32 (dt, 1H, J = 8.1, 1.0 Hz, C^8H), 7.19–7.30 (m, 5H, $C^{14}H$, $C^{14'}H$, $C^{15}H$, $C^{15'}H$, $C^{16}H$), 7.17 (ddd, 1H, J = 8.1, 7.0, 1.2 Hz, C^7H), 7.09 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 6.98 (d, 1H, J = 2.3 Hz, C^2H), 3.79 (s, 2H, $C^{12}H_2$), 2.97–3.00 (m, $C^{10}H_2$, $C^{11}H_2$), 1.63 (br s, 1H, NH).

N-(2-(1H-indol-3-yl)ethyl)-N-benzylpivalamide (97b2)



Prepared according to **General Procedure C** from *N*-Bn-tryptamine **148b** and pivaloyl chloride. Purification *via* trituration in Et_2O afforded **97b2** as a 68 (**A**) : 32 (**B**) mixture of rotamers and as a white solid (220 mg, 54%).

mp 148–150 °C

IR 3290 (br, N–H), 1607 (C=O).

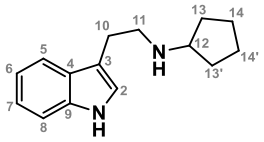
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.20–8.41 (br s, 0.68H, NH (**A**)), 7.96–8.13 (br s, 0.32H, NH (**B**)), 7.45–7.56 (m, 1H, C^5H (**A**), C^5H (**B**)), 7.08–7.38 (m, 3H, C^6H (**A**), C^6H (**B**), C^7H (**A**), C^7H (**B**), C^8H (**A**), C^8H (**B**)), 6.94 (d, 1H, J = 2.4 Hz, C^2H (**A**), C^2H (**B**)), 4.70 (2H, s, $C^{12}H_2$ (**A**), $C^{12}H_2$ (**B**)), 3.58–3.67 (m, 2H, $C^{11}H_2$), 3.04–3.12 (m, 2H, $C^{10}H_2$), 1.36 (s, 6.12H, $C^{19}H_3$, $C^{19'}H_3$, $C^{19''}H_3$ (**A**)), 1.33 (s, 2.88H, $C^{19}H_3$, $C^{19'}H_3$, $C^{19''}H_3$ (**B**)).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: [data for the Major rotamer (**A**)] 178.2 (C^{17}), 136.6 (C^9), 129.0 ($C^{14/14'/15/15'/16}$), 127.7 (C^4), 127.6 ($C^{14/14'/15/15'/16}$), 127.4 ($C^{14/14'/15/15'/16}$), 122.3 (C^2), 119.6 (C^7), 119.1 (C^6), 111.5 (C^8), 48.6 (C^{11}), 39.5 (C^{18}), 29.1 (C^{19}, $C^{19'}$, $C^{19''}$), 23.6 (C^{10}, only visible on HSQC).

Note: C^3, C^5, C^{12}, C^{13} were not observed by ^{13}C NMR

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}ON_2^+$) requires **m/z** 357.1937, found **m/z** 357.1924.

N-(2-(1H-indol-3-yl)ethyl)cyclopentanamine (148c)

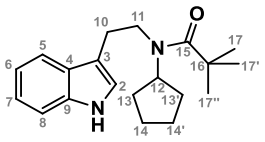


Prepared according to **General Procedure B** from tryptamine **86** and cyclopentanone. **148c** was obtained as a pale brown solid and was used in the next step without further purification (4.97 g, 87%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.64–8.80 (br s, 1H, NH), 7.66 (d, 1H, J = 8.0 Hz, C^5H), 7.36 (d, 1H, J = 8.0 Hz, C^8H), 7.22 (td, 1H, J = 7.5, 1.0 Hz, C^7H), 7.14 (td, 1H, J = 7.5 Hz, 1.0 Hz, C^6H), 7.01 (d, 1H, J = 2.0 Hz, C^2H), 3.12 (p, 1H, J = 7.0 Hz, $C^{12}H$), 2.98–3.04 (m, 4H, $C^{10}H_2$, $C^{11}H_2$), 1.82–1.93 (m, 2H, C^{13}Ha, $C^{13'}$Ha), 1.60–1.75 (m, 2H, C^{14}Ha, $C^{14'}$Ha), 1.45–1.60 (2H, m, C^{14}Hb, $C^{14'}$Hb), 1.25–1.40 (m, 3H, C^{13}Hb, $C^{13'}$Hb, NH).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 136.7 (C^9), 127.7 (C^4), 122.3 (C^2), 122.1 (C^7), 119.4 (C^6), 119.2 (C^5), 114.1 (C^3), 111.5 (C^8), 60.1 (C^{12}), 49.0 (C^{11}), 33.4 (C^{13}, $C^{13'}$), 26.3 (C^{10}), 24.4 (C^{14}, $C^{14'}$).

N-(2-(1H-indol-3-yl)ethyl)-N-cyclopentylpivalamide (97c1)



Prepared according to **General Procedure C** from **148c**. Purification *via* recrystallization in EtOAc gave **97c1** as a light brown solid (350 mg, 41%).

mp 150–152 °C

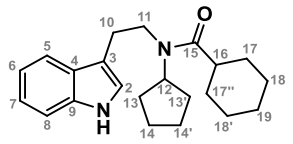
IR 3279 (br, N–H), 1601 (C=O).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.25–8.50 (br s, 1H, NH), 7.73 (d, 1H, J = 8.0 Hz, C^5H), 7.36 (1H, dt, J = 8.0, 1.0 Hz, C^8H), 7.18 (1H, ddd, J = 8.0, 7.0, 1.5 Hz, C^7H), 7.12 (1H, ddd, J = 8.0, 7.0, 1.5 Hz, C^6H), 7.04 (d, 1H, J = 2.0 Hz, C^2H), 4.43–4.61 (m, 1H, $C^{12}H$), 3.36–3.53 (m, 2H, $C^{11}H_2$), 3.03–3.10 (m, 2H, $C^{10}H_2$), 1.59–1.94 (m, 8H, $C^{13}H_2$, $C^{13'}H_2$, $C^{14}H_2$, $C^{14'}H_2$), 1.36 (s, 9H, $C^{17}H_3$, $C^{17'}H_3$, $C^{17''}H_3$).

^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 177.8 (C^{15}), 136.6 (C^9), 127.8 (C^4), 122.3 (C^2), 122.1 (C^7), 119.5 (C^6), 119.4 (C^5), 114.2 (C^3), 111.5 (C^8), 59.3 (C^{12}), 45.4 (C^{11}), 39.5 (C^{16}), 29.9 (C^{13}, $C^{13'}$), 29.2 (C^{17}, $C^{17'}$, $C^{17''}$), 25.2 (C^{10}), 24.3 (C^{14}, $C^{14'}$).

HRMS (ES^+) exact mass calculated for $[M\text{-}H]^+$ ($C_{20}H_{27}ON_2^+$) requires **m/z** 311.2129, found **m/z** 311.2127.

N-(2-(1H-indol-3-yl)ethyl)-N-cyclopentylcyclohexanecarboxamide (97c2)



XX

Prepared according to **General Procedure C** from **148c**. Purification *via* recrystallization in EtOAc gave **97c2** as a 58 (**A**) : 42 (**B**) mixture of rotamers and as a light brown solid (570 mg, 61%).

mp 144–146 °C

IR 3255 (br, N–H), 1611 (C=O).

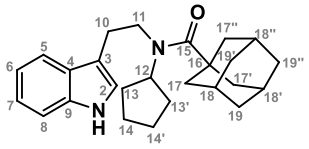
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.64–8.78 (br s, 0.42H, NH (**B**)), 8.39–8.51 (br s, 0.58H, NH (**A**)), 7.74 (d, 0.58H, J = 8.0 Hz, C^5H (**A**)), 7.61 (d, 0.42H, J = 8.0 Hz, C^5H (**B**)), 7.40 (d, 0.42H, J = 8.0 Hz, C^8H (**B**)), 7.35 (d, 0.58H, J = 8.0 Hz, C^8H (**A**)), 7.22 (dt, 0.42H, J = 7.0, 1.0 Hz, C^7H (**B**)), 7.14–7.19 (m, 1H, C^7H (**A**), C^6H (**B**)), 7.11 (ddd, 0.58H, J = 8.0 Hz, 7.0 Hz, 1.0 Hz, C^6H (**A**)), 7.02 (d, 0.58H, J = 2.0 Hz, C^2H (**A**)), 7.01 (d, 0.42H, J = 2.0 Hz, C^2H (**B**)), 4.56 (p, 0.42H, J = 8.5 Hz, $C^{12}H$ (**B**)), 4.23, 0.58H, J = 8.5 Hz, $C^{12}H$ (**A**)), 3.40–3.53 (m, 2H, $C^{11}H_2$ (**A**), $C^{11}H_2$ (**B**)), 2.97–3.06 (m, 2H, $C^{10}H_2$ (**A**), $C^{10}H_2$ (**B**)), 2.59 (tt, 0.58H, J = 11.5, 3.5 Hz, $C^{16}H$ (**A**)), 2.28 (tt, 0.42H, J = 9.5, 4.5 Hz, $C^{16}H$ (**B**)), 0.90–1.97 (m, 18H, $C^{13}H_2$ (**A**), $C^{13}H_2$ (**B**), $C^{13'}H_2$ (**A**), $C^{13'}H_2$ (**B**), $C^{14}H_2$ (**A**), $C^{14}H_2$ (**B**), $C^{14'}H_2$ (**A**), $C^{14'}H_2$ (**B**), $C^{17}H_2$ (**A**), $C^{17}H_2$ (**B**), $C^{17'}H_2$ (**A**), $C^{17'}H_2$ (**B**), $C^{18}H_2$ (**A**), $C^{18}H_2$ (**B**), $C^{18'}H_2$ (**A**), $C^{18'}H_2$ (**B**), $C^{19}H_2$ (**A**), $C^{19}H_2$ (**B**)).

^{13}C NMR ($CDCl_3$, 400 MHz) δ_C: 177.2 (C^{15} (**B**)), 176.6 (C^{15} (**A**)), 136.8 (C^9 (**B**)), 136.6 (C^9 (**A**)), 127.8 (C^4 (**A**)), 127.4 (C^4 (**B**)), 122.7 (C^2 (**B**)), 122.4 (C^2 (**A**)), 122.3 (C^7 (**B**)), 122.0 (C^7 (**A**)), 119.7 (C^6 (**B**)), 119.5 (C^5 (**A**)), 119.4 (C^6 (**A**)), 118.5 (C^5 (**B**)), 114.1 (C^3 (**A**)), 112.5 (C^3 (**B**)), 111.9 (C^8 (**B**)), 111.4 (C^8 (**A**)), 58.6 (C^{12} (**A**)), 57.1 (C^{12} (**B**)), 45.7 (C^{11} (**B**)), 43.9 (C^{11} (**A**)), 42.0 (C^{16} (**B**)), 41.5 (C^{16} (**A**)), 30.6 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**B**)), 30.3 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**A**)), 29.9 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**B**)),

29.8 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**A**)), 27.8 (C10 (**B**)), 26.3 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**B**), 2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**A**)), 26.1 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**A**)), 25.5 (C10 (**A**)), 24.2 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**B**)), 24.1 (2 x $C^{13/13'/14/14'/17/17'/18/18'/19}$ (**A/B**)).

HRMS (ES^+) exact mass calculated for $[M-H]^+$ ($C_{21}H_{30}ON_2^+$) requires **m/z** 337.2285, found **m/z** 337.2287.

(3r,5r,7r)-N-(2-(1H-indol-3-yl)ethyl)-N-cyclopentyladamantane-1-carboxamide (97c3)



Prepared according to **General Procedure C** from **148c**. Purification *via* recrystallization in EtOAc gave **97c3** as a light brown solid (480 mg, 45%)

IR 3280 (br, N–H), 1597 (C=O).

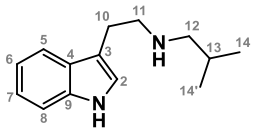
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04–8.13 (br s, 1H, NH), 7.69–7.75 (d, 1H, J = 8.0 Hz, C^5H), 7.35 (dt, 1H, J = 8.0, 1.0 Hz, C^8H), 7.18 (ddd, 1H, J = 8.0, 7.0, 1.5 Hz, C^7H), 7.12 (1H, ddd, J = 8.0 Hz, 7.0, 1.0 Hz, C^6H), 7.04 (d, 1H, J = 2.5 Hz, C^2H), 4.50–4.84 (br s, 1H, $C^{12}H$), 3.30–3.47 (m, 2H, $C^{11}H_2$), 2.96–3.04 (m, 2H, $C^{10}H_2$), 2.07 (app s, 9H, $C^{17}H_2$, $C^{17'}H_2$, $C^{17''}H_2$, $C^{18}H$, $C^{18'}H$, $C^{18''}H$), 1.55–1.95 (m, 14H, $C^{13}H_2$, $C^{13'}H_2$, $C^{14}H_2$, $C^{14'}H_2$, $C^{19}H_2$, $C^{19'}H_2$, $C^{19''}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.2 (C^{15}), 136.5 (C^9), 127.9 (C^4), 122.2 (C^7), 122.1 (C^2), 119.6 (C^6), 119.6 (C^5), 114.6 (C^3), 111.4 (C^8), 59.3 (C^{12} (only visible on HSQC)), 45.8 (C^{11} (only visible on HSQC)), 39.8 (C^{17}, $C^{17'}$, $C^{17''}$), 37.1 (C^{19}, $C^{19'}$, $C^{19''}$), 30.0 (C^{13}, $C^{13'}$, $C^{13''}$), 29.0 (C^{18}, $C^{18'}$, $C^{18''}$), 25.4 (C^{10}), 24.4 (C^{14}, $C^{14'}$).

C^{16} could not be observed

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{26}H_{35}ON_2^+$) requires **m/z** 413.2563, found **m/z** 413.2558.

N-(2-(1H-indol-3-yl)ethyl)-2-methylpropan-1-amine (148d)



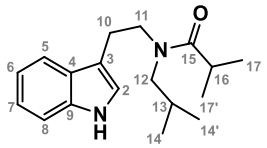
Prepared according to **General Procedure B** from tryptamine **86** and *i*-butyraldehyde. **148d** was used in the next step without further purification (393 mg, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.18–8.30 (br s, 1H, NH), 7.64 (br d, 1H, J = 7.8 Hz, C^5H), 7.36 (br d, 1H, J = 8.1 Hz, C^8H), 7.20 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.03 (d, 1H, J = 2.2 Hz, C^2H), 2.95–3.00 (m, 4H, $C^{10}H_2$, $C^{11}H_2$), 2.47 (d, 2H, J = 6.9 Hz, $C^{12}H_2$), 1.75 (n, 1H, $C^{13}H$, J = 6.7 Hz), 0.88 (d, 6H, J = 6.6 Hz, $C^{14}H_3$, $C^{14'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 136.5 (C^9), 127.6 (C^4), 122.1 (C^7), 122.0 (C^2), 119.3 (C^6), 119.0 (C^5), 114.3 (C^3), 111.3 (C^8), 57.9 (C^{12}), 50.3 (C^{11}), 28.4 (C^{13}), 25.9 (C^{10}), 20.8 (C^{14}, $C^{14'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}N_2^+$) requires **m/z** 217.1699, found **m/z** 217.1698.

N-(2-(1H-indol-3-yl)ethyl)-N-isobutylisobutyramide (97d1)



Prepared according to **General Procedure C** from amine **148d** and *i*-butyryl chloride. Purification *via* recrystallization from Et_2O gave **97d1** as a 53 (**A**) : 47 (**B**) mixture of rotamers and as an off-white solid (150 mg, 29%).

mp 97–99 °C

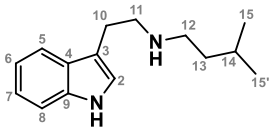
IR 3265 (br, N–H), 2961, 2929, 2871 (C–H), 1619 (C=O), 1457.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.08–8.15 (br s, 0.47H, NH (**B**)), 7.97–8.06 (br s, 0.53H, NH (**A**)), 7.72 (d, 0.53H, J = 7.8 Hz, C^5H (**A**)), 7.56 (d, 0.47H, J = 7.8 Hz, C^5H (**B**)), 7.38 (d, 0.47H, J = 8.1 Hz, C^8H (**B**)), 7.35 (d, 0.53H, J = 8.0 Hz, C^8H (**A**)), 7.10–7.24 (m, 2H, C^6H (**A**,**B**), C^7H (**A**,**B**)), 7.03 (d, 0.53H, J = 2.3 Hz, C^2H (**A**)), 6.99 (d, 0.47H, J = 2.3 Hz, C^2H (**B**)), 3.56–3.65 (m, 2H, $C^{11}H_2$ (**A**,**B**)), 3.25 (d, 0.94H, J = 7.5 Hz, $C^{12}H_2$ (**B**)), 3.05 (d, 1.06H, J = 7.6 Hz, $C^{12}H_2$ (**A**)), 2.97–3.02 (m, 2H, $C^{10}H_2$ (**A**,**B**)), 2.80 (hept, 0.53H, J = 6.7 Hz, $C^{16}H$ (**A**)), 2.65 (hept, 0.47H, J = 6.6 Hz, $C^{16}H$ (**B**)), 2.02 (hept, 0.53H, J = 6.9 Hz, $C^{13}H$ (**A**)), 1.90 (hept, 0.47H, J = 6.9 Hz, $C^{13}H$ (**B**)), 1.14 (d, 3.18H, J = 6.7 Hz, $C^{17}H_3$, $C^{17'}H_3$ (**A**)), 1.00 (d, 2.82H, J = 6.7 Hz, $C^{17}H_3$, $C^{17'}H_3$ (**B**)), 0.89 (app t, 6H, J = 6.6 Hz, $C^{14}H_3$ (**A**,**B**), $C^{14'}H_3$ (**A**,**B**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.8 (C^{15} (**B**)), 177.6 (C^{15} (**A**)), 136.43 (C^9 (**B**)), 136.38 (C^9 (**A**)), 127.7 (C^4 (**A**)), 127.2 (C^4 (**B**)), 122.4 (C^7 (**B**)), 122.3 (C^2 (**B**)), 122.1 (C^7 (**A**)), 122.0 (C^2 (**A**)), 119.8, (C^6 (**B**)), 119.5, (C^6 (**A**)), 119.2 (C^5 (**A**)), 118.4 (C^5 (**B**)), 113.7 (C^3 (**A**)), 112.5 (C^3 (**B**)), 111.5 (C^8 (**B**)), 111.2 (C^8 (**A**)), 55.6 (C^{12} (**A**)), 52.7 (C^{12} (**B**)), 48.6 (C^{11} (**B**)), 47.8 (C^{11} (**A**)), 30.4 (C^{16} (**B**)), 30.3 (C^{16} (**A**)), 28.5 (C^{13} (**B**)), 27.2 (C^{13} (**A**)), 25.2 (C^{10} (**B**)), 23.4 (C^{10} (**A**)), 20.3 (C^{14}, $C^{14'}$(**B**)), 20.1 (C^{14}, $C^{14'}$ (**A**)), 19.8 (C^{17}, $C^{17'}$ (**A**, **B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}ON_2^+$) requires **m/z** 287.2118, found **m/z** 287.2119.

N-(2-(1H-indol-3-yl)ethyl)-3-methylbutan-1-amine (148e)



Prepared according to **General Procedure B** from tryptamine **86** and *i*-valeraldehyde. **148e** was used in the next step without further purification (554 mg, 96%).

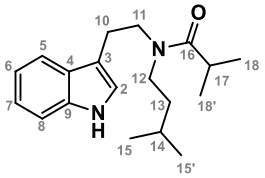
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.26–8.39 (br s, 1H, NH), 7.64 (br d, 1H, J = 7.9 Hz, C^5H), 7.36 (br d, 1H, J = 8.1 Hz, C^8H), 7.20 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz, C^7H), 7.13 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.03 (d, 1H, J = 2.3 Hz, C^2H), 2.97–3.01 (m, 4H, $C^{10}H_2$, $C^{11}H_2$), 2.62–2.68 (m, 2H, $C^{12}H_2$), 1.35–1.41 (m, 2H, $C^{13}H_2$), 1.57 (n, 1H, J = 6.6 Hz, $C^{14}H$), 0.88 (d, 6H, J = 6.6 Hz, $C^{15}H_3$, $C^{15'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 136.5 (C^9), 127.6 (C^4), 122.1 (C^7, C^2), 119.3 (C^6), 119.0 (C^5), 114.2 (C^3), 111.3 (C^8), 50.2 (C^{11}), 48.3 (C^{12}), 39.4 (C^{13}), 26.4 (C^{14}), 26.0 (C^{10}), 21.2 (C^{15}, $C^{15'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N_2^+$) requires **m/z** 231.1856, found **m/z** 231.1856.

All other data in agreement with literature.[9]

N-(2-(1H-indol-3-yl)ethyl)-N-isopentylisobutyramide (97e1)



Prepared according to **General Procedure C** from amine **148e** and *i*-butyryl chloride. Purification *via* recrystallization from Et_2O gave **97e1** as an unassignable 1 : 1 mixture of rotamers and as colorless prisms (240 mg, 33%).

mp 109–111 °C

IR 3260 (br, N–H), 2959, 2930, 2870 (C–H), 1617 (C=O), 1457, 1430.

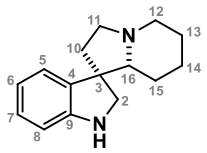
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.21–8.31 (br s, 0.5H, NH), 8.11–8.21 (br s, 0.5H, NH), 7.70 (d, 0.5H, J = 7.8 Hz, C^5H), 7.57 (d, 0.5H, J = 7.8 Hz, C^5H), 7.39 (br d, 0.5H, J = 8.1 Hz, C^8H), 7.36 (br d, 0.5H, J = 8.1 Hz, C^8H), 7.09–7.24 (m, 2H, C^7H, C^6H), 7.02 (d, 0.5H, J = 2.3 Hz, C^2H), 7.00 (d, 0.5H, J = 2.4 Hz, C^2H), 3.54–3.65 (m, 2H, $C^{11}H_2$), 3.37–3.42 (m, 1H, $C^{12}H_2$), 3.16–3.22 (m, 1H, $C^{14}H$), 2.98–3.04 (m, 2H, $C^{10}H_2$), 2.74 (hept, 0.5H, J = 6.7 Hz, $C^{17}H$), 2.60 (hept, 0.5H, J = 6.8 Hz, $C^{17}H$), 1.48–1.63 (m, 1H, $C^{14}H$), 1.38–1.48 (m, 2H, $C^{13}H_2$), 1.16 (d, 3H, J = 6.6 Hz, $C^{18}H_3$, $C^{18'}H_3$), 0.98 (d, 3H, J = 6.7 Hz, $C^{18}H_3$, $C^{18'}H_3$), 0.92 (d, 3H, J = 6.6 Hz $C^{15}H_3$, $C^{15'}H_3$), 0.89 (d, 3H, J = 6.5 Hz $C^{15}H_3$, $C^{15'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.2 (C^{16}), 177.0 (C^{16}), 136.5 (C^9), 136.4 (C^9), 127.7 (C^4), 127.2 (C^4), 122.4 (C^2), 122.3 (C^7), 122.1 (C^7), 122.1 (C^2), 119.7, (C^6), 119.4, (C^6), 119.1 (C^5), 118.3 (C^5), 113.6 (C^3), 112.4 (C^3), 111.5 (C^8), 111.2 (C^8), 48.1(C^{11}), 47.3 (C^{11}), 46.9 (C^{12}), 44.5 (C^{12}), 38.7 (C^{13}), 36.7 (C^{13}), 30.34 (C^{17}), 30.26 (C^{17}), 26.4 (C^{14}), 26.2 (C^{14}), 25.5 (C^{10}), 23.8 (C^{10}), 22.7 (C^{15}, $C^{15'}$), 22.6 (C^{15}, $C^{15'}$), 20.0 (C^{18}, $C^{18'}$), 19.7 (C^{18}, $C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{28}ON_2Na^+$) requires **m/z** 323.2094, found **m/z** 323.2095.

6.2.9 Synthesis of spirocyclic indoline products

(3R,8a'R)-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (126)



Prepared according to **General Procedure E** (0.1 mol% catalyst, 3.00 equiv. TMDS, –15 °C, 1 h) from **126**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave **125** as a yellow oil that crystallized upon standing, and can be further recrystallized from pentane (105 mg, 90%, isolated d.r. >95 : 5).

mp 74–76 °C

IR 3248 (br, N–H), 2931, 2854, 2785 (C–H), 1606, 1489, 1455.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.09 (ddd, 1H, J = 7.4, 1.3, 0.5 Hz, C^5H), 6.86 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.76 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (ddd, 1H, J = 7.8, 1.0, 0.5 Hz, C^8H), 3.81 (d, 1H, J = 9.4 Hz, C^2Ha), 3.58–3.73 (br s, 1H, NH), 3.22 (d, 1H, J = 9.4 Hz, C^2Hb), 3.11–3.20 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.22–2.33 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 1.86–2.01 (m, 2H, $C^{12}Ha$, $C^{10}Hb$), 1.80 (dd, 1H, J = 11.1, 2.7 Hz, $C^{16}H$), 1.71–1.78 (m, 1H, $C^{14}Ha$), 1.59–1.66 (m, 1H, $C^{13}Ha$), 1.45–1.59 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.37 (tdd, 1H, J = 12.7, 11.1, 3.8 Hz, $C^{15}Hb$), 1.09 (qt, 1H, J = 12.8, 4.2 Hz, $C^{14}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.8 (C^9), 134.4 (C^4), 127.9 (C^7), 123.0 (C^5), 118.8 (C^6), 109.7 (C^8), 74.9 (C^{16}), 57.7 (C^2), 54.3 (C^{12}), 54.2 (C^{11}), 53.9 (C^3), 38.0 (C^{10}), 25.5 (C^{13}), 25.4 (C^{15}), 24.3 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2^+$) requires **m/z** 229.1699, found **m/z** 229.1696.

Data for X-ray

CCDC Number : 1906300

Crystal data

Chemical formula	$C_{16.88}H_{22.50}N_{2.25}$
M_r	256.88
Crystal System, space group	Trigonal, *R*3
Temperature (K)	150
a, *b*, *c* (Å)	24.4741 (6), 24.4741 (6), 11.2577 (3)
α, β, γ (°)	90, 90,120
V (Å^3)	5839.7 (3)
Z	16
Radiation type	Cu *Kα*
U (mm^{-1})	0.53
Crystal size (mm)	0.20 × 0.10 × 0.05

Data collection

Diffractometer	Unknown
Absorption correction	Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	
No. of measured	
independent and observed	
[*I*> 2.0σ(*I*)] reflections	6372, 2692, 2402
*R*int	0.014
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.629

Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.036, 0.094, 0.99
No. of reflections	2692
No. of parameters	158

No. restraints	4
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å^{-3})	0.30, –0.18
Absolute structure	–
Structure parameter	–

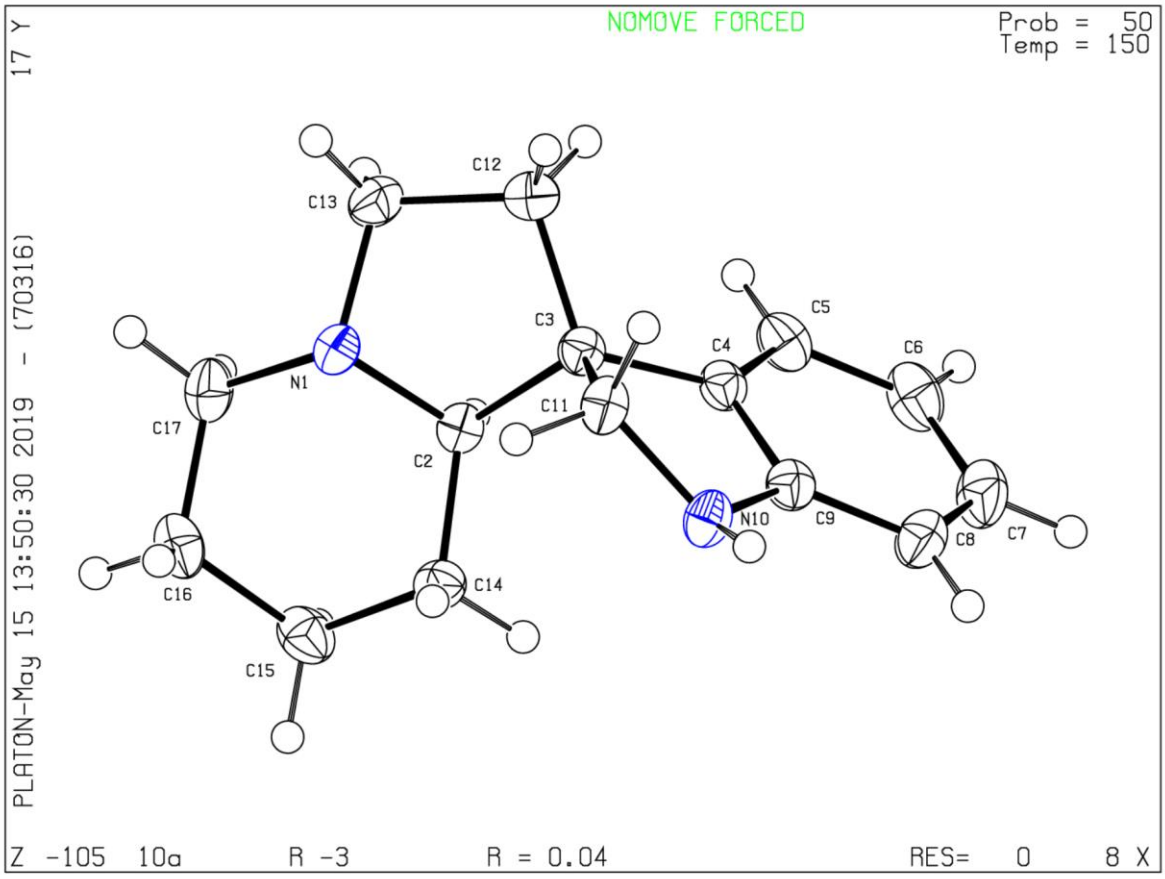


Table i: Selected geometric parameters (Å, º)

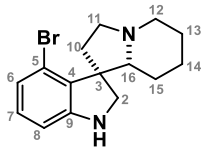
N1—C2	1.4640 (12)	C5—C6	1.3964 (16)
N1—C13	1.4641 (13)	C6—C7	1.3873 (18)
N1—C17	1.4596 (13)	C7—C8	1.3923 (17)
C2—C3	1.5460 (13)	C8—C9	1.3890 (15)
C2—C14	1.5188 (14)	C9—N10	1.3903 (13)
C3—C4	1.5149 (14)	N10—C11	1.4634 (13)
C3—C11	1.5457 (13)	C12—C13	1.5357 (15)
C3—C12	1.5505 (14)	C14—C15	1.5292 (15)

C4—C5	1.3816 (15)	C15—C16	1.5281 (16)
C4—C9	1.4019 (14)	C16—C17	1.5227 (17)
C2—N1—C13	104.37 (8)	C4—C5—C6	119.32 (11)
C2—N1—C17	112.32 (8)	C5—C6—C7	120.02 (10)
C13—N1—C17	113.93 (8)	C6—C7—C8	121.21 (10)
N1—C2—C3	102.26 (8)	C7—C8—C9	118.48 (10)
N1—C2—C14	110.47 (8)	C4—C9—C8	120.62 (10)
C3—C2—C14	119.04 (8)	C4—C9—N10	110.73 (9)
C2—C3—C4	111.77 (8)	C8—C9—N10	128.63 (10)
C2—C3—C11	112.60 (8)	C9—N10—C11	106.79 (8)
C4—C3—C11	100.47 (8)	C3—C11—N10	104.33 (8)
C2—C3—C12	101.89 (8)	C3—C12—C13	105.70 (9)
C4—C3—C12	117.61 (9)	C12—C13—N1	104.27 (8)
C11—C3—C12	112.98 (9)	C2—C14—C15	109.97 (9)
C3—C4—C5	131.10 (10)	C14—C15—C16	110.91 (9)
C3—C4—C9	108.43 (9)	C15—C16—C17	110.74 (9)
C5—C4—C9	120.35 (10)	C16—C17—N1	110.06 (9)

Table ii: Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N10—H101···N1^{i}	0.88	2.19	3.0400 (17)	164 (1)

(3R,8a'R)-4-bromo-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132a)



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131a**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave **132a** as a thick oil that crystallized upon standing to give colourless prisms (114 mg, 87%)

mp 131–133 °C

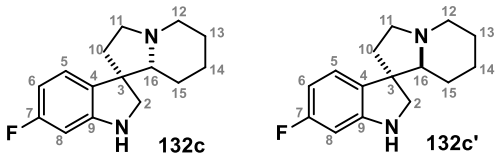
IR 3221 (br, N–H), 2932, 2853, 2796 (C–H), 1599, 1570, 1480, 1445.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.84–6.91 (m, 2H, C^6H, C^7H), 6.86 (dd, 1H, J = 7.0, 1.7 Hz, C^8H), 3.87 (d, 1H, J = 9.5 Hz, C^2Ha), 3.67–3.82 (br s, 1H, NH), 3.21 (d, 1H, J = 9.5 Hz, C^2Hb), 3.09–3.19 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.97 (ddd, 1H, J = 13.6, 8.7, 1.5 Hz, $C^{10}Ha$), 2.52 (app q, 1H, J = 9.1 Hz, $C^{11}Hb$), 2.17 (dd, 1H, J = 11.1, 2.8 Hz, $C^{16}H$), 2.05 (ddd, 1H, J = 12.2, 10.9, 3.1 Hz, $C^{12}Hb$), 1.70–1.78 (m, 1H, $C^{14}Ha$), 1.59–1.67 (m, 2H, $C^{13}Ha$,$C^{10}Hb$), 1.43–1.59 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.37 (tdd, 1H, J = 12.6, 11.1, 3.8 Hz, $C^{15}Hb$), 1.12 (qt, 1H, J = 12.8, 4.1 Hz, $C^{14}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 154.0 (C^9), 130.0 (C^4), 129.5 (C^7), 123.3 (C^6), 119.2 (C^5), 108.7 (C^8), 70.6 (C^{16}), 58.2 (C^2), 55.3 (C^3), 54.3 (C^{11}), 53.8 (C^{12}), 34.8 (C^{10}), 25.3 (C^{13}), 25.0 (C^{15}), 24.1 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}N_2Br^+$) requires **m/z** 307.0804, found **m/z** 307.0804.

(3R,8a'R)-6-fluoro-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132c) and (3R,8a'S)-6-fluoro-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132c')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131c**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **132c'** as a thick yellow oil (6 mg, 5%).

Data for **132c'**:

IR 3151 (br, N–H), 2933, 2854, 2801 (C–H), 1618, 1496, 1457.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.94 (dd, 1H, J = 8.1, 5.6 Hz, C^5H), 6.38 (ddd, 1H, J = 9.5, 8.1, 2.3 Hz, C^6H), 6.28 (dd, 1H, J = 9.9, 2.3 Hz, C^8H), 3.83 (d, 1H, J = 9.5 Hz, C^2Ha), 3.62–3.86 (br s, 1H, NH), 3.24 (d, 1H, J = 9.5 Hz, C^2Hb), 3.09–3.19 (m, 2H, C^{11}Ha, C^{12}Ha), 2.15–2.31 (m, 2H, C^{11}Hb, C^{10}Ha), 1.96 (ddd, 1H, J = 12.1, 11.0, 3.1 Hz, C^{12}Hb), 1.83–1.92 (m, 1H, C^{10}Hb), 1.71–1.79 (m, 2H, C^{16}H, C^{14}Ha), 1.58–1.65 (m, 1H, C^{13}Ha), 1.43–1.58 (m, 2H, C^{13}Hb, C^{15}Ha), 1.34 (tdd, 1H, J = 12.7, 11.1, 3.8 Hz, C^{15}Hb), 1.09 (qt, 1H, J = 12.8, 4.1 Hz, C^{14}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 163.5 (d, J = 241.3 Hz, C^7), 153.1 (d, J = 11.7 Hz, C^9), 129.5 (d, J = 2.1 Hz, C^4), 123.3 (d, J = 10.5 Hz, C^5), 104.7 (d, J = 22.8 Hz, C^6), 97.0 (d, J = 26.0 Hz, C^8), 74.9 (C^{16}), 58.2 (C^2), 54.2 (C^{12}), 53.9 (C^{11}), 53.2 (C^3), 37.9 (C^{10}), 25.4 (C^{13}), 25.2 (C^{15}), 24.2 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}N_2F^+$) requires **m/z** 247.1605, found **m/z** 247.1606.

Further elution [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] afforded the Major isomer **123c** as a thick yellow oil (92 mg, 84%).

Data for **132c**:

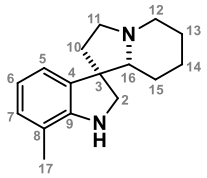
IR 3274 (br, N–H), 2932, 2854, 2784 (C–H), 1613, 1493, 1453.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.16 (br t, 1H, *J* = 6.9 Hz, C^5H), 6.39 (ddd, *J* = 9.6, 8.2, 2.4 Hz, C^6H), 6.28 (dd, 1H, *J* = 9.9, 2.4 Hz, C^8H), 3.48–3.83 (br s, 1H, NH), 3.53 (s, 2H, C^2H_2), 3.09–3.21 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.20 (app q, 1H, *J* = 8.9 Hz, $C^{11}Hb$), 2.08 (dt, 1H, *J* = 12.5, 8.2 Hz, $C^{10}Ha$), 1.87–1.98 (m, 2H, $C^{10}Hb$, $C^{12}Ha$), 1.78 (d, 1H, *J* = 11.0 Hz, $C^{16}H$), 1.65–1.72 (m, 1H, $C^{14}Ha$), 1.54–1.61 (m, 1H, $C^{13}Ha$), 1.40–1.50 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.16 (qt, 1H, *J* = 13.0, 4.0 Hz, $C^{14}Hb$), 0.87–0.98 (m, 1H, $C^{15}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 163.3 (d, *J* = 240.9 Hz, C^7), 152.5 (d, *J* = 11.5 Hz, C^9), 130.9 (C^4), 125.8 (d, J = 10.1 Hz, C^5), 104.7 (d, *J* = 22.2 Hz, C^6), 96.8 (d, *J* = 25.9 Hz, C^8), 74.2 (C^{16}), 59.8 (C^2), 54.2 (C^{12}), 53.9 (C^{11}), 53.3 (C^3), 38.7 (C^{10}), 26.4 (C^{15}), 25.4 (C^{13}), 24.2 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}N_2F^+$) requires **m/z** 247.1605, found **m/z** 247.1604.

(3R,8a'R)-7-methyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132d)



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131d**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2M)] gave the Major isomer **132d** as a thick yellow oil (61 mg, 80%).

Note: A pure sample of the minor isomer **132d'** could not be obtained.

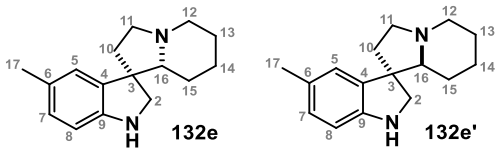
IR 3370 (br, N–H), 2930, 2854, 2784 (C–H), 1601, 1481, 1462, 1440, 1380, 1327.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.96 (dd, 1H, *J* = 7.4, 1.2 Hz, C^5H), 6.90 (dt, 1H, *J* = 7.5, 1.0 Hz, C^7H), 6.71 (t, 1H, *J* = 7.4 Hz, C^6H), 3.88 (d, 1H, *J* = 9.6 Hz, C^2Ha), 3.27–3.59 (br s, 1H, NH), 3.24 (d, 1H, *J* = 9.6 Hz, C^2Hb), 3.14–3.22 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.31 (dt, 1H, *J* = 8.2, 9.3 Hz, $C^{11}Hb$), 2.24 (dd, 1H, *J* = 9.6, 2.4 Hz, $C^{10}Ha$), 2.14 (s, 3H, $C^{17}H_3$), 2.00 (td, 1H, *J* = 11.7, 3.3 Hz, $C^{12}Hb$), 1.89–1.97 (m, 1H, $C^{10}Hb$), 1.85 (dd, 1H, *J* = 11.1, 2.8 Hz, $C^{16}H$), 1.71–1.80 (m, 1H, $C^{14}Ha$), 1.61–1.67 (m, 1H, $C^{13}Ha$), 1.46–1.60 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.41 (tdd, 1H, *J* = 12.7, 11.0, 3.8 Hz, $C^{15}Hb$), 1.10 (qt, 1H, *J* = 12.7, 4.2 Hz, $C^{14}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.2 (C^9), 133.6 (C^4), 128.8 (C^7), 120.4 (C^5), 119.1 (C^8), 119.0 (C^6), 74.8 (C^{16}), 59.5 (C^2), 54.3 (C^{12}), 54.2 (C^3), 54.1 (C^{11}), 38.1 (C^{10}), 25.3 (C^{13}, C^{15}), 24.2 (C^{14}), 16.8 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

(3R,8a'R)-5-methyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132e) and (3R,8a'S)-5-methyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132e')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131e**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **132e'** as a thick yellow oil (16 mg, 9%).

Data for **132e'**:

IR 3273 (br, N–H), 2931, 2855, 2782 (C–H), 1616, 1494, 1441.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.09 (br s, 1H, C^5H), 6.84 (ddd, 1H, J = 7.7, 1.8, 0.9 Hz, C^7H), 6.54 (d, 1H, J = 7.8 Hz, C^8H), 3.22–3.69 (m, 3H, C^2H_2, NH), 3.12–3.21 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.28 (s, 3H, $C^{17}H_3$), 2.21–2.32 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 2.08–2.24 (m, 2H, $C^{12}Ha$, $C^{10}Hb$), 1.80 (dd, 1H, J = 11.1, 2.6 Hz, $C^{16}H$), 1.65–1.73 (m, 1H, $C^{14}Ha$), 1.55–1.62 (m, 1H, $C^{13}Ha$), 1.41–1.55 (m, 2H, $C^{15}Ha$, $C^{13}Hb$), 1.17 (qt, 1H, J = 12.8, 4.0 Hz, $C^{14}Hb$), 1.00 (tdd, 1H, J = 12.8, 11.1, 3.8, $C^{15}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 148.9 (C^9), 135.7 (C^4), 128.2 (C^6), 127.9 (C^7), 125.8 (C^5), 109.5 (C^8), 74.6 (C^{16}), 60.1 (C^2), 54.4 (C^{12}), 54.3 (C^{11}), 54.1 (C^3), 38.7 (C^{10}), 26.7 (C^{15}), 25.4 (C^{13}), 24.4 (C^{14}), 21.0 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1857.

Further elution [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] afforded the Major isomer **132e** as a thick yellow oil (134 mg, 78%).

Data for **132e**:

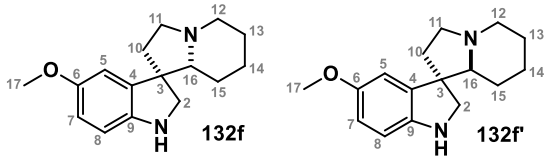
IR 3235 (br, N–H), 2929, 2855, 2784 (C–H), 1617, 1495, 1382.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.89–6.92 (m, 1H, C^5H), 6.86 (ddd, 1H, J = 7.8, 1.8, 0.8 Hz, C^7H), 6.56 (d, 1H, J = 7.8 Hz, C^8H), 3.80 (d, 1H, J = 9.4 Hz, C^2Ha), 3.37–3.66 (br s, 1H, NH), 3.20 (d, 1H, J = 9.4 Hz, C^2Hb), 3.11–3.21 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.29 (s, 3H, $C^{17}H_3$), 2.21–2.32 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 1.98 (ddd, 1H, J = 12.1, 10.9, 3.1 Hz, $C^{12}Ha$), 1.85–1.92 (m, 1H, $C^{10}Hb$), 1.79 (dd, 1H, J = 11.1, 2.7 Hz, $C^{16}H$), 1.71–1.78 (m, 1H, $C^{14}Ha$), 1.59–1.66 (m, 1H, $C^{13}Ha$), 1.46–1.59 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.38 (tdd, 1H, J = 12.6, 11.0, 3.8 Hz, $C^{15}Hb$), 1.10 (qt, 1H, J = 12.8, 4.1 Hz, $C^{14}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 149.4 (C^9), 134.7 (C^4), 128.2 (C^7), 128.1 (C^6), 123.6 (C^5), 109.7 (C^8), 74.9 (C^{16}), 58.0 (C^2), 54.3 (C^{12}), 54.2 (C^{11}), 54.0 (C^3), 37.9 (C^{10}), 25.4 (C^{13}), 25.4 (C^{15}), 24.3 (C^{14}), 21.0 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

(3R,8a'R)-5-methoxy-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132f) and (3R,8a'S)-5-methoxy-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132f')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, –15 °C, 1 h) from **131f**. Purification *via* FCC [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **131f'** as a thick yellow oil (18 mg, 7%).

Data for **132f'**:

IR 3365 (br, N–H), 2932, 2853, 2828, 2781 (C–H), 1596, 1489, 1468, 1437.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.93 (d, 1H, J = 2.7 Hz, C^5H), 6.61 (dd, J = 8.4, 2.6 Hz, C^7H), 6.56 (d, 1H, J = 8.3 Hz, C^8H), 3.73 (s, 3H, $C^{17}H_3$), 3.45–3.51 (2*d, roof effect, 2H, J = 9.2 Hz, C^2H_2), 3.09–3.19 (m, 2H, C^{11}Ha, C^{12}Ha), 2.19 (app q, 1H, J = 8.7 Hz, C^{11}Hb), 2.08 (dt, 1H, J = 13.1, 8.6 Hz, C^{10}Ha), 1.88–1.96 (m, 2H, C^{10}Hb, C^{12}Ha), 1.81 (d, 1H, J = 11.1 Hz, $C^{16}H$), 1.65–1.71 (m, 1H, C^{14}Ha), 1.53–1.60 (m, 1H, C^{13}Ha), 1.41–1.52 (m, 2H, C^{13}Hb, C^{15}Ha), 1.16 (qt, 1H, J = 12.9, 3.9 Hz, C^{14}Hb), 0.87–0.98 (qd, 1H, J = 12.6, 3.7 Hz, C^{15}Hb)

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 153.7 (C^6), 145.1 (C^9), 137.4 (C^4), 112.7 (C^7), 112.1 (C^5), 110.1 (C^8), 74.0 (C^{16}), 59.9 (C^2), 56.3 (C^{17}), 54.6 (C^3), 54.2 (C^{12}), 54.0 (C^{11}), 38.6 (C^{10}), 26.5 (C^{15}), 25.4 (C^{13}), 24.3 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}O_1N_2^+$) requires **m/z** 259.1805, found **m/z** 259.1807.

Further elution [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **132f** as a thick yellow oil (215 mg, 83%).

Data for **132f**:

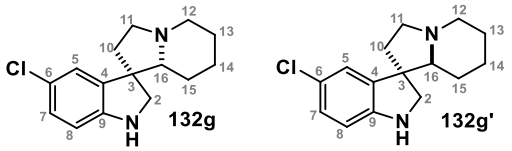
IR 3252 (br, N–H), 2931, 2853, 2829, 2784 (C–H), 1596, 1492, 1471, 1450, 1436.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.70 (d, 1H, J = 2.2 Hz, C^5H), 6.63 (dd, roof effect, 1H, J = 8.4, 2.5 Hz, C^7H), 6.59 (d, roof effect, 1H, J = 8.4 Hz, C^8H), 3.80 (d, 1H, J = 9.6 Hz, C^2Ha), 3.77 (s, 3H, $C^{17}H_3$), 3.44 (br s, 1H, NH), 3.21 (d, 1H, J = 9.6 Hz, C^2Hb), 3.10–3.19 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.18–2.32 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 1.97 (ddd, 1H, J = 12.1, 10.9, 3.1 Hz, $C^{12}Ha$), 1.86–1.95 (m, 1H, $C^{10}Hb$), 1.79 (dd, 1H, J = 11.2, 2.7 Hz, $C^{16}H$), 1.71–1.78 (m, 1H, $C^{14}Ha$), 1.59–1.66 (m, 1H, $C^{13}Ha$), 1.46–1.58 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.38 (tdd, 1H, J = 12.6, 11.0, 3.8 Hz, $C^{15}Hb$), 1.09 (qt, 1H, J = 12.8, 4.1 Hz, $C^{14}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 153.8 (C^6), 145.6 (C^9), 136.4 (C^4), 112.6 (C^7), 110.5 (C^5), 110.0 (C^8), 74.8 (C^{16}), 58.2 (C^2), 56.1 (C^{17}), 54.5 (C^{12}), 54.3 (C^{11}), 54.2 (C^3), 37.8 (C^{10}), 25.5 (C^{15}), 25.4 (C^{13}), 24.3 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}O_1N_2^+$) requires **m/z** 259.1805, found **m/z** 259.1806.

(3R,8a'R)-5-chloro-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132g) and (3R,8a'S)-5-chloro-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132g')



Prepared according to **General Procedure F** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131g**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2M)] gave the minor isomer **132g'** as a yellow oil (18 mg, 21%).

Data for **132g'**:

IR 3222 (br, N–H), 2932, 2854, 2786 (C–H), 1616, 1495.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.24 (d, 1H, J = 2.3 Hz, C^5H), 6.96 (dd, 1H, J = 8.3, 2.2 Hz, C^7H), 6.50 (d, 1H, J = 8.3 Hz, C^8H), 3.52 (d, roof effect, 1H, J = 9.3 Hz, C^2Ha), 3.50 (d, roof effect, 1H, J = 9.1 Hz, C^2Hb), 3.09–3.19 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.20 (q, 1H, J = 8.9 Hz, $C^{11}Hb$), 2.09 (dt, 1H, J = 13.2, 8.6 Hz, $C^{10}Ha$), 1.88–1.95 (m, 2H, $C^{10}Hb$, $C^{12}Ha$), 1.80 (d, 1H, J = 10.7 Hz, $C^{16}H$,), 1.70 (dt, 1H, J = 13.2, 3.4 Hz, $C^{14}Ha$), 1.54–1.60 (m, 1H, $C^{13}Ha$), 1.43–1.52 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.16 (qt, 1H, J = 12.9, 3.9 Hz, $C^{14}Hb$), 0.95 (qd, 1H, J = 12.7, 3.8 Hz, $C^{15}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 149.7 (C^9), 137.4 (C^4), 127.2 (C^7), 125.4 (C^5), 123.2 (C^6), 109.9 (C^8), 73.8 (C^{16}), 59.2 (C^2), 54.2 (C^3), 54.0 (C^{12}), 53.7 (C^{11}), 38.6 (C^{10}), 26.2 (C^{15}), 25.2 (C^{13}), 24.1 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}N_2Cl^+$) requires **m/z** 263.1310, found **m/z** 263.1310.

Further elution [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **123g** as a yellow oil (29 mg, 33% corrected yield).

Data for **132g**:

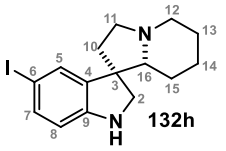
IR 3225 (br, N–H), 1618, 1499, 1466.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.01 (d, 1H, J = 2.1 Hz, C^5H), 6.97 (dd, 1H, J = 8.2, 2.2 Hz, C^7H), 6.52 (d, 1H, J = 8.2 Hz, C^8H), 3.82 (d, 1H, J = 9.6 Hz, C^2Ha), 3.54–3.73 (br s, 1H, NH), 3.22 (d, 1H, J = 9.5 Hz, C^2Hb), 3.09–3.19 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.16–2.32 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 1.84–2.01 (m, 2H, $C^{10}Hb$, $C^{12}Hb$), 1.71–1.79 (m, 2H, $C^{16}H$, $C^{14}Ha$), 1.58–1.66 (m, 1H, $C^{13}Ha$), 1.43–1.58 (m, 2H, $C^{13}Hb$, $C^{15}Ha$), 1.35 (tdd, 1H, J = 12.6, 11.0, 3.8 Hz, $C^{15}Hb$), 1.10 (qt, 1H, J = 12.8, 4.1 Hz, $C^{14}Hb$).

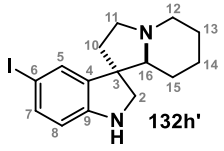
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.2 (C^9), 136.2 (C^4), 127.5 (C^7), 123.1 (C^5), 123.1 (C6), 110.2 (C^8), 74.7 (C^{16}), 57.9 (C^2), 54.1 (C^{12}), 54.0 (C^3), 53.9 (C^{11}), 37.8 (C^{10}), 25.3 (C^{13}), 25.2 (C^{15}), 24.1 (C^{14}).

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{15}H_{20}N_2Cl^+$) requires **m/z** 263.1310, found **m/z** 163.1312.

(3R,8a'R)-5-iodo-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132h) and (3R,8a'S)-5-iodo-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (132h')



132h



132h'

Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **131h**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **132h'** as a thick yellow oil (6 mg, 6%).

Data for **132h'**:

IR 3243 (br, N–H), 2935, 2855, 2781 (C–H), 1616, 1497.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.53 (d, 1H, J = 1.8 Hz, C^5H,), 7.28 (dd, J = 8.2, 1.9 Hz, C^7H), 6.39 (d, 1H, J = 8.2 Hz, C^8H), 3.46–3.52 (m, 2H, C^2H_2), 3.39–3.87 (br s, 1H, NH), 3.09–3.19 (m, 2H, C^{11}Ha, C^{12}Ha), 2.19 (app q, 1H, J = 8.9 Hz, C^{11}Hb), 2.08 (dt, 2H, J = 13.2, 8.6 Hz, C^{10}Ha), 1.87–1.95 (m, 2H, C^{10}Hb, C^{12}Ha), 1.78 (d, 1H, J = 11.0 Hz, $C^{16}H$), 1.66–1.73 (m, 1H, C^{14}Ha), 1.53–1.60 (m, 1H, C^{13}Ha), 1.41–1.53 (m, 2H, C^{13}Hb, C^{15}Ha), 1.15 (qt, 1H, J = 12.9, 4.0 Hz, C^{14}Hb), 0.95 (qd, 1H, J = 12.7, 3.9 Hz, C^{15}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.9 (C^9), 138.4 (C^4), 136.4 (C^7), 133.9 (C^5), 111.4 (C^8), 79.7 (C^6), 74.0 (C^{16}), 59.3 (C^2), 54.17 (C^{12}), 54.12 (C^3), 53.8 (C^{11}), 38.8 (C^{10}), 26.4 (C^{15}), 25.3 (C^{13}), 24.2 (C^{14}).

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{15}H_{20}N_2I^+$) requires **m/z** 355.0666, found **m/z** 355.0666.

Further elution [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **132h** as an off-white solid (71 mg, 71%).

Data for **132h**:

mp 62–64 °C

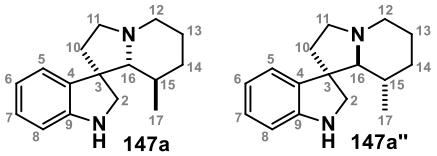
IR 3222 (br, N–H), 2932, 2854, 2786 (C–H), 1616, 1495.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.24–7.30 (m, 2H, C^5H, C^7H), 6.38 (d, 1H, J = 8.0 Hz, C^8H), 3.78 (d, 1H, J = 9.5 Hz, C^2Ha), 3.55–3.77 (br s, 1H, NH), 3.20 (d, 1H, J = 9.5 Hz, C^2Hb), 3.09–3.18 (m, 2H, C^{11}Ha, C^{12}Ha), 2.14–2.30 (m, 2H, C^{10}Ha, C^{11}Hb), 1.96 (ddd, 1H, J = 12.2, 11.0, 3.1 Hz, C^{12}Hb), 1.87 (dt, 1H, J = 13.3, 8.6 Hz, C^{10}Hb), 1.69–1.79 (m, 2H, C^{16}H, C^{14}Ha), 1.57–1.65 (m, 1H, C^{13}Ha), 1.42–1.56 (m, 2H, C^{13}Hb, C^{15}Ha), 1.33 (tdd, 1H, J = 12.6, 11.0, 3.8 Hz, C^{15}Hb), 1.09 (qt, 1H, J = 12.8, 4.1 Hz, C^{14}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.4 (C^9), 137.2 (C^4), 136.4 (C^7), 131.7 (C^5), 111.6 (C^8), 79.1 (C^6), 74.8 (C^{16}), 57.7 (C^2), 54.1 (C^{12}), 53.94 (C^{11}), 53.90 (C^3), 37.9 (C^{10}), 25.3 (C^{13}), 25.2 (C^{15}), 24.1 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}N_2I^+$) requires **m/z** 355.0666, found **m/z** 355.0666.

(3R,8'R,8a'R)-8'-methyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (147a) and (3R,8'S,8a'S)-8'-methyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (147a")



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **134a**. Purification *via* FCC [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **147a"** (much less polar, 3rd most abundant isomer by crude NMR) as a thick pale yellow oil (2 mg, 6%).

Data for **147a"**:

IR 3251 (br, N–H), 2926, 2869, 2849 (C–H), 1613 (C=O), 1498.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.25-7.28 (m, 1H, C^5H), 7.02 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.71 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.60 (dd, 1H, J = 7.8, 1.0 Hz, C^8H), 3.60 (d, 1H, J = 9.6 Hz, C^2Ha), 3.50 (d, 1H, J = 9.6 Hz, C^2Hb), 3.08–3.16 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.18 (dt, 1H, J = 10.1, 8.3 Hz, $C^{11}Hb$), 2.07 (ddd, 1H, J = 12.9, 10.0, 7.9 Hz, $C^{10}Ha$), 1.98 (ddd, 1H, J = 12.9, 8.0, 1.8 Hz, $C^{10}Hb$), 1.88–1.95 (m, 1H, $C^{12}Hb$), 1.56–1.69 (m, 3H, $C^{13}H_2$, $C^{14}Ha$), 1.44–1.51 (m, 2H, $C^{15}H$, $C^{16}H$), 0.86–0.88 (m, 1H, $C^{14}Hb$), 0.67 (d, 1H, J = 5.9 Hz, $C^{17}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 151.0 (C^9), 135.7 (C^4), 127.5 (C^7), 125.4 (C^5), 118.7 (C^6), 109.4 (C^8), 80.1 (C^{16}), 60.5 (C^2), 54.14 (C^{11}), 54.11 (C^3), 54.0 (C^{12}), 43.1 (C^{10}), 34.5 (C^{14}), 33.2 (C^{15}), 25.7 (C^{13}), 18.4 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

Further elution [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **147a** as a yellow solid (21 mg, 66%). Pure samples of the two remaining diastereoisomers could not be obtained.

Data for **147a**:

mp 136–139 °C (sublimation)

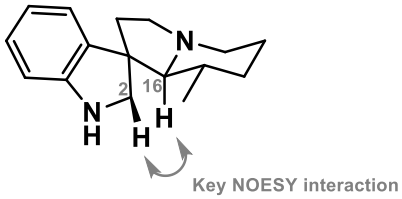
IR 3197 (br, N–H), 2921, 2871, 2800 (C–H), 1608, 1489, 1471, 1379, 1325.

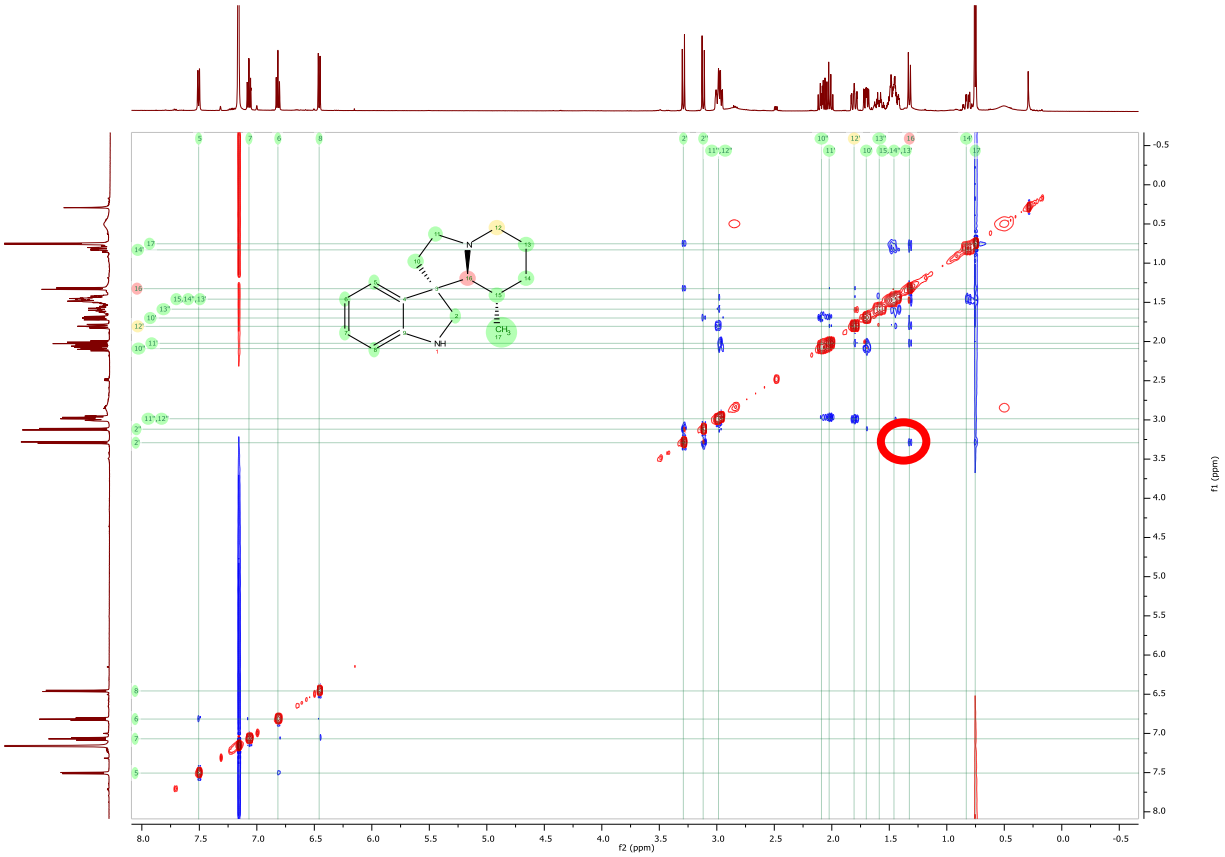
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.07 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.02 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.72 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.59 (d, 1H, J = 7.4 Hz, C^8H), 3.90 (d, 1H, J = 9.6 Hz, C^2Ha), 3.74 (br s, 1H, NH), 3.30 (d, 1H, J = 9.6 Hz, C^2Hb), 3.09–3.18 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.31 (app q, 1H, J = 9.1, $C^{11}Hb$), 2.04–2.09 (m, 2H, $C^{10}H_2$), 2.00 (td, 1H, J = 11.4, 3.5, $C^{12}Hb$), 1.82 (d, 1H, J = 9.6 Hz, $C^{16}H$), 1.53–1.72 (m, 4H, $C^{13}H_2$, $C^{14}Hb$, $C^{15}H$), 0.93 (tdd, J = 12.7, 11.3, 4.6 Hz, 1H, $C^{14}Hb$), 0.52 (d, 1H, J = 6.5 Hz, $C^{17}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 151.2 (C^9), 136.2 (C^4), 127.7 (C^7), 123.1 (C^5), 118.7 (C^6), 109.6 (C^8), 78.4 (C^{16}), 57.4 (C^2), 54.2 (C^{12}), 54.1 (C^3), 53.5 (C^{11}), 41.4 (C^{10}), 34.5 (C^{14}), 33.2 (C^{15}), 25.7 (C^{13}), 18.7 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

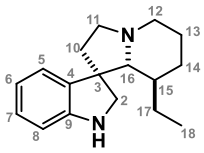
Key NOESY interactions :



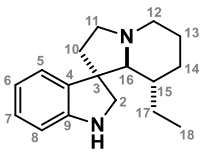


Note: NOESY was taken in C_6D_6 so that $C^{16}H$ was isolated in the 1H NMR. Only this isomer would show a $C^{16}H$-$C^{2}H$ interaction without displaying a $C^{5}H$-$C^{16}H$ or $C^{5}H$-$C^{17}H_3$ interaction.

(3R,8'R,8a'R)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (147b) and (3R,8'S,8a'S)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (147b")



147b



147b"

Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, 0 °C, 1 h) from **134b**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **147b"** (much less polar, 3rd most abundant isomer by crude NMR) as a thick pale yellow oil (15 mg, 8%).

Data for **147b"**:

IR 3236 (br, N–H), 2957, 2930, 2875, 2855, 2788 (C–H), 1607, 1489, 1464.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.24-7.27 (m, 1H, C^5H), 7.01 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.70 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.60 (br d, 1H, J = 7.8 Hz, C^8H), 3.63–3.73 (s, 1H, NH), 3.59 (d, 1H, J = 9.5 Hz, C^2Ha), 3.48 (d, 1H, J = 9.5 Hz, C^2Hb), 3.12–3.16 (m, 1H, $C^{12}Ha$), 3.07–3.12 (m, 1H, $C^{11}Ha$), 2.17 (dt, 1H, J = 10.2, 8.3 Hz, $C^{11}Hb$), 1.96–2.08 (m, 2H, $C^{10}H_2$), 1.87–1.95 (m, 2H, $C^{12}Hb$, $C^{14}Ha$), 1.62–1.68 (m, 1H, $C^{13}Ha$), 1.53–1.62 (m, 2H, $C^{13}Hb$, $C^{16}H$), 1.30–1.39 (m, 2H, $C^{15}H$, $C^{17}Ha$), 1.23–1.29 (m, 1H, $C^{14}Hb$), 0.74–0.86 (m, 1H, $C^{17}Hb$), 0.59 (t, 3H, J = 7.3 Hz, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.9 (C^9), 135.8 (C^4), 127.4 (C^7), 125.2 (C^5), 118.8 (C^6), 109.5 (C^8), 78.5 (C^{16}), 60.8 (C^2), 54.3 (C^{11}), 54.13 (C^3), 54.12 (C^{12}), 43.5 (C^{10}), 39.7 (C^{15}), 30.0 (C^{14}), 25.7 (C^{13}), 24.5 (C^{17}), 11.1 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2^+$) requires **m/z** 257.2012, found **m/z** 257.2013.

Trituration of the main FCC fraction in pentane gave the Major isomer **147b** as a crystalline colourless solid (134 mg, 68%). Pure samples of the two remaining diastereoisomers could not be obtained.

Data for **147b**:

mp 145–150 °C (sublimation).

IR 3236 (br, N–H), 2957, 2930, 2875, 2855, 2788 (C–H), 1607, 1489, 1464.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.06 (dd, 1H, *J* = 7.5, 1.2 Hz, C^5H), 7.01 (td, 1H, *J* = 7.6, 1.3 Hz, C^7H), 6.70 (td, 1H, *J* = 7.4, 1.0 Hz, C^6H), 6.59 (d, 1H, *J* = 7.6 Hz, C^8H), 3.89 (d, 1H, *J* = 9.6 Hz, C^2Ha), 3.74 (br s, 1H, NH), 3.30 (d, 1H, *J* = 9.7 Hz, C^2Hb), 3.09–3.18 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 2.31 (td, 1H, *J* = 9.6, 8.2 Hz, $C^{11}Hb$), 2.10 (td, 1H, *J* = 13.3, 8.4 Hz, $C^{10}Ha$), 1.96–2.05 (m, 3H, $C^{10}Hb$, $C^{12}Hb$, $C^{16}H$), 1.89–1.96 (m, 1H, $C^{14}Ha$), 1.65–1.73 (m, 1H, $C^{13}Ha$), 1.56 (qt, 1H, *J* = 13.2, 4.1 Hz, $C^{13}Hb$), 1.45 (dtd, 1H, *J* = 12.7, 9.1, 3.6 Hz, $C^{15}H$), 1.15–1.24 (m, 1H, $C^{17}Ha$), 0.85 (tdd, 1H, *J* = 13.0, 11.3, 4.1 Hz, $C^{14}Hb$), 0.61–0.68 (m, 4H, $C^{17}Hb$, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.0 (C^9), 136.6 (C^4), 127.6 (C^7), 123.0 (C^5), 118.7 (C^6), 109.5 (C^8), 75.9 (C^{16}), 57.3 (C^2), 54.3 (C^{12}), 54.1 (C^3), 53.6 (C^{11}), 41.8 (C^{10}), 39.9 (C^{15}), 29.8 (C^{14}), 25.6 (C^{13}), 24.5 (C^{17}), 11.0 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2^+$) requires **m/z** 257.2012, found **m/z** 257.2013.

Data for X-Ray:

CCDC Number : 1906301

Crystal data

Chemical formula	$C_{17}H_{24}N_2$
M_r	256.39
Crystal System, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	150
a, *b*, *c* (Å)	8.0763 (2), 11.2330 (2), 15.6700 (3)

α, β, γ (°)	90, 90, 90
V (Å^3)	1421.60 (3)
Z	4
Radiation type	Cu *Kα*
U (mm^{-1})	0.53
Crystal size (mm)	0.20 × 0.10 × 0.05

Data collection

Diffractometer	Unknown
Absorption correction	Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)
T_{min}, T_{max}	0.76, 0.97
No. of measured	9501, 2941, 2777
independent and observed	
[*I*> 2.0σ(*I*)] reflections	
R_{int}	0.040
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.630

Refinement

$R[F^2 > 2\sigma(F^2)]$, *w*$R(F^2)$, *S*	0.037, 0.099, 1.01
No. of reflections	2940
No. of parameters	176
No. restraints	4
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å^{-3})	0.25, –0.17
Absolute structure	Parsons, Flack & Wagner (2013) 1061 Friedel Pairs
Structure parameter	–

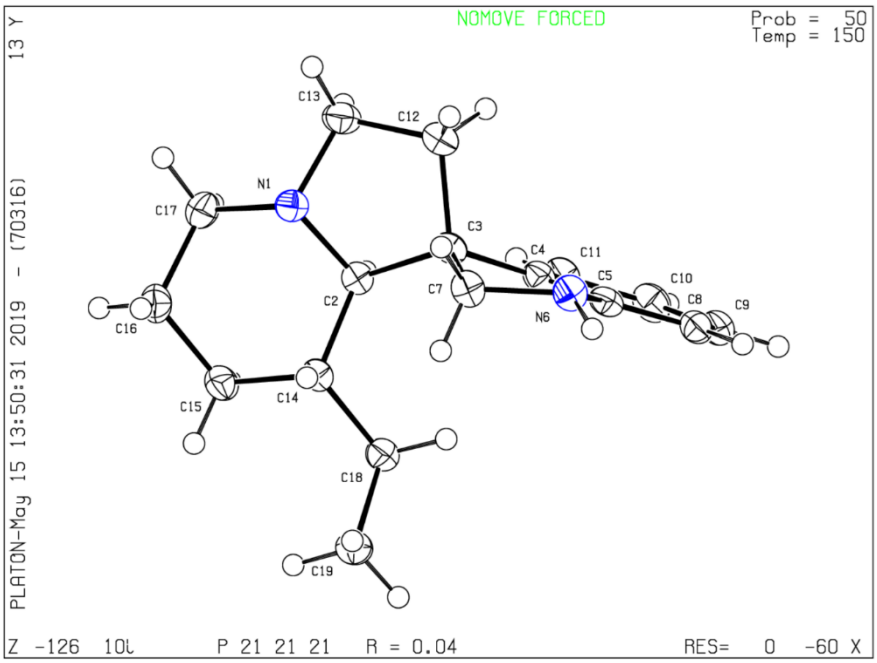


Table iii: Selected geometric parameters (Å, º)

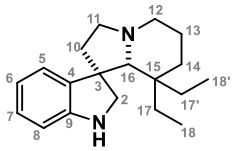
N1—C2	1.4700 (18)	C5—C8	1.395 (2)
N1—C13	1.4616 (19)	N6—C7	1.4683 (19)
N1—C17	1.4658 (18)	C8—C9	1.390 (2)
C2—C3	1.5497 (18)	C9—C10	1.386 (2)
C2—C14	1.5280 (19)	C10—C11	1.400 (2)
C3—C4	1.518 (2)	C12—C13	1.527 (2)
C3—C7	1.5527 (19)	C14—C15	1.5404 (19)
C3—C12	1.571 (2)	C14—C18	1.531 (2)
C4—C5	1.401 (2)	C15—C16	1.527 (2)
C4—C11	1.385 (2)	C16—C17	1.517 (2)
C5—N6	1.388 (2)	C18—C19	1.524 (2)
C2—N1—C13	104.27 (12)	N6—C5—C8	128.93 (14)
C2—N1—C17	112.49 (11)	C5—N6—C7	107.85 (12)
C13—N1—C17	113.10 (12)	C3—C7—N6	104.37 (11)
N1—C2—C3	102.88 (11)	C5—C8—C9	118.59 (14)
N1—C2—C14	110.17 (12)	C8—C9—C10	121.41 (15)
C3—C2—C14	119.44 (12)	C9—C10—C11	119.84 (15)
C2—C3—C4	116.22 (12)	C10—C11—C4	119.41 (15)

C2—C3—C7	115.63 (12)	C3—C12—C13	105.54 (12)
C4—C3—C7	100.83 (12)	C12—C13—N1	103.71 (12)
C2—C3—C12	102.27 (12)	C2—C14—C15	108.58 (12)
C4—C3—C12	111.17 (12)	C2—C14—C18	113.47 (13)
C7—C3—C12	111.04 (12)	C15—C14—C18	111.41 (12)
C3—C4—C5	108.95 (13)	C14—C15—C16	112.34 (13)
C3—C4—C11	130.62 (14)	C15—C16—C17	110.05 (13)
C5—C4—C11	120.32 (14)	C16—C17—N1	109.55 (13)
C4—C5—N6	110.61 (13)	C14—C18—C19	112.40 (13)
C4—C5—C8	120.42 (14)		

Table iv: Hydrogen-bond geometry (Å, º)

N6—H61···N1^{i}	0.87	2.24	3.093 (2)	167 (1)

(3R,8a'R)-8',8'-diethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (147c)



Prepared according to **General Procedure E** (5 mol% catalyst, 3.00 equiv. TMDS, rt, 6 h) from **134c**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **147c** as a white solid (97 mg, 94%). A pure sample of the minor isomer could not be obtained.

mp 143–145 °C

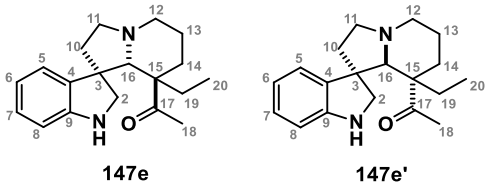
IR 3290 (br, N–H), 2932, 2877, 2845, 2792 (C_{Ar}–H), 1607, 1478, 1465.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.11 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.03 (td, 1H, J = 7.6, 1.2 Hz, C^7H), 6.71 (td, 1H J = 7.4, 1.0 Hz, C^6H), 6.62 (dd, 1H, J = 7.8, 0.9 Hz, C^8H), 4.14 (d, 1H, J = 9.6 Hz, C^2Ha), 3.20–3.34 (m, 2H, $C^{11}Ha$, $C^{12}Ha$), 3.18 (d, 1H, J = 9.6 Hz, C^2Hb), 1.97–2.39 (m, 4H, $C^{10}Ha$, $C^{11}Hb$, $C^{12}Hb$, $C^{17}Ha$), 1.83–1.95 (m, 1H, $C^{10}Hb$), 1.57–1.76 (m, 2H, $C^{13}Ha$, $C^{17}Hb$), 1.42–1.53 (m, 2H, $C^{13}Hb$, $C^{14}Ha$), 1.20 (dq, 1H, J = 15.2, 7.7 Hz, $C^{17'}Ha$), 0.96–1.10 (m, 2H, $C^{14}Hb$, $C^{17'}Hb$), 0.78 (t, 3H, J = 7.6 Hz, $C^{18}H_3$), 0.39 (t, 3H, J = 7.5 Hz, $C^{18'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.2 (C^9), 136.4 (br, C^4), 127.9 (C^7), 123.2 (C^5), 118.6 (C^6), 109.8 (C^8), 77.0 (C^{16}), 58.6 (C^2), 55.7 (C^{12}), 54.4 (C^3), 53.5 (C^{11}), 41.6 (br, C^{10}), 40.0 (C^{15}), 31.2 (C^{14}), 28.4 ($C^{17'}$), 24.7 (C^{17}), 21.6 (C^{13}), 8.4 (C^{18}), 7.8 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{29}N_2^+$) requires **m/z** 285.2325, found **m/z** 285.2324.

1-((3R,8'R,8a'S)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-8'-yl)ethan-1-one (147e) and 1-((3R,8'S,8a'R)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-8'-yl)ethan-1-one (147e')



Prepared according to **General Procedure E** (5 mol% catalyst, 3 equiv. TMDS, rt, 6 h) from **134e**. Purification *via* prep TLC [96 : 4 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave the minor isomer **147e'** as a yellow oil that crystallized upon standing into a white solid (15 mg, 10%), followed by the Major isomer **147e**, obtained as a thick yellow oil that crystallized upon standing into a white solid (82 mg, 55%). The Major isomer could be recrystallyzed from EtOAc.

Data for **147e'**:

mp 100–102 °C

IR 3367 (br, N–H), 2928, 2851, 2787, 2729 (C–H), 1696 (C=O), 1607, 1488, 1464.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.00–7.07 (m, 2H, C^5H, C^7H), 6.71 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.60 (dt, 1H, J = 7.8, 0.8 Hz, C^8H), 3.85 (d, 1H, J = 9.6 Hz, C^2Ha), 3.73 (br s, 1H, NH), 3.25 (ddt, 1H, J = 10.9, 4.0, 1.8 Hz, $C^{12}Ha$), 3.16 (ddd, 1H, J = 9.4, 7.9, 3.4 Hz, $C^{11}Ha$), 3.14 (d, 1H, J = 9.7 Hz, C^2Hb), 2.63 (s, 1H, $C^{16}H$), 2.36 (dt, 1H, J = 9.4, 8.6 Hz, $C^{11}Hb$), 2.19–2.31 (m, 2H, $C^{12}Hb$, $C^{19}Ha$), 2.11 (ddd, 1H, J = 12.2, 8.5, 3.3 Hz, $C^{10}Ha$), 2.03 (dq, 1H, J = 13.8, 7.5 Hz, $C^{19}Hb$), 1.84 (dt, 1H, J = 12.7, 8.2 Hz, $C^{10}Hb$), 1.73 (dtd, 1H, J = 13.1, 3.3, 1.4 Hz, $C^{14}Ha$), 1.59–1.68 (m, 2H, $C^{13}H_2$), 1.58 (s, 3H, $C^{18}H_3$), 1.47 (tdd, 1H, J = 13.1, 4.1, 1.0 Hz, $C^{14}Hb$), 0.84 (t, 3H, J = 7.4 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 211.3 (C^{17}), 151.2 (C^9), 134.8 (C^4), 128.3 (C^7), 123.2 (C^5), 118.9 (C^6), 110.4 (C^8), 76.8 (C^{16}), 58.2 (C^2), 55.2 (C^{15}), 55.1 (C^{12}), 54.3 (C^3), 53.3 (C^{11}), 40.9 (C^{10}), 31.1 (C^{14}), 26.1 (C^{18}), 21.5 (C^{13}), 19.6 (C^{19}), 9.5 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}ON_2^+$) requires **m/z** 299.2118, found **m/z** 299.2119.

Data for **147e**:

mp 98–100 °C (sublimation).

IR 3373 (br N–H), 2930, 2732 (C_{Ar}–H), 1688 (C=O), 1607, 1488, 1464.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.19 (ddd, 1H, J = 7.3, 1.3, 0.5 Hz, C^5H), 7.04 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.70 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.57 (dd, 1H, J = 7.7, 0.8 Hz, C^8H), 3.42–3.57 (br s, 1H, NH), 3.29–3.39 (m, 3H, C^2H_2, C^{11}Ha), 3.15–3.21 (m, 1H, C^{12}Ha), 2.56 (s, 1H, $C^{16}H$), 2.31 (ddd, 1H, J = 10.5, 9.4, 6.7 Hz, C^{11}Hb), 2.07–2.17 (m, 5H, C^{10}Ha, C^{12}Hb, $C^{18}H_3$), 1.84 (ddd, 1H, J = 13.0, 10.4, 4.8 Hz, C^{10}Hb), 1.63–1.70 (m, 1H, C^{14}Ha), 1.53 (dd, 1H, J = 15.2, 7.7 Hz, C^{19}Ha), 1.43–1.50 (m, 2H, $C^{13}H_2$), 1.32–1.43 (m, 1H, C^{14}Hb), 0.73–0.86 (m, 1H, C^{19}Hb), 0.63 (t, 3H, J = 7.4 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 214.2 (C^{17}), 151.4 (C^9), 135.2 (C^4), 128.1 (C^7), 126.6 (C^5), 118.5 (C^6), 109.5 (C^8), 78.5 (C^{16}), 59.3 (C^2), 55.4 (C^{11}), 54.2 (C^{15}), 53.8 (C^3), 53.1 (C^{12}), 38.8 (C^{10}), 32.1 (C^{14}), 27.4 (C^{18}), 21.4 (C^{13}), 20.1 (C^{19}), 9.1 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}ON_2^+$) requires **m/z** 299.2118, found **m/z** 299.2118.

Data for X-Ray:

CCDC Number : 1906302

Crystal data

Chemical formula	$C_{19}H_{26}N_2O$
M_r	298.43
Crystal System, space group	Monoclinic, $P2_1/c$
Temperature (K)	150
a, b, c (Å)	8.39958 (15), 11.3007 (3), 16.6383 (3)
α, β, γ (°)	90, 94.3159 (18), 90
V (Å^3)	1580.53 (3)
Z	4
Radiation type	Cu $K\alpha$
U (mm^{-1})	0.60
Crystal size (mm)	0.20 × 0.10 × 0.05

Data collection

Diffractometer	Oxford diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO* (Agilent, 2011)
T_{min}, T_{max}	0.84, 0.97
No. of measured independent and observed [I> 2.0σ(I)] reflections	10459, 3271, 3031
R_{int}	0.028
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.629

Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.046, 0.125, 0.98
No. of reflections	3261
No. of parameters	202
No. restraints	3

H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å□ ^{3})	0.35, –0.20
Absolute structure	–
Structure parameter	–

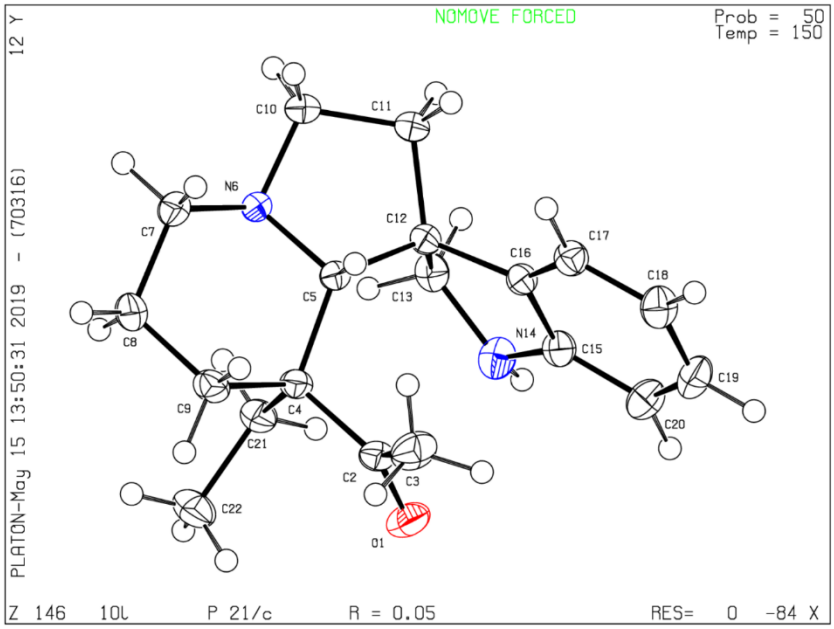


Table v: Selected geometric parameters (Å, º)

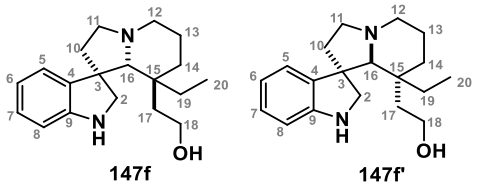
O1—C2	1.2112 (16)	C11—C12	1.5455 (16)
C2—C3	1.5094 (19)	C12—C13	1.5499 (17)
C2—C4	1.5393 (17)	C12—C16	1.5135 (16)
C4—C5	1.5637 (16)	C13—N14	1.4662 (17)
C4—C9	1.5549 (17)	N14—C15	1.3887 (17)
C4—C21	1.5410 (17)	C15—C16	1.3970 (17)
C5—N6	1.4662 (14)	C15—C20	1.3915 (18)
C5—C12	1.5600 (16)	C16—C17	1.3820 (17)
N6—C7	1.4624 (15)	C17—C18	1.3931 (18)
N6—C10	1.4712 (15)	C18—C19	1.386 (2)
C7—C8	1.5192 (17)	C19—C20	1.393 (2)
C8—C9	1.5267 (18)	C21—C22	1.5334 (17)

C10—C11	1.5254 (18)		
O1—C2—C3	119.11 (12)	C11—C12—C5	99.73 (9)
O1—C2—C4	121.64 (12)	C11—C12—C13	112.43 (10)
C3—C2—C4	119.15 (11)	C5—C12—C13	117.39 (10)
C2—C4—C5	110.54 (9)	C11—C12—C16	115.05 (10)
C2—C4—C9	108.22 (10)	C5—C12—C16	112.29 (9)
C5—C4—C9	104.68 (9)	C13—C12—C16	100.72 (9)
C2—C4—C21	109.03 (10)	C12—C13—N14	104.52 (10)
C5—C4—C21	113.25 (10)	C13—N14—C15	107.54 (10)
C9—C4—C21	110.96 (10)	N14—C15—C16	110.67 (11)
C4—C5—N6	110.39 (9)	N14—C15—C20	128.87 (12)
C4—C5—C12	123.50 (10)	C16—C15—C20	120.43 (12)
N6—C5—C12	103.43 (9)	C12—C16—C15	109.09 (10)
C5—N6—C7	112.12 (9)	C12—C16—C17	130.23 (11)
C5—N6—C10	106.04 (9)	C15—C16—C17	120.68 (11)
C7—N6—C10	111.32 (10)	C16—C17—C18	119.27 (12)
N6—C7—C8	110.83 (10)	C17—C18—C19	119.86 (12)
C7—C8—C9	110.41 (10)	C18—C19—C20	121.48 (13)
C8—C9—C4	111.02 (10)	C19—C20—C15	118.26 (13)
N6—C10—C11	105.87 (10)	C4—C21—C22	114.73 (11)
C10—C11—C12	106.81 (10)		

Table vi: Hydrogen-bond geometry (Å, º)

N14—H141···O1^{i}	0.87	2.38	3.2518 (18)	177 (1)

2-((3R,8'S,8a'R)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-8'-yl)ethan-1-ol (147f) and 2-((3R,8'R,8a'S)-8'-ethyl-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-8'-yl)ethan-1-ol (147f')



Prepared according to **General Procedure E** (5 mol% catalyst, 4.00 equiv. TMDS, rt, 24 h) from **134f**. Purification *via* FCC [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **147f'** as a yellow oil that crystallized upon standing into an amorphous solid (9 mg, 9%).

Data for **147f'**:

IR 3357 (br, N–H), 2940, 2873 (C–H), 1607 (C=O), 1478, 1462.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.09 (dd, 1H, J = 7.4, 1.2 Hz, C^5H), 7.04 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.72 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (app d, 1H, J = 6.64 Hz, C^8H), 4.46 (d, 1H, J = 9.6 Hz, C^2Ha), 3.89 (td, 1H, J = 12.0, 3.6 Hz, $C^{18}Ha$), 3.69 (ddd, 1H, J = 12.0, 6.0, 3.0 Hz, $C^{18}Hb$), 3.30 (d, 1H, J = 9.6 Hz, C^2Hb), 3.23–3.27 (m, 1H, $C^{12}Ha$), 3.18 (ddd, 1H, J = 9.9, 7.7, 4.2 Hz, $C^{11}Ha$), 2.37 (dt, 1H, J = 9.9, 8.5 Hz, $C^{11}Hb$), 2.24–2.31 (m, 1H, $C^{17}Ha$), 2.22 (s, 1H, $C^{16}H$), 2.10–2.17 (m, 2H, $C^{10}Ha$, $C^{12}Hb$), 1.88–1.99 (m, 2H, $C^{10}Hb$, $C^{13}Ha$), 1.57–1.64 (m, 2H, $C^{13}Hb$, $C^{14}Ha$), 1.50 (dt, 1H, J = 14.8, 3.3 Hz, $C^{17}Hb$), 1.21 (ddd, 1H, J = 14.0, 5.6, 1.8 Hz, $C^{14}Hb$), 1.15 (dt, 1H, J = 14.9, 7.4 Hz, $C^{19}Ha$), 0.97 (dt, 1H, J = 14.7, 7.5 Hz, $C^{19}Hb$), 0.53 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.9 (C^9), 136.7 (C^4), 127.9 (C^7), 122.9 (C^5), 118.7 (C^6), 109.9 (C^8), 79.0 (C^{16}), 59.9 (C^{18}), 58.3 (C^2), 55.6 (C^{12}), 54.4 (C^3), 53.0 (C^{11}), 41.5 (C^{10}), 41.4 (C^{15}), 37.2 (C^{17}), 34.9 (C^{14}), 34.0 (C^{19}), 23.7 (C^{13}), 7.7 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{29}ON_2^+$) requires **m/z** 301.2274, found **m/z** 301.2274.

Further elution [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **147f** as an amorphous that crystallized upon standing into a yellow solid (40 mg, 41%).

Data for **147f**:

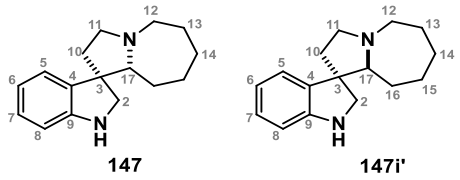
IR 3327 (br, N–H, O–H), 2936, 2880, 2794 (C–H), 1607, 1482, 1463.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.15 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.08 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.76 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (app d, 1H, J = 7.6 Hz, C^8H), 4.11 (d, 1H, J = 9.7 Hz, C^2Ha), 3.81–3.89 (br s, 1H, NH), 3.13–3.29 (m, 5H, C^2Hb, $C^{11}Ha$, $C^{12}Ha$, $C^{18}H_2$), 2.25–2.32 (m, 2H, $C^{10}Hb$, $C^{11}Ha$), 2.23 (td, 1H, J = 7.7, 5.8 Hz, $C^{19}Ha$), 2.18 (s, 1H, $C^{16}H$), 1.98 (ddd, 1H, J = 12.4, 10.9, 3.4 Hz, $C^{12}Hb$), 1.77–1.87 (m, 1H, $C^{10}Hb$), 1.56–1.73 (m, 2H, $C^{13}Ha$, $C^{19}Hb$), 1.48–1.56 (m, 2H, $C^{14}Ha$, $C^{17}Ha$), 1.42 (dp, 1H, J = 13.0, 3.3 Hz, $C^{13}Hb$), 1.06 (ddd, 1H, J = 14.0, 10.0, 4.1 Hz, $C^{17}Hb$), 0.88 (td, 1H, J = 13.6, 4.0 Hz, $C^{14}Hb$), 0.78 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 152.0 (C^9), 135.6 (C^4), 128.1 (C^7), 123.2 (C^5), 118.4 (C^6), 109.9 (C^8), 77.6 (C^{16}), 59.0 (C^{18}), 58.1 (C^2), 55.9 (C^{12}), 54.5 (C^3), 53.7 (C^{11}), 41.0 (C^{10}), 39.8 (C^{15}), 38.7 (C^{17}), 32.4 (C^{14}), 24.4 (C^{19}), 21.6 (C^{13}), 8.1 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{29}ON_2^+$) requires **m/z** 301.2274, found **m/z** 301.2275.

(3R,9a'R)-2',3',5',6',7',8',9',9a'-octahydrospiro[indoline-3,1'-pyrrolo[1,2-a]azepine] (147i) and (3R,9a'S)-2',3',5',6',7',8',9',9a'-octahydrospiro[indoline-3,1'-pyrrolo[1,2-a]azepine] (147i')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **134i**. Purification *via* prep TLC [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave the minor isomer **147i'** as a yellow oil (6 mg, 12%), followed by the Major isomer **147i**, obtained as a yellow oil (14 mg, 28%).

Data for **147i'**:

IR 3374 (br, N–H), 2926, 2858, 2803 (C–H), 1608, 1488, 1463.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.09 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.05 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.75 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.63 (app d, 1H, J = 7.8 Hz, C^8H), 3.84 (d, 1H, J = 9.6 Hz, C^2Ha), 3.58–3.75 (br s, 1H, NH), 3.26 (d, 1H, J = 9.6 Hz, C^2Hb), 3.14 (ddd, 1H, J = 9.5, 8.1, 4.4 Hz, $C^{11}Ha$), 3.05 (ddd, 1H, J = 12.6, 6.0, 1.3 Hz, $C^{12}Ha$), 2.56 (td, 1H, J = 9.3, 7.4 Hz, $C^{11}Hb$), 2.31–2.38 (m, 2H, $C^{12}Hb$, $C^{17}H$), 2.22 (ddd, 1H, J = 13.4, 9.2, 4.4 Hz, $C^{10}Ha$), 1.95 (dt, 1H, J = 13.1, 7.8 Hz, $C^{10}Hb$), 1.73–1.83 (m, 1H, $C^{13}Ha$), 1.56–1.74 (m, 5H, $C^{13}Hb$, $C^{14}H_2$, $C^{15}Ha$, $C^{16}Ha$), 1.48–1.56 (m, 1H, $C^{16}Hb$), 1.35-1.43 (m, 1H, $C^{15}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.7 (C^9), 134.7 (C^4), 127.9 (C^7), 123.2 (C^5), 118.8 (C^6), 109.7 (C^8), 77.0 (C^{17}), 57.2 (C^2), 56.1 (C^3), 55.5 (C^{12}), 55.2 (C^{11}), 39.6 (C^{10}), 27.6 (C^{16}), 27.4 (C^{13}), 26.6 (C^{14}), 25.4 (C^{15}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

Data for **147i**:

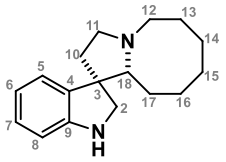
IR 3373 (br, N–H), 2924, 2854, 2794 (C–H), 1607, 1487, 1463.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.24–7.26 (m, 1H, C^5H), 7.03 (td, 1H, J = 7.5, 1.3 Hz, C^7H), 6.74 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.63 (d, 1H, J = 7.3 Hz, C^8H), 3.60–3.68 (br s, 1H, NH), 3.49 (d, roof effect, 1H, J = 9.1 Hz, C^2Ha), 3.45 (d, 1H, J = 9.0 Hz, C^2Hb), 3.17 (ddd, 1H, J = 9.2, 7.8, 3.2 Hz, $C^{11}Ha$), 3.05 (ddd, 1H, J = 12.4, 6.0, 3.9 Hz, $C^{12}Ha$), 2.47 (td, 1H, J = 9.1, 8.0 Hz, $C^{11}Hb$), 2.37 (dd, 1H, J = 10.3, 2.1 Hz, $C^{17}H$), 2.32 (ddd, 1H, J = 12.5, 9.7, 2.7 Hz, $C^{12}Hb$), 2.18 (ddd, 1H, J = 12.8, 8.9, 7.8 Hz, $C^{10}Ha$), 1.94 (ddd, 1H, J = 12.9, 8.0, 3.3 Hz, $C^{10}Hb$), 1.72–1.82 (m, 1H, $C^{13}Ha$), 1.56–1.69 (m, 4H, $C^{13}Hb$, $C^{14}Ha$, $C^{15}H_2$), 1.35–1.44 (m, 3H, $C^{14}Ha$, $C^{16}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.4 (C^9), 134.9 (C^4), 127.6 (C^7), 125.6 (C^5), 118.8 (C^6), 109.6 (C^8), 75.5 (C^{17}), 60.6 (C^2), 56.3 (C^3), 55.7 (C^{12}), 55.3 (C^{11}), 39.3 (C^{10}), 30.5 (C^{16}), 27.9 (C^{13}), 26.5 (C^{14}), 25.8 (C^{15}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires **m/z** 243.1856, found **m/z** 243.1856.

(3R,10a'R)-2',3',6',7',8',9',10',10a'-octahydro-5'H-spiro[indoline-3,1'-pyrrolo[1,2-a]azocine] (147j)



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **134j**. Purification *via* FCC [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **147j** as a yellow oil (47 mg, 49%). The minor diastereoisomer was not recovered after FCC.

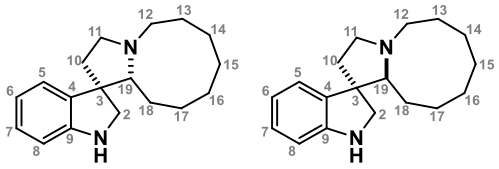
IR 3259 (br, N–H), 2920, 2851, 2800 (C–H), 1606, 1488, 1452.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.02–7.08 (m, 2H, C^5H, C^7H), 6.75 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.65 (dd, 1H, J = 8.1, 1.0 Hz, C^8H), 3.78 (d, 1H, J = 9.4 Hz, C^2Ha), 3.60–3.76 (br s, 1H, NH), 3.26 (d, 1H, J = 9.4 Hz, C^2Hb), 3.13 (ddd, 1H, J = 9.5, 7.8, 3.6 Hz, $C^{11}Ha$), 3.04 (ddd, 1H, J = 13.3, 6.7, 4.5 Hz, $C^{12}Ha$), 2.61–2.73 (m, 3H, $C^{11}Hb$, $C^{12}Hb$, $C^{18}H$), 2.06 (ddd, 1H, J = 12.3, 8.4, 3.7 Hz, $C^{10}Ha$), 1.92 (dt, 1H, J = 12.8, 8.1 Hz, $C^{10}Hb$), 1.45–1.80 (m, 9H, $C^{13}H_2$, $C^{14}H_2$, $C^{15}Ha$, $C^{16}H_2$, $C^{17}H_2$), 1.31–1.42 (m, 1H, $C^{15}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.4 (C^9), 135.6 (C^4), 127.8 (C^7), 123.4 (C^5), 118.8 (C^6), 109.7 (C^8), 72.8 (C^{18}), 57.2 (C^2), 56.7 (C^3), 54.8 (C^{11}), 54.3 (C^{12}), 38.6 (C^{10}), 28.4 (C^{17}), 27.1 (C^{13}), 26.6 (C^{16}), 26.0 (C^{14}), 25.2 (C^{15}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2^+$) requires **m/z** 257.2012, found **m/z** 257.2008.

(3R)-2',3',5',6',7',8',9',10',11',11a'-decahydrospiro[indoline-3,1'-pyrrolo[1,2-a]azonine] (147k) and (3R,11a'S)-2',3',5',6',7',8',9',10',11',11a'-decahydrospiro[indoline-3,1'-pyrrolo[1,2-a]azonine] (147k')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **134k**. Purification *via* FCC [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **147k'** as a yellow oil (11 mg, 15%).

Data for **147k'**:

mp 62-64 °C

IR 3376 (br, N–H), 2916, 2846, 2793 (C–H), 1607, 1485, 1462.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.09 (d, 1H, J = 7.4, C^5H), 7.04 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.72 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.66 (br d, 1H, J = 7.7 Hz, C^8H), 3.34 (d, 1H, J = 8.4 Hz, C^2Ha), 3.25–3.31 (m, 2H, C^2Hb, $C^{11}Ha$), 2.86–2.97 (m, 3H, $C^{12}H_2$, $C^{19}H$), 2.49 (td, 1H, J = 9.9, 7.0 Hz, $C^{11}Hb$), 2.36 (td, 1H, J = 11.7, 7.5 Hz, $C^{10}H_2$), 1.96–2.07 (m, 1H, aliphatic CH), 1.78 (dd, 1H, J = 12.2, 6.2 Hz, $C^{10}Hb$), 1.06–1.75 (m, 11H, aliphatic CH_2).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 152.2 (C^9), 132.8 (C^4), 127.7 (C^7), 125.6 (C^5), 118.4 (C^6), 109.8 (C^8), 70.7 (C^{19}), 61.8 (C^2), 58.9 (C^{12}), 56.6 (C^3), 53.7 (C^{11}), 36.5 (C^{10}), 33.8 (aliphatic CH_2), 29.4 (aliphatic CH_2), 28.2 (aliphatic CH_2), 27.4 (aliphatic CH_2), 25.3 (aliphatic CH_2), 24.1 (aliphatic CH_2).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2^+$) requires **m/z** 271.2169, found **m/z** 271.2168.

Further elution [95 : 5 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **147k** as a yellow oil that crystallized upon standing (41 mg, 56%).

Data for **147k**:

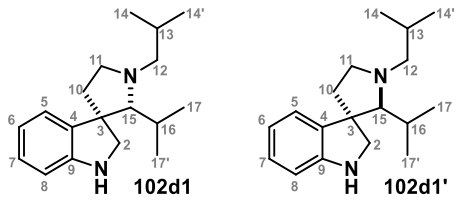
IR 3374 (br, N–H), 2917, 2847, 2801 (C–H), 1607, 1486, 1461, 1445.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.05 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.99 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 6.74 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.65 (br d, 1H, J = 7.7 Hz, C^8H), 3.66 (d, 1H, J = 9.1 Hz, C^2Ha), 3.24 (d, 1H, J = 9.1 Hz, C^2Hb), 3.36–3.96 (br s, 1H, NH), 3.17 (ddd, 1H, J = 9.3, 6.5, 4.1 Hz, $C^{11}Ha$), 2.96–3.02 (m, 2H, $C^{12}H_2$), 2.94 (dd, 1H, J = 6.7, 3.5 Hz, $C^{19}H$), 2.66 (td, 1H, J = 9.0, 7.3 Hz, $C^{11}Hb$), 1.93–1.99 (m, 2H, $C^{10}H_2$), 1.78–1.89 (m, 1H, $C^{15}Ha$), 1.63–1.78 (m, 3H, $C^{14}Ha$, $C^{17}Ha$, $C^{18}Ha$), 1.51–1.62 (m, 4H, $C^{13}H_2$, $C^{16}H_2$), 1.35–1.51 (m, 4H, $C^{14}Hb$, $C^{15}Hb$, $C^{17}Hb$, $C^{18}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.8 (C^9), 136.9 (C^4), 127.6 (C^7), 123.2 (C^5), 118.1 (C^6), 109.7 (C^8), 72.1 (C^{19}), 57.0 (C^2), 55.8 (C^3), 54.8 (C^{12}), 52.4 (C^{11}), 39.2 (C^{10}), 29.6 (C^{18}), 29.2 (C^{16}), 27.6 (C^{13}), 26.0 (C^{14}), 24.5 (C^{15}), 23.4 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2^+$) requires **m/z** 271.2169, found **m/z** 271.2163.

(2'R,3R)-1'-isobutyl-2'-isopropylspiro[indoline-3,3'-pyrrolidine] (102d1) and (2'S,3R)-1'-isobutyl-2'-isopropylspiro[indoline-3,3'-pyrrolidine] (102d1')



Prepared according to **General Procedure E** (5 mol% catalyst, 3.00 equiv. TMDS, rt, 24 h) from **97d1**. Purification *via* prep TLC [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave the Major isomer **102d1** first as a yellow oil (7 mg, 31%), followed by the minor isomer **102d1'**, obtained as a yellow oil (6 mg, 27%).

Data for **102d1**:

IR 3377 (br, N–H), 2953, 2869, 2796 (C–H), 1607, 1486, 1461.

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.00–7.05 (m, 2H, C^5H, C^7H), 6.74 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (dt, 1H, J = 7.5, 1.0 Hz, C^8H), 3.76 (d, 1H, J = 9.1 Hz, C^2Ha), 3.32 (d, 1H, J = 9.1 Hz, C^2Hb), 3.12 (ddd, 1H, J = 9.6, 6.9, 4.0 Hz, $C^{11}Ha$), 2.75 (d, 1H, J = 3.0 Hz, $C^{15}H$), 2.56 (dd, 1H, J =11.6, 4.3 Hz, $C^{12}Ha$), 2.41–2.50 (m, 2H, $C^{11}Hb$, $C^{12}Hb$), 1.76–1.96 (m, 4H, $C^{10}H_2$, $C^{13}H$, $C^{16}H$), 1.02 (d, 3H, J = 6.6 Hz, $C^{14}H_3$), 0.90–0.94 (m, 9H, $C^{14'}H_3$, $C^{17}H_3$, $C^{17'}H_3$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 150.4 (C^9), 138.0 (C^4), 127.5 (C^7), 123.5 (C^5), 118.7 (C^6), 109.7 (C^8), 76.7 (C^{15}), 66.1 (C^{12}), 56.3 (C^2), 55.5 (C^3), 51.5 (C^{11}), 39.8 (C^{10}), 30.4 (C^{16}), 28.5 (C^{13}), 22.5 (C^{17}), 21.6 ($C^{14'}$), 20.6 (C^{14}), 18.6 ($C^{17'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{29}N_2^+$) requires **m/z** 273.2325, found **m/z** 273.2327.

Data for **102d1'**:

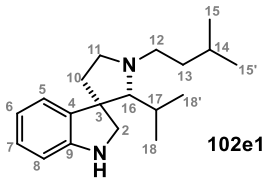
IR 3374 (br, N–H), 2954, 2926, 2869 (C–H), 1608, 1488, 1461.

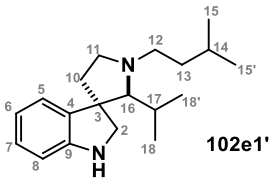
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.19 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.04 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.72 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (dd, 1H, J = 7.7, 1.0 Hz, C^8H), 3.65–3.73 (br s, 1H, NH), 3.40 (d, 1H, J = 8.6 Hz, C^2Ha), 3.30 (d, 1H, J = 8.6 Hz, C^2Hb), 3.20–3.26 (m, 1H, $C^{11}Ha$), 2.54 (d, 1H, J = 4.4 Hz, $C^{15}H$), 2.39–2.48 (m, 2H, $C^{12}H_2$), 2.23–2.34 (m, 2H, $C^{10}Ha$, $C^{11}Hb$), 1.74–1.83 (m, 2H, $C^{10}Hb$, $C^{13}H$), 1.50 (qd, 1H, J = 6.9, 4.4 Hz, $C^{16}H$), 1.01 (d, 3H, J = 6.6 Hz, $C^{14}H_3$), 0.88 (d, 3H, J = 6.7 Hz, $C^{17}H_3$), 0.87 (d, 3H, J = 6.7 Hz, $C^{14'}H_3$), 0.60 (d, 3H, J = 6.9 Hz, $C^{17'}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 152.4 (C^9), 133.2 (C^4), 127.7 (C^7), 125.2 (C^5), 118.6 (C^6), 109.7 (C^8), 77.5 (C^{15}), 68.0 (C^{12}), 62.4 (C^2), 55.9 (C^3), 52.2 (C^{11}), 37.6 (C^{10}), 30.9 (C^{16}), 28.3 (C^{13}), 22.6 ($C^{17'}$), 21.5 ($C^{14'}$), 20.5 (C^{14}), 18.7 (C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{29}N_2^+$) requires **m/z** 273.2325, found **m/z** 273.2325.

(2'R,3R)-1'-isopentyl-2'-isopropylspiro[indoline-3,3'-pyrrolidine] (102e1) and (2'R,3R)-1'-isopentyl-2'-isopropylspiro[indoline-3,3'-pyrrolidine] (102e1')





Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 6 h) from **97e1**. Purification *via* prep TLC [96 : 4 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave the minor isomer **102e1'** eluted first as a yellow oil (14 mg, 30%), followed by the Major isomer **102e1**, obtained as a yellow oil (24 mg, 52%).

Data for **102e1'**:

IR 3361 (br, N–H), 2955 (C–H), 1608, 1486, 1462.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.01–7.06 (m, 2H, C^5H, C^7H), 6.74 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.63 (dd, 1H, J = 8.0, 1.0 Hz, C^8H), 3.81 (d, 1H, J = 9.3 Hz, C^2Ha), 3.45–3.95 (br s, 1H, NH), 3.30 (d, 1H, J = 9.3 Hz, C^2Hb), 3.12–3.26 (m, 1H, $C^{11}Ha$), 2.75-2.89 (m, 1H, $C^{12}Ha$), 2.66 (d, 1H, J = 4.6 Hz, $C^{16}H$), 2.50–2.59 (m, 2H, $C^{11}Hb$, $C^{12}Hb$), 1.86–1.97 (m, 3H, $C^{10}H_2$, $C^{17}H$), 1.65 (n, 1H, J = 6.7 Hz, $C^{14}H$), 1.42–1.53 (m, 2H, $C^{13}H_2$), 0.96 (d, 3H, J = 6.6 Hz, $C^{18}H_3$), 0.94 (d, 3H, J = 6.6 Hz, $C^{15}H_3$), 0.93 (d, 3H, J = 6.5 Hz, $C^{15'}H_3$), 0.86 (d, 3H, J = 7.0 Hz, $C^{18'}H_3$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 150.6 (C^9), 136.8 (C^4), 127.7 (C^7), 123.0 (C^5), 118.7 (C^6), 109.7 (C^8), 77.7 (C^{16}), 56.3 (C^{12}), 55.8 (C^3), 55.7 (C^2), 51.7 (C^{11}), 40.0 (C^{10}), 38.4 (C^{13}), 29.9 (C^{17}), 26.5 (C^{14}), 23.03 (C^{15}), 22.95 ($C^{15'}$), 22.2 ($C^{18'}$), 19.5 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{31}N_2^+$) requires **m/z** 287.2482, found **m/z** 287.2482.

Data for **102e1**:

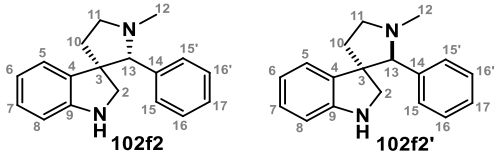
IR 3391 (broad, N-H), 2954, 2868, 2794 (C-H), 1608, 1486, 1463.

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.18 (dd, 1H, *J* = 7.4, 1.4 Hz, C^5H), 7.04 (td, 1H, *J* = 7.6, 1.3 Hz, C^7H), 6.71 (td, 1H, *J* = 7.4, 1.1 Hz, C^6H), 6.64 (dd, 1H, *J* = 7.7 Hz, C^8H), 3.54-3.86 (br s, 1H, NH), 3.43 (d, 1H, *J* = 8.6 Hz, C^2Ha), 3.33 (d, 1H, *J* = 8.6 Hz, C^2Hb), 3.26 (ddd, 1H, J = 8.7, 6.9, 2.4 Hz, $C^{11}Ha$), 2.83 (td, 1H, *J* = 11.3, 6.4 Hz, $C^{12}Ha$), 2.47 (d, 1H, *J* = 5.8 Hz, $C^{16}H$), 2.43 (ddd, 1H, *J* = 11.4, 9.6, 4.7 Hz, $C^{12}Hb$), 2.25–2.35 (m, 2H, $C^{11}Hb$, $C^{10}Ha$), 1.80 (ddd, 1H, *J* = 12.1, 6.2, 2.4 Hz, $C^{10}Hb$), 1.64 (n, 1H, *J* = 6.7 Hz, $C^{14}H$), 1.53 (n, 1H, *J* = 6.7 Hz, $C^{17}H$), 1.37–1.49 (m, 2H, $C^{13}H_2$), 0.91 (d, 6H, *J* = 6.7 Hz, $C^{15}H_3$, $C^{15'}H_3$), 0.89 (d, 3H, *J* = 6.8 Hz, $C^{18}H_3$), 0.52 (d, 3H, *J* = 6.8 Hz, $C^{18'}H_3$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 152.3 (C^9), 133.2 (C^4), 127.8 (C^7), 125.2 (C^5), 118.6 (C^6), 109.6 (C^8), 78.0 (C^{16}), 62.6 (C^2), 57.6 (C^{12}), 55.8 (C^3), 52.2 (C^{11}), 38.5 (C^{13}), 37.9 (C^{10}), 31.2 (C^{17}), 26.4 (C^{14}), 23.2 (C^{15}), 22.9 ($C^{15'}$), 22.2 (C^{18}), 19.2 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{31}N_2^+$) requires **m/z** 287.2482, found **m/z** 287.2481.

(2'R,3R)-1'-methyl-2'-phenylspiro[indoline-3,3'-pyrrolidine] (102f2) (2'S,3R)-1'-methyl-2'-phenylspiro[indoline-3,3'-pyrrolidine] (102f2')



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f2**. Purification *via* FCC [99 : 1 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **102f2** as a yellow oil (26 mg, 46%).

Data for **102f2**:

IR 3374 (br, N–H), 3046, 2940, 2837, 2773, 1606, 1525, 1484, 1340, 1315.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.02–7.13 (m, 6H, C^5H, $C^{15}H$, $C^{15'}H$, $C^{16}H$, $C^{16'}H$, $C^{17}H$), 6.88 (td, 1H, J = 7.4, 1.0 Hz, C^7H), 6.62 (tt, 1H, J = 7.4, 0.9 Hz, C^6H), 6.37 (dd, 1H, J = 7.8, 0.9 Hz, C^8H), 3.73 (d, 1H, J = 9.3 Hz, C^2Ha), 3.58 (d, 1H, J = 9.3 Hz, C^2Hb), 3.44 (td, 1H, J = 8.7, 3.1 Hz, $C^{11}Ha$), 3.31 (s, 1H, $C^{13}H$), 2.53 (q, 1H, J = 8.8 Hz, $C^{11}Hb$), 2.36 (dt, 1H, J = 12.9, 8.4 Hz, $C^{10}Ha$), 2.25 (s, 3H, $C^{12}H_3$), 2.08 (ddd, 1H, J = 12.5, 8.9, 3.1 Hz, $C^{10}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.0 (C^9), 139.0 (C^{14}), 134.3 (C^4), 128.6 ($C^{15/16}$, $C^{15'/16'}$), 127.5 (C^7), 127.3 ($C^{15/16}$, $C^{15'/16'}$), 126.9 (C^{17}), 125.7 (C^5), 118.4 (C^6), 109.4 (C^8), 81.7 (C^{13}), 59.9 (C^2), 57.3 (C^3), 54.9 (C^{11}), 41.2 (C^{12}), 38.1 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}N_2^+$) requires **m/z** 265.1699, found **m/z** 265.1695.

Further elution [99 : 1 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **102f2'** as a yellow oil (21 mg, 37%).

Data for **102f2'**:

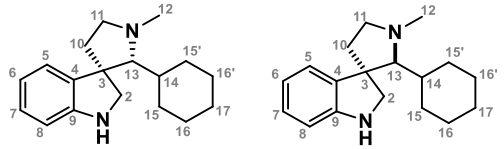
IR 3289 (br, N–H), 3048, 2935, 2844, 2770, 1606, 1484.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.28 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.19–7.24 (m, 3H, $C^{Ar}H$), 7.01–7.08 (m, 3H, $C^{Ar}H$), 6.83 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.50 (app d, 1H, J = 7.7 Hz, C^8H), 3.45 (d, 1H, J = 9.9 Hz, C^2Ha), 3.32–3.40 (m, 2H, $C^{11}Ha$, $C^{13}H$), 3.11 (d, 1H, J = 9.9 Hz, C^2Hb), 2.57 (q, 1H, J = 8.8 Hz, $C^{11}Hb$), 2.37 (ddd, 1H, J = 13.1, 9.0, 3.0 Hz, $C^{10}Ha$), 2.28 (s, 3H, $C^{12}H_3$), 2.11 (td, 1H, J = 13.1, 8.5 Hz, $C^{10}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.6 (C^9), 138.5 (C^{14}), 135.3 (C^4), 128.1 (C^7), 128.0 ($C^{15/16}$, $C^{15'/16'}$), 127.9 ($C^{15/16}$, $C^{15'/16'}$), 127.2 (C^{17}), 123.1 (C^5), 119.1 (C^6), 110.4 (C^8), 80.9 (C^{13}), 57.4 (C^2), 56.8 (C^3), 55.4 (C^{11}), 41.1 (C^{12}), 39.4 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}N_2^+$) requires **m/z** 265.1699, found **m/z** 265.1700.

(2'R,3R)-2'-cyclohexyl-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f3) (2'S,3R)-2'-cyclohexyl-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f3')



102f3 **102f3'**

Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f3**. Purification *via* prep TLC [96 : 4 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave the Major isomer **102f3** first as a yellow oil (18 mg, 61%), followed by the minor isomer **102f3'**, obtained as a yellow oil (5 mg, 17%).

Data for **102f3**:

IR 3372 (br, N–H), 2924, 2850, 2782, 1607, 1488, 1461.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.01–7.06 (m, 2H, C^5H, C^7H), 6.73 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.63 (dt, 1H, J = 7.5, 0.9, C^8H), 3.81 (d, 1H, J = 9.3 Hz, C^2Ha), 3.31 (d, 1H, J = 9.3 Hz, C^2Hb), 3.17 (ddd, 1H, J = 10.2, 6.9, 5.6 Hz, $C^{11}Ha$), 2.54 (dt, 1H, J = 10.0, 7.5 Hz, $C^{11}Hb$), 2.52 (s, 3H, $C^{12}H_3$), 2.50 (d, 1H, J = 4.6 Hz, $C^{13}H$), 1.90–2.03 (m, 2H, $C^{10}H_2$), 1.44–1.75 (m, 6H, $C^{14}H$, $C^{15}Ha$, $C^{15'}Ha$, $C^{16}Ha$, $C^{16'}Ha$, $C^{17}Ha$), 1.07–1.29 (m, 5H, $C^{15}Hb$, $C^{15'}Hb$, $C^{16}Hb$, $C^{16'}Hb$, $C^{17}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 150.6 (C^9), 136.6 (C^4), 127.7 (C^7), 122.9 (C^5), 118.8 (C^6), 109.7 (C^8), 78.5 (C^{13}), 56.4 (C^2), 56.3 (C^3), 55.3 (C^{11}), 44.6 (C^{12}), 40.5 (C^{10}), 40.1 (C^{14}), 32.5 (C^{15}), 30.2 ($C^{15'}$), 27.2 (C^{16}), 26.9 (C^{17}), 26.7 ($C^{16'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2^+$) requires **m/z** 271.2169, found **m/z** 271.2163.

Data for **102f3'**:

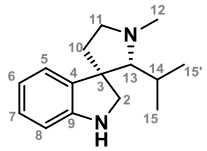
IR 3376 (br, N–H), 2922, 2849, 2778 (C_{Ar}–H), 1607, 1486, 1462.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.19 (dd, 1H, J = 7.4, 1.3 Hz, C^5H), 7.04 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.72 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.64 (br d, 1H, J = 7.8 Hz, C^8H), 3.59–3.79 (br s, 1H, NH), 3.46 (d, 1H, J = 8.8 Hz, C^2Ha), 3.39 (d, 1H, J = 8.8 Hz, C^2Hb), 3.21 (ddd, 1H, J = 9.5, 7.2, 2.6 Hz, $C^{11}Ha$), 2.47 (s, 3H, $C^{12}H_3$), 2.38 (td, 1H, J = 9.8, 6.7 Hz, $C^{11}Hb$), 2.19–2.27 (m, 2H, $C^{13}H$, $C^{10}Ha$), 1.84 (ddd, 1H, J = 12.5, 6.7, 2.6 Hz, $C^{10}Hb$), 1.77–1.81 (m, 1H, $C^{15}Ha$), 1.42–1.68 (m, 4H, 4 protons among $C^{16}H_2$/$C^{16'}H_2$/$C^{17}H_2$), 1.25 (s, 1H, $C^{14}H$), 0.99–1.13 (m, 3H, $C^{15}Hb$, $C^{15'}Ha$, 1 proton among $C^{16}H_2$/$C^{16'}H_2$/$C^{17}H_2$), 0.89–0.95 (m, 1H, 1 proton among $C^{16}H_2$/$C^{16'}H_2$/$C^{17}H_2$), 0.84 (qd, 1H, J = 11.9, 2.7 Hz, $C^{15'}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 152.0 (C^9), 133.6 (C^4), 127.8 (C^7), 125.2 (C^5), 118.7 (C^6), 109.7 (C^8), 79.6 (C^{13}), 62.7 (C^2), 56.6 (C^3), 55.8 (C^{11}), 45.5 (C^{12}), 41.2 (C^{14}), 39.0 (C^{10}), 32.9 ($C^{15'}$), 29.9 (C^{15}), 26.93, 26.88, 26.80 (C^{16}/$C^{16'}$/C^{17}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2^+$) requires **m/z** 271.2169, found **m/z** 271.2168.

(2'R,3R)-2'-isopropyl-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f4)



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f4**. Purification *via* prep TLC [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M), triple elution] gave **102f4** as a pale yellow oil (29 mg, 78%). A pure sample of the minor diastereoisomer could not be obtained.

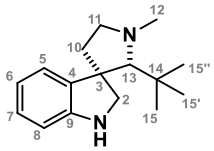
IR 3376 (br, N–H), 2957, 2871, 2784 (C–H), 1607, 1487, 1461.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.01–7.07 (m, 2H, C^5H, C^7H), 6.74 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.64 (dt, 1H, J = 7.6, 0.8 Hz, C^8H), 3.84 (d, 1H, J = 9.3 Hz, C^2Ha), 3.30 (d, 1H, J = 9.3 Hz, C^2Hb), 3.16 (ddd, 1H, J = 9.9, 6.6, 5.1 Hz, $C^{11}Ha$), 2.46–2.55 (m, 4H, $C^{11}Hb$, $C^{12}H_3$), 2.45 (d, 1H, J = 3.8 Hz, $C^{13}H$), 1.88-2.00 (m, 3H, $C^{10}H_2$, $C^{14}H$), 0.96 (d, 3H, J = 6.8 Hz, $C^{15}H_3$), 0.92 (d, 3H, J = 7.1 Hz, $C^{15'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.8 (C^9), 136.4 (C^4), 127.8 (C^7), 123.0 (C^5), 118.8 (C^6), 109.7 (C^8), 79.0 (C^{13}), 56.6 (C^2), 56.2 (C^3), 55.3 (C^{11}), 44.1 (C^{12}), 40.3 (C^{10}), 28.8 (C^{14}), 22.3 ($C^{15'}$), 19.3 (C^{15}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N_2^+$) requires **m/z** 231.1856, found **m/z** 231.1851.

(2'R,3R)-2'-(tert-butyl)-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f5)



Prepared according to **General Procedure E** (5 mol% catalyst, 3.00 equiv. TMDS, rt, 24 h) from **97f5**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave **102f5** as a pale yellow oil (35 mg, 71%).

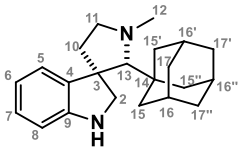
IR 3266 (br, N–H), 2988, 2947, 2867, 2787 (C–H), 1606, 1483, 1459.

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.00–7.06 (m, 2H, C^7H, C^5H), 6.74 (td, 1H, J = 7.4, 1.1 Hz, C^6H), 6.64 (dt, 1H, J = 7.3, 1.0 Hz, C^8H), 4.06 (d, 1H, J = 9.1 Hz, C^2Ha), 3.31 (d, 1H, J = 9.1 Hz, C^2Hb), 3.12–3.21 (m, 1H, $C^{11}Ha$), 2.63–2.72 (m, 5H, $C^{11}Hb$, $C^{13}H$, $C^{12}H_3$), 2.04 (dt, 1H, J = 12.5, 6.3 Hz, $C^{10}Ha$), 1.87 (dt, 1H, J = 12.3, 6.8 Hz, $C^{10}Hb$), 0.99 (s, 3H, $C^{15}H_3$, $C^{15'}H_3$, $C^{15''}H_3$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 150.1 (C^9), 137.3 (C^4), 127.6 (C^7), 122.6 (C^5), 118.8 (C^6), 109.8 (C^8), 81.5 (C^{13}), 57.6 (C^3), 56.1 (C^2), 55.0 (C^{11}), 46.4 (C^{12}), 39.7 (C^{10}), 36.4 (C^{14}), 29.0 (C^{15}, $C^{15'}$, $C^{15''}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}N_2^+$) requires **m/z** 245.2012, found **m/z** 245.2008.

(2'R,3R)-2'-((3R,5R,7R)-adamantan-1-yl)-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f6)



Prepared according to **General Procedure E** (5 mol% catalyst, 3.00 equiv. TMDS, rt, 24 h) from **97f6**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] followed by trituration in cold pentane gave **102f6** as a white solid (98 mg, 88%).

IR 3246 (br, N–H), 2900, 2847, 2786, 1605, 1489, 1455.

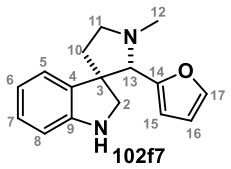
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.06 (dd, 1H, J = 7.5, 1.4 Hz, C^5H), 7.03 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.74 (td, 1H, J = 7.5, 1.1 Hz, C^6H), 6.64 (dd, 1H, J = 7.7, 1.0 Hz, C^8H), 4.22 (d, 1H, J = 8.9 Hz, C^2Ha), 3.45–3.95 (br s, 1H, NH), 3.32 (d, 1H, J = 8.9 Hz, C^2Hb), 3.05–3.14 (m, 1H, $C^{11}Ha$), 2.60–2.70 (m, 4H, $C^{11}Hb$, $C^{12}H_3$), 2.51 (s, 1H, $C^{13}H$), 2.00 (dt, 1H, J = 11.8, 5.8 Hz, $C^{10}Ha$), 1.90–1.95 (m, 3H, $C^{16}H$, $C^{16'}H$, $C^{16''}H$), 1.82 (dt, 1H, J = 12.2, 7.1 Hz, $C^{10}Hb$), 1.61–1.71 (m, 12H, $C^{15}H_2$, $C^{15'}H_2$, $C^{15''}H_2$, $C^{17}H_2$, $C^{17'}H_2$, $C^{17''}H_2$).

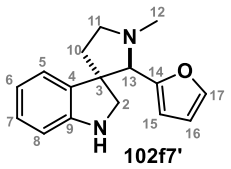
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.1 (C^9), 137.0 (C^4), 127.4 (C^7), 122.7 (C^5), 118.7 (C^6), 109.8 (C^8), 81.3 (C^{13}), 57.8 (C^3), 56.2 (C^2), 55.1 (C^{11}), 47.2 (C^{12}), 40.3 (C^{15}, $C^{15'}$, $C^{15''}$), 39.0 (C^{10}), 37.3 (C^{17}, $C^{17'}$, $C^{17''}$), 28.8 (C^{16}, $C^{16'}$, $C^{16''}$).

C^{14} was not well observed, but could be at 39.6 (broad signal).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{31}N_2^+$) requires **m/z** 323.2482, found **m/z** 323.2480.

(2'R,3R)-2'-(furan-2-yl)-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f7) and (2'S,3R)-2'-(furan-2-yl)-1'-methylspiro[indoline-3,3'-pyrrolidine] (102f7')





Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f7**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave **102f7** and **12f7'** as 58 (**A**): 42 (**B**) mixture of non-separable diastereoisomers.

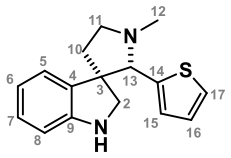
IR 3379 (br, N–H), 2958, 2842, 2778 (C–H), 1604, 1491, 1478.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.35–7.37 (m, 0.42H, $C^{17}H$ (**B**)), 7.22–7.24 (m, 0.58H, $C^{17}H$ (**A**)), 7.20 (dd, 0.42H, J = 7.4, 1.2 Hz, C^5H (**B**)), 7.05 (td, 0.58H, J = 7.6, 1.3 Hz, C^7H (**A**)), 6.89–6.98 (1H, m, C^5H (**A**), C^7H (**B**)), 6.80 (td, 0.42H, J = 7.4, 1.0 Hz, C^6H (**B**)), 6.56–6.63 (m, 1H, C^6H (**A**), C^8H (**B**)), 6.54 (d, 0.58H, J = 7.7 Hz, C^8H (**A**)), 6.29 (dd, 0.42H, J = 3.2, 1.8 Hz, $C^{16}H$ (**B**)), 6.16 (dd, 0.58H, J = 3.2, 1.8 Hz, $C^{16}H$ (**A**)), 6.06 (d, 0.42H, J = 3.2 Hz, $C^{15}H$ (**B**)), 5.91 (d, 0.58H, J = 3.2 Hz, $C^{15}H$ (**A**)), 3.69 (d, 0.58H, J = 9.1 Hz, C^2Ha (**A**)), 3.48–3.58 (m, 2H, C^2Ha (**B**), C^2Hb (**A**), $C^{13}H$ (**A**), $C^{13}H$ (**B**)), 3.23–3.33 (m, 1.42H, C^2Hb (**B**), $C^{11}Ha$ (**A**), $C^{11}Ha$ (**B**)), 2.55–2.68 (m, 1H, $C^{11}Hb$ (**A**), $C^{11}Hb$ (**B**)), 2.40 (dt, 0.58H, J = 12.9, 8.6 Hz, $C^{10}Ha$ (**A**)), 2.33 (s, 3H, $C^{12}H_3$ (**A**), $C^{12}H_3$ (**B**)), 2.14–2.32 (m, 0.84H, $C^{10}H_2$ (**B**)), 2.08 (ddd, 0.58H, J = 12.9, 8.1, 3.0 Hz, $C^{10}Hb$ (**A**)).

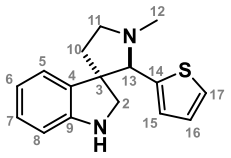
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 153.8 (C^{14} (**A**)), 152.9 (C^{14} (**B**)), 151.2 (C^9 (**B**)), 151.1 (C^9 (**A**)), 142.3 (C^{17} (**B**)), 141.4 (C^{17} (**A**)), 135.5 (C^4 (**A**)), 133.4 (C^4 (**B**)), 128.0 (C^7 (**B**)), 127.7 (C^7 (**A**)), 124.9 (C^5 (**A**)), 122.9 (C^5 (**B**)), 119.0 (C^6 (**B**)), 118.8 (C^6 (**A**)), 110.14 (C^8 (**B**)), 110.10 (C^{16} (**A**)), 110.08 (C^{16} (**B**)), 109.5 (C^8 (**A**)), 108.5 (C^{15} (**B**)), 108.1 (C^{15} (**A**)), 74.2 (C^{13} (**B**)), 73.8 (C^{13} (**A**)), 60.9 (C^2 (**A**)), 58.1 (C^2 (**B**)), 56.8 (C^3 (**A**)), 56.3 (C^3 (**B**)), 54.9 (C^{11} (**B**)), 54.5 (C^{11} (**A**)), 40.98, 40.96 (C^{12} (**A**,**B**)), 39.3 (C^{10} (**B**)), 38.2 (C^{10} (**A**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}ON_2^+$) requires **m/z** 255.1492, found **m/z** 245.1489.

(2'S,3R)-1'-methyl-2'-(thiophen-2-yl)spiro[indoline-3,3'-pyrrolidine] (102f8) and (2'R,3R)-1'-methyl-2'-(thiophen-2-yl)spiro[indoline-3,3'-pyrrolidine] (102f8')



102f8



102f8'

Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f8**. Purification *via* FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the Major isomer **102f8** as a yellow oil that turned into an amorphous solid upon standing (37 mg, 47%).

Data for **102f8**:

IR 3373 (br, N–H), 2939, 2837, 2774 (C–H), 1606, 1485, 1463.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.15 (ddd, 1H, J = 7.4, 1.4, 0.6 Hz, C^5H), 7.06 (ddd, 1H, J = 5.1, 1.3, 0.6 Hz, $C^{17}H$), 6.98 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.79 (dd, 1H, J = 5.1, 3.5 Hz, $C^{16}H$), 6.73 (ddd, 1H, J = 3.5, 1.3, 0.6 Hz, $C^{15}H$), 6.68 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.48 (br d, 1H, J = 7.8 Hz, C^8H), 3.66 (d, 1H, J = 9.3 Hz, C^2Ha), 3.64 (s, 1H, $C^{13}H$), 3.55 (d, 1H, J = 9.3 Hz, C^2Hb), 3.48–3.58 (br s, 1H, NH), 3.41 (ddd, 1H, J = 9.5, 8.3, 3.7 Hz, $C^{11}Ha$), 2.54 (td, 1H, J = 9.2, 7.9 Hz, $C^{11}Hb$), 2.38 (dt, 1H, J = 12.8, 8.1 Hz, $C^{10}Ha$), 2.32 (s, 3H, $C^{12}H_3$), 2.07 (ddd, 1H, J = 12.8, 9.1, 3.7 Hz, $C^{10}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.3 (C^9), 142.5 (C^{14}), 133.8 (C^4), 127.9 (C^7), 125.85 (C^5), 125.83 (C^{16}), 125.78 (C^{15}), 125.0 (C^{17}), 118.7 (C^6), 109.5 (C^8), 76.8 (C^{13}), 59.3 (C^2), 57.2 (C^3), 54.3 (C^{11}), 41.4 (C^{12}), 37.7 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2S^+$) requires **m/z** 271.1264, found **m/z** 271.1261.

Further elution FCC [98 : 2 CH_2Cl_2/NH_3 in MeOH (2 M)] gave the minor isomer **102f8'** as a yellow oil that turned into an amorphous solid upon standing (35 mg, 45%).

Data for **102f8'**:

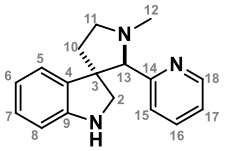
IR 3375 (br, N–H), 2942, 2841, 2778, 1607, 1487, 1462,

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.23 (dd, 1H, J = 7.4, 1.3, C^5H), 7.20 (dd, 1H, J = 5.1, 1.2, $C^{17}H$), 7.07 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.89 (dd, 1H, J = 5.1, 3.5 Hz, $C^{16}H$), 6.82 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.63 (dt, 1H, J = 3.5, 1.0 Hz, $C^{15}H$), 6.55 (br d, 1H, J = 7.8 Hz, C^8H), 3.72 (s, 1H, $C^{13}H$), 3.63 (d, 1H, J = 9.8 Hz, C^2Ha), 3.35 (ddd, 1H, J = 9.7, 8.1, 3.8 Hz, $C^{11}Ha$), 3.18 (d, 1H, J = 9.8 Hz, C^2Hb), 2.97–3.21 (br s, 1H, NH), 2.58–2.66 (m, 1H, $C^{11}Hb$), 2.41 (s, 3H, $C^{12}H_3$), 2.33 (ddd, 1H, J = 12.8, 8.9, 3.7 Hz, $C^{10}Hb$), 2.13 (dt, 1H, J = 13.1, 8.2 Hz, $C^{10}Ha$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 151.5 (C^9), 143.0 (C^{14}), 134.8 (C^4), 128.1 (C^7), 126.6 (C^{16}), 125.1 (C^{15}), 124.4 (C^{17}), 123.0 (C^5), 119.0 (C^6), 110.3 (C^8), 76.5 (C^{13}), 57.4 (C^2), 57.0 (C^3), 55.0 (C^{11}), 41.6 (C^{12}), 38.9 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2S^+$) requires **m/z** 271.1264, found **m/z** 271.1259.

(2'R,3R)-1'-methyl-2'-(pyridin-2-yl)spiro[indoline-3,3'-pyrrolidine] (102f9)



Prepared according to **General Procedure E** (1 mol% catalyst, 3.00 equiv. TMDS, rt, 1 h) from **97f9**. Purification *via* FCC [97 : 3 CH_2Cl_2/NH_3 in MeOH (2 M)] gave **102f9** as a brown oil that could be crystallized into light brown prisms from EtOAc (121 mg, 91%).

mp 88–92 °C

IR 3293 (br, N–H), 3049, 2938, 2841, 2779 (C–H), 1606, 1590, 1570, 1486, 1464, 1434.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.37 (br d, 1H, J = 4.9 Hz, $C^{18}H$), 7.35 (td, 1H, J = 7.7, 1.8 Hz, $C^{16}H$), 7.09 (br d, 1H, J = 8.0 Hz, C^5H), 7.00 (d, 1H, J = 7.5 Hz, $C^{15}H$), 6.96 (ddd, 1H, J = 7.5, 4.8, 1.2 Hz, $C^{17}H$), 6.83 (td, 1H, J = 7.6, 1.3 Hz, C^7H), 6.54 (td, 1H, J = 7.4, 1.0 Hz, C^6H), 6.36 (d, 1H, J = 7.6 Hz, C^8H), 3.96 (d, 1H, J = 9.3 Hz, C^2Ha), 3.57 (s, 1H, $C^{13}H$), 3.55 (d, 1H, J = 9.3 Hz, C^2Hb), 3.44 (td, 1H, J = 8.6, 3.2 Hz, $C^{11}Ha$), 2.58 (q, 1H, J = 8.6 Hz, $C^{11}Hb$), 2.35 (dt, 1H, J = 12.9, 8.3 Hz, $C^{10}Ha$), 2.29 (s, 3H, $C^{12}H_3$), 2.12 (ddd, 1H, 12.6, 8.8, 3.3 Hz, $C^{10}Hb$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.8 (C^{14}), 151.0 (C^9), 148.5 (C^{18}), 135.2 (C^{16}), 134.0 (C^4), 127.5 (C^7), 125.4 (C^{15}), 122.8 (C^5), 122.2 (C^{17}), 121.9 (C^6), 109.7 (C^8), 82.5 (C^{13}), 59.7 (C^2), 57.5 (C^3), 55.0 (C^{11}), 41.3 (C^{12}), 38.4 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}N_3^+$) requires **m/z** 266.1652, found **m/z** 266.1649.

Data for X-ray

CCDC Number : 1906303

Crystal data

Chemical formula	$C_{17}H_{19}N_3$
M_r	265.36
Crystal System, space group	Monoclinic, $P2_1/c$
Temperature (K)	150
a, b, c (Å)	12.7067 (2), 9.2266 (1), 12.4900 (3)
α, β, γ (°)	90, 104.1523 (16), 90
V (Å^3)	1419.88 (2)
Z	4
Radiation type	Cu $K\alpha$
U (mm^{-1})	0.58
Crystal size (mm)	0.20 × 0.10 × 0.05

Data collection

Diffractometer	Oxford diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO* (Agilent, 2011)
T_{min}, T_{max}	0.88, 0.94
No. of measured independent and observed [I> 2.0σ(I)] reflections	14017, 2947, 2760
R_{int}	0.023
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.630

Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.038, 0.097, 1.00
No. of reflections	2947
No. of parameters	184
No. restraints	3

H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å^{-3})	0.23, –0.25
Absolute structure	–
Structure parameter	–

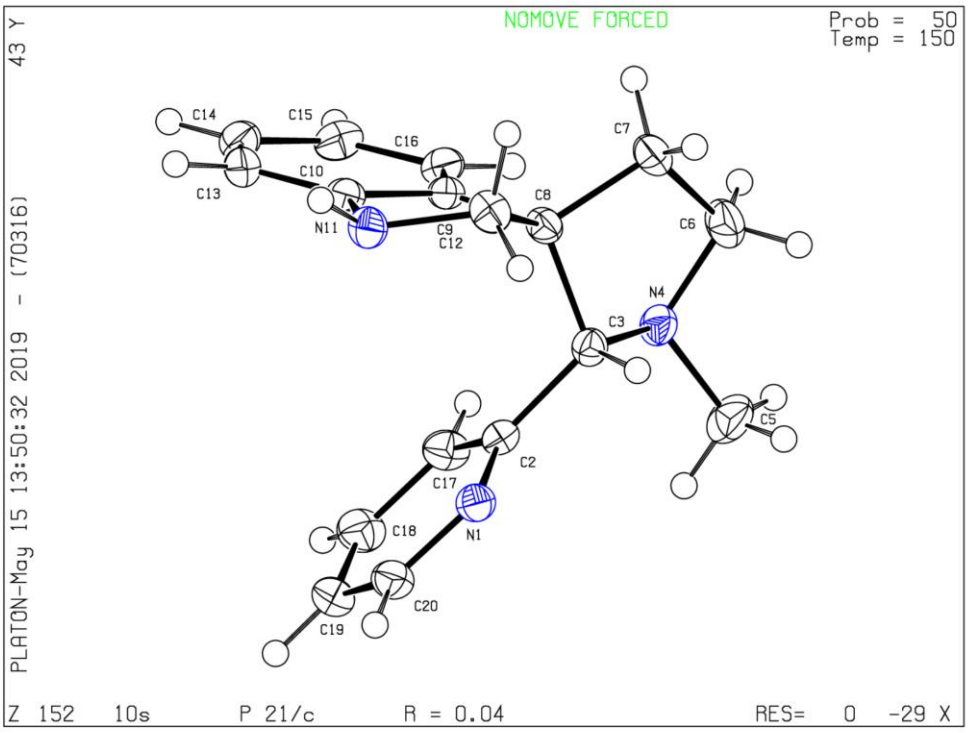


Table vii: Selected geometric parameters (Å, º)

N1—C2	1.3434 (13)	C9—C10	1.4000 (14)
N1—C20	1.3435 (14)	C9—C16	1.3831 (14)
C2—C3	1.5110 (13)	C10—N11	1.3923 (14)
C2—C17	1.3946 (15)	C10—C13	1.3901 (15)
C3—N4	1.4621 (13)	N11—C12	1.4704 (13)
C3—C8	1.5608 (14)	C13—C14	1.3883 (17)
N4—C5	1.4524 (14)	C14—C15	1.3898 (16)
N4—C6	1.4651 (14)	C15—C16	1.3946 (16)
C6—C7	1.5310 (16)	C17—C18	1.3863 (16)
C7—C8	1.5389 (13)	C18—C19	1.3838 (17)

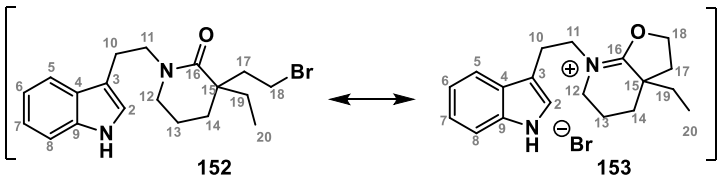
C8—C9	1.5116 (14)	C19—C20	1.3817 (16)
C8—C12	1.5425 (14)		
C2—N1—C20	117.21 (9)	C9—C8—C12	101.19 (8)
N1—C2—C3	116.14 (9)	C8—C9—C10	108.73 (9)
N1—C2—C17	122.32 (9)	C8—C9—C16	131.12 (9)
C3—C2—C17	121.54 (9)	C10—C9—C16	120.13 (9)
C2—C3—N4	113.02 (8)	C9—C10—N11	110.87 (9)
C2—C3—C8	115.80 (8)	C9—C10—C13	120.92 (10)
N4—C3—C8	100.94 (8)	N11—C10—C13	128.21 (9)
C3—N4—C5	114.99 (9)	C10—N11—C12	106.87 (8)
C3—N4—C6	105.57 (8)	C8—C12—N11	104.66 (8)
C5—N4—C6	111.89 (9)	C10—C13—C14	118.31 (10)
N4—C6—C7	105.66 (8)	C13—C14—C15	121.22 (10)
C6—C7—C8	105.25 (8)	C14—C15—C16	120.09 (10)
C7—C8—C3	100.58 (8)	C15—C16—C9	119.30 (10)
C7—C8—C9	114.66 (8)	C2—C17—C18	119.27 (10)
C3—C8—C9	112.26 (8)	C17—C18—C19	118.81 (10)
C7—C8—C12	114.07 (8)	C18—C19—C20	118.15 (10)
C3—C8—C12	114.71 (8)	C19—C20—N1	124.20 (10)

Table viii: Hydrogen-bond geometry (Å, º)

N11—H111···N1^{i}	0.89	2.32	3.1853 (16)	162 (1)

6.2.10 Synthesis of compounds towards natural products

1-(2-(1H-indol-3-yl)ethyl)-3-(2-bromoethyl)-3-ethylpiperidin-2-one (152)



PPh_3 (150 mg, 0.572 mmol) was added to a solution of **134f** (120 mg, 0.382 mmol) and CBr_4 (190 mg, 0.573 mmol) in CH_2Cl_2 (6 mL). The resulting solution was stirred for 1 h at rt before being concentrated *in vacuo*. Direct purification *via* FCC (100% EtOAc until all O=PPh_3 is eluted, then 4 : 1 $CHCl_3$/MeOH) gave a 5 : 1 equilibrium of **152** and **153**, respectively, as a hygroscopic white solid.

Imidate form 153:

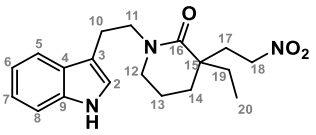
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H:10.00 (br s, 1H, NH), 7.53 (dt, 1H, J = 8.0, 0.9 Hz, C^8H), 7.45 (d, 1H, J = 7.9 Hz, C^5H), 7.16 (br d, 1H, J = 2.5 Hz, C^2H), 7.13 (ddd, 1H, J = 8.2, 7.0, 1.2 Hz, C^7H), 7.06 (ddd, 1H, J = 8.0, 7.0, 1.0 Hz, C^6H), 4.27–4.38 (m, 1H, $C^{18}H_2$), 4.08 (dt, 1H, J = 13.2, 6.5 Hz, C^{11}Ha), 3.78 (dt, 1H, J = 14.1, 7.1 Hz, C^{11}Hb), 3.68–3.74 (m, 1H, C^{12}Ha), 3.54–3.60 (m, 1H, C^{12}Hb), 3.14 (td, 2H, J = 6.7, 4.0 Hz, $C^{10}H_2$), 2.00–2.12 (m, 1H, $C^{17}H_2$), 1.87–1.95 (m, 2H, C^{13}Ha, C^{14}Ha), 1.69–1.79 (m, 2H, C^{13}Hb, C^{14}Hb), 1.15–1.22 (m, 2H, $C^{19}H_2$), 0.77 (t, 3H, J= 7.4 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 182.1 (C^{16}), 136.5 (C^9), 127.0 (C^4), 124.0 (C^2), 122.1 (C^7), 119.4 (C^6), 117.9 (C^5), 112.4 (C^8), 108.8 (C^3), 75.0 (C^{18}), 52.3 (C^{11}), 49.2 (C^{12}), 46.0 (C^{15}), 32.7 (C^{17}), 25.5 (C^{14}), 24.50 (C^{19}), 22.45 (C^{10}), 17.4 (C^{13}), 7.8 (C^{20}).

Bromide form 152:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H [selected peaks]: 8.35 (br s, 1H, NH), 7.64 (dd, 1H, J = 8.0, 1.1 Hz, C^5H), 7.39 (ddd, 1H, J = 8.1, 1.0, 0.9 Hz, C^8H), 3.41 (ddd, 1H, J = 12.1, 9.6, 5.2 Hz, C^{18}Ha), 3.34 (ddd, 1H, J = 12.0, 9.6, 5.2 Hz, C^{18}Hb), 3.00 (td, 1H, J = 7.4, 0.8 Hz, $C^{10}H_2$), 2.17 (ddd, 1H, J = 13.6, 11.8, 5.1 Hz, C^{17}Ha).

1-(2-(1H-indol-3-yl)ethyl)-3-ethyl-3-(2-nitroethyl)piperidin-2-one (154)



$AgNO_2$ (220 mg, 1.43 mmol) was added to the 5 : 1 mixture of **152** and **153**, respectively, in CH_2Cl_2 (6 mL). The yellow solution was protected from the light and stirred for 1 h at rt before being directly purified *via* FCC (1 : 1 Et_2O/petroleum ether 30–40 °C), giving **154** as a pale yellow oil (62 mg, 47% over two steps).

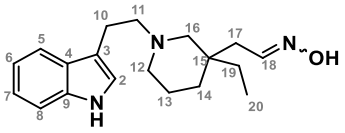
IR 3283 (br, N–H), 2942, 1611 (C=O), 1551 (NO_2), 1384 (NO_2).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 (br s, 1H, NH), 7.65 (br d, 1H, J = 7.9 Hz, C^5H), 7.35 (ddd, 1H, J = 8.1, 1.0, 1.0 Hz, C^8H), 7.19 (ddd, 1H, J = 8.2, 7.2, 1.2 Hz, C^7H), 7.13 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.06 (d, 1H, J = 2.3 Hz, C^2H), 4.37 (m, 2H, $C^{18}H_2$), 3.79 (dt, 1H, J = 13.2, 7.5 Hz, $C^{11}Ha$), 3.55 (dt, 1H, J = 13.1, 6.9 Hz, $C^{11}Hb$), 3.20 (t, 2H, J = 6.0 Hz, $C^{12}H_2$), 3.02 (t, J = 7.1 Hz, $C^{10}H_2$), 2.11–2.17 (m, 2H, $C^{17}H_2$), 1.66–1.81 (m, 4H, $C^{19}Ha$, $C^{13}H_2$, $C^{14}Ha$), 1.45–1.57 (m, 2H, $C^{19}Hb$, $C^{14}Hb$), 0.85 (t, 3H, J = 7.5 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 172.7 (C^{16}), 136.4 (C^9), 127.6 (C^4), 122.24 (C^7), 122.19 (C^2), 119.6 (C^6), 118.8 (C^5), 113.1 (C^3), 111.4 (C^8), 72.8 (C^{18}), 48.7 (C^{12}), 48.4 (C^{11}), 43.7 (C^{15}), 35.1 (C^{17}), 30.5 (C^{14}), 30.3 (C^{19}), 23.1 (C^{10}), 19.5 (C^{13}), 8.3 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}O_3N_3^+$) requires **m/z** 344.19687, found **m/z** 344.19673.

2-(1-(2-(1H-indol-3-yl)ethyl)-3-ethylpiperidin-3-yl)acetaldehyde oxime (156)



TMDS (170 μL, 0.962 mmol) was added to a solution of **154** (110 mg, 0.320 mmol) and $IrCl(CO)(PPh_3)_2$ (12.5 mg, 0.016 mmol) in toluene-d_8 (5 mL). The yellow solution was stirred for 16 h at rt before being concentrated *in vacuo* and directly purified *via* FCC (gradient, from 97 : 3 $CHCl_3$/MeOH to 95 : 5 $CHCl_3$/MeOH), followed by prep TLC (1 : 1 EtOAc/acetone), giving **156** as a 1 : 1 mixture of **E** and **Z** isomers and as a pale yellow oil (15 mg, 15%).

IR 3414, 3057 (br, N–H, O–H), 2855, 2805, 1457.

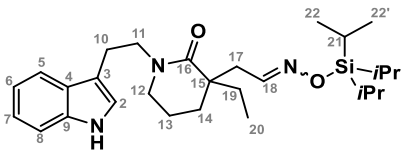
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.00 (2*br s, 1H, NH), 7.60–7.65 (m, 1H, C^5H), 7.47 (t, 0.5H, J = 6.9 Hz, $C^{18}H$ (**E** isomer)), 7.34 (dt, 1H, J = 8.1, 0.9 Hz, C^8H), 7.18 (ddd, 1H, J = 8.2, 7.0, 1.3 Hz, C^7H), 7.11 (ddt, 1H, J = 8.1, 7.0, 1.1 Hz, C^6H), 7.00–7.05 (m, 1H, C^2H), 6.88 (t, 0.5H, J = 6.1 Hz, $C^{18}H$ (**Z** isomer)), 2.80–2.99 (m, 2H, $C^{10}H_2$), 2.52–2.79 (m, 3.5H, $C^{11}H_2$, $C^{12}Ha$, $C^{17}Ha$ (**Z** isomer)), 2.08–2.44 (m, 5.5H, $C^{12}Hb$, $C^{16}H_2$, $C^{17}Hb$ (**Z** isomer), $C^{17}H_2$ (**E** isomer)), 1.56–1.83 (m, 2H, $C^{13}H_2$), 1.28–1.51 (m, 4H, $C^{14}H_2$, $C^{19}H_2$), 0.86 (2*t, 3H, J = 7.6 Hz, $C^{20}H_3$,).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 151.0, 150.6 (C^{18}), 136.5 (C^9), 128.0, 127.9 (C^4), 122.1 (C^7), 122.0, 121.9 (C^2), 119.5, 119.4 (C^6), 119.2 (C^5), 115.1, 114.8 (C^3), 111.4 (C^8), 63.1, 62.9 (C^{16}), 60.0, 59.9 (C^{11}), 55.1, 54.7 (C^{12}), 36.7 (C^{15}), 34.9 (C^{17}, **E** isomer), 33.9 (C^{14}), 30.4 (C^{17}, **Z** isomer), 23.0, 22.9 (C^{10}), 22.2, 22.1 (C^{13}), 7.8, 7.6 (C^{20}).

Notes: C^{19} were not be observed by ^{13}C NMR spectroscopic analysis. In this NMR spectrum, most signals could not be attributed to the **E** or **Z** isomers. 151.0, 150.6 (C^{18}) should be read as 151.0 (C^{18}, **E** or **Z** isomer), 150.6 (C^{18}, **E** or **Z** isomer).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{28}ON_3^+$) requires **m/z** 314.22269, found **m/z** 314.22283.

2-(1-(2-(1H-indol-3-yl)ethyl)-3-ethyl-2-oxopiperidin-3-yl)acetaldehyde O-triisopropylsilyl oxime (158)



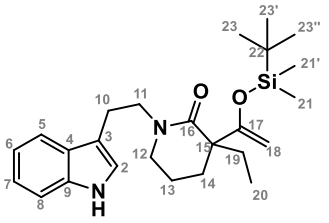
DBU (5.6 μL, 39 μmol) and TIPSCl (4.2 μL, 0.26 mmol) were sequentially added to a solution of **154** (9.0 mg, 26 μmol) in d_8-toluene (0.5 mL, NMR tube) at rt. Monitoring by ^{1}H NMR showed complete conversion to the silyl nitronate after 10 min (appearance of a triplet at 6.40 ppm, 1H, J = 6.6Hz, $C^{18}H$). Vaska's complex (<1 mg, 1 mol%) and TMDS (15 μL, 78 μmol) were then added, and the resulting solution mixture was left to stir at rt for 16 h. It was then directly purified *via* FCC (2 : 1 pentane/Et_2O) to give **158** as a yellow oil (1.8 mg, 15%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H [selected peaks]: 7.94–8.00 (2*br s, 1H, NH), 7.68 (d, 1H, J = 7.8 Hz, C^5H), 7.50 (dd, 0.5H, J = 7.4, 5.8 Hz, $C^{18}H$ (**E** isomer)), 7.34–7.38 (m, 1H, C^8H), 7.19 (ddd, 1H, J = 8.2, 6.9, 1.2 Hz, C^7H,), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.04–7.07 (m, 1H, C^2H), 6.91 (dd, 0.5H, J = 6.3, 5.2 Hz, $C^{18}H$ (**Z** isomer)), 3.63–3.68 (m, 2H, $C^{11}H_2$), 3.13–3.22 (m, 2H, $C^{12}H_2$), 3.02 (td, 2H, J = 7.6, 2.7 Hz, $C^{10}H_2$), 2.76 (dd, roof effect, 0.5H, J = 14.8, 6.4 Hz, C^{17}Ha, (**Z** isomer)), 2.68 (dd, roof effect, 0.5H, J = 14.8, 5.2 Hz, C^{17}Hb (**Z** isomer)), 2.58 (dd, 0.5H, J = 13.9, 5.8 Hz, C^{17}Ha (**E** isomer)), 2.32 (dd, 0.5H, J = 13.9, 7.4 Hz, C^{17}Hb (**E** isomer)), 1.58–1.85 (m, 4H, $C^{13}H_2$, $C^{14}H_2$, $C^{19}H_2$), 1.18–1.32 (m, 3H, $C^{21}H_3$), 1.07 (2*d, 18H, 3*$C^{22}H_3$, 3*$C^{22'}H_3$), 0.94 (t, 3H, J = 7.4 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 173.5, 173.4 (C^{16}), 153.3 (C^{18}, **E** isomer), 153.1 (C^{18}, **Z** isomer), 136.3 (C^9), 127.5, 127.5 (C^4), 122.1 (C^7, C^2), 122.0 (C^2), 119.4 (C^6), 118.9 (C^5), 113.40, 113.38 (C^3), 111.2 (C^8), 49.0, 48.9 (C^{12}), 48.7, 48.6 (C^{11}), 44.6, 44.5 (C^{15}), 38.3 (C^{17}, **E** isomer), 33.6 (C^{17}, **Z** isomer), 29.8 (3*C^{21}), 23.2 (C^{10}), 18.0 (3*C^{22}, $C^{22'}$), 8.7, 8.6 (C^{20})

Notes: C^{13}, C^{14}, C^{19} were not be assigned by ^{13}C NMR spectroscopic analysis. In this NMR spectrum, most signals could not be attributed to the **E** or **Z** isomers. 173.5, 173.4 (C^{16}) should be read as 173.5 (C^{16}, **E** or **Z** isomer), 173.4 (C^{16}, **E** or **Z** isomer).

1-(2-(1H-indol-3-yl)ethyl)-3-(1-((tert-butyldimethylsilyl)oxy)vinyl)-3-ethylpiperidin-2-one (159)



NEt_3 (89 μL, 0.64 mmol) and TBSOTf (88 μL, 0.38 mmol) were sequentially added to a solution of **134e** (0.10 g, 0.32 mmol) in CH_2Cl_2 (2 mL) at 0 °C. The resulting reaction mixture was allowed to reach rt overnight, before being directly purified *via* FCC (3 : 1 petroleum ether 30–40 °C/EtOAc), giving **159** as a white solid (106 mg, 78%).

mp 134–136°C.

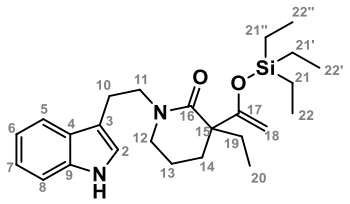
IR 3272 (br, N–H), 2930, 2857 (C–H), 1615 (C=O, amide), 1492, 1460.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.25 (br s, 1H, NH), 7.70 (app d, 1H, J = 7.8 Hz, C^5H), 7.36 (ddd, 1H, J = 8.1, 1.0, 0.9 Hz, C^8H), 7.18 (ddd, 1H, J = 8.2, 7.1, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.05 (d, 1H, J = 2.3 Hz. C^2H), 4.17–4.20 (m, 1H, $C^{18}Ha$), 4.12–4.16 (m, 1H, $C^{18}Hb$), 3.71 (ddd, 1H, J = 13.1, 9.3, 6.1 Hz, $C^{11}Ha$), 3.59 (ddd, 1H, J = 13.1, 9.2, 6.2 Hz, $C^{11}Hb$), 3.22–3.29 (m, 2H, $C^{12}H_2$), 2.95–3.11 (m, 2H, $C^{10}H_2$), 1.83–2.08 (m, 3H, $C^{13}Ha$, $C^{14}Ha$, $C^{19}Ha$), 1.45–1.75 ($C^{13}Hb$, $C^{14}Hb$, $C^{19}Hb$), 0.90–0.96 (m, 12H, $C^{20}H_3$, $C^{23}H_3$, $C^{23'}H_3$, $C^{23''}H_3$), 0.21 (s, 3H, $C^{21}H_3$), 0.19 (s, 3H, $C^{21'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.7 (C^{16}), 160.2 (C^{17}), 136.4 (C^9), 127.6 (C^4), 122.3 (C^2), 122.0 (C^7), 119.4 (C^6), 119.0 (C^5), 113.4 (C^3), 111.3 (C^8), 90.1 (C^{18}), 53.6 (C^{15}), 48.77 (C^{12}), 48.75 (C^{11}), 29.8 (C^{19}), 28.3 (C^{14}), 26.0 (C^{22}), 25.8 (C^{23}, $C^{23'}$, $C^{23''}$), 23.1 (C^{10}), 19.6 (C^{13}), 9.9 (C^{20}), –4.6 (C^{21}), –4.8 ($C^{21'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{39}O_2N_2Si^+$) requires **m/z** 427.27753, found **m/z** 427.27738.

1-(2-(1H-indol-3-yl)ethyl)-3-(1-((tert-butyldimethylsilyl)oxy)vinyl)-3-ethylpiperidin-2-one (159')



NEt_3 (45 μL, 0.32 mmol) and TESOTf (44 μL, 0.19 mmol) were sequentially added to a solution of **134e** (50 mg, 0.16 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The resulting solution was allowed to reach rt overnight, before being directly purified *via* FCC (4 : 1 petroleum ether 30–40 °C/EtOAc), giving **159'** as a colourless oil (68 mg, 99%).

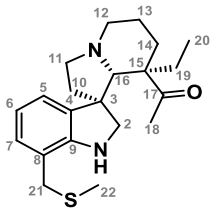
IR 3298 (br, N–H), 2930, 2967, 2877 (C–H), 1619 (C=O, amide), 1493, 1459.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.47 (br s, 1H, NH), 7.70 (app d, 1H, *J* = 7.8 Hz, C^5H), 7.36 (ddd, 1H, *J* = 8.1, 1.0, 0.9 Hz, C^8H), 7.18 (ddd, 1H, *J* = 8.2, 7.1, 1.3 Hz, C^7H), 7.11 (ddd, 1H, *J* = 8.0, 7.0, 1.1 Hz, C^6H), 7.04 (d, 1H, *J* = 2.3 Hz, C^2H), 4.17 (d, 1H, *J* = 1.9 Hz, $C^{18}Ha$), 4.14 (d, 1H, J = 2.1 Hz, $C^{18}Hb$), 3.75 (ddd, 1H, *J* = 13.0, 9.6, 6.0 Hz, $C^{11}Ha$), 3.57 (ddd, 1H, *J* = 13.0, 9.4, 6.1 Hz, $C^{11}Hb$), 3.21–3.31 (m, 2H, $C^{12}H_2$), 2.94–3.12 (m, 2H, $C^{10}H_2$), 1.88–2.10 (m, 3H, $C^{13}Ha$, $C^{14}Ha$, $C^{19}Ha$), 1.57–1.76 ($C^{13}Hb$, $C^{14}Hb$, $C^{19}Hb$), 0.99 (t, 9H, *J* = 7.9 Hz, $C^{22}H_3$, $C^{22'}H_3$, $C^{22''}H_3$), 0.93 (t, 3H, *J* = 7.3 Hz, $C^{20}H_3$), 0.72 (q, 6H, *J* = 7.6 Hz, $C^{21}H_2$, $C^{21'}H_2$, $C^{21''}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.7 (C^{16}), 160.4 (C^{17}), 136.4 (C^9), 127.6 (C^4), 122.3 (C^2), 121.9 (C^7), 119.3 (C^6), 118.9 (C^5), 113.2 (C^3), 111.3 (C^8), 89.5 (C^{18}), 53.6 (C^{15}), 48.8 (C^{11}, C^{12}), 29.7 (C^{19}), 28.3 (C^{14}), 23.4 (C^{10}), 19.7 (C^{13}), 9.9 (C^{20}), 6.9 (C^{22}, $C^{22'}$, $C^{22''}$), 5.0 (C^{21}, $C^{21'}$, $C^{21''}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{39}O_2N_2Si^+$) requires **m/z** 427.27753, found **m/z** 427.27728.

1-((3R,8'R,8a'S)-8'-ethyl-7-((methylthio)methyl)-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizin]-8'-yl)ethan-1-one (171)



$(COCl)_2$ (3.2 μL, 37 μmol) was added to a solution of DMSO (5.2 μL, 74 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C. The resulting solution was stirred for 5 min before **147e** (10 mg, 34 μmol) in CH_2Cl_2 (0.5 mL) was added. Stirring was maintained for 10 further min and NEt_3 (45 μL, 320 μmol) was added. The reaction mixture was allowed to reach rt, quenched with H_2O (0.5 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 0.5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification *via* prep TLC (9 : 1 CH_2Cl_2/MeOH) gave **171** as a yellow oil (2.3 mg, 19%).

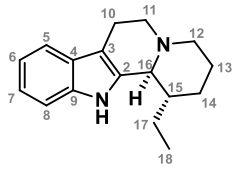
IR 3352 (br, N–H), 2931 (C–H), 1694 (C=O), 1599, 1456.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.98 (dd, 1H, *J* = 7.5, 1.2 Hz, C^5H), 6.86 (dd, 1H, *J* = 7.4, 1.1 Hz, C^7H), 6.67 (t, 1H, *J* = 7.5 Hz, C^6H), 4.32 (br s, 1H, NH), 3.91 (d, 1H, *J* = 9.9 Hz, C^2Ha), 3.61 (d, strong roof effect, 1H, *J* = 13.3 Hz, $C^{21}Ha$), 3.58 (d, strong roof effect, 1H, *J* = 13.3 Hz, $C^{21}Hb$), 3.23 (ddt, 1H, *J* = 11.0, 3.9, 1.7 Hz, $C^{12}Ha$), 3.19 (d, 1H, *J* = 9.9 Hz, C^2Hb), 3.16 (ddd, 1H, *J* = 9.3, 7.7, 3.3 Hz, $C^{11}Ha$), 2.63 (s, 1H, $C^{16}H$), 2.37 (app q, 1H, *J* = 8.8 Hz, $C^{11}Hb$), 2.29 (dt, 1H, J = 14.3, 7.2 Hz, $C^{19}Ha$), 2.23 (td, 1H, *J* = 11.4, 3.9 Hz, $C^{12}Hb$), 2.01–2.13 (m, 2H, $C^{10}Ha$, $C^{19}Hb$), 1.95 (s, 3H, $C^{22}H_3$), 1.85 (dt, 1H, J = 12.7 Hz, $C^{10}Hb$) 1.68–1.73 (m, 1H, $C^{14}Ha$), 1.57–1.67 (m, 2H, $C^{13}H_2$), 1.55 (s, 3H, $C^{18}H_3$), 1.46 (td, 1H, *J* = 13.2, 4.1 Hz, $C^{14}Hb$), 0.84 (t, 3H, *J* = 7.4 Hz, $C^{20}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 211.4 (C^{17}), 150.1 (C^{9}), 135.4 (C^{4}), 129.0 (C^{7}), 122.3 (C^{5}), 119.0 (C^{8}), 118.6 (C^{6}), 77.2 (C^{16}), 58.3 (C^{2}), 55.12 (C^{15}), 55.08 (C^{12}), 54.3 (C^{3}), 53.3 (C^{11}), 41.1 (C^{10}), 35.2 (C^{21}), 31.1 (C^{14}), 26.1 (C^{18}), 21.6 (C^{13}), 19.7 (C^{19}), 14.8 (C^{22}), 9.6 (C^{20}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{31}ON_2S^+$) requires **m/z** 359.21516, found **m/z** 359.21530.

(1SR,12bSR)-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (173)



$(COCl)_2$ (3.6 μL, 42 μmol) was added to a solution of DMSO (6.0 μL, 85 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C. The resulting solution was stirred for 5 min before **147e** (11.5 mg, 39 μmol) in CH_2Cl_2 (0.5 mL) was added. Stirring was maintained for 10 further min and NEt_3 (51 μL, 0.37 mmol) was added. The reaction mixture was allowed to reach rt, quenched with H_2O (0.5 mL), the layers separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 0.5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification *via* prep TLC (9 : 1 CH_2Cl_2/MeOH) gave **173** as a yellow oil (2.3 mg, 24%).

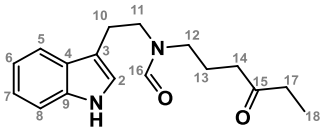
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.80 (br s, 1H, NH), 7.48 (app d, 1H, J = 7.7 Hz, C^5H), 7.32 (ddd, 1H, J = 8.1, 1.0, 0.9 Hz, C^8H), 7.14 (ddd, 1H, J = 8.1, 7.1, 1.3 Hz, C^7H), 7.09 (ddd, 1H, J = 8.0, 7.1, 1.1 Hz, C^6H), 3.69 (d, 1H, J = 6.0 Hz, $C^{16}H$), 3.23–3.28 (m, 1H, $C^{11}Ha$), 2.86–3.00 (m, 3H, $C^{10}Ha$, $C^{11}Hb$, $C^{12}Ha$), 2.64–2.72 (m, 2H, $C^{10}Hb$, $C^{12}Hb$), 1.81–1.91 (m, 2H, $C^{15}H$, $C^{17}Ha$), 1.58–1.74 (m, 4H, $C^{13}H_2$, $C^{14}Ha$, $C^{17}Hb$), 1.32–1.40 (m, 1H, $C^{14}Hb$), 1.03 (t, 3H, J = 7.3 Hz, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 135.8 (C^9), 134.7 (C^2), 127.5 (C^4), 121.5 (C^7), 119.4 (C^6), 118.2 (C^5), 110.8 (C^8), 109.1 (C^3), 61.0 (C^{16}), 51.9 (br, C^{12}), 50.9 (C^{11}), 38.6 (C^{15}), 27.8 (br, C^{14}), 25.5 (C^{17}), 22.2 (C^{13}), 20.2 (C^{10}), 11.6 (C^{18}).

Note: Slight differences were observed with the literature, in particular for carbons and protons in close proximity to the tertiary amine. We believe this is due to a slightly different protonation state.

All other data in agreement with literature.[10]

N-(2-(1H-indol-3-yl)ethyl)-N-(4-oxohexyl)formamide (176)



A suspension of **147e** (4.5 mg, 15 μmol) and MnO_2 (fine powder, 24 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) was stirred at rt for 8 h. The suspension was filtered on celite®, rinsed with CH_2Cl_2 and concentrated *in vacuo*. Purification *via* prep TLC gave **176** as a 3 : 2 mixture of rotamers (2.3 mg, 53%) and as a yellow oil.

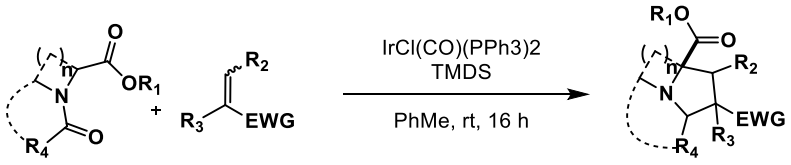
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.97–8.08 (m, 1.4H, NH, $C^{16}H$ (**B**)), 7.77 (s, 0.6H, $C^{16}H$ (**A**)), 7.66 (app d, 0.4H, J = 7.8 Hz, C^5H (**B**)), 7.56 (app d, 0.6H, J = 7.9 Hz, C^5H (**A**)), 7.35–7.39 (m, 1H, C^8H), 7.18–7.24 (m, 1H, C^7H), 7.11–7.16 (m, 1H, C^6H), 7.07 (d, 0.4H, J = 2.4 Hz, C^2H (**B**)), 6.97 (d, 0.6H, J = 2.3 Hz, C^2H (**A**)), 3.60–3.64 (m, 0.8H, $C^{11}H_2$ (**B**)), 3.53 (t, 1.2H, J = 7.0 Hz, $C^{11}H_2$ (**A**)), 3.38 (dd, 1.2H, J = 7.9, 6.6 Hz, $C^{12}H_2$ (**A**)), 3.17 (t, 0.8H, J = 7.1Hz, $C^{12}H_2$ (**B**)), 2.32–2.47 (m, 4H, $C^{14}H_2$, $C^{17}H_2$), 1.86 (p, 1.2H, J = 7.1 Hz, $C^{13}H_2$ (**A**)), 1.79 (p, 0.8H, J = 7.0 Hz, $C^{13}H_2$ (**B**)), 1.05 (t, 1.8H, J = 7.3 Hz, $C^{18}H_3$ (**A**)), 1.04 (t, 1.2H, J = 7.3 Hz, $C^{18}H_3$ (**B**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 211.0 (C^{15} (**A**)), 210.2 (C^{15} (**B**)), 163.3 (C^{16} (**A**)), 163.0 (C^{16} (**B**)), 136.5 (C^9 (**A**)), 136.3 (C^9 (**B**)), 127.5 (C^4 (**B**)), 127.0 (C^4 (**A**)), 122.6 (C^2 (**A**)), 122.5 (C^7 (**A**)), 122.3 (C^7 (**B**)), 122.1 (C^2 (**B**)), 119.8 (C^6 (**A**)), 119.7 (C^6 (**B**)), 118.9 (C^5 (**B**)), 118.5 (C^5 (**A**)), 113.0 (C^3 (**B**)), 111.9 (C^3 (**A**)), 111.5 (C^8 (**A**)), 111.3 (C^8 (**B**)), 47.8 (C^{11} (**A**)), 47.1 (C^{12} (**B**)), 43.1 (C^{11} (**B**)), 41.5 (C^{12} (**A**)), 39.4 (C^{14} (**A**)), 38.4 (C^{14} (**B**)), 36.2 (C^{17} (**B**)), 36.2 (C^{17} (**A**)), 25.1 (C^{10} (**A**)), 23.4 (C^{10} (**B**)), 22.6 (C^{13} (**B**)), 21.6 (C^{13} (**A**)), 8.0 (C^{18} (**A**)), 7.9 (C^{18} (**B**)).

All other data in agreement with literature.[11]

6.3 Experimental Details for Chapter 3

6.3.1 General Procedure F: cycloaddition of amides and lactams

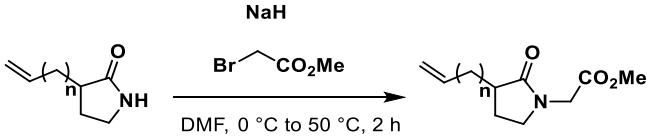


The amide (0.25 mmol), the coupling partner (0.28 mmol) and Vaska's complex (2.0 mg, 1 mol%) were loaded in a dried Schlenk tube under inert conditions. Toluene (1 mL) was introduced under a positive flow of nitrogen, followed by TMDS (88 μL, 0.50 mmol). The Schlenk tube was connected to a nitrogen line equipped with an oil bubbler, allowing gas to escape the reaction vessel. Upon addition of TMDS, bubbling should be observed within 10–15 s. The resulting solution was stirred for 16 h.

Note: For oily or liquid amides/lactams, Vaska's complex was introduced after the toluene. Sometimes poor conversion was observed when the iridium catalyst was added in neat substrate.

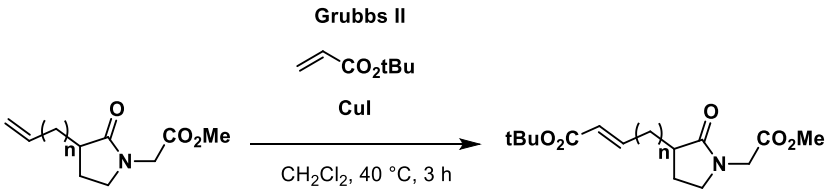
The reaction mixture was then loaded on a small Silica gel column (bubbling can occur), the reaction vessel rinsed with 8 : 1 EtOAc/MeOH, and this was also loaded on the silica gel column. Elution was performed with the above solvent (3 × 5 mL). The resulting solution was then concentrated *in vacuo*. Purification *via* FCC afforded the corresponding product.

6.3.2 General Procedure G: alkylation of lactams



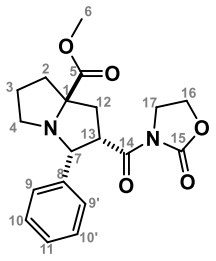
The lactam was dissolved in anhydrous DMF (4 mL/mmol substrate). NaH was added carefully portionwise (2.00 equiv.), and the resulting suspension was placed in a pre-heated oil bath at 50 °C for 30 min (to help dissolution of the sodium salt). The reaction mixture was then cooled down to 0 °C, and methyl bromoacetate was added dropwise. The reaction flask was placed back in the oil bath, and left to stir at 50 °C for 2 h. It was cooled down to rt, and quenched with saturated NH_4Cl (1mL/mmol substrate). Extraction with EtOAc (3 × 10 mL/mmol substrate) was then carried out. The combined organics washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC afforded the corresponding product.

6.3.3 General Procedure H: cross-metathesis



The lactam was dissolved in degassed CH_2Cl_2 (3 mL/mmol substrate). *t*-butyl acrylate was added (3.00 equiv.), followed by CuI (6 mol%) and Grubbs-II (5 mol%). The resulting solution was heated for 3 h at 40 °C. The reaction mixture was cooled down to rt and directly loaded on a Silica Gel Column.

methyl (2S,3R,7aR)-2-(2-oxooxazolidine-3-carbonyl)-3-phenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (198)



Prepared according to **General Procedure F** from **192**. Purification *via* FCC (4 : 1 pentane/EtOAc) gave **198** as a pale yellow oil (77 mg, 86%).

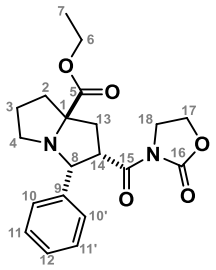
IR 2953, 1778 (C^{14}=O), 1726 (C^{5}=O), 1698 (C^{15}=O), 1478, 1457, 1387, 1366, 1285, 1224, 1197.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.23–7.31 (m, 3H, C^{10}H, $C^{10'}$H, C^{11}H), 7.15–7.19 (2H, m, C^{9}H, $C^{9'}$H), 4.95 (d, 1H, J = 9.4 Hz, C^{7}H), 4.79 (ddd, 1H, J = 11.5, 9.3, 7.6 Hz, C^{13}H), 4.15 (td, 1H, J = 9.0, 5.7 Hz, C^{16}Ha), 3.83 (td, 1H, J = 8.9, 7.9 Hz, C^{16}Hb), 3.77 (s, 3H, $C^{6}H_3$), 3.70 (ddd, 1H, J = 10.9, 9.3, 7.8 Hz, C^{17}Ha), 3.04 (ddd, 1H, J = 10.9, 9.1, 5.6 Hz, C^{17}Hb), 2.65–2.74 (m, 2H, $C^{4}H_2$), 2.45–2.56 (m, 2H, $C^{12}H_2$) 2.35 (ddd, 1H, J = 11.4, 6.7, 3.8 Hz, C^{2}Ha), 1.89–2.06 (m, 3H, C^{2}Hb, $C^{3}H_2$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.1 (C^{5}), 172.0 (C^{14}), 152.8 (C^{15}), 138.1 (C^{8}), 129.4 (C^{9}, $C^{9'}$), 128.2 (C^{10}, $C^{10'}$), 128.1 (C^{11}), 76.1 (C^{1}), 65.2 (C^{7}), 62.1 (C^{16}), 53.0 (C^{13}), 52.4 (C^{6}), 46.4 (C^{4}), 42.7 (C^{17}), 36.1 (C^{12}), 35.8 (C^{2}), 28.0 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_5N_2^+$) requires **m/z** 359.1600, found **m/z** 359.1601.

ethyl (2S,3R,7aR)-2-(2-oxooxazolidine-3-carbonyl)-3-phenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (209)



Prepared according to **General Procedure F** from **200**. Purification *via* FCC (8 : 1 pentane/EtOAc) gave **209** as a pale yellow oil (66 mg, 71%).

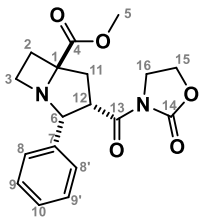
IR 2979, 1778 (C^{15}=O), 1721 (C^{5}=O), 1698 (C^{16}=O), 1457, 1387, 1366, 1284, 1095.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.22–7.30 (m, 3H, C^{11}H, $C^{11'}$H, C^{12}H), 7.14–7.19 (m, 2H, C^{10}H, C10'H), 4.94 (d, 1H, J = 9.3 Hz, C^{8}H), 4.82 (ddd, 1H, J = 11.6, 9.3, 7.4 Hz, C^{14}H), 4.22 (q, 2H, J = 7.1 Hz, $C^{6}H_2$), 4.15 (td, 1H, J = 9.0, 5.6 Hz, C^{17}Ha), 3.82 (td, 1H, J = 8.9, 8.0 Hz, C^{17}Hb), 3.69 (ddd, 1H, J = 11.0, 9.4, 7.9 Hz, C^{18}Ha), 3.02 (ddd, 1H, J = 10.8, 9.1, 5.6 Hz, C^{18}Hb), 2.65–2.73 (m, 2H, $C^{4}H_2$), 2.42–2.54 (m, 2H, $C^{13}H_2$), 2.35 (ddd, 1H, J = 12.2, 7.0, 3.9 Hz, C^{2}Ha), 1.97–2.04 (m, 2H, $C^{3}H_2$), 1.90 (ddd, 1H, J = 12.3, 9.7, 7.9 Hz, C^{2}Hb), 1.32 (t, 3H, J = 7.1 Hz, $C^{7}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 176.4 (C^{5}), 172.0 (C^{15}), 152.9 (C^{16}), 138.3 (C^{9}), 129.3 (C^{10}, $C^{10'}$), 128.2 (C^{11}, $C^{11'}$), 128.0 (C^{12}), 76.1 (C^{1}), 64.9 (C^{8}), 62.1 (C^{17}), 61.0 (C^{6}), 53.1 (C^{14}), 46.1 (C^{4}), 42.6 (C^{18}), 35.9 (C^{13}), 35.5 (C^{2}), 28.0 (C^{3}), 14.4 (C^{7}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}O_5N_2^+$) requires **m/z** 373.1758, found **m/z** 373.1759.

methyl (2R,3S,5S)-3-(2-oxooxazolidine-3-carbonyl)-2-phenyl-1-azabicyclo[3.2.0]heptane-5-carboxylate (210)



Prepared according to **General Procedure F** from **202**. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **210** as a pale yellow oil (60 mg, 69%).

mp 94–96 °C

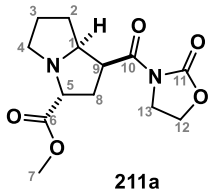
IR Missing

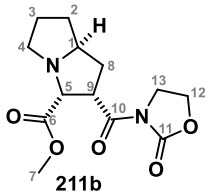
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.24–7.31 (m, 5H, $C^{8}H$, $C^{8'}H$, $C^{9}H$, $C^{9'}H$, $C^{10}H$), 4.98 (roofed d, 1H, J = 9.8 Hz, $C^{6}H$), 4.89 (dt, 1H, J = 9.8, 8.5 Hz, $C^{12}H$), 4.15 (ddd, 1H, J = 9.0, 8.1, 5.6 Hz, $C^{15}Ha$), 3.93 (app q, 1H, J = 8.1 Hz, $C^{3}Ha$), 3.80–3.87 (m, 1H, $C^{16}Ha$), 3.79 (s, 3H, $C^{5}H_3$), 3.71–3.79 (m, 1H, $C^{15}Ha$), 3.42 (ddd, 1H, J = 10.0, 8.6, 5.6 Hz, $C^{16}Hb$), 3.12 (td, 1H, J = 8.2, 3.0 Hz, $C^{3}Hb$), 3.07 (dd, 1H, J = 14.0, 8.3 Hz, $C^{11}Ha$), 2.74 (dt, 1H, J = 10.8, 8.5 Hz, $C^{2}Ha$), 2.62 (dd, 1H, J = 14.0, 8.8 Hz, $C^{11}Hb$), 2.26 (ddd, 1H, J = 11.0, 8.2, 3.0 Hz, $C^{2}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.9 (C^{13}), 174.0 (C^{4}), 152.8 (C^{14}), 135.8 (C^{7}), 129.2 (C^{9}, $C^{9'}$), 128.2 (C^{8}, $C^{8'}$), 127.9 (C^{10}), 75.0 (C^{1}), 70.9 (C^{6}), 61.9 (C^{15}), 52.5 (C^{5}), 52.0 (C^{12}), 44.6 (C^{3}), 42.9 (C^{16}), 38.1 (C^{11}), 27.2 (C^{2}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}O_5N_2^+$) requires **m/z** 345.14450, found **m/z** 345.14448.

methyl (1S,3R,7aS)-1-(2-oxooxazolidine-3-carbonyl)hexahydro-1H-pyrrolizine-3-carboxylate (211a) methyl (2S,3R,7aS)-2-(2-oxooxazolidine-3-carbonyl)hexahydro-1H-pyrrolizine-3-carboxylate (211b)





Prepared according to **General Procedure F** from **207** to afford an 82 : 18 mixture of regioisomers **211a** and **211b**, respectively. Purification *via* FCC (3 : 7 pentane/EtOAc) gave a 93 : 7 mixture of **211a** and **211b**, respectively (46 mg, 65%).

Data for **211a**

IR 2955, 1776 (C^{10}=O), 1738 (C^{6}=O), 1691 (C^{11}=O), 1387, 1266, 1204.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 4.39-4.44 (m, 2H, $C^{12}H_2$), 4.33 (td, 1H, J = 8.0, 6.0 Hz, C^{9}H), 4.16 (td, 1H, J = 8.7, 6.8 Hz, C^{1}H), 3.96–4.09 (m, 2H, $C^{13}H_2$), 3.73 (s, 3H, $C^{7}H_3$), 3.69-3.74 (m, 1H, C^{5}H), 3.21 (ddd, 1H, J = 9.9, 6.1, 4.2 Hz, C^{4}Ha), 2.57–2.63 (m, 2H, C^{4}Hb, C^{8}Ha), 2.22 (ddd, 1H, J = 13.0, 7.6, 6.5 Hz, C^{8}Hb), 1.84–1.91 (m, 2H, $C^{3}H_2$), 1.76 (1H, dtd, J = 12.1, 6.5, 4.4 Hz, C^{2}Ha), 1.20–1.29 (1H, m, C^{2}Hb).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.4 (C^{6}), 173.6 (C^{10}), 153.2 (C^{11}), 67.6 (C^{5}), 66.8 (C^{1}), 62.1 (C^{12}), 55.3 (C^{4}), 52.3 (C^{7}), 45.3 (C^{9}), 42.8 (C^{13}), 32.6 (C^{8}), 28.2 (C^{2}), 27.3 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}O_5N_2^+$) requires **m/z** 283.1288, found **m/z** 283.1288.

Further elution (3 : 7 pentane/EtOAc) gave a 2 : 5 mixture of **211a** and **211b**, respectively.

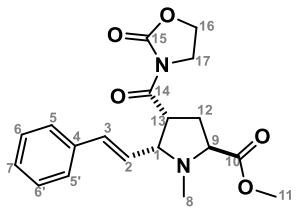
Data for **211b** :

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H [selected peaks]: 4.53 (ddd, 1H, J = 11.5, 9.3, 6.9 Hz, C^9H), 3.92 (d, 1H, J = 9.3 Hz, C^5H), 3.72 (s, 3H, C^7H_3), 3.15 (dt, 1H, J = 11.6, 6.1 Hz, C^4Ha), 2.80 (dt, 1H, J = 10.4, 6.4 Hz, C^4Hb), 2.49 (dt, 1H, J = 11.9, 6.6 Hz, C^8Ha).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C [selected peaks]: 70.6 (C^5), 55.4 (C^4), 48.3 (C^9), 36.9 (C^8).

Scale-up : Reaction performed on 2 mmol scale without further modifications gave 367 mg, 65% (combined).

methyl (2S,4R,5R)-1-methyl-4-(2-oxooxazolidine-3-carbonyl)-5-((E)-styryl)pyrrolidine-2-carboxylate (212)



Prepared according to **General Procedure F** from **208**. Purification *via* FCC (3 : 2 pentane/EtOAc) gave **212** as a pale yellow oil (66 mg, 70%).

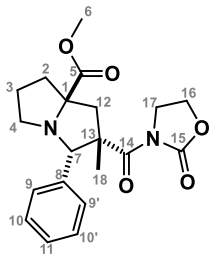
IR 2952 (br, N–H), 1777 (C^{14}=O), 1731 (C^{10}=O), 1696 (C^{15}=O), 1450, 1387, 1361, 1261, 1200, 1171.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.31–7.35 (m, 2H, C^5H, $C^{5'}$H), 7.27–7.31 (m, 2H, C^6H, $C^{6'}$H), 7.21–7.25 (m, 1H, C^7H), 6.56 (d, 1H, J = 15.8 Hz, C^3H), 5.87 (dd, 1H, J = 15.8, 9.5 Hz, C^2H), 4.71 (app q, 1H, J = 9.1 Hz, C^{13}H), 4.18–4.25 (m, 1H, C^{16}Ha), 4.11 (t, 1H, J = 9.5 Hz, C^1H), 3.89–3.95 (m, 2H, C^{16}Hb, C^{17}Ha), 3.87 (dd, 1H, J = 8.3, 2.2 Hz, C^9H), 3.73–3.79 (m, 1H, C^{17}Hb), 3.74 (s, 3H, $C^{11}H_3$), 2.91 (ddd, 1H, J = 13.1, 9.2, 8.3 Hz, C^{12}Ha), 2.35 (s, 3H, C^8H_3), 2.02 (ddd, 1H, J = 13.1, 8.6, 2.2 Hz, C^{12}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 173.8 (C^{10}), 172.5 (C^{14}), 153.2 (C^{15}), 136.5 (C^4), 133.8 (C^3), 128.8 (C^6, $C^{6'}$), 128.0 (C^7), 127.8 (C^2), 126.5 (C^5, $C^{5'}$), 67.2 (C^1), 65.5 (C^9), 62.1 (C^{16}), 51.6 (C^{11}), 46.4 (C^{13}), 42.9 (C^{17}), 35.7 (C^8), 30.1 (C^{12}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}O_5N_2^+$) requires **m/z** 359.1602, found **m/z** 359.1601.

methyl (2S,3S,7aR)-2-methyl-2-(2-oxooxazolidine-3-carbonyl)-3-phenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (214)



Prepared according to **General Procedure F** from **192**. Purification *via* FCC (4 : 1 pentane/EtOAc) gave **214** as a white solid (77 mg, 83%).

mp 98–100 °C

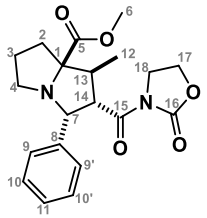
IR 2951 (br, C–H), 1783 (C^{14}=O), 1725 (C^{5}=O), 1680 (C^{15}=O), 1476, 1383, 1360, 1308, 1276, 1201.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.24–7.30 (m, 3H, C^{10}H, $C^{10'}$H, C^{11}H), 7.15–7.19 (m, 2H, C^{9}H, $C^{9'}$H), 4.99 (s, 1H, C^{7}H), 4.08 (td, 1H, J = 8.8, 5.4 Hz, C^{16}Ha), 3.78 (s, 3H, $C^{6}H_3$), 3.73 (ddd, 1H, J = 10.9, 9.0, 8.1 Hz, C^{17}Ha), 3.56 (app q, 1H, J = 8.5 Hz, C^{16}Hb), 3.22 (ddd, 1H, J = 10.9, 8.5, 5.4 Hz, C^{17}Hb), 2.93 (roofed d, 1H, J = 14.1 Hz, C^{12}Ha), 2.84 (roofed d, 1H, J = 14.1 Hz, C^{12}Hb), 2.78–2.85 (m, 1H, C^{4}Ha), 2.52 (dt, 1H, J = 10.7, 6.8 Hz, C^{4}Hb), 2.13 (ddd, 1H, J = 12.8, 7.5, 5.3 Hz, C^{2}Ha), 1.92 (dt, 1H, J = 12.8, 8.2 Hz, C^{2}Hb), 1.68–1.77 (m, 4H, C^{3}Ha, $C^{18}H_3$), 1.55–1.64 (m, 1H, C^{3}Hb).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 178.9 (C^{5}), 174.9 (C^{14}), 151.2 (C^{15}), 139.4 (C^{8}), 129.5 (br, C^{9}, $C^{9'}$), 128.4 (C^{10}, $C^{10'}$), 127.9 (C^{11}), 75.2 (C^{1}), 71.4 (C^{7}), 62.2 (C^{16}), 60.3 (C^{13}), 52.7 (C^{6}), 48.6 (C^{4}), 47.9 (C^{12}), 44.4 (C^{17}), 39.8 (C^{2}), 27.4 (C^{3}), 23.2 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}O_5N_2^+$) requires **m/z** 373.1758, found **m/z** 373.1758.

methyl (1S,2S,3R,7aR)-1-methyl-2-(2-oxooxazolidine-3-carbonyl)-3-phenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (215)



Prepared according to **General Procedure F**. from **192**. Purification *via* FCC (4 : 1 pentane/EtOAc) gave **215** as a pale yellow oil (48 mg, 52%).

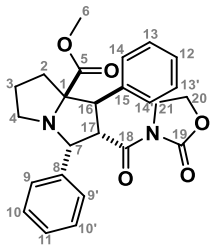
IR 1777 (C^{15}=O), 1724 (C^{5}=O), 1692 (C^{16}=O), 1386, 1221, 703.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.31–7.21 (m, 3H, C^{10}H, $C^{10'}$H C^{11}H), 7.13–7.18 (m, 2H, C^{9}H, $C^{9'}$H), 5.10 (d, 1H, J = 9.5 Hz, C^{7}H), 4.60 (dd, 1H, J = 11.7, 9.5 Hz, C^{14}H), 4.14 (ddd, 1H, J = 9.3, 8.6, 5.7 Hz, C^{17}Ha), 3.85–3.78 (m, 1H, C^{17}Hb), 3.77 (s, 3H, $C^{6}H_3$), 3.67 (ddd, 1H, J = 10.8, 9.3, 7.8 Hz, C^{18}Ha), 2.95 (ddd, 1H, J = 10.8, 9.1, 5.7 Hz, C^{18}Hb), 2.83 (dq, 1H, J = 11.6, 6.7 Hz, C^{13}H), 2.68–2.56 (m, 2H, C^{2}Ha, C^{4}Ha), 2.50 (ddd, 1H, J = 9.2, 7.3, 4.3 Hz, C^{4}Hb), 1.91–2.01 (m, 1H, C^{3}Ha), 1.80–1.90 (m, 1H, C^{3}Hb) 1.72 (ddd, 1H, J = 12.1, 9.5, 7.9 Hz, C^{2}Hb), 0.97 (d, 3H, J = 6.8 Hz, $C^{12}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.0 (C^{5}), 171.7 (C^{15}), 152.8 (C^{16}), 138.2 (C^{8}), 129.4 (C^{9}), 128.1 (C^{10}), 127.9 (C^{11}), 79.9 (C^{1}), 64.8 (C^{7}), 62.1 (C^{17}), 60.1 (C^{14}), 51.9 (C^{6}), 46.11 (C^{4}), 43.20 (C^{13}), 42.5 (C^{18}), 34.2 (C^{2}), 28.0 (C^{3}), 14.3 (C^{12}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}N_2O_5^+$) requires **m/z** 373.1758, found **m/z** 373.1758.

methyl (1R,2S,3R,7aR)-2-(2-oxooxazolidine-3-carbonyl)-1,3-diphenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (216)



Prepared according to **General Procedure F** from **192**. Purification *via* FCC (6 : 1 pentane/EtOAc) gave **216** as a pale yellow oil (69 mg, 64%).

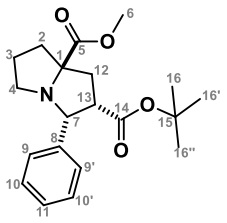
IR 2949 (C–H), 1778 (C^{18}=O), 1727 (C^{5}=O), 1697 (C^{19}=O), 1387, 1280, 1223.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.19–7.36 (m, 10H, C^{9}H, $C^{9'}$H, C^{10}H, $C^{10'}$H, C^{11}H, C^{12}H, C^{13}H, $C^{13'}$H, C^{14}H, $C^{14'}$H), 5.63 (dd, 1H, J = 11.9, 9.5 Hz, C^{17}H), 5.28 (d, 1H, J = 9.5 Hz, C^{7}H), 4.09–4.15 (m, 2H, C^{16}H, C^{20}Ha), 3.84 (app td, 1H, J = 9.0, 7.6 Hz, C^{20}Hb), 3.59 (ddd, 1H, J = 10.9, 9.3, 7.5 Hz, C^{21}Ha), 3.49 (s, 3H, $C^{6}H_3$), 2.91 (ddd, 1H, J = 10.9, 9.2, 6.0 Hz, C^{21}Hb), 2.76 (app dt, 1H, J = 8.4, 7.0 Hz, C^{4}Ha), 2.62–2.67 (m, 1H, C^{2}Ha), 2.55 (ddd, 1H, J = 8.7, 7.3, 3.9 Hz, C^{4}Hb), 2.06–2.13 (m, 1H, C^{3}Ha), 1.88–2.01 (m, 2H, C^{2}Hb, C^{3}Hb).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.9 (C^{5}), 171.1 (C^{18}), 153.1 (C^{19}), 138.3 (C^{8}), 137.1 (C^{15}), 129.4 (C^{9}, $C^{9'}$), 128.6 (C^{10} or C^{13}, $C^{10'}$ or $C^{13'}$), 128.2 (C^{10} or C^{13}, $C^{10'}$ or $C^{13'}$), 128.1 (C^{11} or C^{12}), 127.7 (C^{14}, $C^{14'}$), 127.5 (C^{11} or C^{12}), 81.1 (C^{1}), 64.2 (C^{7}), 62.1 (C^{20}), 57.3 (C^{17}), 53.6 (C^{16}), 51.7 (C^{6}), 45.2 (C^{4}), 42.5 (C^{21}), 34.4 (C^{2}), 28.0 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{27}N_2O_5^+$) requires **m/z** 435.1914, found **m/z** 435.1908.

2-(tert-butyl) 7a-methyl (2S,3R,7aR)-3-phenyltetrahydro-1H-pyrrolizine-2,7a(5H)-dicarboxylate (217)



Prepare according to **General Procedure F** from **192** and the corresponding (2.5 equiv.). Purification *via* FCC (93 : 7 to 90 : 10 pentane/EtOAc) gave **217** as a pale yellow oil (71 mg, 82%).

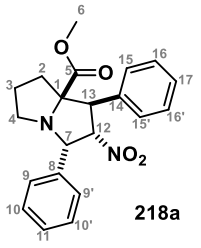
IR 2976, 1727 (C^5=O, C^{14}=O), 1458, 1392, 1156.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.22–7.32 (m, 3H, C^{10}H, $C^{10'}$H, C^{11}H), 7.16–7.20 (m, 2H, C^9H, $C^{9'}$H), 4.66 (d, 1H, J = 8.8 Hz, C^7H), 3.81 (ddd, 1H, J = 13.2, 8.9, 7.2 Hz, C^{13}H), 3.75 (s, 3H, C^6H_3), 2.67–2.73 (m, 1H, C^4Ha), 2.52–2.60 (m, 2H, C^4Hb, C^{12}Ha), 2.29–2.40 (m, 2H, C^2Ha, C^{12}Hb), 1.77–1.93 (m, 3H, C^2Hb, C^3H_2), 0.98 (s, 9H, $C^{16}H_3$, $C^{16'}H_3$, $C^{16''}H_3$).

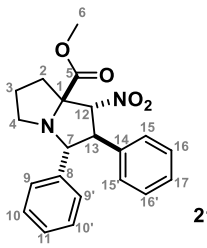
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.7 (C^5), 170.8 (C^{14}), 138.7 (C^8), 129.8 (br, C^9, $C^{9'}$), 128.3 (C^{10}, $C^{10'}$), 127.8 (C^{11}), 80.5 (C^{15}), 75.2 (C^1), 67.6 (C^7), 53.0 (C^{13}), 52.5 (C^6), 47.6 (C^4), 37.2 (C^{12}), 36.5 (C^2), 28.3 (C^3), 27.5 (C^{16}, $C^{16'}$, $C^{16''}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{28}O_4N^+$) requires **m/z** 346.2013, found **m/z** 346.2014.

methyl (1S,2S,3S,7aR)-2-nitro-1,3-diphenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (218a) and methyl (1R,2S,3R,7aR)-1-nitro-2,3-diphenyltetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (218b)



218a



218b

Prepared according to **General Procedure F** from **192**. Purification *via* FCC (9 : 1 pentane/EtOAc) gave **218a** as a pale yellow oil (41 mg, 44%).

Data for **218a**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.26–7.39 (m, 8H, $C^{9}H$, $C^{9'}H$, $C^{10}H$, $C^{10'}H$, $C^{11}H$, $C^{16}H$, $C^{16'}H$, $C^{17}H$), 7.19–7.23 (m, 2H, $C^{15}H$, $C^{15'}H$), 6.36 (dd, 1H, J = 11.1, 8.9 Hz, $C^{12}H$), 5.27 (d, 1H, J = 8.8 Hz, $C^{7}H$), 4.31 (d, 1H, J = 11.2 Hz, $C^{13}H$), 3.43 (s, 3H, $C^{6}H_3$), 2.88 (dt, 1H, J = 8.7, 7.3 Hz, $C^{4}Ha$), 2.73–2.79 (m, 1H, $C^{2}Ha$), 2.61 (td, 1H, J = 8.2, 3.4 Hz, $C^{4}Hb$), 2.17–2.24 (m, 1H, $C^{3}Ha$), 1.96–2.06 (m, 2H, $C^{2}Hb$, $C^{3}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.1 (C^{5}), 134.9 (C^{8}), 134.4 (C^{14}), 129.3 (C^{9}, $C^{9'}$), 129.1 (C^{11}), 128.9 (C^{10} or C^{16}), 128.6 (C^{10} or C^{16}), 128.1 (C^{17}), 127.2 (C^{15}, $C^{15'}$), 94.0 (C^{12}), 80.1 (C^{1}), 65.6 (C^{7}), 53.9 (C^{13}), 51.9 (C^{6}), 44.9 (C^{4}), 34.3 (C^{2}), 27.8 (C^{3}).

All other data in perfect agreement with literature.[12]

Further elution (9 : 1 pentane/EtOAc) gave regioisomer **218b** as a pale yellow oil (41 mg, 44%).

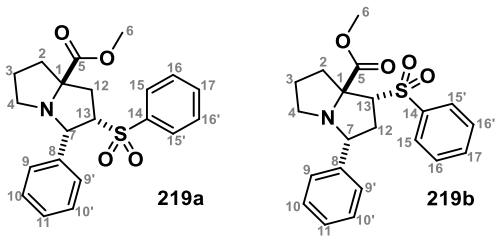
Data for **218b**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.35–7.39 (m, 4H, C^9H, $C^{9'}H$, $C^{15}H$, $C^{15'}H$), 7.25–7.33 (m, 4H, $C^{10}H$, $C^{10'}H$, $C^{16}H$, $C^{16'}H$), 7.17–7.24(m, 2H, $C^{11}H$, $C^{17}H$), 5.95 (d, 1H, J = 10.2 Hz, $C^{12}H$), 4.85 (d, 1H, J = 12.3 Hz, C^7H), 4.44 (dd, 1H, J = 12.3, 10.2 Hz, $C^{13}H$), 3.93 (s, 3H, C^6H_3), 2.64 (ddd, 1H, J = 11.5, 9.1, 5.6 Hz, C^4Ha), 2.45–2.51 (m, 2H, C^2Ha, C^4Hb), 1.86–1.94 (m, 1H, C^3Ha), 1.80–1.86 (m, 1H, C^3Hb), 1.60 (ddd, 1H, J = 13.4, 11.8, 7.2 Hz, C^2Hb).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 173.6 (C^5), 136.4 (C^{14}), 134.9 (C^8), 129.4 (C^9, $C^{9'}$), 129.2 (C^{10} or C^{16}), 128.5 (C^{10} or C^{16}), 128.2 (C^{11} or C^{17}), 128.1 (C^{15}, $C^{15'}$), 127.9 (C^{11} or C^{17}), 97.7 (C^{12}), 76.3 (C^1), 68.0 (C^7), 53.6 (C^6), 51.0 (C^4), 48.2 (C^{13}), 32.2 (C^2), 25.6 (C^3).

All other data in perfect agreement with literature.[12]

methyl (2S,3S,7aR)-3-phenyl-2-(phenylsulfonyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (219a) and methyl (1R,3R,7aS)-3-phenyl-1-(phenylsulfonyl)tetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (219b)



Prepared according to **General Procedure F** from **192**. Purification *via* FCC (98 : 2 to 60 : 40 pentane/EtOAc) gave a 53 : 47 mixture of **219a** (**A**) and **219b** (**B**), respectively, as a white solid (74 mg, 77%).

mp 104–106 °C (from EtOAc).

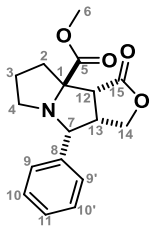
IR 1728 (C^5=O), 1447, 1291 (S=O), 1149, 1086, 721, 690.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.96–8.01 (m, 0.94H, $C^{15}H$ (**B**), $C^{15'}H$ (**B**)), 7.64–7.70 (m, 0.47H, $C^{17}H$ (**B**)), 7.52–7.62 (m, 1.47H, $C^{17}H$ (**A**), $C^{16}H$ (**B**), $C^{16'}H$ (**B**)), 7.42–7.46 (m, 1.06H, $C^{15}H$ (**A**), $C^{15'}H$ (**A**)), 7.23–7.40 (m, 5H, $C^{9}H$ (**B**), $C^{9'}H$ (**B**), $C^{10}H$ (**A**), $C^{10'}H$ (**A**), $C^{10}H$ (**B**), $C^{10'}H$ (**B**), $C^{11}H$ (**A**), $C^{11}H$ (**B**), $C^{16}H$ (**A**), $C^{16'}H$ (**A**)), 7.05–7.09 (m, 1.06H, $C^{9}H$ (**A**), $C^{9'}H$ (**A**)), 4.62 (dd, 0.47H, J = 12.3, 6.2 Hz, $C^{7}H$ (**B**)), 4.51–4.60 (m, 1.06H, $C^{7}H$ (**A**), $C^{13}H$ (**A**)), 4.38 (dd, 0.47H, J = 12.8, 4.0 Hz, $C^{13}H$ (**B**)), 3.76 (s, 1.41H, $C^{6}H_3$ (**B**)), 3.73 (s, 1.59H, $C^{6}H_3$ (**A**)), 2.35–2.78 (m, 5H, $C^{2}H_2$ (**B**), $C^{2}Ha$ (**A**), $C^{4}H_2$ (**A**), $C^{4}H_2$ (**B**), $C^{12}H_2$ (**A**), $C^{12}Ha$ (**B**)), 2.15 (ddd, 0.47H, J = 11.6, 6.3, 4.1 Hz, $C^{12}Hb$ (**B**)), 1.86–1.61 (m, 2.53H, $C^{2}Hb$ (**A**), $C^{3}H_2$ (**A**), $C^{3}H_2$ (**B**)).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.4 (C^5 (**B**)), 174.6 (C^5 (**A**)), 140.7 (C^{14} (**B**)), 139.2 (C^{14} (**A**)), 136.7 (C^8 (**B**)), 134.7 (C^8 (**A**)), 133.9 (C^{17} (**B**)), 133.4 (C^{17} (**A**)), 131.0 (C^9, $C^{9'}$ (**A**)), 129.4 (C^{16}, $C^{16'}$ (**B**)), 129.0 (C^{16} (**A**), $C^{16'}$ (**A**)), 128.7 (C^9, $C^{9'}$ (**B**)), 128.5 (C^{11} (**B**)), 128.4 (C^{11} (**A**)), 128.23 (C^{15} (**A**)), 128.19 (C^{15} (**B**)), 127.99 (C^{10}, $C^{10'}$(**B**)), 127.97 (C^{10}, $C^{10'}$ (**A**)), 76.2 (C^1 (**A**)), 75.7 (C^1 (**B**)), 70.1 (C^7 (**A**)), 68.5 (C^7 (**B**)), 66.2 (C^{13} (**A**)), 64.0 (C^{13} (**B**)), 53.1 (C^6 (**B**)), 52.7 (C^6 (**A**)), 50.4 (C^4 (**B**)), 45.9 (C^4 (**A**)), 36.1 (C^2(**A**)), 35.4 (C^2 (**B**)), 31.6 (C^{12} (**A**)), 29.5 (C^{12} (**B**)), 28.2 (C^3 (**A**)), 26.3 (C^3 (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{24}NO_4S^+$) requires m/z 386.1421, found **m/z** 386.1420.

methyl (3aS,4R,8aR,8bR)-1-oxo-4-phenylhexahydro-3H-furo[3,4-a]pyrrolizine-8a(6H)-carboxylate (220)



Prepared according to **General Procedure F** from **192**. Purification *via* FCC (1 : 4 pentane/EtOAc) gave **220** as a white solid (30 mg, 40%).

mp 90–92 °C

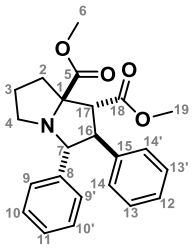
IR 2981, 1765 (C^{15}=O, ester), 1728 (C^{5}=O, ester), 1250, 1161.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34–7.40 (m, 2H, $C^{10}H$, $C^{10'}H$), 7.26–7.32 (m, 1H, $C^{11}H$), 7.20–7.24 (m, 2H, $C^{9}H$, $C^{9'}H$), 4.37 (d, 1H, J = 7.5 Hz, $C^{7}H$), 4.07 (dd, 1H, J = 10.1, 7.6 Hz, $C^{14}Ha$), 3.78 (s, 3H, $C^{6}H_3$), 3.72 (dd, 1H, J = 10.1, 2.6 Hz, $C^{14}Hb$), 3.54 (app qd, 1H, J = 7.7, 2.5 Hz, $C^{13}H$), 3.47 (roofed d, 1H, J = 8.3 Hz, $C^{12}H$), 2.71–2.82 (m, 2H, $C^{4}H_2$), 2.50–2.57 (m, 1H, $C^{2}Ha$), 2.02–2.20 (m, 3H, $C^{2}Hb$, $C^{3}H_2$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.1 (C^{5}), 174.5 (C^{15}), 137.6 (C^{8}), 128.8 (C^{10}), 128.2 (C^{9}), 127.9 (C^{11}), 78.5 (C^{1}), 68.4 (C^{14}), 62.7 (C^{7}), 52.1 (C^{6}), 48.9 (C^{13}), 46.6 (C^{12}), 43.0 (C^{4}), 27. 5 (C^{2}), 26.6 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}NO_4^+$) requires m/z 302.1387, found m/z 302.1387.

dimethyl (1R,2S,3R,7aR)-2,3-diphenyltetrahydro-1H-pyrrolizine-1,7a(5H)-dicarboxylate (221)



Prepared according to **General Procedure F** from **192** and methyl cinnamate (2.5 equiv.). Purification *via* FCC (3 : 1 pentane/EtOAc) gave **221** as a colourless oil that crystallized upon standing (61 mg, 64%). Crystals for X-ray analysis were obtained from slow evaporation from EtOAc.

mp 136–138 °C (significant sublimation happens from 100 °C).

IR 2951, 1734 (C^{14}=O, C^{5}=O), 1436, 1224, 1167.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.36–7.40 (m, 4H, C^{9}H, $C^{9'}$H, C^{14}H, $C^{14'}$H), 7.21–7.26 (m, 4H, C^{10}H, $C^{10'}$H, C^{13}H, $C^{13'}$H), 7.16–7.20 (m, 1H, C^{11}H), 7.11–7.16 (m, 1H, C^{12}H), 4.83 (d, 1H, J = 11.6 Hz, C^{7}H), 3.99 (app roofed t, 1H, J = 11.2 Hz, C^{16}H), 3.92 (d, 1H, J = 11.2 Hz, C^{17}H), 3.89 (s, 3H, $C^{6}H_3$), 3.63 (s, 3H, $C^{19}H_3$), 2.53 (ddd, 1H, J = 11.1, 9.0, 5.8 Hz, C^{4}Ha), 2.47 (ddt, 1H, J = 12.8, 6.0, 1.5 Hz, C^{2}Ha), 2.42 (ddt, 1H, J = 8.9, 5.9, 1.5 Hz, C^{4}Hb), 1.71–1.84 (m, 2H, $C^{3}H_2$), 1.62 (td, 1H, J = 12.4, 7.0 Hz, C^{2}Hb).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 175.4 (C^{5}), 172.5 (C^{18}), 138.9 (C^{15}), 136.1 (C^{8}), 129.7 (C^{9}, $C^{9'}$), 128.7 (C^{14}, $C^{14'}$), 128.3 (C^{10}, $C^{10'}$, C^{13}, $C^{13'}$), 127.7 (C^{11}), 127.0 (C^{12}), 75.5 (C^{1}), 70.3 (C^{7}), 60.2 (C^{17}), 53.1 (C^{6}), 52.0 (C^{19}), 51.0 (C^{4}), 47.0 (C^{16}), 32.9 (C^{2}), 25.6 (C^{3}).

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}O_4N^+$) requires **m/z** 380.1856, found **m/z** 380.1857.

Data for X ray:

Crystal data

Chemical formula	$C_{23}H_{25}NO_4$
M_r	379.44
Crystal System, space group	Monoclinic, $P2_1/c$
Temperature (K)	150
a, *b*, *c* (Å)	10.0439 (1), 18.5010 (3), 10.7555 (2)
α, β, γ (°)	90, 90.7333 (15), 90
V (Å^3)	1998.45 (2)
Z	4
Radiation type	Cu $K\alpha$
U (mm^{-1})	0.695
Crystal size (mm)	0.20 × 0.10 × 0.05

Data collection

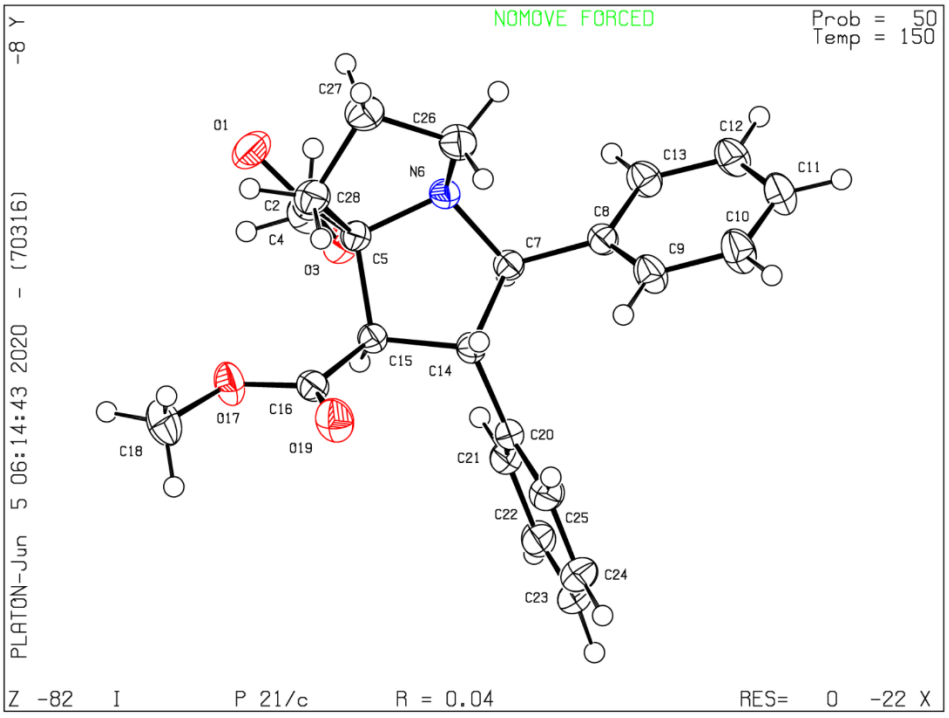
Diffractometer	Unknown
Absorption correction	Multi-scan
T_{min}, T_{max}	0.980, 1.000
No. of measured	14017, 2947, 2760
independent and observed	
R_{int}	–
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	–

Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.0358, 0.0915, 0.985
No. of reflections	4219
No. of parameters	254
No. restraints	3
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å□ ^{3})	–

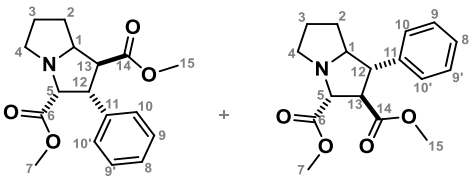
Absolute structure –

Structure parameter –



Selected parameters: Missing

dimethyl (1S,2R,3R)-2-phenylhexahydro-1H-pyrrolizine-1,3-dicarboxylate (222a) and dimethyl (1S,2R,3R)-1-phenylhexahydro-1H-pyrrolizine-2,3-dicarboxylate (222b)



Prepared according to **General Procedure F** from **207** and methyl cinnamate (2.5 equiv.). Purification *via* FCC (3 : 2 pentane/EtOAc) gave a 54 : 46 mixture of **222a** (**A**) and **222b** (**B**), respectively, as a pale yellow oil (25 mg, 33%).

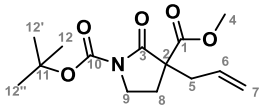
IR 2952, 1736 (C=O), 1437, 1197, 1172.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.30–7.34 (m, 0.92H, C^9H (**B**), $C^{9'}H$ (**B**)), 7.18–7.29 (m, 4.08H, C^8H (**A**), C^8H (**B**), C^9H (**A**), $C^{9'}H$ (**A**), $C^{10}H$ (**A**), $C^{10}H$ (**B**), $C^{10'}H$ (**A**), $C^{10'}H$ (**B**)), 4.19 (td, 0.54H, J = 9.1, 6.4 Hz, C^1H (**A**)), 3.95 (dd, 0.54H, J = 10.1, 8.2 Hz, $C^{12}H$ (**A**)), 3.81–3.90 (m, 2H, C^1H (**B**), C^5H (**A**), C^5H (**B**), $C^{13}H$ (**A**)), 3.79 (s, 1.38H, C^7H_3 (**B**)), 3.66 (s, 1.62H, C^7H_3 (**A**)), 3.57-3.63 (m, 0.46H, $C^{13}H$ (**B**)), 3.57 (s, 1.38H, $C^{15}H_3$ (**B**)), 3.33–3.37 (m, 0.54H, C^4Ha (**A**)), 3.33 (s, 1.62H, $C^{15}H_3$ (**A**)), 3.14–3.21 (m, 0.46H, C^4Ha (**B**)), 3.10 (dd, 0.46H, J = 11.7, 9.7 Hz, $C^{12}H$ (**B**)), 2.83–2.89 (m, 0.46H, C^4Hb (**B**)), 2.69 (td, 0.54H, J = 9.5, 6.1 Hz, C^4Hb (**A**)), 1.91–2.00 (m, 1H, C^3Ha (**A**), C^3Ha (**B**)), 1.81–1.92 (m, 2H, C^2Ha (**A**), C^2Ha (**B**), C^3Hb (**A**), C^3Hb (**B**)), 1.64–1.72 (m, 0.46H, C^2Hb (**B**)), 1.41–1.52 (m, 0.54H, C^2Hb (**A**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 173.1 (C^6 (**A**)), 172.9 (C^6 (**B**), C^{14} (**A**)), 172.5 (C^{14} (**B**)), 138.6 (C^{11} (**B**)), 137.3 (C^{11} (**A**)), 128.9 (C^9 (**B**), $C^{9'}$ (**B**)), 128.6 (C^9 (**A**), $C^{9'}$ (**A**)), 128.0 (C^{10} (**A**), $C^{10'}$ (**A**)), 127.7 (C^{10} (**B**), $C^{10'}$ (**B**)), 127.5 (C^8 (**B**)), 127.3 (C^8 (**A**)), 73.5 (C^5 (**A**)), 72.8 (C^1 (**B**)), 71.3 (C^5 (**B**)), 66.3 (C^1 (**A**)), 56.5 (C^{13} (**B**)), 56.2 (C^4 (**A**)), 56.0 (C^{12} (**B**)), 55.7 (C^4 (**B**)), 52.7 (C^7 (**B**)), 52.3 (C^{15} **(B)**), 52.0 (C^7 (**A**)), 51.5 (C^{15} (**A**)), 50.5 (C^{13} (**A**)), 48.6 (C^{12} (**A**)), 30.5 (C^2 (**B**)), 29.0 (C^2 (**A**)), 26.6 (C^3 (**A**)), 25.5 (C^3 (**B**)).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}O_4N^+$) requires **m/z** 304.1543, found **m/z** 304.1542.

1-(tert-butyl) 3-methyl 3-allyl-2-oxopyrrolidine-1,3-dicarboxylate (S1a)



NaH (440 mg, 11.0 mmol) was added portionwise to a solution of dimethyl allyl malonate **223a** (1.72 g, 10.0 mmol) in anhydrous DMF (10 mL) at 0 °C. The resulting solution was stirred for 30 min at rt and **224** (4.48 g, 20.0 mmol) was then added portionwise. The resulting solution was then stirred for 42 h at 50 °C, before being cooled down to rt and carefully quenched with saturated NH_4Cl. The resulting biphasic mixture was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (10 : 1 pentane/EtOAc) gave **S1a** as a white solid (502 mg, 17%).

mp 44–46 °C

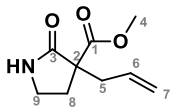
IR 2981, 1787 (C^3=O), 1754 (C^1=O), 1725 (C^{10}=O), 1369, 1310, 1252, 1219.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.70 (dddd, 1H, J = 17.2, 10.2, 7.6, 7.0 Hz, C^6H), 5.09–5.19 (m, 2H, C^7H_2), 3.75 (s, 3H, C^4H_3), 3.69–3.75 (m, 2H, C^9H_2), 2.80 (ddt, 1H, J = 14.1, 7.6, 1.1 Hz, C^5Ha), 2.53 (ddt, 1H, J = 14.1, 7.0, 1.2 Hz, C^5Hb), 2.44 (ddd, 1H, J = 13.2, 6.9, 4.2 Hz, C^8Ha), 1.99 (dt, 1H, J = 13.2, 8.7 Hz, C^8Hb), 1.53 (s, 9H, $C^{12}H_3$, $C^{12'}H_3$, $C^{12''}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.0 (C^1 or C^3), 170.8 (C^1 or C^3), 150.3 (C^{10}), 132.6 (C^6), 120.1 (C^7), 83.6 (C^{11}), 57.5 (C^2), 53.2 (C^4), 44.1 (C^9), 38.7 (C^5), 28.2 (C^{12}, $C^{12'}$, $C^{12''}$), 26.6 (C^8).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}O_5NNa^+$) requires **m/z** 306.1312, found **m/z** 306.1313.

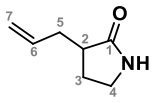
1-(tert-butyl) 3-methyl 3-allyl-2-oxopyrrolidine-1,3-dicarboxylate (225a)



TFA (710 μL, 9.28 mmol) was added to a solution of **S1a** (502 mg, 1.77 mmol) in CH_2Cl_2 (3.5 mL) and the resulting solution was stirred at rt for 30 min before being concentrated *in vacuo* to give **225a** as a pale yellow oil that was used without purification in the next step (460 mg, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.89–7.17 (br s, 1H, NH), 5.72 (ddt, 1H, J = 17.2, 10.0, 7.2 Hz, C^6H), 5.12–5.23 (m, 2H, C^7H_2), 3.77 (s, 3H, C^4H_3), 3.51 (ddd, 1H, J = 9.7, 8.1, 7.2 Hz, C^9Ha), 3.37 (td, 1H, J = 9.3, 3.7 Hz, C^9Hb), 2.73 (dd, 1H, J = 14.0, 7.7 Hz, C^5Ha), 2.52–2.62 (m, 2H, C^5Hb, C^8Ha), 2.20 (ddd, 1H, J = 13.4, 8.9, 7.2 Hz, C^8Hb).

3-allylpyrrolidin-2-one (226a)



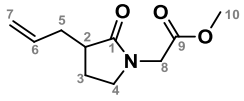
LiCl (75 mg, 1.8 mmol) and water (63 μL, 3.5 mmol) were sequentially added to a solution of **225a** (0.46 g) in DMSO (18 mL). The resulting solution was stirred at 190 °C for 3 h and extracted with EtOAc (3 × 25 mL) when cooled down to rt. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (1 : 4 pentane/EtOAc) gave **226a** as a pale yellow oil (123 mg, 56%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.88–6.13 (br s, 1H, NH), 5.80 (ddt, 1H, J = 17.1, 10.2, 7.0 Hz, C^6H), 5.02–5.15 (m, 2H, C^7H_2), 3.28–3.39 (m, 2H, C^4H_2), 2.58 (dddt, 1H, J = 13.9, 6.8, 4.2, 1.4 Hz, C^5Ha), 2.46 (qd, 1H, J = 8.8, 4.1 Hz, C^2H), 2.21–2.32 (m, 1H, C^3Ha), 2.13–2.22 (m, 1H, C^5Hb), 1.85 (dq, 1H, J = 12.8, 8.5 Hz, C^3Hb).

^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 179.7 (C^1), 135.6 (C^6), 116.9 (C^7), 40.31 (C^2), 40.29 (C^4), 35.0 (C^5), 26.8 (C^3).

All other data in accordance with literature.[13]

methyl 2-(3-(but-3-en-1-yl)-2-oxopyrrolidin-1-yl)acetate (228a)



Prepared according to **General Procedure G** from **226a**. Purification *via* FCC (2 : 3 pentane/EtOAc) gave **228a** as a pale yellow oil (72 mg, 38%).

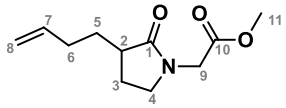
IR 2980, 1749 (C^9=O), 1687 (C^1=O), 1439, 1275, 1211, 1180.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.80 (ddt, 1H, J = 17.1, 10.2, 6.9 Hz, C^6H), 5.10 (app dq, 1H, J = 16.9, 1.6 Hz, C^7Ha), 5.06 (ddt, 1H, J = 10.1, 2.1, 1.1 Hz, C^7Hb), 4.09 (roofed d, 1H, J = 17.7 Hz, C^8Ha), 4.05 (d, 1H, J = 17.7 Hz, C^8Hb), 3.73 (s, 3H, $C^{10}H_3$), 3.35–3.43 (m, 2H, C^4H_2), 2.53–2.63 (m, 2H, C^2H, C^5Ha), 2.16–2.25 (m, 2H, C^3Ha, C^5Hb), 1.76–1.84 (m, 1H, C^3Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.9 (C^1), 169.3 (C^9), 135.6 (C^6), 117.1 (C^7), 52.3 (C^{10}), 46.1 (C^4), 44.2 (C^8), 41.0 (C^2), 35.4 (C^5), 24.2 (C^3).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{15}O_3NNa^+$) requires **m/z** 220.0944, found **m/z** 220.0945.

methyl 2-(3-(but-3-en-1-yl)-2-oxopyrrolidin-1-yl)acetate (228b)



Prepared according to **General Procedure G** from **226b**. Purification *via* FCC (2 : 3 pentane/EtOAc) gave **228b** as a pale yellow oil (77 mg, 56%).

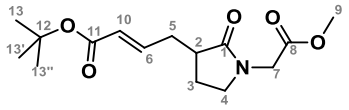
IR 2980, 1748 (C^{10}=O), 1687 (C^{1}=O), 1438, 1281, 1210, 1180.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.81 (ddt, 1H, *J* = 16.9, 10.2, 6.6 Hz, C^{7}H), 5.05 (app dq, 1H, *J* = 17.1, 1.7 Hz, C^{8}Ha), 4.98 (ddt, 1H, *J* = 10.1, 2.2, 1.3 Hz, C^{8}Hb), 4.10 (roofed d, 1H, *J* = 17.5 Hz, C^{9}Ha), 4.03 (d, 1H, *J* = 17.6 Hz, C^{9}Hb), 3.73 (s, 3H, $C^{11}H_3$), 3.35–3.45 (m, 2H, $C^{4}H_2$), 2.47 (qd, 1H, *J* = 9.0, 4.5 Hz, C^{2}H), 2.08–2.28 (m, C^{3}Ha, $C^{6}H_2$), 1.99 (dddd, 1H, *J* = 13.7, 9.3, 6.8, 4.4 Hz, C^{5}Ha), 1.74 (app dq, 1H, *J* = 12.7, 8.6 Hz, C^{3}Hb), 1.43–1.52 (m, 1H, C^{5}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.5 (C^{1}), 169.4 (C^{10}), 138.1 (C^{7}), 115.3 (C^{8}), 52.3 (C^{11}), 46.1 (C^{4}), 44.2 (C^{9}), 40.8 (C^{2}), 31.4 (C^{6}), 30.5 (C^{5}), 25.2 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{17}O_3NNa^+$) requires **m/z** 234.1101, found **m/z** 234.1104.

tert-butyl (E)-4-(1-(2-methoxy-2-oxoethyl)-2-oxopyrrolidin-3-yl)but-2-enoate (230a)



Prepared according to **General Procedure H** from **228a**. Purification *via* FCC (4 : 1 pentane/EtOAc) gave **230a** as a pale yellow oil (9.0 mg, 9%)

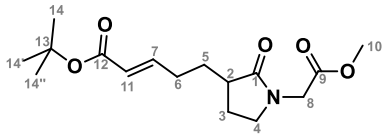
IR 2978, 2932, 1750 (C^{8}=O), 1694 (C^{11}=O), 1693 (C^{1}=O), 1438, 1367, 1275, 1210, 1152.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.81 (dt, 1H, J = 15.6, 7.2 Hz, $C^{6}H$), 5.82 (dt, 1H, J = 15.5, 1.6 Hz, $C^{10}H$), 4.11 (roofed d, 1H, J = 17.6 Hz, $C^{7}Ha$), 4.03 (roofed d, 1H, J = 17.6 Hz, $C^{7}Hb$), 3.73 (s, 3H, $C^{9}H_3$), 3.44 (dt, 1H, J = 9.4, 7.8 Hz, $C^{4}Ha$), 3.38 (td, 1H, J = 9.1, 3.4 Hz, $C^{4}Hb$), 2.76 (dddd, 1H, J = 14.9, 6.8, 4.0, 1.6 Hz, $C^{5}Ha$), 2.62 (qd, 1H, J = 9.0, 4.0 Hz, $C^{2}H$), 2.22–2.31 (m, 2H, $C^{3}Ha$, $C^{5}Hb$), 1.76 (dq, 1H, J = 12.8, 8.5 Hz, $C^{3}Hb$), 1.47 (s, 9H, $C^{13}H_3$, $C^{13'}H_3$, $C^{13''}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.1 (C^{1}), 169.2 (C^{8}), 165.8 (C^{11}), 144.4 (C^{6}), 125.3 (C^{10}), 80.5 (C^{12}), 52.4 (C^{9}), 46.0 (C^{4}), 44.3 (C^{7}), 40.5 (C^{2}), 33.7 (C^{5}), 28.3 (C^{13}, $C^{13'}$, $C^{13''}$), 24.7 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}O_5NNa^+$) requires **m/z** 320.1468, found **m/z** 320.1469.

tert-butyl (E)-5-(1-(2-methoxy-2-oxoethyl)-2-oxopyrrolidin-3-yl)pent-2-enoate (230b)



Prepared according to **General Procedure H** from **228b**. Purification *via* FCC (4 : 1 pentane/EtOAc) gave **230b** as a pale yellow oil (67 mg, 63%)

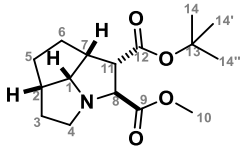
IR 2977, 2932, 1751 (C^{9}=O), 1694 (C^{12}=O), 1693 (C^{1}=O), 1438, 1367, 1285, 1212, 1151.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.85 (dt, 1H, J = 15.7, 6.9 Hz, $C^{7}H$), 5.78 (dt, 1H, J = 15.6, 1.6 Hz, $C^{11}H$), 4.09 (roofed d, 1H, J = 17.6 Hz, $C^{8}Ha$), 4.04 (roofed d, 1H, J = 17.6 Hz, $C^{8}Hb$), 3.73 (s, 3H, $C^{10}H_3$), 3.43 (dt, 1H, J = 9.2, 7.6 Hz, $C^{4}Ha$), 3.39 (td, 1H, J = 9.0, 2.6 Hz, $C^{4}Hb$), 2.47 (qd, 1H, J = 8.8, 5.0 Hz, $C^{2}H$), 2.22–2.37 (m, 3H, $C^{3}Ha$, $C^{6}H_2$), 2.03 (dddd, 1H, J = 13.9, 9.1, 6.9, 5.0 Hz, $C^{5}Ha$), 1.73 (dq, 1H, J = 12.8, 8.5 Hz, $C^{3}Hb$), 1.50–1.61 (m, 1H, $C^{5}Hb$), 1.48 (s, 9H, $C^{14}H_3$, $C^{14'}H_3$, $C^{14''}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.0 (C^{1}), 169.3 (C^{9}), 166.1 (C^{12}), 146.8 (C^{7}), 123.9 (C^{11}), 80.3 (C^{13}), 52.4 (C^{10}), 46.1 (C^{4}), 44.2 (C^{8}), 40.7 (C^{2}), 29.8 (C^{5}), 29.6 (C^{6}), 28.3 (C^{14}, $C^{14'}$, $C^{14''}$), 25.2 (C^{3}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}O_5NNa^+$) requires **m/z** 334.1625, found **m/z** 334.1626.

1-(tert-butyl) 2-methyl (1S,2S,31R,5aS,7aR)-octahydro-2H-cyclopenta[gh]pyrrolizine-1,2-dicarboxylate (231a)



Prepared according to **General Procedure H** from **230a**. Purification *via* FCC (1 : 1 to 1 : 2 pentane/EtOAc) gave **231a** as a pale yellow oil (28 mg, 72%).

IR 2950, 1742 (C^{12}=O, C^{9}=O (shoulder)), 1693 (C^{1}=O), 1368, 1199, 1158.

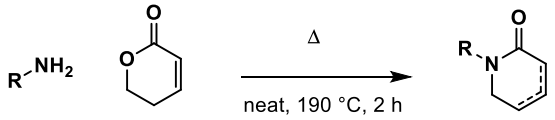
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 4.09 (t, 1H, J = 7.5 Hz, C^{1}H), 3.81 (d, 1H, J = 7.0 Hz, C^{8}H), 3.70 (s, 3H, $C^{10}H_3$), 3.15 (ddd, 1H, J = 10.0, 8.0, 3.1 Hz, C^{4}Ha), 3.04 (qd, 1H, J = 7.5, 3.2 Hz, C^{7}H), 2.82 (t, 1H, J = 7.2 Hz, C^{11}H), 2.60 (td, 1H, J = 9.8, 5.8 Hz, C^{4}Hb), 2.47–2.52 (m, 1H, C^{2}H), 1.90 (ddt, 1H, J = 12.7, 9.9, 7.0 Hz, C^{3}Ha), 1.74–1.81 (m, 2H, C^{5}Ha, C^{6}Ha), 1.54–1.62 (m, 2H, C^{3}Hb,C^{6}Hb), 1.22–1.28 (m, 1H, C^{5}Hb).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 172.3 (C^{9}), 171.3 (C^{12}), 81.0 (C^{13}), 75.7 (C^{1}), 69.9 (C^{8}), 53.7 (C^{4}), 52.3 (C^{11}), 51.9 (C^{10}), 47.4 (C^{7}), 44.0 (C^{2}), 31.7 (C^{6}), 30.8 (C^{5}), 30.6 (C^{3}), 28.1 (C^{14}, $C^{14'}$, $C^{14''}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{26}O_4N^+$) requires **m/z** 296.1856, found **m/z** 296.1858.

6.4 Experimental Details for Chapter 4

6.4.1 General Procedure I: unsaturated δ-valerolactam synthesis



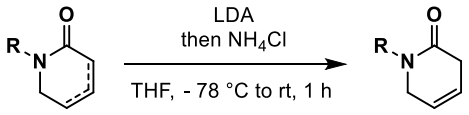
To a microwave vial was added the non-volatile amine (1.00 equiv.) and the dihydropyranone (1.00 equiv., can be purchased or made from a literature procedure)[14]. The vial was sealed, and put under an Argon atmosphere with three vacuum-Argon cycles. It was then placed in a pre-heated oil bath, and behind a blast shield. The reaction was stirred at 190 °C for 3 h before being allowed to room temperature.

Note: a pressure due to the generation of water can build up, the microwave should be checked to resist high pressure, and sized appropriately. Alternatively, the reaction vessel can also be connected to a nitrogen line equipped with a bubbler. It is important to keep oxygen out at those elevated temperatures.

It may be necessary to wrap the oil bath with tin foil to allow the temperature to rise to 190 °C.

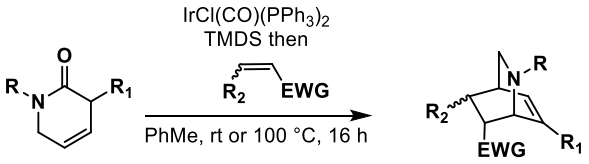
Once the reaction has cooled down to rt, the seal is open, and the gum is dissolved in $CHCl_3$ and loaded on a silica gel column for FCC purification. The product is usually obtained as a mixture of isomers at the double-bond position.

6.4.2 General Procedure J: deconjugation of unsaturated lactams



n-BuLi (2.5 M in hexanes, 1.5 equiv.) was added dropwise to a solution of *i*-Pr_2NH (1.50 equiv.) in THF (10 mL/mmol lactam. After 30 min, a solution of lactam (1.00 equiv.) in THF (1 mL/mmol lactam) was added dropwise. The solution was stirred for 1 h before being quenched with saturated NH_4Cl (1.0 mL/mmol lactam) and allowed to reach rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.0 mL/mmol lactam). The combined organic layers were dried over Na_2SO_4 concentrated *in vacuo*. Purification *via* FCC afforded the corresponding pure β, γ unsaturated δ-valerolactam.

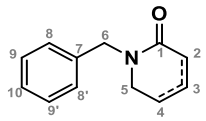
6.4.3 General Procedure K: synthesis of isoquinucleidine products



To a vial was loaded the lactam (0.1 mmol), Vaska's catalyst (0.1 mol%), and toluene (1 mL). TMDS (2 equiv.) was then added, and the resulting solution started bubbling. It was left to stir for 20 min, before the dienophile (1 equiv.) was added. The reaction mixture was then stirred for 16 h at rt or 100 °C. It could then be loaded directly on a silica gel column for FCC purification.

Note: if isomerisation of the dienamine is a problem (see section **4.3.4** of **Chapter 4**), DMSO (100 μL) can be added 5 min after the introduction of TMDS. This will "kill" any catalytically active iridium species in the pot.

1-benzyl-5,6-dihydropyridin-2(1H)-one (335')



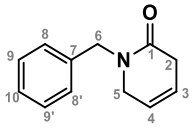
Prepared according to **General Procedure I** from benzylamine and dihydropyranon **328**. Purification *via* FCC (1 : 1 pentane/EtOAc) gave a 1 : 1 mixture of isomers **335** and **335'**, respectively, as a yellow oil (4.49 g, 40%).

Data of conjugated lactam **335'**:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H [selected peaks]: 6.55 (dt, 1H, J = 10.0 Hz, 4.2 Hz, C^3H), 6.00 (dt, 1H, J = 9.8, 1.8 Hz, C^4H), 4.62 (s, 2H, C^6H_2), 3.32 (t, 2H, J = 7.3 Hz, C^5H_2), 2.32 (tdd, 2H, J = 7.2, 4.2, 1.7 Hz, C^2H_2).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 164.7 (C^1), 139.5, (C^3), 137.6 (C^7), 128.7 (C^9, $C^{9'}$), 128.1 (C^8, $C^{8'}$), 127.5 (C^{10}), 125.5 (C^2), 49.8 (C^6), 44.7 (C^5), 24.3 (C^4).

1-benzyl-3,6-dihydropyridin-2(1H)-one (335)



n-BuLi (1.6 M in hexanes, 15.1 mL, 24.2 mmol) was added dropwise to a solution of *i*-Pr_2NH (3.40 mL, 24.2 mmol) in THF (150 mL) at −78 °C. After 30 min, a solution of the mixture of isomers lactam **335** and **335'** (3.02 g, 16.1 mmol) in THF (10 mL) was added dropwise and the reaction was left to stir for 3 h before being quenched with saturated NH_4Cl (20 mL) and allowed to reach rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **335** as a yellow oil (853 mg, 28%).

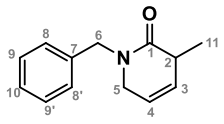
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.24–7.36 (m, 5H, C^8H, $C^{8'}H$, C^9H, $C^{9'}H$, $C^{10}H$), 5.76 (dtt, 1H, J = 10.6, 3.4, 2.0 Hz, C^4H), 5.67 (dtt, 1H, J = 10.1, 3.1, 1.9 Hz, C^3H), 4.67 (s, 2H, C^6H_2), 3.78–3.85 (m, 2H, C^5H_2), 3.02–3.07 (m, 2H, C^2H_2).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 167.3 (C^1), 136.8 (C^7), 128.8 (C^9, $C^{9'}$), 128.2 (C^8, $C^{8'}$), 127.6 (C^{10}), 122.7 (C^4), 120.9 (C^3), 49.8 (C^6), 48.4 (C^5), 32.3 (C^2).

All other data in accordance with literature.

Yasui, Y.; Kakinokihara, I.; Takeda, H.; Takemoto, Y. Preparation of α,β-Unsaturated Lactams through Intramolecular Electrophilic Carbamoylation of Alkenes. *Synthesis* **2009**, *23*, 3989–3993.

1-benzyl-3-methyl-3,6-dihydropyridin-2(1H)-one (S2)



n-BuLi (1.6 M in hexanes, 0.98 mL, 1.57 mmol) was added dropwise to a solution of *i*-Pr_2NH (215 μL, 1.57 mmol) in THF (8 mL) was added at –78 °C. After 30 min, a solution of the mixture of isomers lactam **335** and MeI (280 mg, 1.50 mmol) in THF (5 mL) was added dropwise. After a further 30 min, MeI (93 μL, 1.50 mmol) was added dropwise, and the reaction was left to stir for 3 h before being quenched with saturated NH_4Cl (1 mL) and allowed to reach rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification *via* FCC (3 : 2 pentane/EtOAc) gave **S2** as a yellow oil (217 mg, 78%).

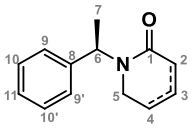
IR 2929, 1642 (C=O), 1492, 1454, 1411, 1325, 1259.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.30–7.35 (m, 2H, C^9H, $C^{9'}H$), 7.25–7.29 (m, 3H, C^8H, $C^{8'}H$, $C^{10}H$), 5.73 (ddt, roof effect, 1H, J = 10.1, 3.7, 2.0 Hz, C^3H), 5.66 (dtd, roof effect, 1H, J = 10.0, 3.1, 1.7 Hz, C^4H), 4.67 (d, major roof effect, 1H, J = 18.7 Hz, C^6Ha), 4.65 (d, major roof effect, 1H, J = 18.7 Hz, C^6Hb), 3.78–3.82 (m, 2H, C^5H_2), 3.00–3.08 (m, 1H, C^2H), 1.36 (d, 3H, J = 7.4 Hz, $C^{11}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 171.1 (C^1), 137.1 (C^7), 129.2 (C^3), 128.8 (C^9, $C^{9'}$), 128.2 (C^8, $C^{8'}$), 127.6 (C^{10}), 119.7 (C^4), 49.9 (C^6), 48.3 (C^5), 36.5 (C^2), 19.5 (C^{11}).

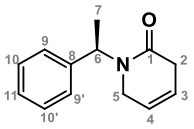
HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}ON^+$) requires **m/z** 202.12264, found **m/z** 202.12288.

(*R*)-1-(1-phenylethyl)-5,6-dihydropyridin-2(1H)-one (S3')



Prepared according to **General Procedure I** from (*R*)-(+)-α-methylamine and dihydropyranone **328**. Purification *via* FCC (3 : 2 pentane/EtOAc) gave **S3** as a mixture of isomers and as a yellow oil that was used in the next step without further characterisation.

(*R*)-1-(1-phenylethyl)-3,6-dihydropyridin-2(1H)-one (S3)



LHMDS (1.0 M in THF, 1.56 mL, 1.56 mmol) was added dropwise to a solution of lactam **S3'** (260 mg, 1.30 mmol) in THF (12 mL) at −78 °C. The reaction was left to stir for 3 h before being quenched with saturated NH_4Cl (1 mL) and allowed to reach rt. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give **S3** as colourless needles (226 mg, 87%).

mp 30–32 °C

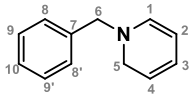
IR 2976, 1639 (C=O), 1481, 1440, 1411, 1325, 1298, 1209, 1183.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.27–7.36 (m, 5H, $C^{9}H$, $C^{9'}H$, $C^{10}H$, $C^{10'}H$, $C^{11}H$), 6.24 (q, 1H, J = 7.1 Hz, $C^{6}H$), 5.74 (dtt, 1H, *J* = 10.8, 3.6, 2.0 Hz, $C^{4}H$), 5.66 (dtt, 1H, *J* = 10.0, 3.4, 1.9 Hz, $C^{3}H$), 3.74 (dtdd, *J* = 17.5, 5.0, 3.0, 2.2 Hz, $C^{5}Ha$), 3.36 (dtdd, 1H, *J* = 17.5, 4.6, 3.3, 1.9 Hz, $C^{5}Hb$), 3.02–3.07 (m, 2H, $C^{2}H_2$), 1.54 (d, 1H, *J* = 7.2 Hz, $C^{7}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 167.2 (C^{1}), 140.1 (C^{8}), 128.6 (C^{10}, $C^{10'}$), 127.6 (C^{9}, $C^{9'}$), 127.5 (C^{11}), 122.4 (C^{4}), 121.3 (C^{3}), 49.7 (C^{6}), 42.4 (C^{5}), 32.9 (C^{2}), 15.3 (C^{7}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}ON^+$) requires m/z 202.1226, found m/z 202.1229.

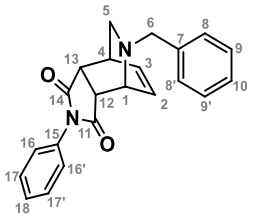
1-benzyl-1,2-dihydropyridine (337)



An NMR tube was charged with lactam **335** (6.9 mg, 0.037 mmol), trimethoxybenzene as an internal standard, deuterated toluene (0.5 mL), TMDS (13 μL, 0.0111 mmol) and Vaska's complex (0.1 mg, 0.0004 mmol). The resultant reaction mixture was monitored by NMR spectroscopic analysis. **^{1}H NMR** (C_7D_8, 400 MHz) δ_H [selected peaks]: 5.83–5.87 (m, 1H, $C^{3}H$), 5.82 (dt, 1H, *J* = 7.3, 1.0 Hz, $C^{1}H$), 4.87–4.93 (m, 1H, $C^{2}H$), 4.70 (ddd, 1H, *J* = 7.0, 5.4, 1.4 Hz, $C^{4}H$), 3.61 (dd, 1H, *J* = 3.9, 1.6 Hz, $C^{5}H_2$), 3.51 (d, 2H, *J* = 3.9, 1.6 Hz, $C^{6}H_2$).

^{13}C NMR ($C^{7}D^{8}$, 101 MHz) δ_C [selected peaks]: 138.8 (C^{1}), 111.7, (C^{2}), 95.6 (C^{4}), 59.3 (C^{6}), 48.0 (C^{5}).

9-benzyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (339)



Prepared according to **General Procedure K** (rt) from **335** and *N*-phenyl maleimide **338**. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **339** as amorphous yellow solid (11.9 mg, 93%).

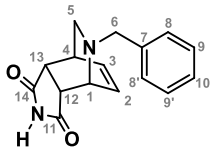
IR 1709 (2 * C=O), 1498, 1382, 1183.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.34–7.40 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.24–7.33 (m, 5H, $C^{8}H$, $C^{8'}H$, $C^{9}H$, $C^{9'}H$, $C^{18}H$), 7.18–7.24 (m, 1H, $C^{10}H$), 7.07–7.12 (m, 2H, $C^{17}H$, $C^{17'}H$), 6.42 (ddd, 1H, J = 8.0, 6.3, 1.5 Hz, $C^{3}H$), 6.29 (ddd, 1H, J = 8.2, 5.2, 1.4 Hz, $C^{2}H$), 3.97 (ddd, 1H, J = 5.4, 4.0, 1.5 Hz, $C^{1}H$), 3.62 (roofed d, 1H, J = 13.1 Hz, $C^{6}Ha$), 3.38–3.46 ($C^{6}Hb$, $C^{12}H$), 3.14–3.19 (m, 1H, $C^{4}H$), 3.04 (dd, 1H, J = 10.1, 2.1 Hz, $C^{5}Ha$), 3.00 (dd, 1H, J = 8.2, 3.2 Hz, $C^{13}H$), 2.03 (dd, 1H, J = 10.1, 2.6 Hz, $C^{5}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.8 (C^{14}), 176.5 (C^{11}), 138.6 (C^{7}), 132.03 (C^{3}), 132.97 (C^{15}), 130.9 (C^{2}), 129.3 (C^{16}, $C^{16'}$), 128.9 (C^{8}, $C^{8'}$), 128.8 (C^{18}), 128.6 (C^{9}, $C^{9'}$), 127.4 (C^{10}), 126.6 (C^{17}, $C^{17'}$), 61.5 (C^{6}), 53.1 (C^{5}), 52.9 (C^{1}), 46.1 (C^{12}), 41.0 (C^{13}), 33.6 (C^{4}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{21}O_2N_2^+$) requires **m/z** 345.1598, found **m/z** 345.1593.

9-benzyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (340)



Prepared according to **General Procedure K** (rt) from **335**. Purification *via* prep TLC (1 : 1 pentane/EtOAc) gave **340** as a yellow oil (10.6 mg, 40%).

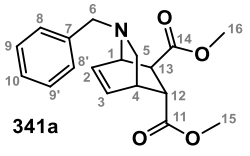
IR 1709 (2 * C=O), 1350, 1185.

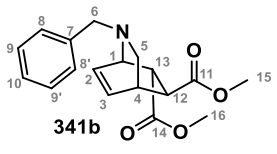
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.23–7.36 (m, 5H, $C^{8}H$, $C^{8'}H$, $C^{9}H$, $C^{9'}H$, $C^{10}H$), 6.43 (ddd, 1H, J = 8.0, 6.3, 1.5 Hz, $C^{3}H$), 6.29 (ddd, 1H, J = 8.2, 5.2, 1.4 Hz, $C^{2}H$), 3.91 (ddd, 1H, J = 5.4, 3.9, 1.5 Hz, $C^{1}H$), 3.63 (roofed d, 1H, J = 13.1 Hz, $C^{6}Ha$), 3.45 (roofed d, 1H, J = 13.1 Hz, $C^{6}Hb$), 3.37 (dd, 1H, J = 8.1, 4.0 Hz, $C^{12}H$), 3.09–3.14 (m, 1H, $C^{4}H$), 3.03 (dd, 1H, J = 10.1, 2.1 Hz, $C^{5}Ha$), 2.94 (dd, 1H, J = 8.1, 3.2 Hz, $C^{13}H$), 2.04 (dd, 1H, J = 10.1, 2.7 Hz, $C^{5}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 178.8 (C^{14}), 177.6 (C^{11}), 138.6 (C^{7}), 132.0 (C^{3}), 130.6 (C^{2}), 128.9 (C^{8}), 128.6 (C^{9}), 127.4 (C^{10}), 61.5 (C^{6}), 52.9 (C^{5}), 52.2 (C^{1}), 47.5 (C^{12}), 42.4 (C^{13}), 33.1 (C^{4}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}O_2N_2^+$) requires **m/z** 269.1285, found **m/z** 269.1285.

dimethyl (1*RS*,4*SR*,5*RS*,6*SR*) 2-benzyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylate (341a) and dimethyl (1*RS*,4*SR*,5*SR*,6*RS*)-2-benzyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylate (342b)





Prepared according to **General Procedure K** (100 °C) from **335**. Purification *via* prep TLC (4 : 1 pentane/EtOAc, double elution) gave **341a** as a yellow oil (top spot, lowest polarity, 3.3 mg, 10%) and **341b** as a yellow oil (bottom spot, highest polarity, 3.1 mg, 10%).

Data for **341a**:

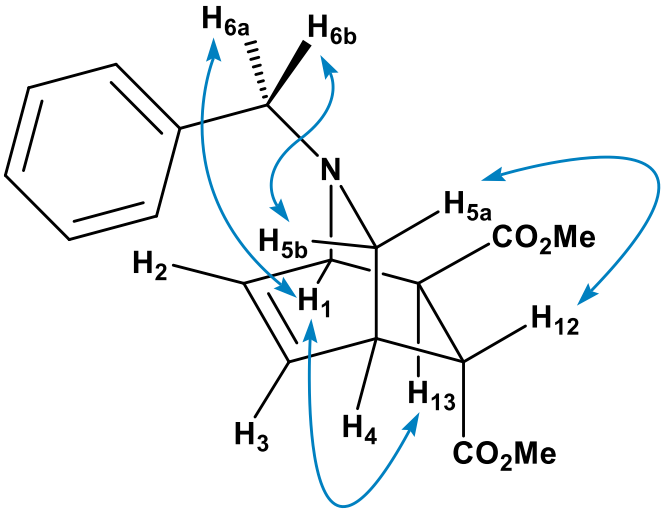
IR 2951, 1735 (2 * C=O), 1435, 1349, 1248, 1198.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.26–7.30 (m, 2H, $C^{9}H$, $C^{9'}H$), 7.20–7.24 (m, 3H, $C^{8}H$, $C^{8'}H$, $C^{10}H$), 6.43 (ddd, 1H, J = 7.9, 6.3, 1.4 Hz, $C^{3}H$), 6.31 (ddd, 1H, J = 8.0, 5.5, 1.4 Hz, $C^{2}H$), 3.79 (ddd, 1H, J = 5.5, 2.8, 1.4 Hz, $C^{1}H$), 3.69 (s, 3H, $C^{16}H_3$), 3.65 (s, 3H, $C^{15}H_3$), 3.49 (roofed d, 1H, J = 13.3 Hz, $C^{6}Ha$), 3.41 (dd, 1H, J = 4.6, 2.5 Hz, $C^{12}H$), 3.35 (dd, 1H, J = 13.3 Hz, $C^{6}Hb$), 3.20 (dd, 1H, J = 9.8, 2.3 Hz, $C^{5}Ha$), 3.01–3.05 (m, 1H, $C^{4}H$), 2.86 (dd, 1H, J = 4.7, 2.8 Hz, $C^{13}H$), 1.88 (dd, 1H, J = 9.8, 2.6 Hz, $C^{5}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.5 (C^{11}), 173.7 (C^{14}), 139.5 (C^{7}), 133.0 (C^{3}), 130.9 (C^{2}), 128.7 (C^{8}), 128.2 (C^{9}), 127.1 (C^{10}), 61.5 (C^{6}), 53.99 (C^{5}), 53.94 (C^{1}), 52.2 (C^{15}), 52.1 (C^{16}), 49.1 (C^{13}), 41.9 (C^{12}), 34.1 (C^{4}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}O_4N^+$) requires **m/z** 316.15433, found **m/z** 316.15402.

Key NOESY interactions :



Data for 341b:

IR 2952, 1733 (2 * C=O), 1435, 1274, 1198, 1028.

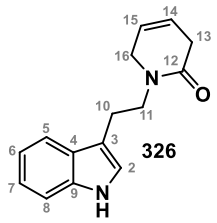
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.27–7.35 (m, 4H, $C^{8}H$, $C^{8'}H$, $C^{9}H$, $C^{9'}H$), 7.20–7.25 (m, 1H, $C^{10}H$), 6.53 (ddd, 1H, J = 8.1, 6.6, 1.5 Hz, $C^{3}H$), 6.24 (ddd, 1H, J = 8.1, 5.3, 1.3 Hz, $C^{2}H$), 3.85 (ddd, 1H, J = 5.3, 3.0, 1.5 Hz, $C^{1}H$), 3.73 (s, 3H, $C^{16}H_3$), 3.67–3.72 (m, 2H, $C^{6}Ha$, $C^{13}H$), 3.64 (s, 3H, $C^{15}H_3$), 3.49 (d, 1H, J = 13.3 Hz, $C^{6}Hb$), 3.43 (roofed d, 1H, J = 13.4 Hz, $C^{6}Hb$), 2.95–2.99 (m, 1H, $C^{4}H$), 2.88–2.93 (m, 2H, $C^{5}Ha$, $C^{12}H$), 1.88 (dd, 1H, J = 10.4, 2.2 Hz, $C^{5}Hb$).

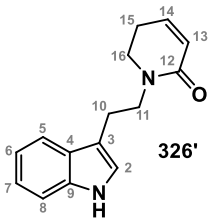
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 173.6 (C^{11}), 173.5 (C^{14}), 139.3 (C^{7}), 134.2 (C^{3}), 131.0 (C^{2}), 128.7 (C^{8}), 128.4 (C^{9}), 127.0 (C^{10}), 61.3 (C^{6}), 53.9 (C^{1}), 52.3 (C^{16}), 52.2 (C^{15}), 50.2 (C^{5}), 46.9 (C^{13}), 43.0 (C^{12}), 33.8 (C^{4}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}O_4N^+$) requires **m/z** 316.1543, found **m/z** 316.1540.

1-(2-(1H-indol-3-yl)ethyl)-3,6-dihydropyridin-2(1H)-one (326)

and 1-(2-(1H-indol-3-yl)ethyl)-5,6-dihydropyridin-2(1H)-one (326')



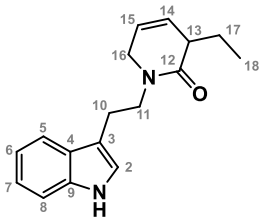


Prepared according to **General Procedure I** from tryptamine **86** and dihydropyranone **328**. Purification via FCC (100% EtOAc) gave an inconsequential 2 : 1 mixture of isomers **326** (**A**) and **326'** (**B**), respectively, as an orange solid (1.23 g, 51%). This can be recrystallised from EtOAc (25 mL/g of product, 78 °C to 0 °C).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.01 (br s, 1H, NH (**A**), NH (**B**)), 7.64–7.70 (m, 1H, C^5H (**A**), C^5H (**B**)), 7.37 (app d, 1H, J = 8.1 Hz, C^8H (**A**), C^8H (**B**)), 7.20 (app ddd, 1H, J = 8.1, 7.0, 1.2 Hz, C^7H (**A**), C^7H (**B**)), 7.13 (ddd, 1H, J = 8.1, 7.0, 1.1 Hz, C^6H (**A**), C^6H (**B**)), 7.07 (app d, 1H, J = 2.4 Hz, C^2H (**A**), C^2H (**B**)), 6.49 (dt, 0.33H, J = 9.7, 4.2 Hz, $C^{14}H$ (**B**)), 5.94 (dt, 0.33H, J = 9.8, 1.8 Hz, $C^{13}H$ (**B**)), 5.74 (dtd, 0.66H, J = 10.8, 3.4, 1.7 Hz, $C^{15}H$ (**A**)), 5.63 (dtd, 0.67H, J = 10.1, 3.1, 1.5 Hz, $C^{14}H$ (**A**)), 3.84 (tdd, 1.33H, J = 5.0, 3.1, 2.1 Hz, $C^{16}H_2$ (**A**)), 3.73 (td, 2H, J = 7.4, 1.5 Hz, $C^{11}H_2$ (**A**), $C^{11}H_2$ (**B**)), 3.27 (t, 0.67H, $C^{16}H_2$ (**B**)), 3.08 (app ddt, 2H, 7.8, 6.9, 2.2 Hz, $C^{10}H_2$ (**A**), $C^{10}H_2$ (**B**)), 2.99 (tdd, 1.33H, J = 5.1, 3.4, 1.9 Hz, $C^{13}H_2$ (**A**)), 2.12–2.24 (m, 0.66H, $C^{15}H_2$ (**B**)).

^{13}C NMR Missing

1-(2-(1H-indol-3-yl)ethyl)-3-ethyl-3,6-dihydropyridin-2(1H)-one (324)



Prepared according to **General Procedure D** from a 2 : 1 mixture of **326** and **326'** and EtI. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **324** as a white solid (1.09 g, 84%).

mp 102–104 °C

IR 3333 (br), 2970, 1625 (C=O), 1498, 1459, 1378, 1341, 1303.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.11 (s, 1H, NH), 7.69 (app dq, 1H, J = 7.8, 0.9 Hz, C^5H), 7.36 (dt, 1H, J = 8.1, 1.0 Hz, C^8H), 7.19 (ddd, 1H, J = 8.1, 7.0, 1.3 Hz, C^7H), 7.12 (ddd, 1H, J = 8.0, 7.0, 1.1 Hz, C^6H), 7.02 (br d, 1H, J = 2.2 Hz, C^2H), 5.70 (2 * d, very strong roof effect, 2H, J = 11.2 Hz, $C^{14}H$, $C^{15}H$), 3.91–3.74 (m, $C^{11}Ha$, $C^{16}H_2$), 3.66 (dt, 1H, J = 13.2, 7.4 Hz, $C^{11}Hb$), 3.11–3.04 (m, 2H, $C^{10}H_2$), 2.94–3.01 (m, 1H, J = 6.7, 3.3, 1.5 Hz, $C^{13}H$), 1.91 (app tt, 1H, J = 13.9, 7.3 Hz, $C^{17}Ha$), 1.73 (dqd, 1H, J = 13.4, 7.5, 4.3 Hz, $C^{17}Hb$), 0.88 (t, 3H, J = 7.5 Hz, $C^{18}H_3$).

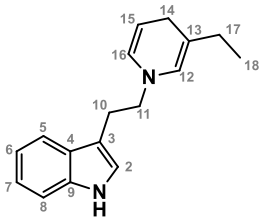
Data in toluene for NMR tube experiment:

^{1}H NMR (C_7D_8, 400 MHz) δ_H: 7.74–7.71 (m, 1H, C^5H), 7.35 (br s, 1H, NH), 7.25–7.16 (m, 2H, C^6H, C^7H), 7.16–7.14 (m, 1H, C^8H), 6.66 (d, 1H, J = 2.3 Hz, C^2H), 5.37 (ddt, 1H, J = 10.1, 3.8, 2.0 Hz, $C^{14}H$), 5.24 (dtd, 1H, J = 10.1, 3.1, 1.6 Hz, $C^{15}H$), 3.79 (ddd, 1H, J = 13.1, 8.4, 6.8 Hz, $C^{11}Ha$), 3.48 (ddd, 1H, J = 13.1, 8.1, 6.8 Hz, $C^{11}Hb$), 3.34 (ddt, 1H, J = 17.6, 4.3, 2.6 Hz, $C^{16}Ha$), 3.22 (dddd, 1H, J = 17.6, 4.5, 3.4, 1.9 Hz, $C^{16}Hb$), 3.00 (dddd, 1H, J = 7.6, 6.7, 2.4, 0.9 Hz, $C^{10}H_2$), 2.87 (tq, 1H, J = 6.0, 4.3, 3.6 Hz, $C^{13}H$), 2.04 (dqd, 1H, J = 13.7, 7.4, 6.3 Hz, $C^{17}Ha$), 1.66 (dqd, 1H, J = 13.3, 7.5, 4.4 Hz, $C^{17}Hb$), 0.88 (t, J = 7.4 Hz, 3H, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.2 (C^{12}), 136.4 (C^4), 127.5 (C^9), 127.1 (C^{14}), 122.2 (C^7), 122.0 (C^1), 121.1 (C^2), 119.4 (C^6), 118.8 (C^5), 113.0 (C^3), 111.3 (C^8), 49.5 (C^{16}), 48.0 (C^{11}), 42.4 (C^{13}), 26.3 (C^{17}), 23.1 (C^{10}), 10.1 (C^{18}).

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}ON_2^+$) requires **m/z** 291.1468, found **m/z** 291.1468.

3-(2-(3-ethylpyridin-1(4H)-yl)ethyl)-1H-indole (344c)

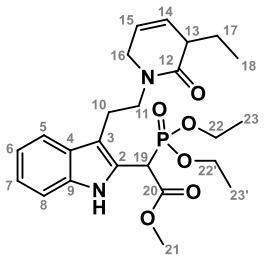


An NMR tube was charged with lactam **326** (2.7 mg, 0.010 mmol), deuterated toluene, TMDS (3.5 μL, 0.030 mmol), Vaska's complex (<0.1 mg, 0.0001 mmol) and the reaction was monitored by NMR spectroscopic analysis.

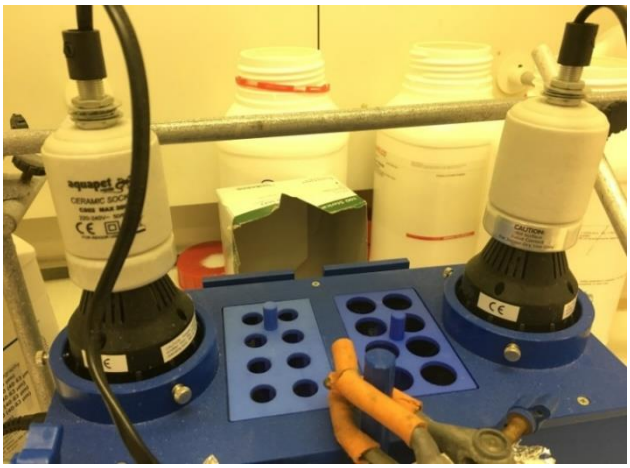
^{1}H NMR (C_7D_8, 400 MHz) δ_H [selected peaks]: 6.40–6.43 (m, 1H, C^2H), 5.61 (dq, 1H, J = 8.0, 1.5 Hz, $C^{16}H$), 5.45 (app q, 1H, J = 1.4 Hz, $C^{12}H$), 4.39 (dt, 1H, J = 7.9, 3.2 Hz, $C^{15}H$), 3.02 (dd, 2H, J = 8.3, 6.4 Hz, $C^{11}H_2$), 2.96–3.02 (m, $C^{14}H_2$), 2.74–2.79 (m, 2H, $C^{10}H_2$), 1.80 (qd, 2H, J = 7.5, 1.2 Hz, $C^{17}H_2$), 0.95 (t, 1H, J = 7.4 Hz, $C^{18}H_3$).

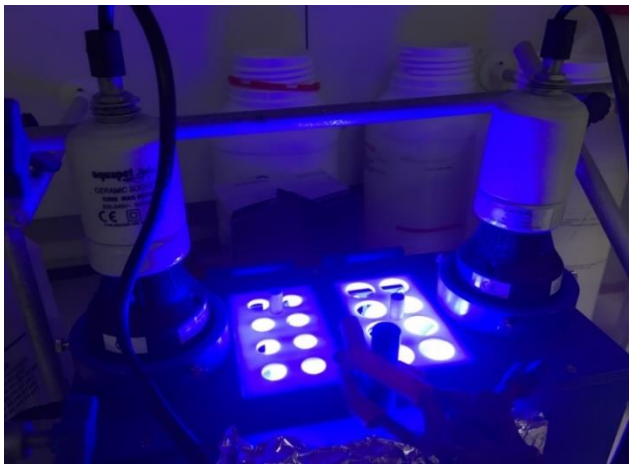
^{13}C NMR (C^7D^8, 101 MHz) δ_C [selected peaks]: 131.3 (C^{16}), 125.4 (C^{12}), 122.0 (C^2), 96.5 (C^{15}), 54.3 (C^{11}), 28.5 (C^{17}), 27.1 (C^{14}), 26.3 (C^{10}).

methyl 2-(diethoxyphosphoryl)-2-(3-(2-(3-ethyl-2-oxo-3,6-dihydropyridin-1(2H)-yl)ethyl)-1H-indol-2-yl)acetate (323)



A vial was charged with phosphono-ester **325** (26.1 mg, 0.0900 mmol), lactam **324** (26.8 mg, 0.100 mmol), amine **350** (5.5 mg, 0.020 mmol), and $Ir(ppy)_3$ (0.9 mg, 0.001 mmol). The vial was flushed with Argon and DCE (0.5 mL) was introduced. The vial was then placed in a photobox (Hepatochem EvoluChem™ PhotoRedOx Duo, equipped with two EvoluChem™ LED 18W lights).and irradiated while stirred and cooled with a ventilator to *ca.* 30 °C for 14 h. It was then directly loaded on a FCC and eluted with EtOAc to give C^2-functionalised **323** as an inconsequential 54 (**A**) : 46 (**B**) mixture of diastereoisomers and as a yellow oil (24.3 mg, 51%).





IR 3256 (br), 2924, 2854, 1738 (C=O, ester), 1636 (C=O, lactam), 1491, 1458, 1247.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 9.20 (s, 0.46H, NH (**B**)), 9.19 (s, 0.54H, NH (**A**)), 7.66–7.72 (app t, 1H, J = 8.8 Hz, C^5H (**A**), C^5H (**B**)), 7.35–7.39 (app ddt, 1H, J = 8.2, 2.0, 0.9 Hz, C^8H (**A**), C^8H (**B**)), 7.16–7.21 (m, 1H, C^7H (**A**), C^7H (**B**)), 7.08–7.13 (m, 1H, C^6H (**A**), C^6H (**B**)), 5.65–5.76 (m, 2H, $C^{14}H$ (**A**), $C^{14}H$ (**B**),

$C^{15}H$ (**A**), $C^{15}H$ (**B**)), 4.73 (d, 0.54H, *J* = 23.8 Hz, $C^{19}H$ (**A**)), 4.72 (d, 0.46H, *J* = 23.7 Hz, $C^{19}H$ (**B**)), 4.07–4.21 (m, 2H, $C^{22}H_2$ (**A**), $C^{22}H_2$ (**B**)), 3.81–4.07 (m, 3.46H, $C^{16}H_2$ (**A**), $C^{16}Ha$ (**B**), $C^{22'}H_2$ (**A**), $C^{22'}H_2$ (**B**)), 3.78 (s, 1.38H, $C^{21}H_3$ (**B**)), 3.77 (s, 1.62H, $C^{21}H_3$ (**A**)), 3.67–3.75 (m, 1H, $C^{16}Hb$ (**B**), $C^{11}Ha$ (**A**)), 3.62 (ddd, 0.54H, *J* = 13.2, 9.6, 6.3 Hz, $C^{11}Hb$ (**A**)), 3.56 (ddd, 0.46H, *J* = 13.2, 9.6, 6.3 Hz, $C^{11}Ha$ (**B**)), 3.46 (ddd, 0.46H, *J* = 13.2, 9.5, 6.8 Hz, $C^{11}Hb$ (**B**)), 2.95–3.12 (m, 3H, $C^{10}H_2$ (**A**), $C^{10}H_2$ (**B**), $C^{13}H$ (**A**), $C^{13}H$ (**B**)), 1.93 (pd, 0.54H, *J* = 7.3, 4.0 Hz, $C^{17}Ha$ (**A**)), 1.90 (pd, 0.46H, *J* = 7.3, 4.0 Hz, $C^{17}Ha$ (**B**)), 1.69–1.81 (m, 1H, $C^{17}Hb$ (**A**), $C^{17}Hb$ (**B**)), 1.32 (t, 1.62H, *J* = 7.1 Hz, $C^{23}H_3$ (**A**)), 1.31 (t, 1.38H, *J* = 7.1 Hz, $C^{23}H_3$ (**B**)), 1.15 (t, 1.38H, *J* = 7.1 Hz, $C^{23'}H_3$ (**B**)), 1.14 (t, 1.62H, *J* = 7.1 Hz, $C^{23'}H_3$ (**A**)), 0.90 (t, 1.38H, *J* = 7.5 Hz, $C^{18}H_3$ (**B**)), 0.89 (t, 1.62H, *J* = 7.5 Hz, $C^{18}H_3$ (**A**)).

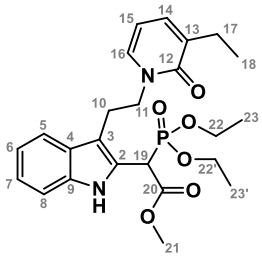
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 170.24 (C^{12} (**A**)), 170.20 (C^{12} (**B**)), 167.6–167.7 (m, C^{20} (**A**), C^{20} (**B**)), 135.92 (C^4 (**A**)), 135.88 (C^4 (**B**)), 127.6 (d, *J* = 2.4 Hz, (C^9 (**B**)), 127.5 (d, *J* = 2.4 Hz, (C^9 (**A**)), 127.3 (C^{14} (**B**)), 127.2 (C^{14} (**A**)), 123.7 (d, *J* = 11.4 Hz, C^2 (**A**)), 123.5 (d, *J* = 11.1 Hz, C^2 (**B**)), 122.6 (C^7 (**A**), C^7 (**B**)), 121.11 (C^{15} (**A**)), 121.07 (C^{15} (**B**)), 119.70 (C^6 (**B**)), 119.67 (C^6 (**A**)), 119.0 (C^5 (**B**)), 118.9 (C^5 (**A**)), 112.09 (d, *J* = 10.0 Hz, (C^3 (**B**)), 112.03 (d, *J* = 9.9 Hz, (C^3 (**A**)), 111.42 (C^8 (**A**)), 111.38 (C^8 (**B**)), 63.8–63.9 (m, C^{22} (**A**), C^{22} (**B**), $C^{22'}$ (**A**), $C^{22'}$ (**B**)), 53.30 (C^{21} (**B**)), 53.28 (C^{21} (**A**)), 50.0 (C^{16} (**A**)), 49.7 (C^{16} (**B**)), 48.4 (d, *J* = 2.8 Hz, C^{11} (**A**)), 48.3 (d, *J* = 2.8 Hz, C^{11} (**B**)), 43.5 (d, *J* = 133.6 Hz, C^{19} (**B**)), 43.4 (d, *J* = 132.9 Hz, C^{19} (**A**)), 42.43 (C^{13} (**B**)), 42.41 (C^{13} (**A**)), 26.3 (C^{17} (**A**)), 26.2 (C^{17} (**B**)), 22.0 (C^{10} (**A**), C^{10} (**B**)), 16.5 (d, *J* = 5.9 Hz, (C^{23} (**A**), C^{23} (**B**)), 16.41 (d, *J* = 5.8 Hz, $C^{23'}$ (**B**)), 16.38 (d, *J* = 5.8 Hz, $C^{23'}$ (**A**)), 10.2 (C^{18} (**B**)), 10.1 (C^{18} (**A**)).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 17.51 (**B**), 17.38 (**A**).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{34}O_6N_2P^+$) requires **m/z** 477.21490, found **m/z** 477.21484.

Note: It is remarkable that C^{11} appears as a doublet. It may be the consequence of the proximity in space with the phosphorus atom. This phenomenon is also observed in pyridone **356** below.

methyl 2-(diethoxyphosphoryl)-2-(3-(2-(3-ethyl-2-oxopyridin-1(2H)-yl)ethyl)-1H-indol-2-yl)acetate (356)



Original procedure to give analytical quantities of the product: A 10 ml vial was charged with **324** (26.8 mg, 100 μmol), Ru(bpy3).6H_2O (0.8 mg, 1 μmol), **350** (55.0 mg, 200 μmol), **325** (28.9 mg, 100 μmol), and DMF (1 ml). The vial was then irradiated for 14 h under the Blue LED "loop" system. The solution was then diluted with EtOAc (5 ml), and extracted with 5% (w/w) LiCl aqueous solution (5 × 3 mL). The organic layer was then concentrated *in vacuo* and purification *via* FCC gave a mixture of desired product **323** and byproduct pyridone **356**. Further purification of the mixture *via* reverse-phase HPLC (1 : 2 MeCN/H_2O) afforded **323** as an inconsequential mixture of two diastereomers and as a yellow oil (1.8 mg, 4%) and **356** as a yellow oil (1.0 mg, 2%).



IR Missing

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 9.20 (s, 1H, NH), 7.64 (dt, 1H, J = 7.8, 1.0 Hz, C^5H), 7.37 (dt, 1H, J = 8.0, 0.9 Hz, C^8H), 7.20 (ddt, 1H, J = 8.1, 7.0, 1.1 Hz, C^7H), 7.15–7.07 (m, 2H, C^6H, $C^{16}H$), 6.89 (dd, 1H, J = 6.8, 2.0 Hz, $C^{14}H$), 5.93 (t, 1H, J = 6.8 Hz, $C^{15}H$), 4.60 (d, 1H, J = 24.0 Hz, $C^{19}H$), 4.32 (ddd, 1H, J = 12.6, 8.5, 5.2 Hz, $C^{11}Ha$), 4.18–3.96 (m, 4H, $C^{11}Hb$, $C^{22}H_2$, $C^{22'}Ha$), 3.94–3.79 (m, 1H, $C^{22'}Hb$), 3.75 (d, 3H, J = 0.5 Hz, $C^{21}H_3$), 3.34–3.19 (m, 1H, $C^{10}Ha$), 3.19–3.06 (m, 1H, $C^{10}Hb$), 2.68–2.54 (m, 2H, $C^{17}H_2$), 1.30 (td, 3H, J = 7.1, 0.6 Hz, $C^{23}H_3$), 1.23 (t, 3H, J = 7.5 Hz, $C^{23'}H_3$), 1.16 (td, 3H, J = 7.0, 0.6 Hz, $C^{18}H_3$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 167.8 (C^{12}), 162.9 (C^{20}), 136.1 (C^4), 135.6 (C^{14}), 135.1 (C^{16}), 124.2 (d, J = 11.5 Hz, C^2), 122.9 (C^7), 120.1 (C^6), 119.0 (C^5), 111.6 (C^8), 105.5 (C^{15}), 64.2- 64.0 (m, C^{22}, $C^{22'}$), 52.9 (C^{21}), 51.2 (d, J = 2.8 Hz, C^{11}), 43.6 (d, J = 132.4 Hz, C^{19}), 23.9 (app s, C^{10}, C^{17}), 16.7 (m, C^{23}, $C^{23'}$) 12.9 (C^{18}).

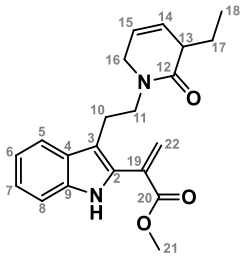
Note : C^3 and C^9 were not observed.

^{31}P NMR ($CDCl^3$, 162 MHz) δ_P: 17.1.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{31}O_6N_2NaP$) requires **m/z** 497.1811,

found **m/z** 497.1809

methyl 2-(3-(2-(3-ethyl-2-oxo-3,6-dihydropyridin-1(2H)-yl)ethyl)-1H-indol-2-yl)acrylate (322)



A round-bottom flask was charged with phosphonate **323** (26.3 mg, 0.055 mmol), paraformaldehyde (16.8 mg, 0.55 mmol), LiBr (5.8 mg, 0.066 mmol), and THF (1.1 mL). NEt_3 (8.0 μL, 0.055 mmol) was added dropwise, and the resulting suspension was stirred at rt for 30 min. The reaction mixture was quickly concentrated at 0 °C, and wet-loaded with small amounts of CH_2Cl_2 on a pipette cold column. Elution with cold 5 : 1 Toluene/EtOAc, followed by concentration at 0 °C (product must not be kept neat more than a handful of minutes or decomposition will happen) gave **322** as a yellow oil (15.9 mg, 81%). It was characterized immediately in deuterated toluene and used in the next 3 h.

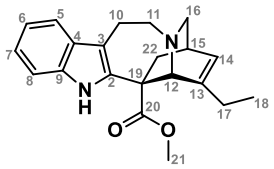
IR 3257 (br), 2963, 1723 (C=O, ester), 1623 (C=O, lactam), 1496, 1457, 1437, 1343, 1286.

^{1}H NMR (C_7D_8, 500 MHz) δ_H: 9.19 (s, 1H, NH), 7.67–7.73 (m, 1H, C^5H), 7.13–7.19 (m, 1H, C^7H, C^6H), 7.00–7.03 (m, 1H, C^8H), 6.56 (s, 1H, C^{22}Ha), 6.52 (s, 1H, C^{22}Hb), 5.33 (ddt, roof effect, 1H, J = 10.2, 3.7, 2.0 Hz, C^{14}H), 5.24 (dtd, roof effect, 1H, J = 10.1, 3.0, 1.6 Hz, C^{15}H), 3.41–3.58 (m, 2H, $C^{11}H_2$), 3.34–3.38 (m, 4H, C^{16}Ha, $C^{21}H_3$), 3.28 (dddd, roof effect, 1H, J = 17.5, 4.9, 3.3, 1.9 Hz, C^{16}Hb), 3.01–3.18 (m, 2H, $C^{10}H_2$), 2.76–2.83 (m, 1H, C13H), 1.92–2.05 (m, 1H, C^{17}Ha), 1.55–1.66 (m, 1H, C^{17}Hb), 0.84 (t, 3H, *J* = 7.4 Hz, $C^{18}H_3$).

^{13}C NMR (C_7D_8, 126 MHz) δ_C: 168.9 (C^{12}), 167.5 (C^{20}), 135.9 (C^9), 131.0 (C^{19}), 130.2 (C^2), 128.4 (C^{22}), 127.6 (C^{14}), 123.2 (C^7), 121.4 (C^{15}), 119.9 (C^6), 119.2 (C^5), 112.6 (C^3), 111.7 (C^8), 51.8 (C^{21}), 49.3 (C^{16}), 47.9 (C^{11}), 42.5 (C^{13}), 26.4 (C^{17}), 23.2 (C^{10}), 10.2 (C^{18}). Note: C^4 is overlapping with some of the deuterated toluene peaks.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{25}O_3N_2$) requires **m/z** 353.1860, found **m/z** 353.1859.

catharanthine (234)



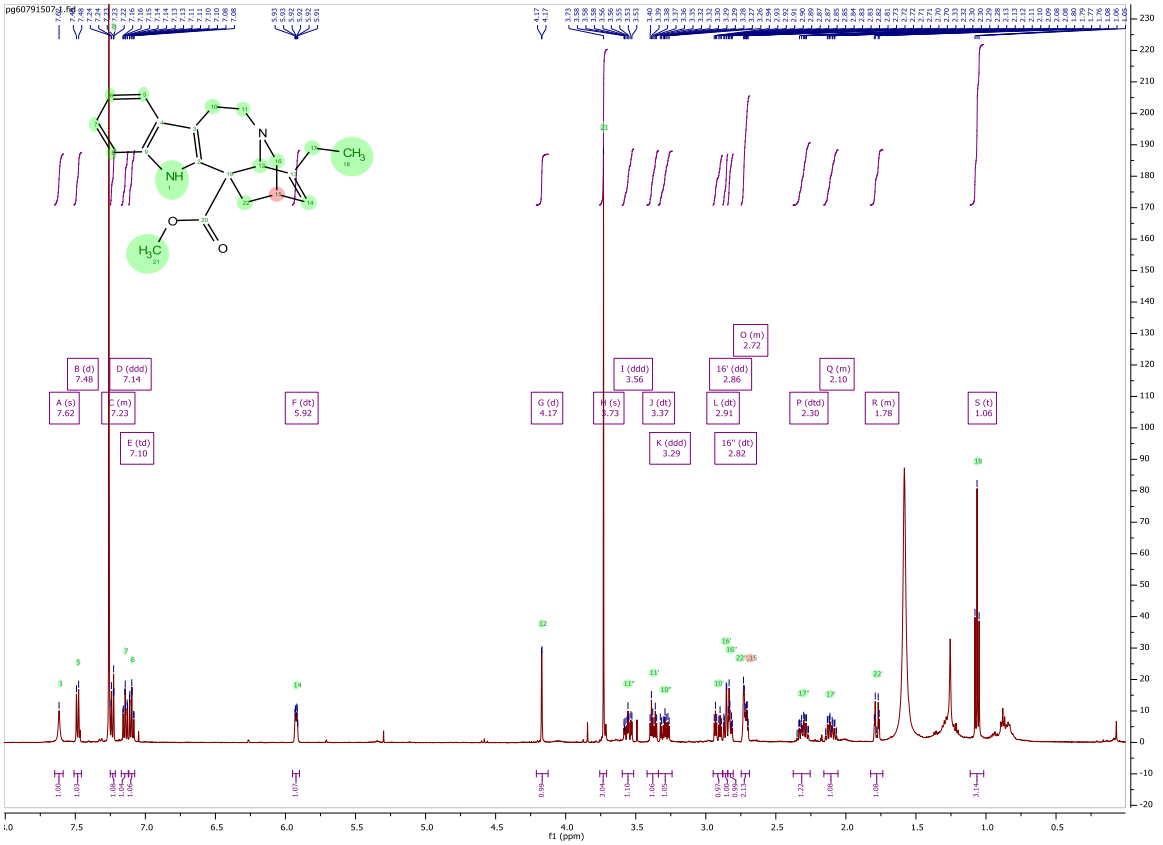
An NMR tube was charged with **322** (5.6 mg, 0.016 mmol), deuterated toluene (0.5 mL), and Vaska's complex (0.1 mg, 0.00016 mmol, 1 mol%). A solution of TMDS (8.5 μL, 0.048 mmol) in deuterated toluene (0.25 mL) was added dropwise over 20 min with the help of a syringe pump. Mild bubbling was observed. The reaction was monitored by NMR. After 2 h at rt, the resulting solution was directly loaded on a prep TLC, and elution with 100% EtOAc gave catharanthine **234** (0.6 mg, 11%, amount was too low to determine physical state).

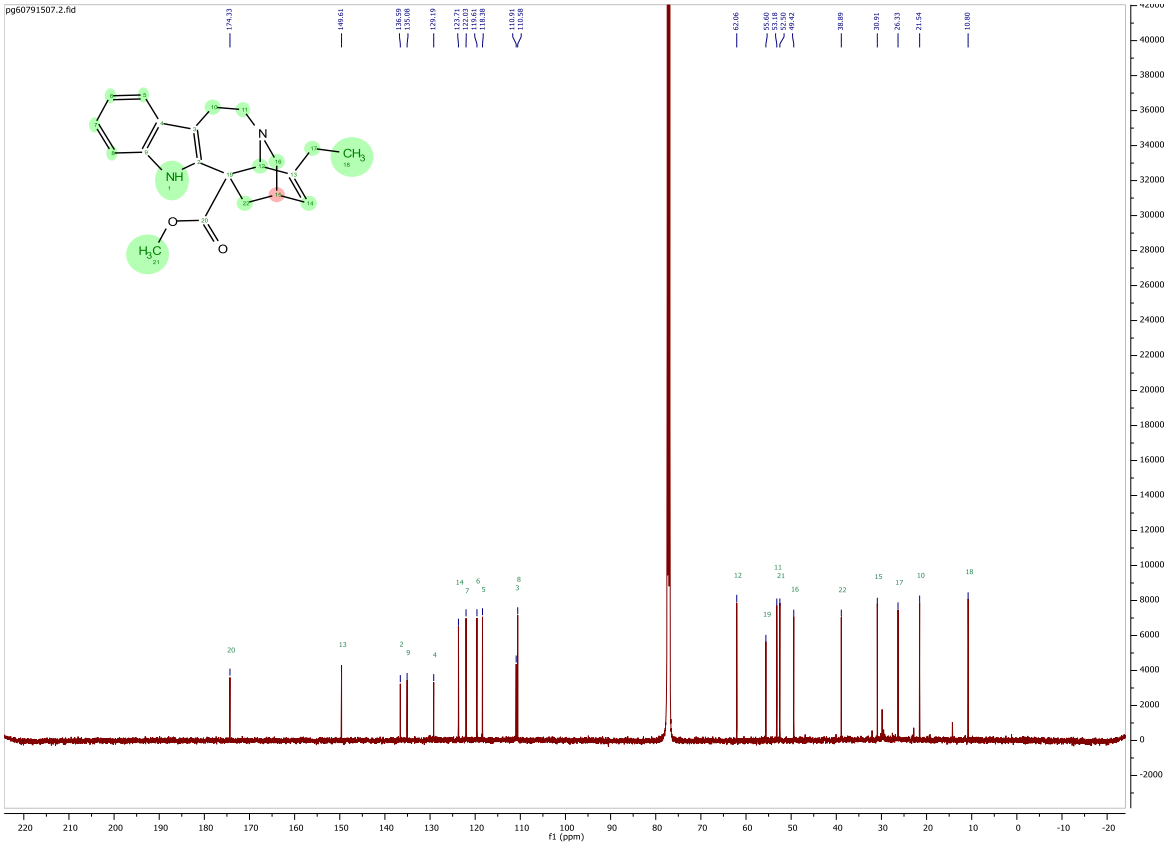
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.61 (s, 1H, NH), 7.48 (d, 1H, J = 7.7 Hz, C^5H), 7.23 (app d, 1H, J = 8.1 Hz, C^8H), 7.14 (ddd, 1H, J = 8.1, 7.1, 1.3 Hz, C^7H), 7.10 (app td, 1H, J = 7.4, 7.0, 1.2 Hz, C^6H), 5.91–5.94 (m, 1H, $C^{14}H$), 4.17 (d, 1H, J = 1.5 Hz, $C^{12}H$), 3.73 (s, 3H, $C^{21}H_3$), 3.56 (ddd, 1H, J = 14.1, 10.5, 3.9 Hz, $C^{11}Ha$), 3.38 (dt, 1H, J = 13.8, 4.6 Hz, $C^{11}Hb$), 3.29 (ddd, 1H, J = 15.4, 10.5, 5.4 Hz, $C^{10}Ha$), 2.91 (dt, 1H, J = 16.5, 4.4 Hz, $C^{10}Hb$), 2.86 (br d, roof effect, 1H, J = 8.6 Hz, $C^{16}Ha$), 2.83 (dt, roof effect, 1H, J = 8.7, 2.7 Hz, $C^{16}Hb$), 2.69–2.75 (m, 2H, $C^{15}H$, $C^{22}Ha$), 2.31 (ddd, 1H, J = 17.1, 7.3, 2.2 Hz, $C^{17}Ha$), 2.11 (ddd, 1H, J = 17.2, 7.4, 1.8 Hz, $C^{17}Hb$), 1.78 (dd, roof effect, 1H, J = 13.9, 3.3 Hz, $C^{22}Hb$), 1.06 (t, 3H, J = 7.3 Hz, $C^{18}H_3$).

Data in toluene for NMR tube experiment: ^{1}H NMR (C_7D_8, 400 MHz) δ_H [selected peaks]: 5.72–5.76 (m, 1H, $C^{14}H$), 4.22 (d, 1H, J = 1.5 Hz, $C^{12}H$), 3.39 (ddd, 1H, J = 12.7, 9.4, 3.9 Hz, $C^{11}Ha$), 3.25 (s, 3H, $C^{21}H_3$), 3.00–3.16 (m, 2H), 2.83 (dt, 1H, J = 12.7, 3.3 Hz), 2.76 (dt, 1H, J = 8.3, 2.8 Hz), 2.66–2.73 (m, 1H), 2.60 (dd, 1H, J = 8.1 Hz, 1.5 Hz), 2.33–2.38 (m, 1H).

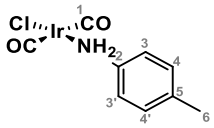
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.3 (C^{20}), 149.6 (C^{13}), 136.6 (C^2), 135.1 (C^9), 129.2 (C^4), 123.7 (C^{14}), 122.0 (C^7), 119.6 (C^6), 118.4 (C^5), 110.9 (C^3), 110.6 (C^8), 62.1 (C^{12}), 55.6 (C^{19}), 53.2 (C^{11}), 52.5 (C^{21}), 49.4 (C^{16}), 38.9 (C^{22}), 30.9 (C^{15}), 26.3 (C^{17}), 21.5 (C^{10}), 10.8 (C^{18}).

All other data in accordance with literature.[15]


pg607915071.fid
A (s) 7.62
B (d) 7.48
C (m) 7.23
D (ddd) 7.14
E (td) 7.10
F (dt) 5.92
G (d) 4.17
H (s) 3.73
I (ddd) 3.56
J (dt) 3.37
K (ddd) 3.29
L (dt) 2.91
16' (dd) 2.86
16'' (dt) 2.82
O (m) 2.72
P (dtd) 2.30
Q (m) 2.10
R (m) 1.78
S (t) 1.06
f1 (ppm)


pg607915072.fid
f1 (ppm)

dicarbonylchloro(p-toluidine) Iridium (I) (370)



WARNING: this reaction must be done with appropriate supervision. A CO gas alarm must be worn around the neck at all time (ask stores downstairs).

According to a literature procedure,[16] a two-necked round-bottom flask equipped with condenser and gas inlet bubbler (glass frit) was charged with iridium chloride trihydrate **19** (1.00 g, 2.84 mmol), LiCl (286 mg, 6.75 mmol), 2-methoxyethanol (39 mL) and water (4.2 mL). Carbon monoxide was passed slowly through the solution *via* the gas inlet, and the solution was stirred and heated at 124 °C. Over the course of 9 h, the solution became a golden yellow colour, from a deep brown-orange (*ca* 30 min), passing through a bright orange (*ca* 1 h), amber (*ca* 2 h), and golden colour (5 h). The carbon monoxide flux was stopped, and the reaction was allowed to cool down to rt. *p*-Toluidine **369** (371 mg, 3.46 mmol) was added to the solution, which was then poured onto water (125 mL). On pouring, the solution turned from a golden yellow colour to a deep blue colour. The resulting suspension was filtered, and the solids rinsed with water (2 × 50 mL), dissolved in toluene, dried over Na_2SO_4 and concentrated *in vacuo* to give **370** as a metallic purple solid (590 mg, 53%).

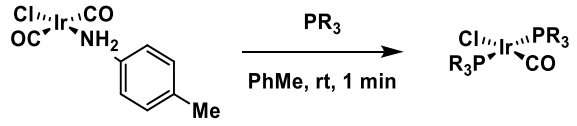
^{1}H NMR ($(CD_3)_2CO$, 400 MHz) δ_H: 7.26 (d, roof effect, 2H, J = 8.2 Hz, C^4H, $C^{4'}H$), 7.20 (d, roof effect, 2H, J = 8.2 Hz, C^3H, $C^{3'}H$), 6.82–7.00 (br s, 2H, NH_2), 2.31 (s, 3H, C^6H_3).

^{13}C NMR ($(CD_3)_2CO$, 101 MHz) δ_C: 145.1 (C^2), 138.1 (C^5) 131.1 (C^4, $C^{4'}$), 122.7 (C^3, $C^{3'}$), 21.1 (C^6).

Note: The carbonyl could not be observed with certainty. Weak signals at 169.2 and 168.7 were however present.

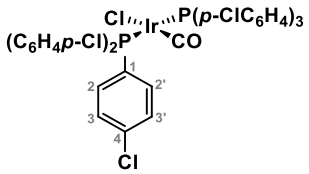
All other data in accordance with literature.[16]

6.4.4 General Procedure L: preparation of Vaska-type iridium complexes



The phosphine/phosphite (2.00 equiv.) was added to a solution of iridium complex **370** (1.00 equiv.) in PhMe (20 mL/mmol **370**). Gas evolved instantly (WARNING: most likely CO gas), and the solution colour became yellow or pale yellow from a purple colour. If the product does not crash out, some pentane (10 to 40 mL/mmol **370**) can be added. The resulting suspension was filtered, and the solids collected, and dried *in vacuo*.

trans-carbonylchlorobis(tris(4-chlorophenyl)phosphine)iridium(I) (371)



Prepared according to **General Procedure L** from tris(4-chlorophenyl)phosphine. Filtration gave **371** as a dark yellow solid (145 mg, 72%).

mp No physical state change up to 205 °C.

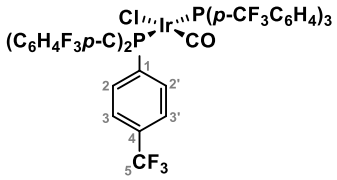
IR (solid) 1964 (C=O), 1479, 1387, 1083, 1012.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.59 (app dt, 12H, J = 8.3, 5.4 Hz, C^3H, $C^{3'}H$), 7.37–7.44 (m, 12H, C^2H, $C^{2'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 137.7 (C^4), 135.9 (t, J = 6.6 Hz, C^3, $C^{3'}$), 129.7 (t, J = 27.6 Hz, C^1), 128.9 (t, J = 5.5 Hz, C^2, $C^{2'}$).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 22.6.

trans-carbonylchlorobis(tris(4-trifluoromethylphenyl)phosphine)iridium(I) (372)



Prepared according to **General Procedure L** from tris(4-trifluoromethylphenyl)phosphine. Filtration gave **372** as a dark yellow solid (143 mg, 59%).

mp No physical state change up to 205 °C.

IR (solid) 1964 (C=O), 1398, 1322, 1169, 1122, 1109, 1061, 1015.

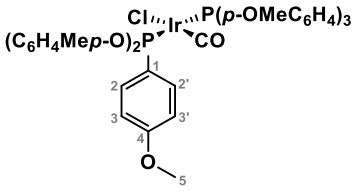
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.74 (app d, roof effect, 12H, J = 7.9 Hz, C^3H, $C^{3'}$H), 7.66 (app dt, roof effect, 12H, J = 8.2, 5.5 Hz, C^2H, $C^{2'}$H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 135.0 (t, J = 5.9 Hz, C^2), 125.7-126.1 (m, C^1, C^3, C^4).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 4.3.

NB: due to high level of multiplicity in the ^{13}C NMR, most carbons could not be observed.

trans-carbonylchlorobis(tris(4-methoxyphenyl)phosphine)iridium(I) (373)



Prepared according to **General Procedure L** from tris(4-methoxyphenyl)phosphine. Filtration gave **373** as a beige solid (141 mg, 72%). The complex most likely forms the oxygen adduct instantly when in solution (see ^{31}P NMR and IR). The characterization data given here is thus most likely assignable to the adduct.

IR (solid) 2000 (C=O), 1965 (C=O), 1594, 1568, 1501, 1289, 1255, 1181, 1101.

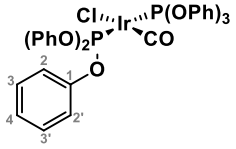
mp No physical state change up to 205 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.41–7.49 (m, 12H, C^2H, $C^{2'}H$), 6.87–6.93 (m, 12H, C^3H, $C^{3'}H$), 3.82 (s, 18H, C^5H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 161.7 (C^4), 136.2 (t, J = 6.4 Hz, C^2), 119.4 (t, J = 31.8 Hz, C^1), 114.0 (t, J = 5.8 Hz, C^3), 55.3 (C^5).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 1.43.

trans-carbonylchlorobis(triphenylphosphite)iridium(I) (374)



Prepared according to **General Procedure L** from triphenylphosphite. Filtration gave **374** as a bright yellow solid (123 mg, 69%).

mp 154-156 °C.

IR (solid) 1999 (C=O), 1587, 1486, 1185, 1161.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.19–7.28 (m, 24H, C^2H, $C^{2'}H$, C^3H, $C^{3'}H$), 7.13–7.18 (m, 6H, C^4H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 150.9 (t, J = 2.7 Hz, C1), 129.7 (C^3), 125.2 (C^4), 121.4 (t, J = 2.7 Hz, C^2).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 104.3.

Data for X-Ray:

Crystal data

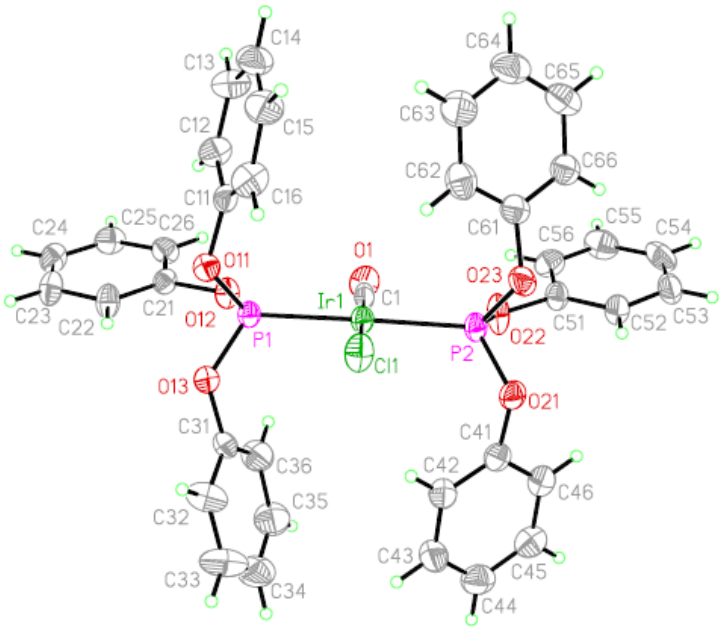
Chemical formula	$C_{37}H_{30}ClIrO_7P_2$
M_r	876.26
Crystal System, space group	Triclinic, *P*-1
Temperature (K)	150
a, *b*, *c* (Å)	9.9241 (5), 10.9830 (5), 16.6727 (6)
α, β, γ (°)	98.045 (3), 98.088 (4), 103.498 (4)
V (Å^3)	1721.08 (2)
Z	2
Radiation type	Cu $K\alpha$
U (mm^{-1})	9.514
Crystal size (mm)	0.05 × 0.03 × 0.01

Data collection

Diffractometer	Unknown
Absorption correction	Semi-empirical from equivalents
T_{min}, T_{max}	0.71, 0.94
No. of measured	7123
independent and observed	

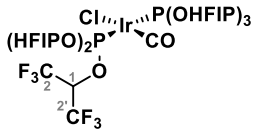
Refinement

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.0345, 0.0781, 1.00
No. of reflections	22574
No. of parameters	433
No. restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Absolute structure	–
Structure parameter	–



Selected parameters: missing

trans-carbonylchlorobis(tris(hexafluoroisopropyl)phosphite)iridium(I) (375)



Prepared according to **General Procedure L** from triphenylphosphite. Filtration gave 375 as a bright yellow solid (48 mg, 36%).

mp 62–64 °C

IR (solid) 2055 (C=O), 1656, 1367, 1297, 1233, 1201, 1112, 1080.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.64 (br sept, 6H, J = 5.2 Hz, C^{1}H, can also be t, J = 6.0 Hz when ^{19}F-decoupled NMR is measured).

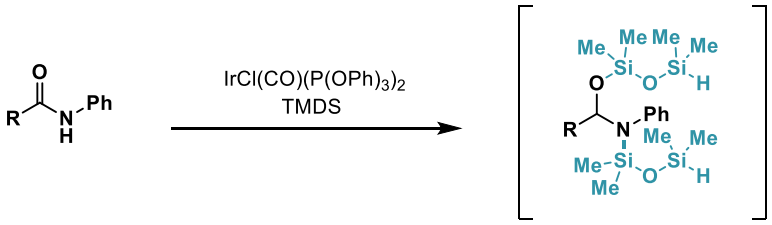
^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: –73.5.

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: Nothing appears consequently to extensive ^{13}C–^{19}F and ^{13}C–^{31}P couplings.

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 112.4.

6.5 Experimental Details for Chapter 5

6.5.1 General Procedure M: secondary amide reduction

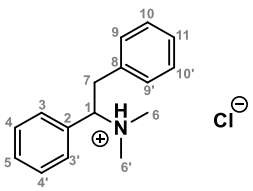


An NMR tube was charged with the secondary amide (0.100 mmol), toluene (0.5 mL), TMDS (3.00 equiv.) and Iridium complex **374** (1 mol%, sometimes referred to as "Super Vaska's"). The NMR tube was closed with a NMR cap, and the resultant solution immediately started bubbling. After 5 minutes, the over-pressure was evacuated by opening and closing the NMR tube. The resulting solution was left still for 72 h.

Tanya Rogova did the subsequent functionalisation.

Note: the conversion of the reaction can be influenced by the shape of the vessel, we found that a small headspace was beneficial. NMR tubes performed the best.

N,N-dimethyl-1,2-diphenylethan-1-ammonium chloride (379a· HCl)



A flame-dried 1 L three-necked round-bottomed flask equipped with a 2.5 cm Teflon-coated magnetic oval stir bar, a 250 mL addition funnel with pressure-equalization arm topped by a rubber septum, an internal

thermometer, and a rubber septum, is charged with dimethylbenzamide **377** (1.49 g, 10.0 mmol) and carbonylchlorobis(triphenylphosphine)iridium(I) **20** (3.90 mg, 5 μmol). CH_2Cl_2 (50 mL) is then added *via* cannula before TMDS (3.53 mL, 20.0 mmol) is added in one portion. The reaction is monitored by TLC using 50% EtOAC-pentane as the eluent. After 40 minutes and upon completion, the flask is immersed in a –78 °C dry ice/acetone cooling bath. While the solution is cooling, benzylmagnesium chloride (2.0 M in THF, 10.0 mL, 20.0 mmol) (Note 9) is transferred *via* cannula to the addition funnel. The Grignard reagent is then added dropwise over 10 minutes to the vigorously stirred reaction mixture. Subsequently, the cooling bath is removed and stirring is continued for a further 4 hours over which time the reaction temperature reaches rt. The reaction vessel is then placed in an ice bath and while the temperature is decreasing, 25.0 mL of saturated aqueous NH_4Cl is added to the addition funnel. Once the internal temperature has reached 5 °C, the aqueous NH_4Cl solution is slowly added to the stirred reaction mixture (Note 13). The mixture is then transferred to a 1 L separatory funnel, and the layers are partitioned, then the aqueous layer is extracted once with CH_2Cl_2 (200 mL). The combined organic layers are dried over anhydrous Na_2SO_4 (10 g), filtered *via* gravity filtration and the filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 500 mbar, then 23 mbar) to afford an orange oil (approximately 4.0 g). The residue is transferred to a 50 mL round-bottomed flask, dissolved in Et_2O (20 mL), and the flask is cooled in an 0 °C ice bath. HCl in dioxane (4.0 M, 3.75 mL, 15.0 mmol) is added in one portion to the vigorously stirred ethereal solution. The resulting suspension is filtered through a sintered glass funnel, under vacuum, and the solids washed twice with Et_2O (10 mL then 5 mL). The filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 20 mbar), Et_2O (5 mL) is added and the resulting suspension is filtered again under vacuum. The combined solids (2.6 g) are suspended in EtOAc (26 mL) in a 50.0 mL beaker. The suspension is heated to 60 °C, then the minimum volume of MeOH (5.2 mL) is added to dissolve the solids. The solution is left to cool to rt for 4 hours (Note 21), then placed in a –15 °C freezer for 14 hours. The resulting crystals are collected by vacuum filtration on a sintered glass funnel (porosity 2) and rinsed with ice-cold Et_2O (5 mL). The mother liquour is concentrated on a rotary evaporator under reduced pressure (40 °C, 600 then 28 mbar), and the recrystallisation is repeated a further two times (1 mL of EtOAc and 0.2 mL of MeOH per gram of material). The collected solids (1.83 g, 0.24 g, 0.02 g from each respective crop) are then

combined, dissolved in MeOH (25 mL) and concentrated on a rotary evaporator under reduced pressure (40 °C, 300 then 28 mbar) affording the desired product **379a**·HCl (2.10 g, 80%) as a colourless powder.

mp 206–208 °C (though visible sublimation happens from ~ 150 °C)

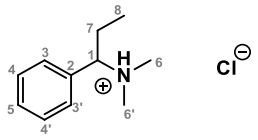
IR 3046, 2959, 2578, 2465, 2362, 1457, 1162, 1075, 1030, 1003, 960, 922

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.32–7.42 (m, 5H, C^2H, C^3H, $C^{3'}H$, C^4H, $C^{4'}H$), 7.04–7.11 (m, 3H, C^9H, $C^{9'}H$), 6.93–6.99 (m, 2H, $C^{10}H$, $C^{10'}H$), 4.25 (dd, 1H, J = 11.6, 3.5 Hz, C^1H), 3.83 (dd, 1H, J = 13.0, 3.5 Hz, C^7Ha), 3.42 (dd, 1H, J = 13.0, 11.6 Hz, C^7Hb), 2.73 (s, 6H, C^6H3, $C^{6'}H3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 135.4 (C^2), 131.1 (C^8), 130.3 (C^5), 130.0 (C^3, $C^{3'}$), 129.41 (C^4, $C^{4'}$), 129.35 (C^{10}, $C^{10'}$), 128.6 (C^9, $C^{9'}$), 127.1 (C^{11}), 72.8 (C^1), 42.9 (br, C^6), 39.2 (br, $C^{6'}$), 37.4 (C^7).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}N$) requires **m/z** 226.1590, found **m/z** 226.1591.

N,N-dimethyl-1-phenylpropan-1- ammonium chloride (379b·HCl)



Full procedure as published:

To a flame-dried 1 L three-necked round-bottomed flask equipped with a 3.5 cm Teflon-coated magnetic oval stir bar, a 250 mL addition funnel with pressure-equalization arm topped by a rubber septum, an internal thermometer, and a rubber septum, is charged dimethylbenzamide **377** (14.9 g, 100 mmol) (Note 2) and carbonylchlorobis(triphenylphosphine)iridium(I) **20** (39.0 mg, 0.05 mmol) under a nitrogen atmosphere (Note 3). CH_2Cl_2 (500 mL) (Note 4) is then added *via* cannula before 1,1,3,3-tetramethyldisiloxane (35.3 mL, 200 mmol) (Note 5) is added over 3 minutes (Note 6).

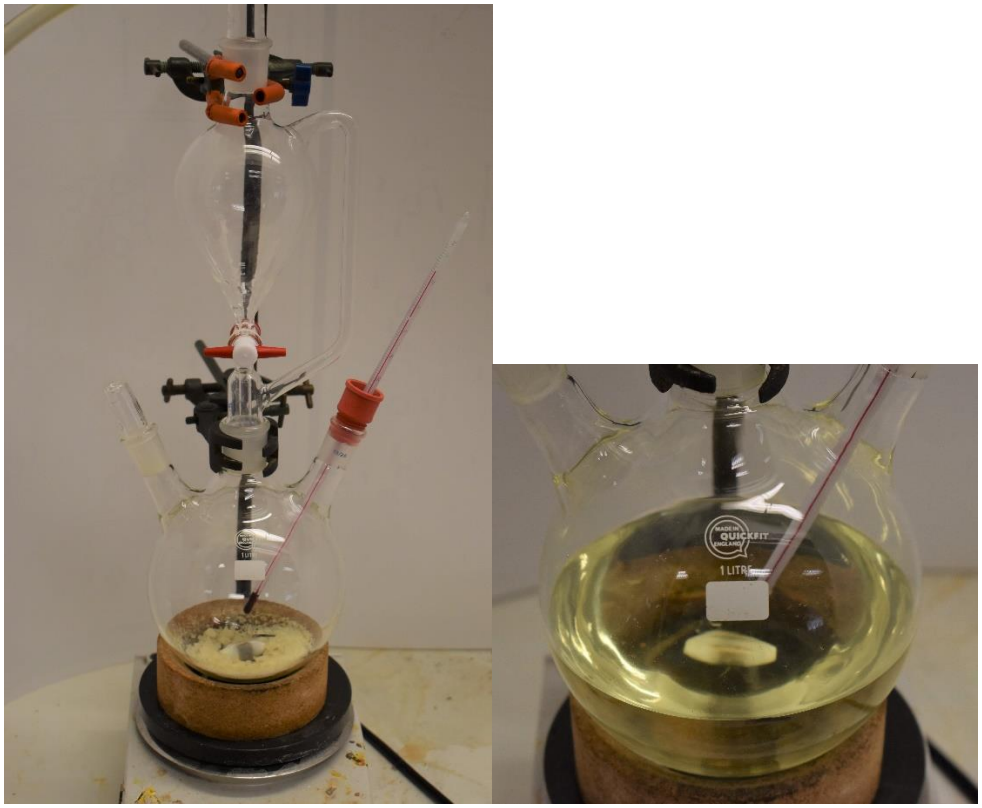


Figure i Reaction set-up, with starting material and catalyst (top). Before the addition of TMDS (bottom)

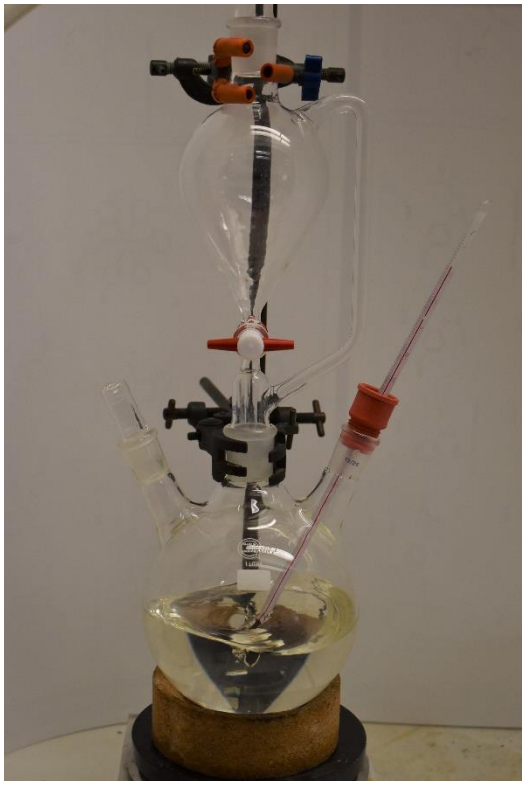


Figure ii Reaction mixture 40 minutes after the addition of TMDS

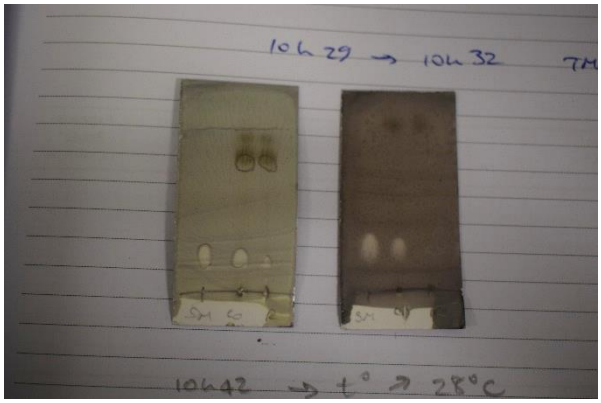


Figure iii TLC after 10 minutes (left) and 40 minutes (right) demonstrating absence of SM (white spot in vanillin stain).

The reaction is monitored by silica gel TLC using 50% EtOAC-pentane as the eluent (Note 7). After 45 minutes (Note 8) and upon completion, the flask is immersed in a –78 °C dry ice/acetone cooling bath. While the solution is cooling, ethylmagnesium bromide (3.0 M in THF, 36.7 mL, 110 mmol) (Note 9) is transferred *via* cannula to the addition funnel. The Grignard reagent is then added dropwise over 10 minutes to the vigorously stirred (1100 rpm) reaction mixture (Note 10).

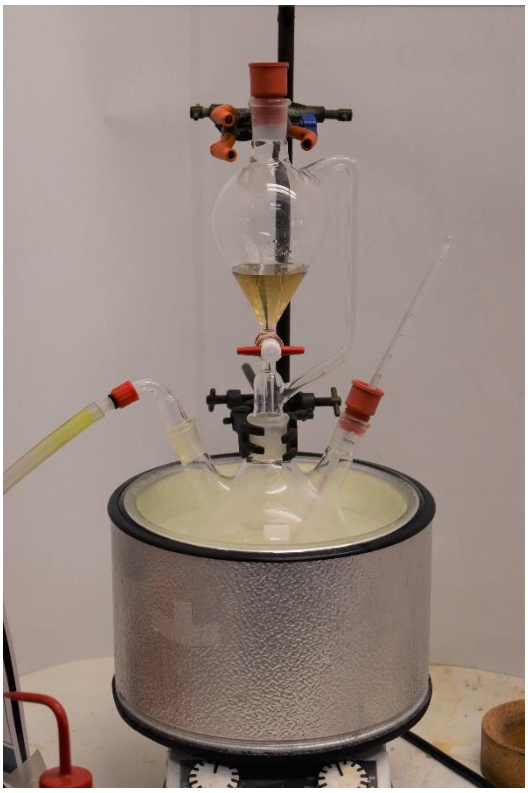


Figure iv Reaction mixture just before addition of the Grignard reagent

Subsequently, the cooling bath is removed and stirring is maintained for a further 4 hours over which time the reaction temperature reaches 23 °C (Note 11).

The reaction vessel is then placed in an ice bath, and while the temperature is decreasing, 250 mL of saturated aqueous NH_4Cl is added to the addition funnel.

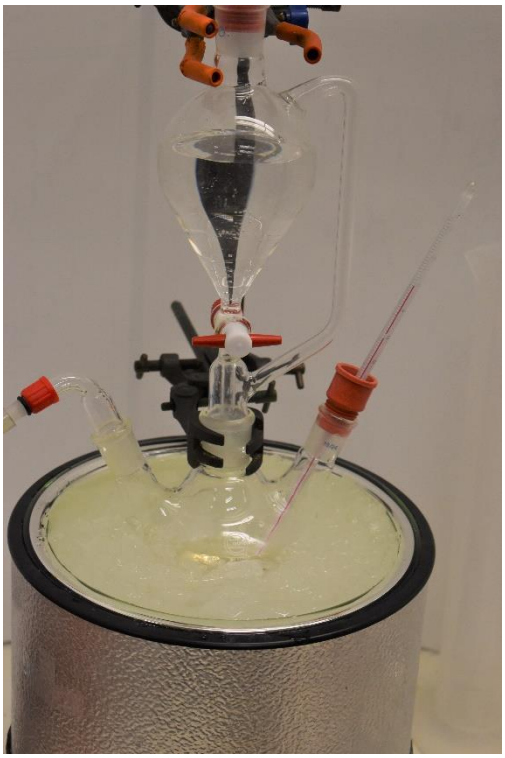


Figure v Reaction mixture 4 h after the addition of Grignard reagent, cooling down to 0 °C

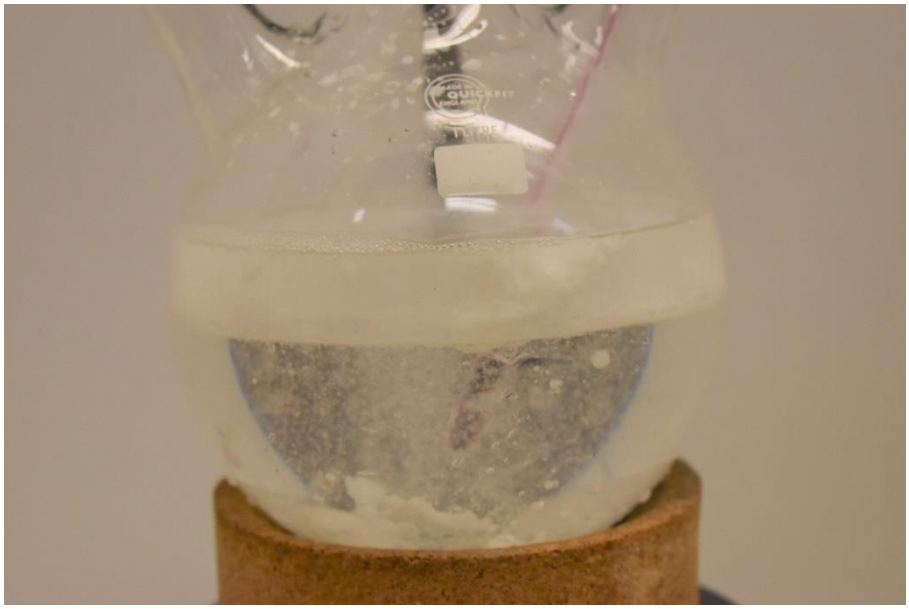


Figure vi Reaction mixture upon quenching with saturated NH_4Cl

Once the internal temperature has reached 5 °C, the aqueous NH_4Cl solution is slowly added to the stirred reaction mixture (Note 12). Following this, the mixture is then transferred to a 1 L separatory funnel, water (200 mL) and CH_2Cl_2 (100 mL) were used to wash the flask, and the layers are partitioned, then the aqueous layer is extracted once with CH_2Cl_2 (200 mL). The combined organic layers are dried over anhydrous Na_2SO_4 (100 g), filtered *via* gravity filtration and the filtrate is concentrated on a rotary evaporator under reduced pressure (40 °C, 500 mbar, then 41 mbar) to afford a colourless oil (approximately 35 g). The residue is transferred to a 500 mL round-bottomed flask, dissolved in Et_2O (200 mL) (Note 13), and the flask is cooled in a 0 °C ice bath.

HCl in dioxane (4.0 M, 37.5 mL, 150 mmol) (Note 14) is added continuously over 1 minute to the vigorously stirred (1100 rpm) ethereal solution (Note 15).



Figure vii Addition of the HCl in dioxane solution (top) leading to the precicpitation of the HCl salt (bottom)

The resulting biphasic solution is concentrated on a rotary evaporator under reduced pressure (40 °C, 500 mbar, then 46 mbar). To the resulting mixture (solid in an oil) is then added EtOAc (200 mL) (Note 16), and the suspension is heated at 70 °C. MeOH (3.5 mL) (Note 17) is added dropwise until all solids dissolved. The resulting hot solution is then placed in a fridge at -15 °C and left to crystallise for 16 hours (Note 18). The crystals obtained are then filtered in a sinter funnel (porosity 2), under vacuum, and transferred to a crystallizer and placed under high vacuum (2 mbar) for 6 hours (10.6 g obtained).



Figure viii Resuspension in hot EtOAc (top) followed by dissolution in EtOAc/MeOH (bottom)

The mother liquour is concentrated on a rotary evaporator under reduced pressure (40 °C, 500 mbar, then 44 mbar), and crystallisation from hot EtOAc (200 mL)/MeOH (4.0 mL) as described previously gives a second crop of crystals (3.0 g). Finally, the mother liquour is once more concentrated on a rotary evaporator under reduced pressure (40 °C, 500 mbar, then 54 mbar), and diethyl ether (200 mL) is added to produce a suspension who is sonicated for 1 minute, then placed at -15 °C for 16 h. Final filtration as previously described yields 1.3 g. The crops are combined and made homogenous to afford the desired product **379b**·HCl (14.9 g, 75%) as white crystals (Note 19 and 20).

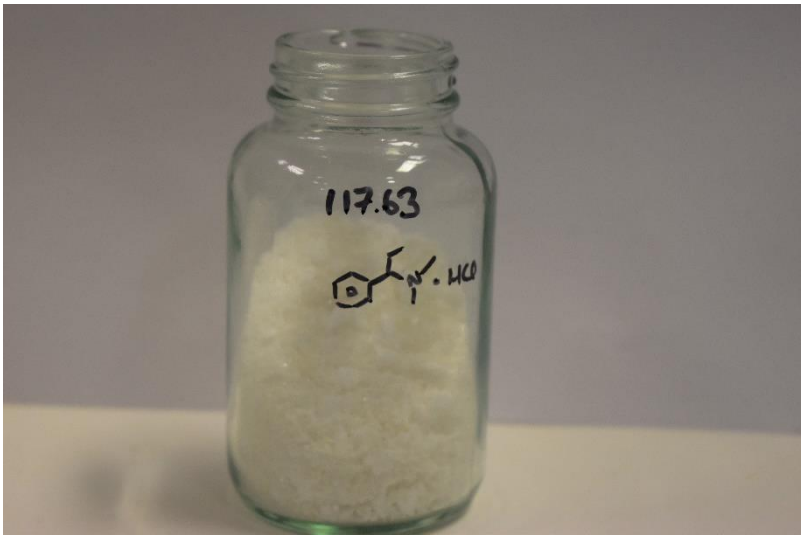


Figure ix. Purified product

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with N,N-dimethylbenzamide, carbonylchlorobis(triphenylphosphine)iridium, (I), dichloromethane, 1,1,3,3-Tetramethyldisiloxane, ethylmagnesium bromide (3.0 M in diethyl ether), diethyl ether, hydrochloric acid in dioxane (4.0 M),

ethyl acetate, and methanol. It should be noted that higher catalysts loading can potentially generate a significant amount of flammable hydrogen gas. It is advisable to conduct these experiments in a large flask, adequately vented to a standard inert gas manifold or bubbler into a fume hood.

2. N,N-Dimethylbenzamide (>99%) was purchased from Sigma-Aldrich. An insoluble impurity was removed by dissolving the amide in hot EtOAc (200 mL per 25 grams of starting material) and filtering on cotton wool.
3. Carbonylchlorobis(triphenylphosphine)iridium (I) was purchased from Alfa Aesar and used as received.
4. Dichloromethane was purchased from Sigma-Aldrich, dried by sitting over activated 4Å molecular sieves (1g/10 mL of solvent) for 24 hours, and was degassed by sparging with Argon for 2 hours prior to starting the reaction.
5. 1,1,3,3-Tetramethyldisiloxane was purchased from Sigma-Aldrich and used as received.
6. Over *circa* 15 minutes, the yellow colour of the solution was observed to fade and some gas evolution was observed. The temperature of the reaction increased to 26 °C.
7. TLC was performed using 50% EtOAc-pentane as the eluent. An aliquot (50 μL) of the reaction mixture was diluted in CH_2Cl_2 (150 μL) before spotting on the TLC plate and elution. The tertiary amide starting material could be visualised under a UV lamp and with a vanillin stain (R_f = 0.2).
8. Complete disappearance of starting material was observed after 45 minutes.
9. Ethylmagnesium bromide (3.0 M in diethyl ether) was purchased from Sigma-Aldrich and used as received.
10. The addition was started 15 minutes after the flask was immersed into the −78 °C bath. The reaction temperature was kept below −50 °C at all times during the addition.
11. The temperature reached 20 °C after 3 hours. The reaction mixture remains colourless.
12. The addition was started 10 minutes after the flask was immersed into the 0° C bath. The reaction temperature was kept below 10 °C at all times during the addition. The first drops were carefully added, and overall the addition lasted 10 minutes. A significant amount of gas evolved at this stage, including ammonia, the reaction mixture should be kept in a fumehood at all time.
13. Diethyl ether was purchased from Sigma-Aldrich and used as received.
14. Hydrochloric acid in dioxane (4.0 M) was purchased from Fluorochem ltd. and used as received.

15. Immediate formation of a white solid was observed. Vigorous stirring was necessary to maintain homogeneity during precipitation. A suspension is not obtained, but rather a biphasic mixture.
16. Ethyl acetate was purchased from Sigma-Aldrich and used as received.
17. Methanol was purchased from Sigma-Aldrich and used as received.
18. The crystallization was not seeded or initiated.
19. The yield and purity of the sample was evaluated on the combined homogenized crops, and the purity was found to be 97.6% with quantitative NMR using 15.2 mg of compound **379b**·HCl and 18.4 mg of standard (trimethoxybenzene). A second reaction on identical scale provided 15.6 g (78%) of the desired product **379b**·HCl, whose purity was evaluated to be 97.2%.
20.

mp 160–162 °C

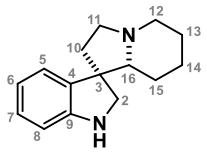
IR 3407, 2972, 2861, 1635, 1460, 1172

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 12.16–12.60 (br s, 1H, NH), 7.40–7.45 (m, 5H, C^3H, $C^{3'}H$, C^4H, $C^{4'}H$, C^5H), 3.93 (dd, 1H, J = 11.7, 3.8 Hz, C^1H), 2.72 (br s, 3H, C^6H_3), 2.56 (br s, 3H, $C^{6'}H_3$), 2.38–2.49 (m, 1H, C^7Ha), 2.17 (ddq, 1H, J = 13.1, 11.8, 7.3 Hz, C^7Hb), 0.75 (t, 3H, J = 7.3 Hz, C^8H_3).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 131.2 (C^2), 130.2 (C^5), 129.8 (C^3, $C^{3'}$), 129.5 (C^4, $C^{4'}$), 72.6 (C^1), 42.4 (br, C^6), 39.1 (br, $C^{6'}$), 23.8 (C^7), 10.8 (C^8).

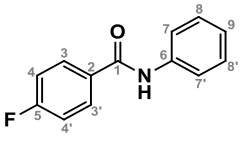
HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{18}N$) requires **m/z** 164.1434, found **m/z** 164.1435.

Large scale procedure for (3R,8a'R)-2',3',6',7',8',8a'-hexahydro-5'H-spiro[indoline-3,1'-indolizine] (126)



To a solution of indole-tethered lactam **125** (3.00 g, 12.4 mmol, 1 equiv.) in CH_2Cl_2[1] (24.7 mL, 0.5 M), was added Vaska's catalyst as a solution (240 μg in 1.0 mL of CH_2Cl_2).[2] The solution was cooled down to −15 °C with a cryostat, and TMDS (6.57 mL, 37.2 mmol, 3 equiv.) was added over a minute. The resulting solution was stirred at −15 °C for 6 h. It was then concentrated *in vacuo*, and directly loaded on a Flash Chromatography Column. Elution with 98 : 2 CH_2Cl_2 : NH_3 in MeOH (2 M) afforded **126** as a yellow oil that crystallized upon standing, and can be further recrystallized from pentane (2.43 g, 86%).

4-fluoro-N-phenylbenzamide (380a)



Prepared according to **General Procedure C** from aniline and *p*-fluorobenzoic acid by Tanya Rogova.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.85–7.93 (m, 2H, C3H, C3'H), 7.73 (br s, 1H, NH), 7.57–7.67 (m, 2H, C^8H, $C^{8'}$H), 7.33–7.43 (m, 2H, C4H, C4'H), 7.11–7.22 (m, 3H, C^7H, $C^{7'}$H, C^9H).

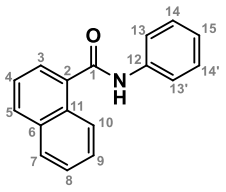
[1] The dichloromethane was obtained from Sigma-Aldrich, allowed to sit on MS (3A) for 24 h and sparged with Argon for 30 minutes before the reaction.
[2] The solution was made from the dissolution of 2.4 mgs of catalyst in 10 mL of CH_2Cl_2.

Data in toluene-d_8:

^{1}H NMR (C_7D_8, 400 MHz) δ_H: 7.47–7.53 (m, 2H, C^{3}H, C$^{3'}$H), 7.30 (ddd, 2H, J = 10.3, 5.3, 2.6 Hz, C^{4}H, C$^{4'}$H), 7.08–7.17 (m, 2H, C^{8}H, C$^{8'}$H), 6.88–6.95 (m, 1H, C^{9}H), 6.60–6.68 (m, 2H, C^{7}H, C$^{7'}$H).

All other data in accordance with literature.[17]

N-phenyl-1-naphthamide (380b)



Prepared according to **General Procedure C** from aniline and *1*-naphthoyl chloride. [3]

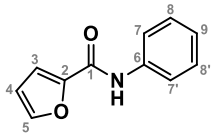
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.33–8.40 (m, 1H), 7.97 (d, 1H, J = 8.1 Hz), 7.90 (dd, 1H, J = 6.8, 2.8 Hz), 7.64–7.81 (m, 4H), 7.5–7.61 (m, 2H), 7.50 (t, 1H, J = 7.6 Hz), 7.40 (t, 2H, J = 7.6 Hz), 7.23–7.15 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 167.7, 138.2, 134.7, 133.9, 131.2, 130.2, 129.3, 128.6, 127.5, 126.8, 125.4, 125.2, 124.9, 124.8, 120.1.

All other data in accordance with literature.[17]

[3] This compound could not be assigned due to all signals overlapping.

N-phenylfuran-2-carboxamide (380c)



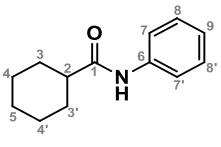
Prepared according to **General Procedure C** from aniline and 2-furanoyl chloride. Product **380c** was isolated as a white solid (405 mg, 43%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.13 (br s, 1H, NH), 7.63–7.71 (m, 2H, C^7H, $C^{7'}H$), 7.49 (dd, 1H, J = 1.7, 0.8 Hz, C^5H), 7.32–7.38 (m, 2H, C^8H, $C^{8'}H$), 7.23 (dd, 1H, J = 3.5, 0.8 Hz, C^3H), 7.09–7.18 (m, 1H, C^9H), 6.54 (dd, 1H, J = 3.5, 1.8 Hz, C^4H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 156.2 (C^1), 148.0 (C^6), 144.3 (C^5), 137.5 (C^2), 129.2 (C^8, $C^{8'}$), 124.6 (C^9), 120.1 (C^7, $C^{7'}$), 115.3 (C^3), 112.7 (C^4).

All other data in accordance with literature.[18]

N-phenylcyclohexanecarboxamide (380d)



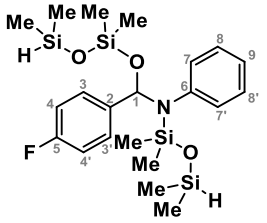
Prepared according to **General Procedure C** from aniline and cyclohexanecarbonyl chloride. Product **380d** was isolated as a white solid.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.49–7.56 (m, 2H, C^7H, $C^{7'}H$), 7.28–7.36 (m, 2H, C^8H, $C^{8'}H$), 7.19 (s, 1H, NH) 7.05–7.12 (m, 1H, C^9H), 2.23 (tt, 1H, J = 11.7, 3.5 Hz, C^2H), 1.91–2.03 (m, 2H, C^3Ha, $C^{3'}Ha$), 1.84 (dq, 1H, J = 13.6, 3.8 Hz, C^4Ha, $C^{4'}Ha$), 1.65–1.74 (m, 1H, C^5Ha), 1.46–1.62 (m, 2H, C^3Hb, $C^{3'}Hb$), 1.20–1.40 (m, 3H, C^1Hb, C^4Hb, $C^{4'}Hb$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 175.0 (C^1), 138.2 (C^6), 129.1 (C^8), 124.2 (C^9), 119.9 (C^7), 46.7 (C^2), 29.8, (C^3), 25.8 (C^4, C^5).

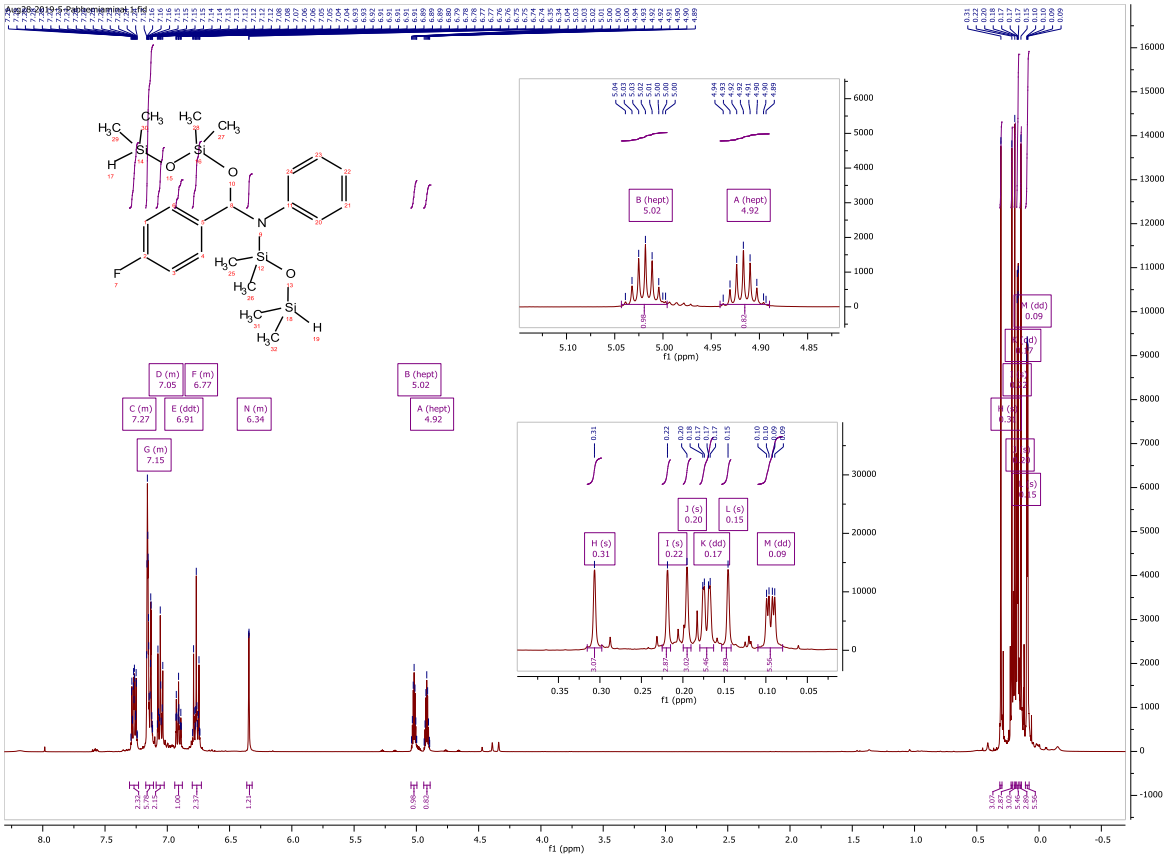
All other data in accordance with literature.[19]

N-((4-fluorophenyl)((1,1,3,3-tetramethyldisiloxaneyl)oxy)methyl)-1,1,3,3-tetramethyl-N-phenyldisiloxan-1-amine 381a)



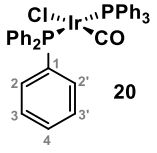
An NMR tube was charged with secondary amide **380a** (12.0 mg, 56 μmol), deuterated benzene (0.5 mL), TMDS (30 μL, 168 μmol) and Iridium complex **374** (0.9 mg, 1.1 μmol). The resultant reaction mixture was monitored by NMR spectroscopic analysis. After 72 h, the reaction mixture was carefully blown with a light nitrogen flow. The resulting oil was redissolved in deuterated benzene, and bis-silylated hemiaminal **381a** could be observed as the sole species.

^{1}H NMR (C_6D_6, 400 MHz) δ_H: 7.23–7.30 (m, 2H, C^3H, $C^{3'}H$), 7.11–7.17 (m, 2H, C^7H, $C^{7'}H$), 7.02–7.09 (m, 2H, C^8H, $C^{8'}H$), 6.91 (ddt, 1H, J = 7.8, 6.8, 1.3 Hz, C^9H), 6.73–6.80 (m, 2H, C^4H, $C^{4'}H$), 6.34 (s, 1H, C^1H), 5.02 (hept, 1H, J = 2.8 Hz, Si–H), 4.92 (hept, 1H, J = 2.8 Hz, Si–H), 0.31 (s, 3H, O–Si–CH_3), 0.22 (s, 3H, O–Si–CH_3), 0.20 (s, 3H, O–Si–CH_3), 0.17 (app dd, 6H, J = 2.8, 0.8 Hz, 2* H–Si–CH_3), 0.15 (s, 3H, Si–CH_3), 0.09 (app dd, 6H, J = 2.8, 1.2 Hz, 2* H–Si–CH_3).


B (hept)
5.02
A (hept)
4.92
H (s)
0.31
I (s)
0.22
J (s)
0.20
K (dd)
0.17
L (s)
0.15
M (dd)
0.09
D (m)
7.05
F (m)
6.77
C (m)
7.27
E (ddt)
6.91
N (m)
6.34
G (m)
7.15
f1 (ppm)

6.6 Vaska's complex synthesis

Vaska's complex



20

Prepared according to a modified literature procedure.[20]

DMF (42 mL) was thoroughly degassed by 3 Freeze-Pump-Thaw cycles, before $IrCl3(xH_2O)$ (2.00 g, 2.84 mmol) and PPh_3 (3.73 g, 14.2 mmol) were added. The flask containing the resulting dark solution was equipped with a condenser, evacuated and filled with Nitrogen, and heated at 160 °C for 11 h. It was left to cool down to around 50 °C, and MeOH (100 mL, degassed by sparging with nitrogen for 20 minutes) was carefully added. The yellow solution should become cloudy and yellow crystals should start forming. It was left in the refrigerator (0 °C) for around 4 h before being filtered under nitrogen (special sintered funnel required), and the solids washed with MeOH (20 mL). The resulting solids (still on the sintered funnel) are then dissolved in chloroform (around 80 mL, degassed by sparging for 20 minutes) until the solution passing is no longer deep yellow (some beige solids might be left, depending on the batch of Iridium chloride), and collected in a flasked under nitrogen. Pentane (300 mL) is then added, and Vaska's complex should slowly crash out/crystallise. It can be filtered (open to air), dried and stored in a close vessel. Over time (around a year), the complex will oxidise in air to the Oxygen adduct (around 5.20 ppm in the 31P NMR).

mp 215 °C.

IR (solid) 1949 (C=O), 1479, 1435, 1387, 1097.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.69-7.77 (m, 12H, C^3H, $C^{3'}H$), 7.34-7.44 (m, 18H, C^2H, $C^{2'}H$, C^4H).

^{31}P NMR ($CDCl_3$, 162 MHz) δ_P: 23.88.

6.7 References for Chapter 6

(1) Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(2) Hoefgen,B.; Decker, M.; Mohr, P.; Schramm, A. M.; Rostom, S. A. F.; El-Subbagh, H.; Schweikert, P. M.; Rudolf, D. R.; Kassack, M. U.; Lehmann J. Dopamine/Serotonin Receptor Ligands. 10:1 SAR Studies on Azecine-type Dopamine Receptor Ligands by Functional Screening at Human Cloned D1, D2L, and D5 Receptors with a Microplate Reader Based Calcium Assay Lead to a Novel Potent D1/D5 Selective Antagonist. *J. Med. Chem.* **2006**, *49*, 760-769.

(3) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R., I.; Trevitt, G.; Dixon, D. J. Enantioselective Brønsted Acid-Catalyzed *N*-Acyliminium Cyclization Cascades. *J. Am. Chem. Soc.* **2009**, *131*, 31, 10796–10797.

(4) Desmaële, D.; Mekouar, K.; d'Angelo, J. Stereocontrolled Elaboration of Quaternary Carbon Centers through the Asymmetric Michael-Type Alkylation of Chiral Imines/Secondary Enamines: Enantioselective Synthesis of (+)-Vincamine. *J. Org. Chem.* **1997**, *62*, 3890–3901.

(5) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 13436 –13440.

(6) Temme, O.; Taj, S.-A.; Andersson,P. G. Highly Enantioselective Intermolecular Cu(I)-Catalyzed Cyclopropanation of Cyclic Enol Ethers. Asymmetric Total Synthesis of (+)-Quebrachamine**.** *J. Org. Chem.*, 1998, **63**, 6007–6015.

(7) Herrmann, J. L.; Schlessinger, R. H. Methods for alkylating lactones. *J. Chem. Soc. Chem. Commun.,* **1973**, 711.

(8) Kawanishi, K.; Uhara, Y.; Hashimoto, Y. Alkaloids from the hallucinogenic plant Virola Sebifera. Phytochemistry **1985**, *24*, 6, 1373-1375.

(9) Qu, S.-J.; Wang, G.-F.; Duan, W.-H.; Yao, S.-Y.; Zuo, J.-P.; Zhuo, C.-J. P.; Tan,C.-H.; Zhu, D.-Y. *Bioorg. Med. Chem.* **2011**, *19*, 3120–3127.

(10) M. Lounasmaa, R. Jokela, B. Tirkkonen and T. Tamminem, Conformational Studies of 1- and 3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizines. *Heterocycles*, **1985**, 23, 1367-1371.

(11) Massiot, G.; Sousa Oliveira, F.; Levy, J. Synthesis in the indole series viii (1): a novel approach to indoloquinolizidines through alkylation-cyclization of an enamine derived from tryptamine. *Tetrahedron Lett.*, 1982, **23**, 177–180.

(12) Felluga, F.; Pitacco, G.; Visintin, C.; Valentin, E. Synthesis of Polysubstituted Pyrrolizidines from Proline Derivatives and Conjugated Nitroolefins. *Helv. Chimica Acta* **1997**, *80*, 1457–1472.

(13) Koukhi, N.; Vaultier, M.; Carrié, R. Synthesis and Reactivity of Methyl γ-Azido Butyrates and Ethyl δ-Azido Valerates and of the corresponding acid chlorides as useful reagents for the aminoalkylation. *Tetrahedron* **1987**, *43*, 8, 1811-1822.

(14) Nakagawa, M.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. Synthesis of 5,6-Dihydro-2-pyrone and 2-Pyrone. *Synthesis*, **1974**, *7*, 510−511.

(15) Reding, M. T.; Fukuyama, T. Stereocontrolled Total Synthesis of (±)-Catharanthine via Radical Mediated Indole Formation. *Org. Lett.,* **1999,** *1*, 7, 973−976.

(16) Klabunde, U.; Forster, D.; Weinreis, W. O. Dicarbonylchloro(p-toluidine)iridium(I). *Inorganic Syntheses* **1974**, *15*, 82−84.

(17) Xiao, F.; Liu, Y. Tang, C.; Deng, G.-J. Peroxide-Mediated Transition-Metal-Free Direct Amidation of Alcohols with Nitroarenes. *Org. Lett.* **2012**, *14*, 4, 984–987.

(18) Zhu, Y.-P.; Sergeyev, S.; Franck, P.; Orru, R. V. A.; Maes, B. U. W. Amine Activation: Synthesis of *N*-(Hetero)arylamides from Isothioureas and Carboxylic Acids. *Org. Lett.* **2016**, *18*, 4602−4605.

(19) Song, W.; Dong, K.; Li, M. Visible Light-Induced Amide Bond Formation. *Org. Lett.* **2020**, *22*, 2, 371–375.

(20) Vrieze, K.; Collman, J. P. ; Sears, C. T., Jr.; Kubota, M. Trans-Chlorocarbonylbis(Tri-Phenylphosphine)Iridium. Inorg. Synth. **1968**, *11*, 101−104.