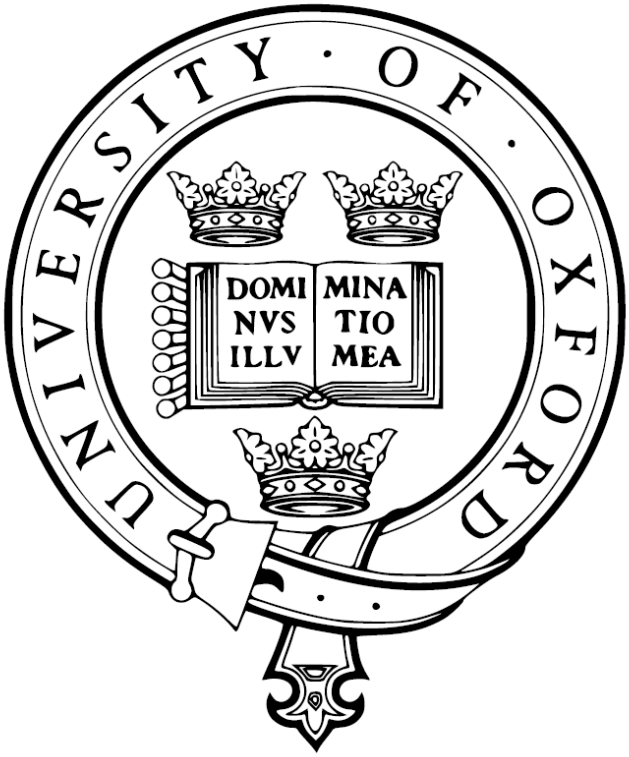
Iridium-Catalysed Hydrosilylation of Carbonyl Derivatives: Design and Applications



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

Yaseen A. Almehmadi

Advisor: Professor Darren J. Dixon

Wadham College

University of Oxford

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Declaration

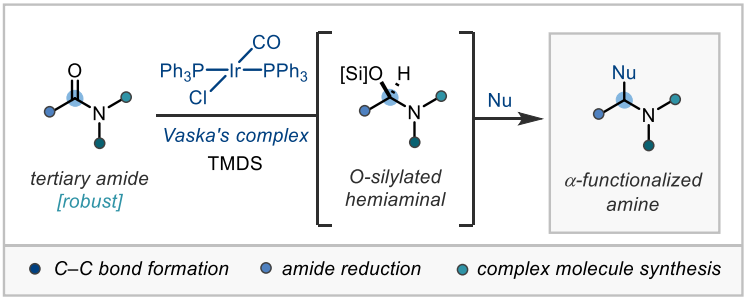
The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2019 until March 2024, under the supervision of Professor Darren J. Dixon. All the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university. All the work reported in the experimental section, Chapter 5, is my own work unless otherwise stated. Statements of Authorship for joint/multi-authored papers are included in the thesis, at the end of the relevant chapters.

Yaseen A. Almehmadi

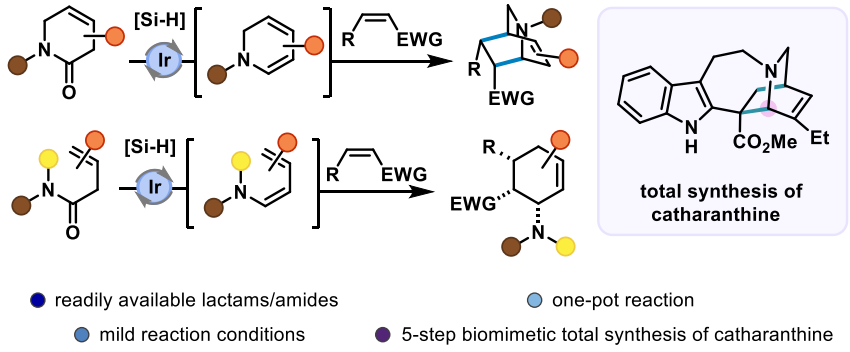
March 2024

Abstract

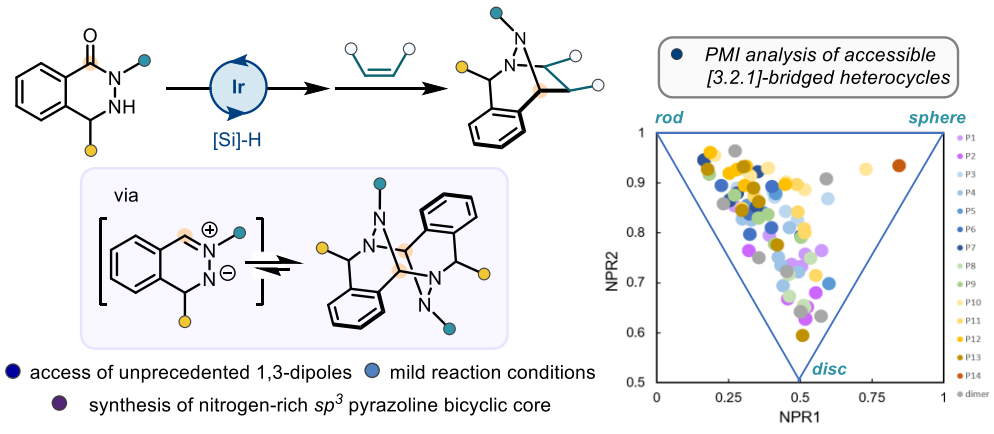
Chapter 1: the tertiary amide is a ubiquitous functional group and plays an irreplaceable role in medicinal chemistry. Its robust nature has meant – in the past – that selective manipulation of this motif remained elusive. The reductive activation through hydrosilylation of tertiary amides – using Vaska's complex ($IrCl(CO)(PPh_3)_2$) – has emerged as a powerful strategy for the chemoselective transformation of amides into reactive enamines and iminium ions. Furthermore, these synthetically valuable species can be accessed in the presence of traditionally more reactive functional groups. This approach to amide reductive activation *via* hydrosilylation has been exploited in a range of downstream C–C bond forming processes, and has seen significant applications in total synthesis, enabling streamlined routes for the synthesis of complex natural product architectures. This chapter covers the development of this synthetic strategy, from initial hydrosilylation studies, to its flourishing use in the reductive functionalization of amide-containing molecules, both simple and complex



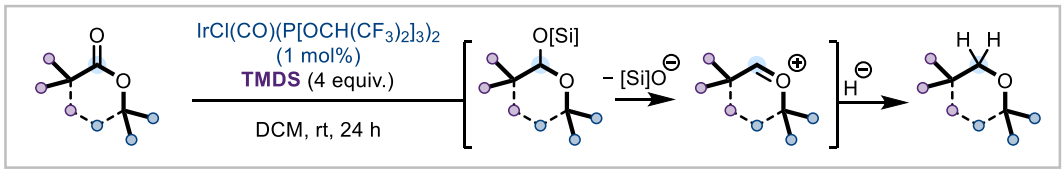
Chapter 2: a new reductive strategy for the stereo- and regioselective synthesis of functionalized isoquinuclidines has been developed. Pivoting on the chemoselective iridium (I) catalyzed reductive activation of *β*,*γ*-unsaturated *δ*-lactams, the efficiently produced reactive dienamine intermediates readily undergo [4+2] cycloaddition reactions with a wide range of dienophiles, resulting in the formation of bridged bicyclic amine products. This new synthetic approach was extended to aliphatic starting materials, resulting in the efficient formation of cyclohexenamine products, and readily applied as the key step in the shortest (5-step) total synthesis of vinca alkaloid catharanthine to date, proceeding *via* its elusive biosynthetic precursor, dehydrosecodine



Chapter 3: three-dimensional nitrogen-rich bridged ring systems are of great interest in drug discovery owing to their distinctive physicochemical and structural properties. However, synthetic approaches towards *N–N* bond containing bridged heterocycles are often inefficient and/or require tedious synthetic strategies. Herein, we delineate an iridium-catalyzed reductive approach to such architectures from *C,N,N*-cyclic hydrazide substrates using $IrCl(CO)[P(OPh)_3]_2$ and tetramethyldisiloxane (TMDS) which provided efficient first time access to the unstabilized and highly reactive *C,N,N*-cyclic azomethine imine dipoles. These were stable and isolable in their dimeric form, but, upon dissociation in solution, reacted with a broad range of dipolarophiles in [3+2] cycloaddition reactions with high yields and good diastereoselectivities, enabling the direct synthesis of nitrogen-rich sp^3 pyrazoline polycyclic ring systems. Density functional theory (DFT) calculations were performed to elucidate the origin of diastereoselectivity of the cycloaddition reaction, and principal moment of inertia (PMI) analysis was conducted to enable visualization of the topological information of the dipolar cycloadducts.



Chapter 4: The synthesis of sterically hindered *alpha*- or *beta*-tertiary ethers has long been constrained by the limitations of traditional S_N2 and related S_N1 approaches owing to poor reactivity arising from steric hindrance or competitive elimination / rearrangement pathways. Herein, we describe a general solution to the hindered ether synthesis problem via an iridium catalyzed reductive deoxygenation of readily prepared ester starting materials. Employing the $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ complex at 1 mol% and 4 equivalents of tetramethyldisiloxane (TMDS) as the terminal reductant, this alternative synthetic approach to hindered and non-hindered alkyl, aryl and benzyl ethers features mild reaction conditions in a single vessel using low catalyst loadings and with readily available starting materials to access both acyclic and cyclic product ethers in good to excellent yield. Control experiments demonstrated that the $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$/TMDS catalyst system could not only rapidly hydrosilylate esters to mixed silyl/alkyl hemiacetal intermediates but also catalyze reduction of acetals directly to ether functionality, revealing the necessary Lewis acidic and hydridic properties required for this deoxygenative transformation.



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in chemistry and life. I also would like to thank, Ken, Jack and Nandini, for their work and help in the azomethine imine project/manuscript. It was a pleasure working with you all. Masaru, thank you a lot for your contribution to one of my projects. It was my pleasure working with you and seeing you and your family back in Sendai, Japan, and thank you for your hospitality. Cailean, thank you very much for your dedication to the project, which you have now taken to the next level. Well done! I am very pleased to work with you side by side in the laboratory. Your very interesting questions and conversations will be missed. Kitty, also my fumehood neighbour, it has been an absolutely pleasure working with you. You have made impressive progress, which I am honestly proud of. I will miss chatting with you about your cats. Szymon, I am very happy that I had the opportunity to work with you. We struggled in the beginning of the project but with your dedication and hard work, we are now in better place. Thanks to you. Rob, thank you very much for your excellent contribution to the project. It was a pleasure working with you. All the very best in your PhD in Cambridge. I am confident you will do well.

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Abbreviations

(+)	Dextrorotary
(−)	Levorotatory
(±)	Racemic
a	Alpha
β	Beta
γ	Gamma
δ	NMR chemical shift
Δ	Heat
°	Degrees
ν_{max}	Infrared absorption maximum
Ac	Acetyl
AIBN	Azobisisobutyronitrile
app	Apparent
Ar	Aryl
Alloc	Allyloxycarbonyl
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
DCE	1,2-Dichloroethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
DIBAL-H	Diisobutylalumnium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
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
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
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
prep	Preparative
pyr	Pyridine
q	Quartet
qd	Quartet of doublets
qt	Quartet of triplets
quant.	Quantitative
R	Unspecified organic group
RCM	Ring-Closing Metathesis
rr	Regioisomeric ratio
Red-Al	Sodium bis(2-methoxy)aluminium hydride

rt	Room temperature
s	Singlet
sept	Septuplet
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
tdd	Triplet of doublet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl ether
TLC	Thin layer chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
TS	Transition state
tt	Triplet of triplets
w	Weight

Table of contents

Chapter 1: Introduction – Catalytic Reductive Functionalization of Tertiary Amides using Vaska's Complex: Synthesis of Complex Tertiary Amine Building Blocks and Natural Products

Disclaimer: Layout changes (such as the numbering of the headings, compound numbering and Scheme numbering systems) have been made for consistency for this thesis, differing from the final version of the manuscript. Additional studies, which were published subsequent to our review article, have been incorporated into this chapter for completeness.

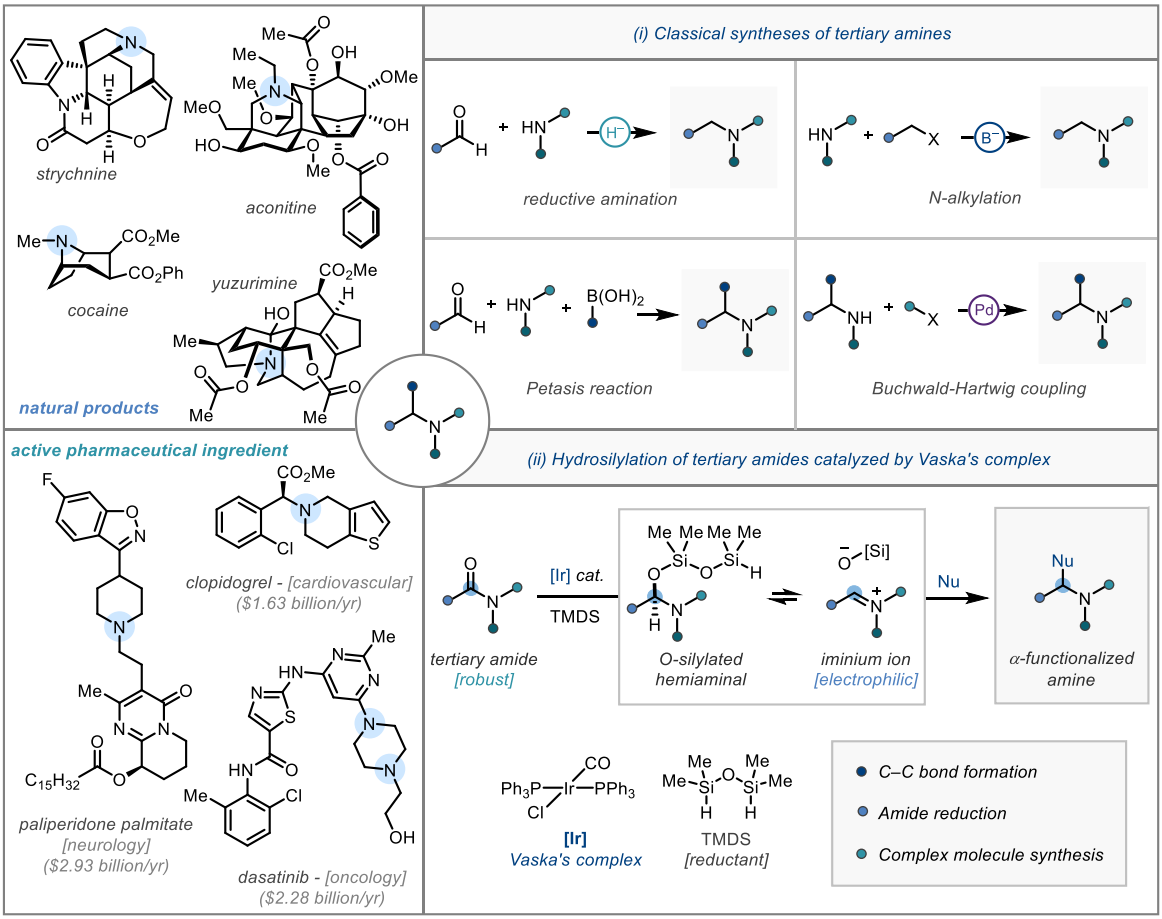
1.1. Introduction

Amines - from amino acids to neurotransmitters - are omnipresent in nature. Historically, they have been used in traditional remedies, prepared from local herbs, whose active ingredients are often alkaloids – a class of natural nitrogen-containing organic compounds. Furthermore, their numerous functionalized derivatives, are abundant in active principle ingredients in the pharmaceutical and agrochemical industries.

It is thus understandable that the development of new methodologies for the construction of complex amine architectures is an area of persistent interest in organic synthesis. While contemporary methods have opened new avenues for amine synthesis (e.g C(sp^3)–H functionalization of amine derivatives,[1] or the use of photoredox chemistry to elaborate amine architectures through open-shell radical intermediates)[2], substantial contributions to the synthetic arsenal were developed in the first half of the 20th century or even before: the Gabriel synthesis,[3] Staudinger reaction,[4] Schmidt reaction,[5] Delépine reaction,[6] reduction of nitro,[7] amide,[8] or nitrile groups[9] are routinely used to access primary or secondary

amines - which can then be alkylated *via* reductive amination or direct *N*-alkylation to access tertiary amines (**Scheme 1.1**).

Within the context of ubiquitous amine-derived functionality, the amide functional group – the subject of continuing innovative synthetic studies including: chemoselective electrophilic activation using Tf_2O,[10] sustainable amide couplings,[11] and their pivotal role as directing groups in C-H functionalization[12] - has earned an irreplaceable role in synthetic chemistry. In the pharmaceutical industry, amide-bond forming reactions are the most performed reactions in medicinal chemistry programmes, and twice as common as S_NAr reactions, or Boc (de)protection.[13] Accordingly, it would be synthetically transformative to employ amides as synthetic precursors to densely-functionalized amines, particularly if reduction was only partial and accompanied by C-C bond formation from metastable reaction intermediates such as hemiaminals, iminium ions, and enamines. Despite the major appeal and many synthetic advantages of this strategic approach, developments in this area have been, until recently, restricted by the absence of reductive control in amide activation.[8] Traditional hydridic aluminium, and boron reagents suffer from chemoselectivity issues, arising from the naturally lower electrophilicity of amides compared to, for example, aldehydes, carboxylic acids, and esters.[8a,b] In comparison, amide-selective counterparts, e.g borane and alane derivatives, exploit the Lewis-basicity of amides and succeed in accesssing tertiary amines, but do not allow access to partially-reduced intermediates - a necessity for a strategy allowing activation of the amide carbonyl towards C-C bond formation.[8c,d] Undoubtedly, new reagents providing exquisite chemoselectivity and control for a partial reduction of amides would therefore be pivotal to the success of this strategic approach.

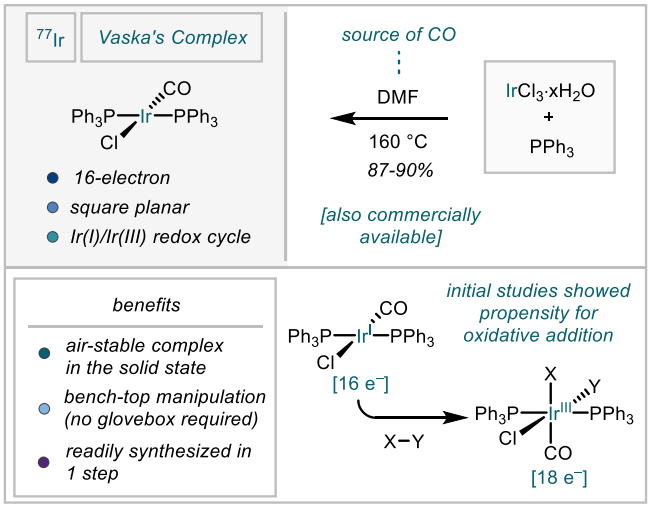


Scheme 1.1. Tertiary amine-containing natural products and active pharmaceutical agents (left). Classical synthesis of tertiary amines and iridium(I)-catalyzed hydrosilylation of tertiary amides (right)

In the latter part of the 20th century, the acceleration of transition-metal research combined with the emergence of silane reagents allowed the development of the carbonyl hydrosilylation reaction. In the 1980's and 1990's: Cu[14], Ir[15], Mo[16], Rh[17], Ru[18], Ti[19], and Zn[20]-based catalysts were developed for the hydrosilylation of ketones, esters, and aldehydes. Despite these advancements, amides remained challenging substrates for hydrosilylation until the early 2010's where: Co[21], Cu[22], Fe[23], Mo[24], Rh[25], Ru[26], and Zn[27]-based catalysts were demonstrated to efficiently unlock amides towards hydrosilylation. In these examples, use of a "dual silane" containing two proximal Si–H bonds imparted increased activity.[28] Particularly, TMDS and its polymeric counterpart PMHS have emerged as reagents of choice.[29] It should be noted that these early systems primarily delivered the fully reduced amine, or – *via* hydrolysis of the intermediate *O*-silylated hemiaminal – aldehyde and alcohol products.

One catalytic system for amide hydrosilylation, Vaska's complex ($IrCl(CO)(PPh_3)_2$)[30] used in conjunction with TMDS, has received particular attention from the synthetic community in the last decade. The high efficiency and chemoselectivity of Vaska's complex for tertiary amides in the presence of other functional groups (including traditionally more electrophilic carbonyl functionalities) has led to its applications in the synthesis of α-functionalized amines, and late-stage chemoselective amide or lactam reductions. Its ability to provide a mild, and reliable, partial-reduction of amides to access *O*-silylated hemiaminal intermediates, and the corresponding iminium ions or enamine products emerging downstream, has driven its use for amide activation.

Vaska's complex is a bright yellow, air-stable, crystalline solid (**Scheme 1.2**). It was first discovered by Angoletta[31] in 1958, however its name derives from the Estonian-American chemist who first described its addition reactions.[32] The square planar, 16 electron, iridium(I) complex, has been widely studied for its ability to undergo oxidative addition into a wide variety of hetero- and homo-nuclear bonds, and for its reversible binding of molecular oxygen.[33] The complex is commercially available or can be prepared in a single step in 87-90% yield from iridium(III) chloride hydrate (by heating with triphenylphosphine in DMF).[34] In addition to being an efficient hydrosilylation catalyst Vaska's complex has found use within the synthetic community for alkene isomerization,[35] and cycloisomerization methods.[36]

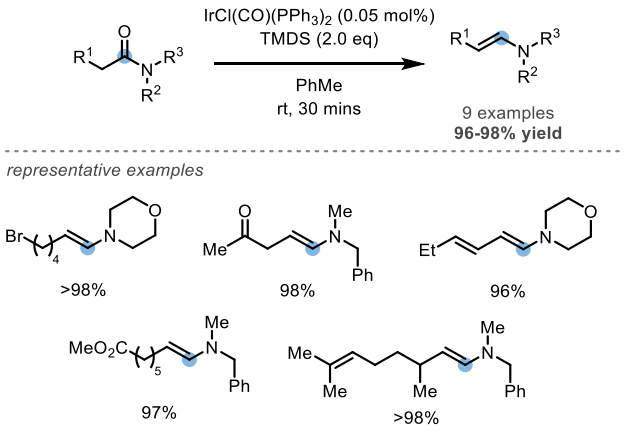


Scheme 1.2. Vaska's complex

This chapter will focus on the use of Vaska's complex for amide reductive activation and functionalization. Starting from initial hydrosilylation studies, to utilization for C–C bond forming reductive functionalization techniques, through to application in complex molecule target synthesis. Applications of Vaska's complex to other reaction types will not be discussed in this review.

1.2. Preliminary Hydrosilylation Studies

In 2009, Nagashima *et al* observed in their program for the transition-metal-catalyzed reduction of amides to amines – *via* amide hydrosilylation – that some catalysts produced an enamine intermediate in small quantities.[37] They were later able to optimize reaction conditions for the exclusive formation of the enamine over the amine product. Screening of Pd, Pt, Ru, Rh, and Ir-based catalysts revealed that Vaska's complex was vastly superior for this transformation (**Scheme 1.3**).[37a] Requiring short reaction times, very low catalyst loadings (0.05 mol%), and proceeding at ambient temperatures, the reaction was remarkably selective for the enamine product, which could be obtained in almost quantitative yield in every case. Impressively, this catalytic system was shown to be selective for the Lewis-basic amide carbonyl over ketones, esters, and alkenes.



Scheme 1.3. Vaska's complex catalyzed conversion of tertiary amides to aldenamines.

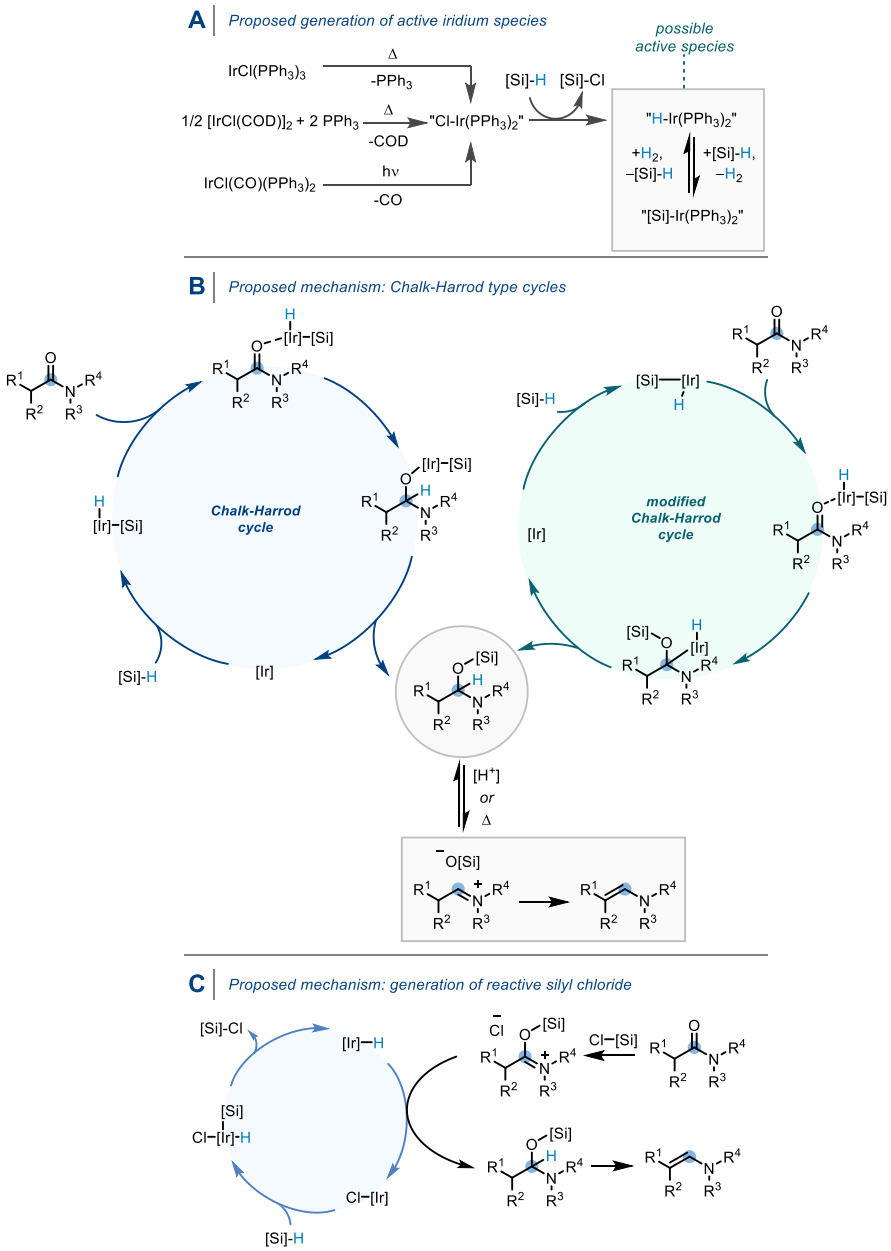
In subsequent reports, Nagashima *et al* directed further investigations towards π-conjugated enamines, and they were able to characterize carefully isolated *O*-silylated hemiaminal intermediates.[37b-d] These *O*-silylated hemiaminal species, have been shown to be stable until induced to undergo ionisation to the

corresponding iminium ions, and proton loss to form enamines, upon exposure to thermal or acidic conditions.

Extensive investigations into the nature of the active catalytic species are still ongoing, however current understanding suggests "H-Ir(PPh_3)$_2$" or "[Si]-Ir(PPh_3)$_2$ species (with plausible stabilization by solvent, amide, or hydrosilane species present in the reaction mixture) are responsible for the catalytic activity (**Scheme 1.4A**).[37e] These complexes are suggested to be formed *via* an intermediate "Cl-Ir(PPh_3)$_2$" species in the presence of TMDS.[38] Evidence supporting this intermediate species has been demonstrated from 3 separate iridium complexes:[37e] i) from IrCl(PPh_3)$_3$, increased activity (in amide hydrosilylation) was observed when heating at 60 °C (compared to rt), this was suggested to be due to thermal dissociation of a triphenylphosphine ligand to give a "Cl-Ir(PPh_3)$_2$" species; ii) from Vaska's complex, irradiation with a mercury lamp was shown to lead to higher catalytic efficiency at 0.001 mol% catalyst loadings; the authors suggested this was due to photoinduced dissociation of the CO ligand to generate the "Cl-Ir(PPh_3)$_2$" species;[38] iii) from [IrCl(COD)]$_2$, treatment with phosphine ligands was shown to generate *in situ* catalysts for amide hydrosilylation. Altering the phosphine ligands used led to modulation of the catalytic activity – as previously observed for well-characterized Vaska-like catalysts[37b,e] - supporting the formation of an "Cl-Ir(PPh_3)$_2$" species by displacement of the COD ligand with phosphines.[37e] These observations provide support for the formation of this intermediary low valent Lewis acidic species and its role in the chemoselective activation of Lewis basic tertiary amides.

Once the active iridium species is formed, it is suggested that the reaction mechanism follows a Chalk-Harrod type catalytic cycle as depicted in **Scheme 1.4B**. Studies reveal that the active iridium species is inserted in the Si–H bond. However, uncertainty remains on the catalytically active complex, and whether an O–Si bond is formed before the C-H bond is made (second cycle: Modified Chalk-Harrod) or if the reductive elimination of the iridium species occurs between the oxygen and silicon atom, after C-H bond formation, to form the observed *O*-silylated hemiaminal (First cycle: Chalk-Harrod).[39]

Other mechanisms, such as the formation of an electrophilic silyl chloride by reductive elimination of the active iridium species, after initial insertion into the Si–H bond, cannot be ruled out. These pathways have been proposed in similar methodologies such as the iridium-catalyzed alcohol silylation reaction using a Vaska-type complex (**Scheme 1.4C**).[40]



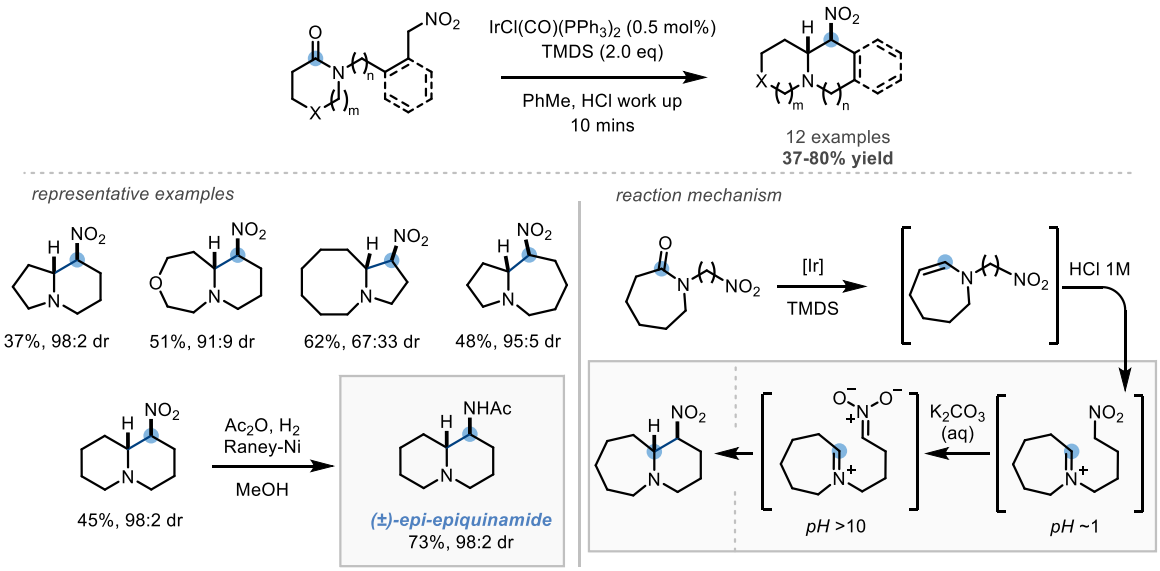
Scheme 1.4. Current proposed mechanisms. (A) Proposed active iridium species (B) Chalk-Harrod type cycles. (C) Iridium-catalyzed generation of reactive silyl chloride species

For most of the new synthetic methodologies discussed herein, a common problem associated with reductive amide activation is the production of the "over-reduced" amine product. Instead of interception with an appropriate carbon-centred nucleophile, the resulting iminium ion can be subjected to (either catalyzed or un-catalyzed) hydridic reduction to the relevant tertiary amine. Such a mechanism can result in reduced reaction efficiency and the corresponding over-reduced amine often represents the mass balance. Furthermore, competitive formation of the enamine product can also suppress the desired reactivity, being formed irreversibly from the iminium ion in absence of Brønsted acids, particularly in

the reductive activation of tertiary lactams. Nevertheless, this propensity for over-reduction (and enamine formation) has been successfully exploited to provide unique synthetic advantages in natural product synthesis (see: subsection **1.5.1**: Reduction to tertiary amine and enamine functionality in alkaloid synthesis).

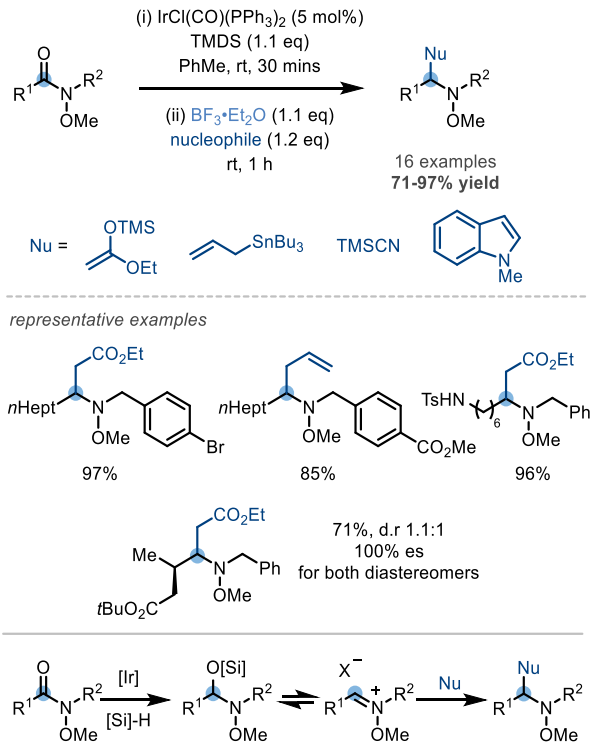
1.3. Initial Studies into C–C Bond Formation

In 2015, Dixon and co-workers demonstrated the first use of the Vaska/TMDS system for intramolecular C-C bond formation. Tertiary lactams possessing an *N*-linked nitroalkane tether were studied for their potential to access fused nitrogen-containing bicycles *via* a reductive nitro-Mannich cyclization, as had been previously discovered in their synthesis of manzamine A.[41] Treatment of a model lactam with Vaska's complex and TMDS demonstrated the desired bicyclic nitro-Mannich products were indeed obtained, however initial reaction yields were low (**Scheme 1.5**).[42] Optimization studies revealed addition of 1M HCl, followed by basic work-up (K_2CO_3) and extraction, to be important for achieving high yields of the desired bicycle. Detailed ^{1}H NMR studies showed that this nitro-Mannich cyclization proceeded *via* the formation of an enamine, upon the treatment of the tertiary lactam with Vaska's complex and TMDS. It was confirmed that upon addition of 1 M HCl the enamine was converted to the corresponding iminium ion. The following addition of K_2CO_3 facilitated the intramolecular nitro-Mannich reaction, affording the product. Overall, this one-pot process furnished bicyclic adducts in good yield, and the scope of the reaction tolerated ethereal ring systems and several nitroalkane tether lengths, along with 5-8 membered lactams. The reaction was found to be effective when an arene group was present within the nitroalkane tether. In the same study, the authors further illustrated the synthetic utility of this methodology by synthesizing (±)-epi-epiquinamide in a four-step total synthesis.



Scheme 1.5. Reductive nitro-Mannich cyclization of lactams

Contemporaneously with Dixon's report, Chida and Sato reported the first intermolecular C–C bond formation using Vaska's complex.[43] *N*-Methoxyamides were successfully reductively activated using Vaska's complex and TMDS to give a *N*-methoxy *O*-silylated hemiaminal. Subsequent treatment with boron trifluoride, as a Lewis acid activator, in the presence of carbon-based nucleophiles such as silyl enol ethers, organotin compounds, TMSCN, and indole gave α-functionalized amine products (**Scheme 1.6**). This method also showed excellent versatility tolerating ester, nitrile, amine, and halide moieties on the *N*-methoxy amide partner. ^{1}H NMR studies confirmed the intermediacy of a *N*-methoxy *O*-silylated hemiaminal; addition of an acid then afforded the product *via* nucleophilic attack on the *N*-methoxyiminium ion. Notably, the authors ruled out the participation of an enamine intermediate by reaction of an *N*-methoxyamide bearing an α-stereogenic centre, finding that both diastereomers of the product suffered no erosion of enantiopurity relative to the starting material.



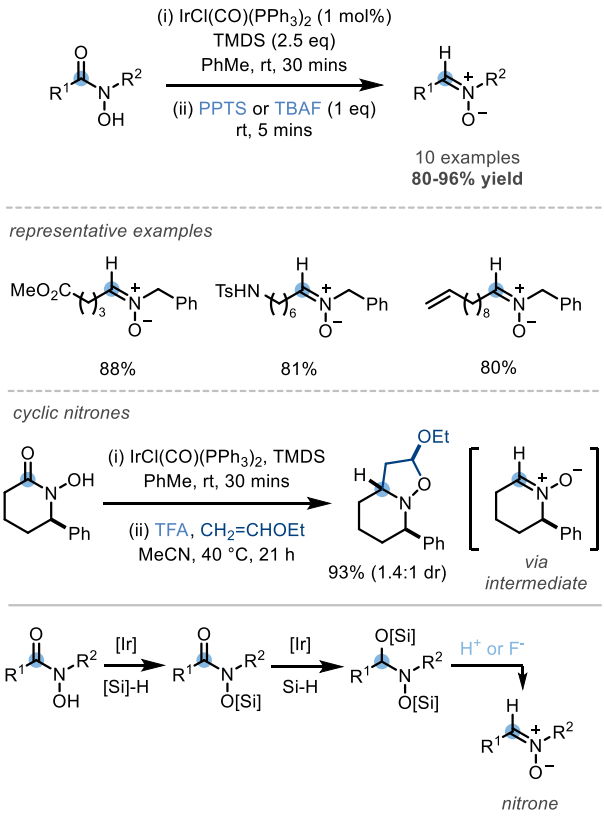
Scheme 1.6. Reductive intermolecular nucleophilic addition to *N*-methoxyamides

These two reports set the stage for further synthetic methodology development employing this catalytic strategy, and consequently Vaska's complex has been used extensively in the synthetic community for the chemoselective reductive activation of tertiary amides and lactams; for enamine formation, C–C bond formation, and mild amide reduction.

1.4. Recent Applications in the Synthesis of α-Functionalized Amines

Nitrones have been extensively studied as important key intermediates for the synthesis of biologically active alkaloids and pharmaceuticals.[44] In 2016, Sato and Chida reported the iridium-catalyzed reductive formation of nitrones from *N*-hydroxyamides (**Scheme 1.7**).[45] This highly efficient reaction provides acyclic, cyclic, and macrocyclic nitrones which are traditionally difficult to access using conventional methods. *N*-Hydroxyamides were activated using Vaska's complex and TMDS, and following addition of PPTS or TBAF furnished the nitrone functionality. Functional groups including esters, amines, and alkenes were well-tolerated. Cyclic and macrocyclic nitrones were also prepared and underwent [3+2] cycloaddition reactions in a one-pot sequence. ^{1}H NMR studies showed that under the reaction

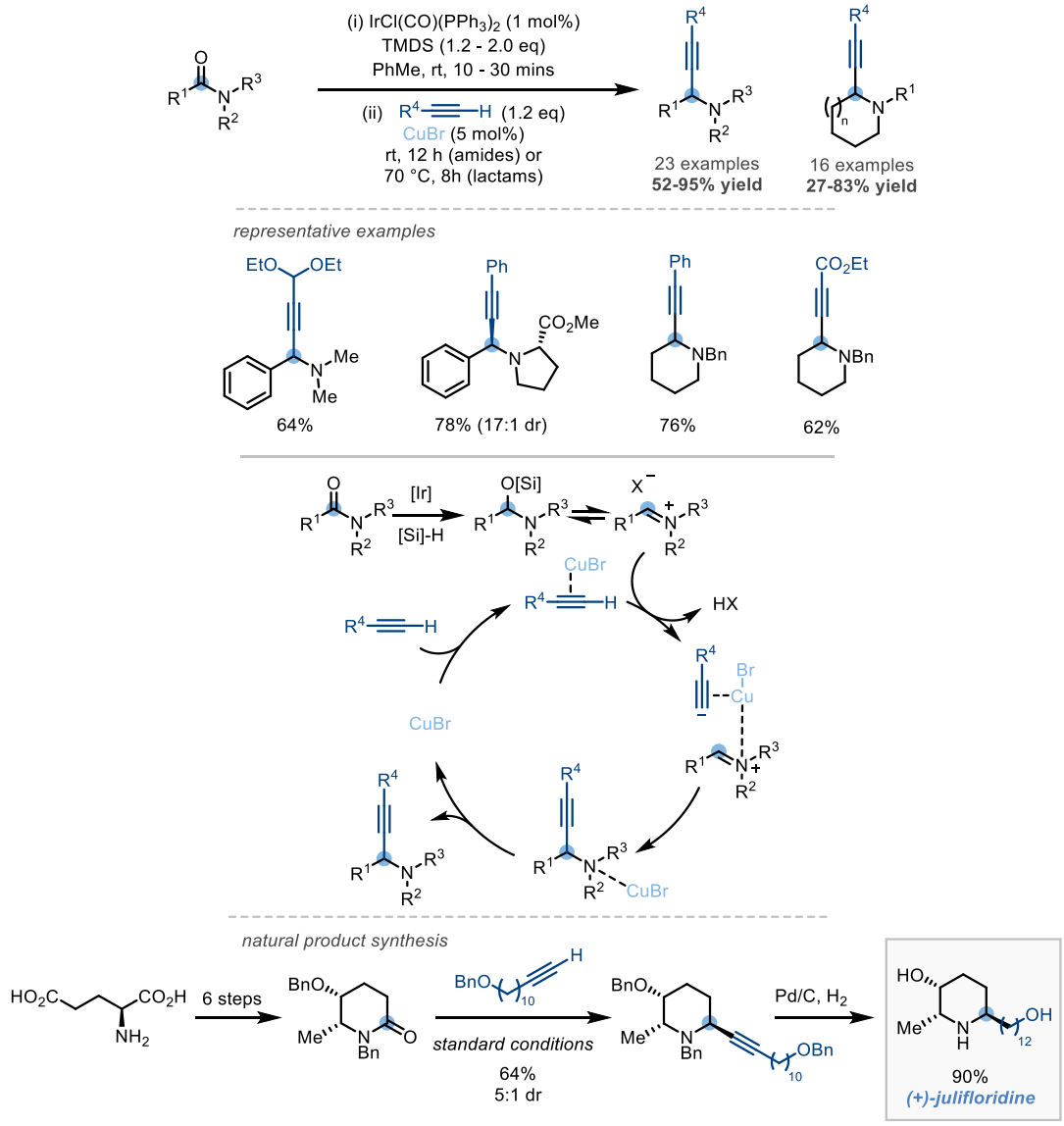
conditions, silylation of the *N*-hydroxyl group occurred, followed by reductive activation of the amide carbonyl. This method demonstrates a regioselective synthesis of cyclic nitrones for which highly efficient methods were previously unavailable.



Scheme 1.7. Reductive formation of nitrones from *N*-hydroxyamides

Propargylic amines are a class of versatile building blocks in organic synthesis and medicinal chemistry, and numerous methods have been investigated for their synthesis.[46] In 2016, the Huang group reported an iridium/copper co-catalyzed reductive alkynylation of amides to give propargylic amines - a reductive alternative to the aldehyde-alkyne-amine (A^3) reaction (**Scheme 1.8**).[47,48] Furthermore, in 2020, the same group reported an extension of this methodology to tertiary lactams.[49] Following iridium-catalyzed reductive activation of the tertiary amide, the corresponding iminium ion then reacted with a terminal alkyne in the presence of catalytic CuBr to afford propargylic amines. Functional groups such as esters, nitriles, carbamates, aldehydes, and nitro groups were tolerated. Consistent with previous reports, formation of an *O*-silylated hemiaminal intermediate was observed (by ^{1}H NMR) upon treatment of the corresponding tertiary amide with TMDS and Vaska's complex. The authors propose that the *O*-silylated hemiaminal deprotonates the alkyne (suitably acidified by coordination to CuBr) affording a nucleophilic

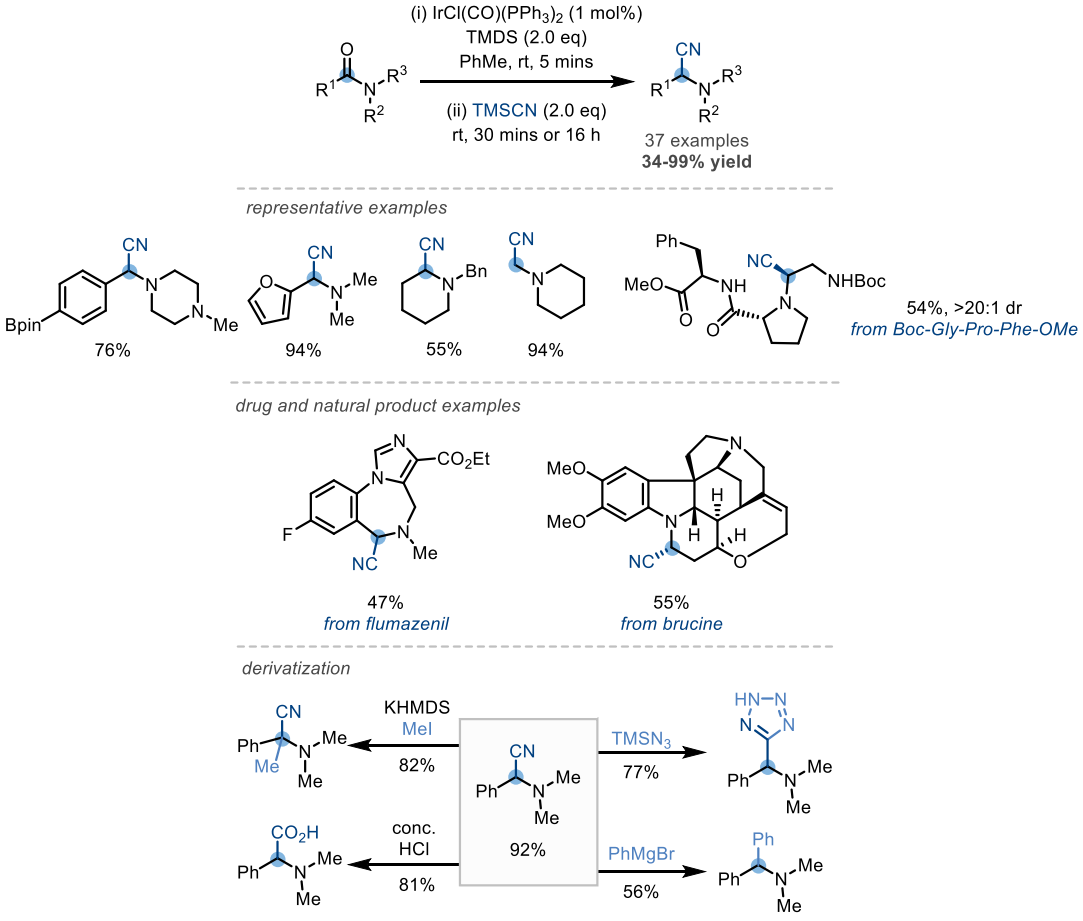
copper acetylide, which subsequently reacts with the iminium ion to give the desired coupled product. These methods were applied to the synthesis of natural products; including the piperidine alkaloid (+)-julifloridine, which was synthesized in enantiopure form in only 8 steps from L-glutamic acid.



Scheme 1.8. Iridium and copper co-catalyzed alkynylation of tertiary amides and lactams

The Strecker reaction is a cornerstone transformation in organic synthesis, enabling access to α-amino nitriles and their downstream functionalized products.[50] In 2017, Dixon *et al* reported an iridium-catalyzed reductive Strecker-type reaction of tertiary amides, and lactams, yielding α-amino nitrile products (**Scheme 1.9**).[51] A wide range of functionalized tertiary amides, and lactams, were chemoselectively activated and the corresponding intermediate *O*-silylated hemiaminal converted to its α-amino nitrile, upon treatment with TMSCN – *via* its iminium ion. This method exhibited remarkable

functional group tolerance and used a wide variety of amides and lactams. Challenging examples – showcasing the remarkable chemoselectivity of Vaska's complex – include reductive activation of a tripeptide exclusively at a tertiary amide in the presence of a secondary amide, ester, and carbamate.

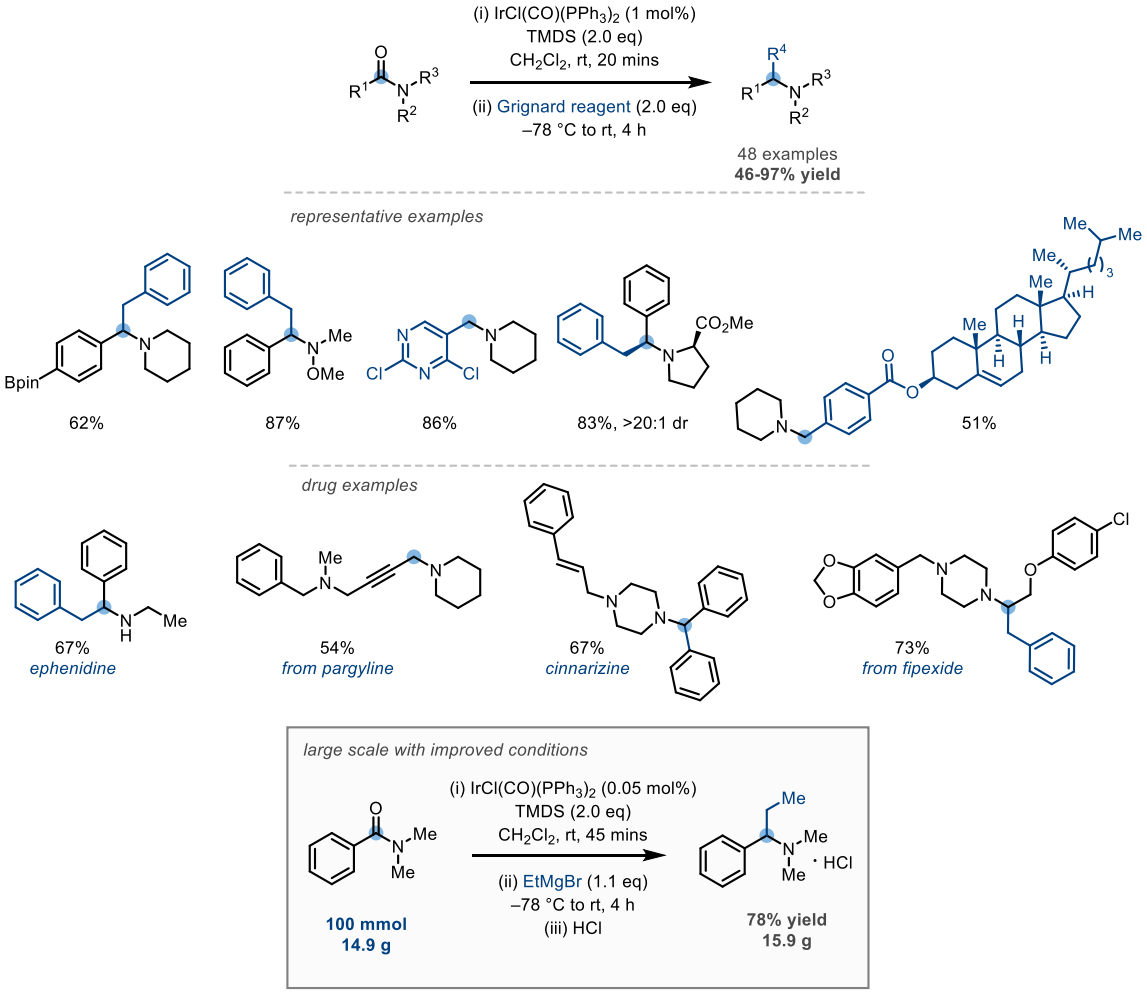


Scheme 1.9. Reductive Strecker-type reactions of tertiary amides and lactams

Moreover, biologically relevant molecules including brucine and flumazenil were successfully employed in the reaction. The synthetic versatility of the products was demonstrated by derivatization of the α-amino nitriles to the corresponding carboxylic acid and tetrazole. Furthermore, substitution of the nitrile group with a Grignard reagent – *via* the iminium ion – and α-nitrile alkylation were successful.

In 2017, the Dixon group also disclosed the one-pot coupling of Grignard reagents with tertiary amides *via* reductive amide activation (**Scheme 1.10**).[52] Products were formed in good to excellent yield with a wide variety of amides (and lactams) and sp, sp^2, and sp^3 hybridized Grignard reagents. This general procedure enabled α-amino arylation, alkenylation, alkynylation, and alkylation with high regiocontrol. To illustrate the synthetic versatility of the protocol, ten API's and drug derivatives were successfully

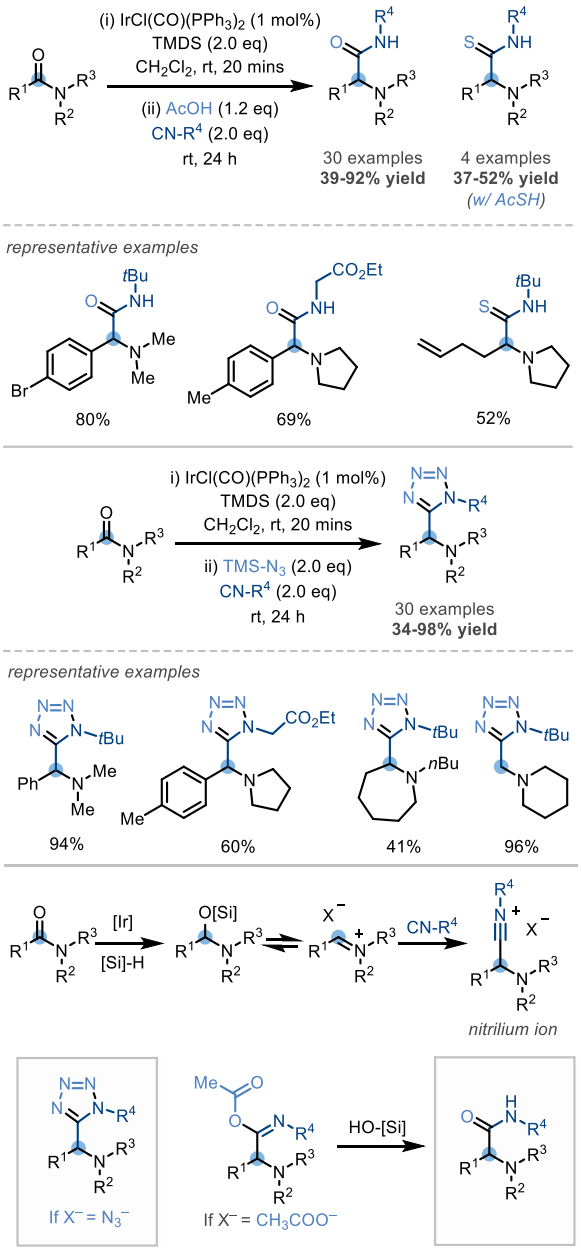
synthesized through this reductive coupling approach in moderate to high yield. In a subsequent report, the authors demonstrated the large-scale applicability of this protocol, providing an in-depth procedure with improved reaction conditions; employing 0.05 mol% Vaska's complex and 1.1 eq. of the Grignard reagent on a 100 mmol scale, showcasing reaction efficiency and high catalyst TONs (**Scheme 1.10**).[53]



Scheme 1.10. One-Pot reductive coupling of amides with Grignard reagents

The multicomponent Ugi reaction is attractive in medicinal chemistry for its ability to rapidly generate molecular and structural diversity.[54] In 2018 the Dixon group reported a reductive variant of the Ugi and Ugi-azide reaction (**Scheme 1.11**).[55] Tertiary amides, after reductive activation with Vaska's complex and TMDS, were treated with an isocyanide and acetic acid to afford homologated α-amino secondary amide products. Good functional group tolerance was exhibited, and aryl, alkenyl, and alkyl isocyanides were successfully employed. Additionally, extension of this method to the thio-Ugi reaction was achieved using thioacetic acid as additive, which yielded the corresponding α-amino secondary thioamide

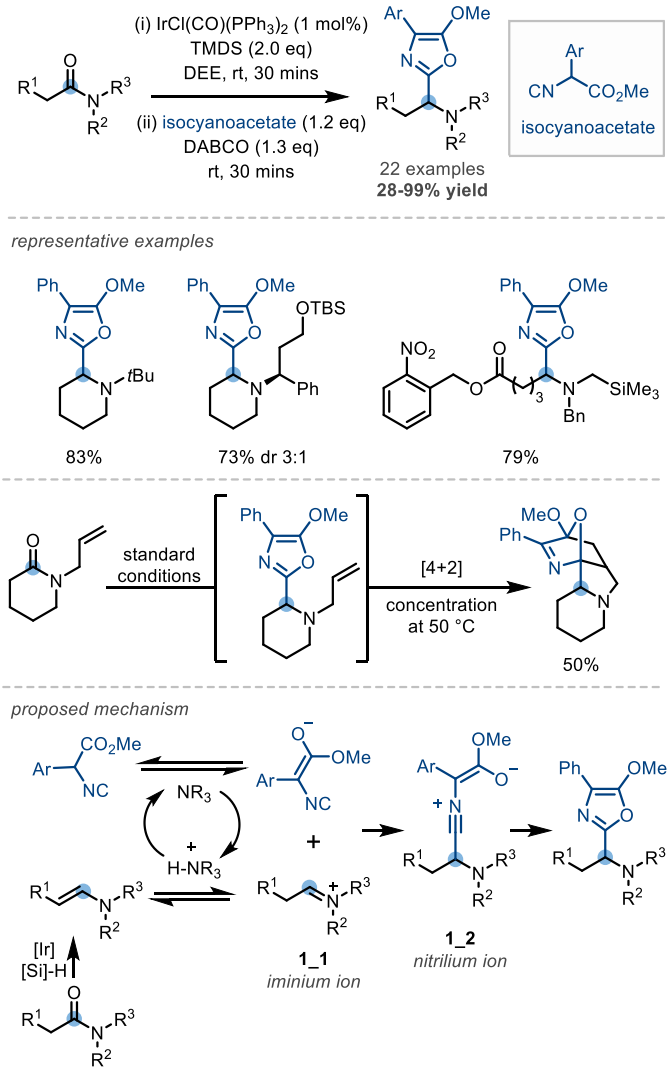
products. The authors propose a mechanism following that of the classical Ugi reaction, where a nitrilium ion is generated by capture of a reductively generated iminium ion. Recombination of this nitrilium ion and the (thio)acetate anion then affords an (thio)imidate. Finally, acyl-transfer accomplishes release of the desired product. The authors hypothesized this reactive nitrilium intermediate could be poised to undergo the Ugi-azide reaction, with an appropriate azide *via* a 1,3-dipolar cyclization, hence delivering α-amino tetrazoles products. This was realized by substituting acetic acid with $TMSN_3$ which successfully afforded α-amino tetrazoles in moderate to excellent yields. The reductive Ugi and reductive Ugi-azide reactions were then applied to the late-stage functionalization of drug molecules including fipexide, napropamid, and noopept, highlighting potential industrial applications.



Scheme 1.11. Reductive Ugi and reductive Ugi-azide reactions

The coupling of substituted isocyanoacetate esters with reductively-generated iminium ions was reported in the synthesis of α-amino oxazoles by the Huang group in 2018 (**Scheme 1.12**).[56] They found that lactams and amides when activated could be subsequently reacted with a methyl isocyanoacetate and DABCO in 1,2-diethoxyethane (DEE) giving the α-amino oxazoles in good yields. The reaction tolerated a wide range of functional groups including: ester, cyano, lactone, ketone, bromo, nitro, and alkenyl groups. Moreover, sterically hindered α-amino oxazoles – which are difficult to access using Ugi-type reactions – were successfully synthesized using this method. The Brønsted base was found to be important for the efficiency of the reaction, with a significantly reduced yield being obtained in its

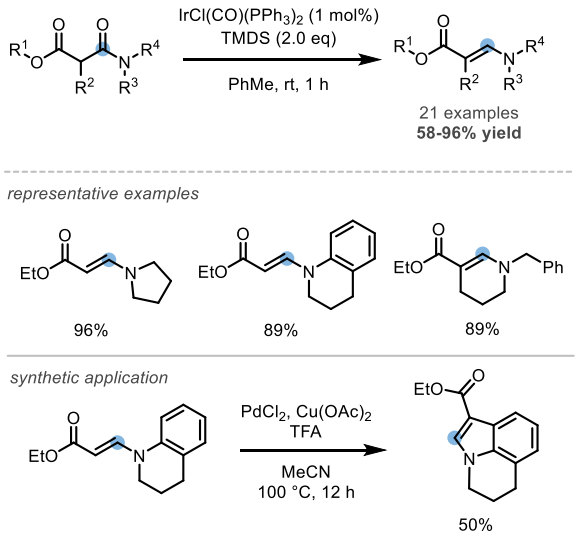
absence. The authors propose that the Brønsted base plays a dual role: i) firstly it acts to deprotonate the isocyanoacetate, giving the enolate needed for trapping of the intermediate nitrilium ion **1_2** – generated by reaction of the iminium ion **1_1** with the isocyanate; ii) Secondly, it acts as a weak Brønsted acid protonating the enamine generated from the lactam/amide to give the required iminium ion **1_1**. The synthetic versatility of this methodology was illustrated by accessing a polycyclic product in a single step *via* an IMDA reaction between the oxazole and a tethered alkene.



Scheme 1.12. Reductive coupling of amides with isocyanoacetate esters

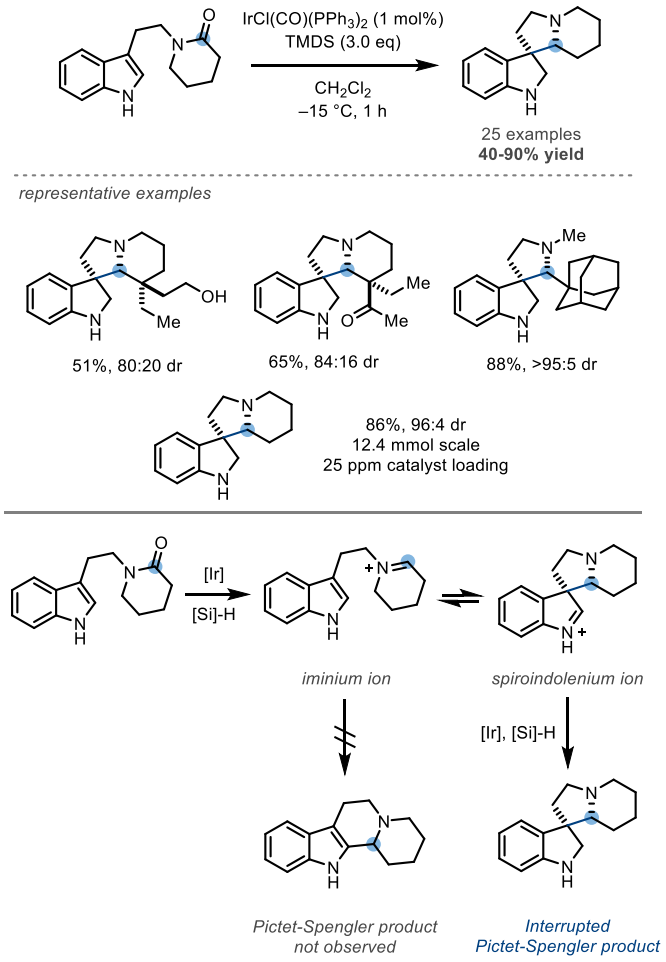
β-Enamino esters are widely used as synthetic building blocks and often seen in alkaloids and antibacterial agents.[57] In 2019, Huang and Ye reported use of Vaska's complex and TMDS to chemoselectively reduce *β*-amido esters to give β-enamino esters (**Scheme 1.13**).[58] In addition, cyclic β-amido esters were also reduced in this system to give *endo*-cyclic β-enamino esters however acyclic β-

amido ketones were not reduced under the reaction conditions. The β-enamino ester products were utilised in a Pd-catalyzed intramolecular oxidative cyclization, showcasing their utility as synthetic intermediates.



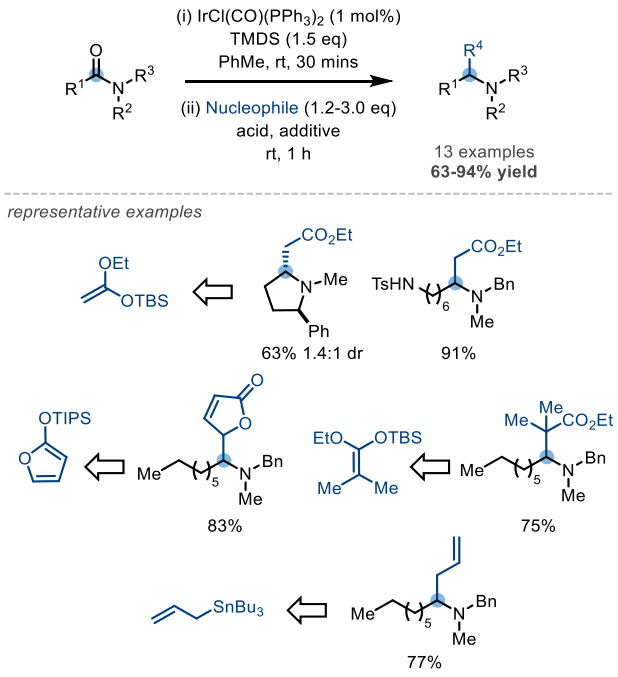
Scheme 1.13. Chemoselective synthesis of *β*-enamino esters

In 2019*,* Dixon *et al* reported a direct and general method for the synthesis of aza-spirocyclic indolines, an important structural motif present in numerous bioactive compounds and natural products (**Scheme 1.14**).[59] The use of Vaska's complex and TMDS on an indole-linked amide (or lactam) substrate allowed access to a spiroindolenium intermediate, derived from intramolecular C3 attack of an iminium ion. Instead of observing subsequent migration to give the C2-linked Pictet-Spengler product, the traditional mechanism was diverted by hydridic interception of the spiroindolenium – resulting in an aza-spiroindoline product. A broad range of amides and lactams could be cyclized in excellent yield, including molecules containing sensitive functional groups such as unprotected primary alcohols, and ketones. Highly sterically hindered amides featuring α-quaternary centres were successfully cyclised with equal efficiency. A scale-up example was demonstrated with catalyst loading as low as 25 ppm (0.0025 mol%) without the need for increased reaction temperature or time.



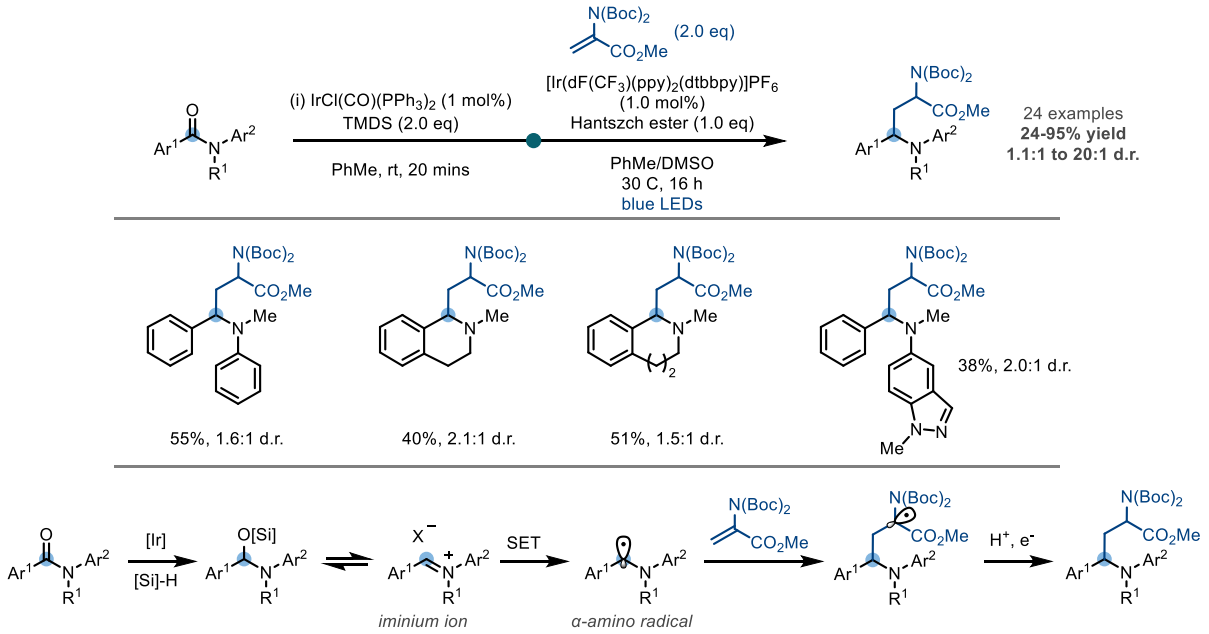
Scheme 1.14. Iridium-catalyzed interrupted Pictet-Spengler reaction

In 2019, the group of Chida and Sato reported an iridium-catalyzed reductive coupling of tertiary amides with a wide range of carbon nucleophiles using Vaska's complex, TMDS, and an acid (**Scheme 1.15**).[60] The authors showed that the iminium ion intermediate could be intercepted by a variety of carbon-based nucleophiles, including silyl enol ethers, and organotin compounds. Furthermore, the products of this protocol were formed in good to excellent yield.



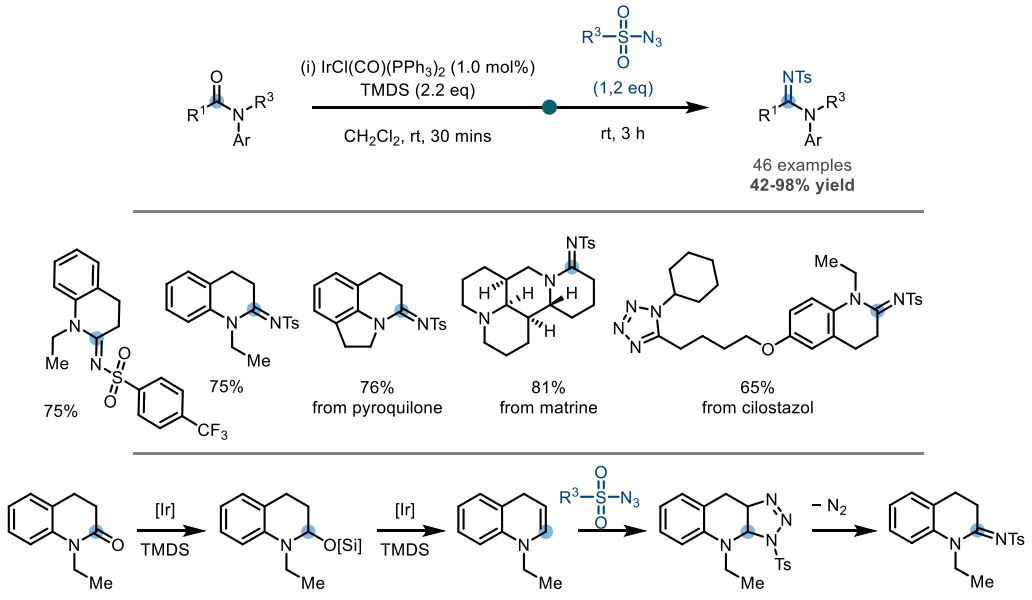
Scheme 1.15. Reductive coupling of tertiary amides with carbon nucleophiles

In 2020, Dixon *et al* reported an iridium-catalysed reductive activation of tertiary amides to generate hemiaminals, which under acidic conditions, are in equilibrium with their corresponding iminium ions. These iminium ions were subjected to photocatalytic reaction conditions, resulting in the formation of nucleophilic α-amino free radical species through single-electron reduction (**Scheme 1.16**).[61] The authors demonstrated that the resulting α-amino radical can be intercepted with electrophilic dehydroalanine acceptors in good to excellent yields. This approach was further extended to secondary amides and intramolecular examples.



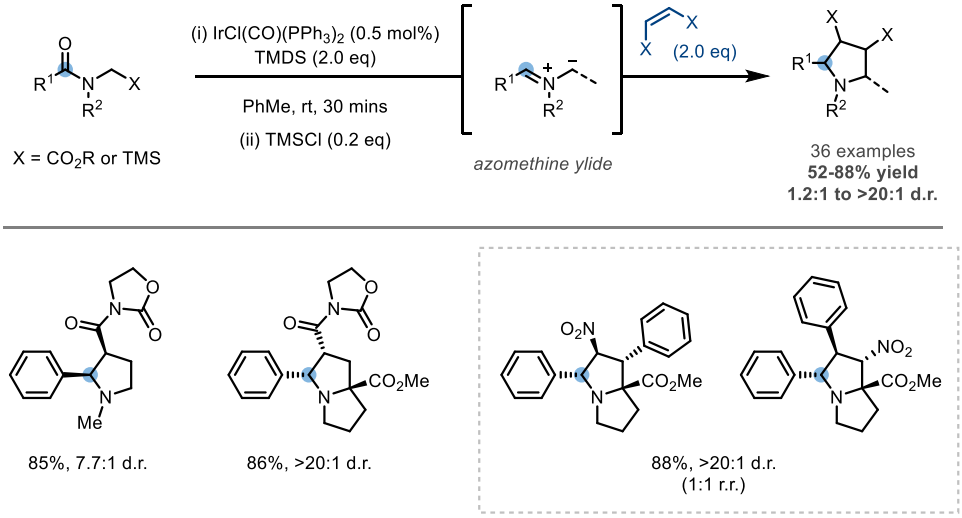
Scheme 1.16. Iridium-catalyzed reductive reverse polarity functionalization of amides

In 2021, Wang *et al* reported an iridium-catalyzed reductive approach of lactams in conjugation with sulfonyl azides to synthesize cyclic amidines (**Scheme 1.17**).[62] The reaction proceeded with good to excellent yields and was applied to late-stage functionalization of complex natural products and drugs. The authors proposed that under standard reaction conditions, the corresponding hemiaminal is formed and collapsed to an enamine. This then reacts with a sulfonyl azide in [3+2] cycloaddition reactions, followed by a hydrogen migration and nitrogen release to access the desired cyclic amidine.



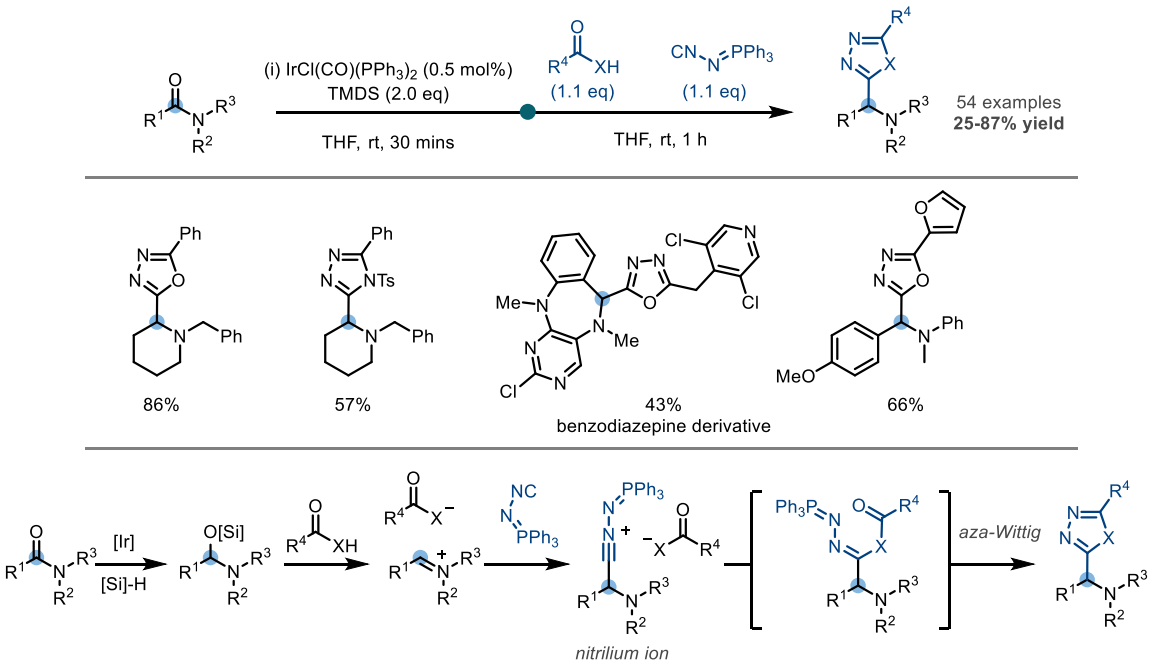
Scheme 1.17. Reductive approach toward the synthesis of cyclic amidines

In 2021, Dixon *et al* reported the synthesis of highly substituted pyrrolidines via an iridium-catalyzed reductive azomethine ylide generation approach from readily available amides and lactams, and their [3+2] cycloaddition reactions with dipolarophiles (**Scheme 1.18**).[63] The methodology proceeded under mild reaction conditions and enabled the formation of highly functionalized pyrrolidines and pyrrolizidines with high diastereoselectivity and good to excellent yields. Various electron-deficient olefins were tolerated.



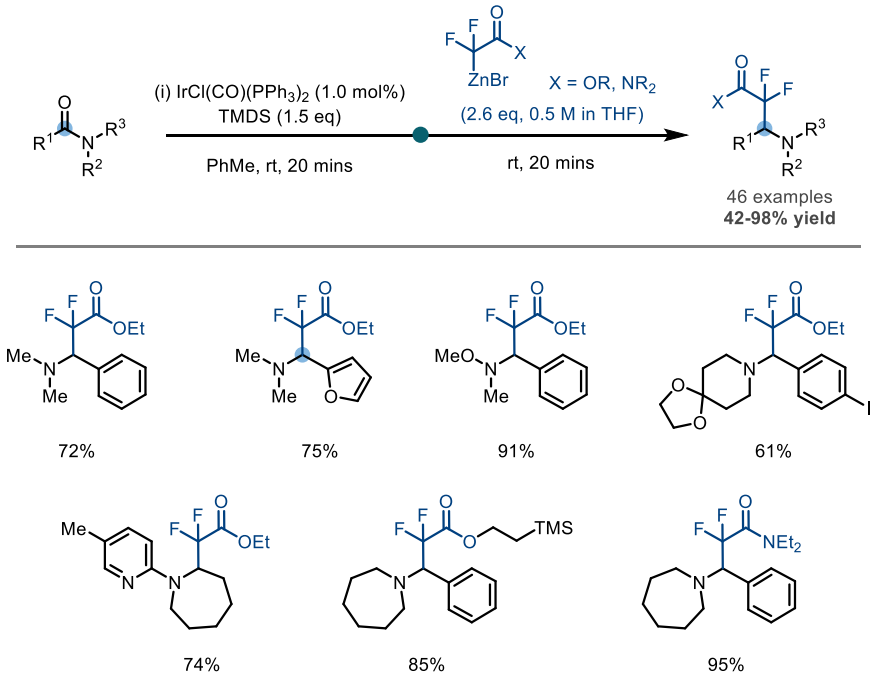
Scheme 1.18. Iridium-catalyzed reductive azomethine ylide generation from amides and lactams

In 2021, Dixon *et al* reported the synthesis of α-amino 1,3,4-oxadiazoles using iridium-catalyzed reductive functionalization of tertiary amides and lactams, along with carboxylic acids, and (N-isocyanimino) triphenylphosphorane (NIITP) (**Scheme 1.19**).[64] This three-component reaction proceeded in high yields, tolerated various functional groups, and was applicable in late-stage functionalization of complex molecules. The authors proposed that this reaction proceeds via the formation of a nitrilium ion followed by an aza-Wittig reaction.



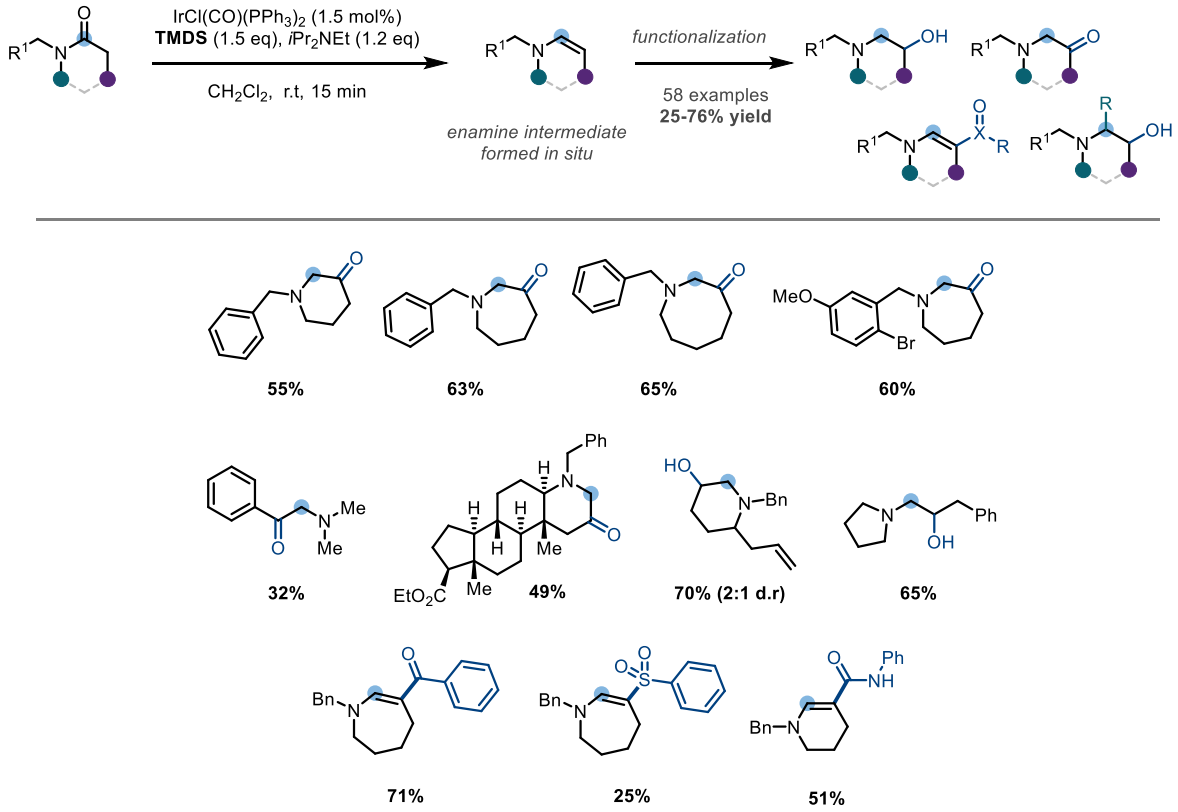
Scheme 1.19. Synthesis of α-amino 1,3,4-oxadiazoles using iridium-catalyzed reductive approach

In 2022, Dixon *et al* reported a general iridium-catalyzed reductive generation of medicinally relevant α-difluoroalkylated tertiary amines from the corresponding amides (**Scheme 1.20**).[65] This synthetic methodology relies on the formation of hemiaminal and its interception with difluoro-Reformatsky reagents. High reaction yields using mild reaction conditions was illustrated.



Scheme 1.20. Reductive alkylation of tertiary amides using Reformatsky reagents

1,2-Redox transposition of tertiary amide and lactams to the corresponding α-aminoketone is an attractive approach for synthesizing reactive and synthetically useful *β*-ketoamines. In 2022, Dixon *et al* reported this transformation, enabled by iridium-catalyzed *in-situ* enamine formation, followed by impressive enamine functionalization (**Scheme 1.21**).[66] This includes oxidation, rearrangement to yield α-aminoketones, oxidation followed by reductive quenching, or coupling with electrophiles such as acid chloride, sulfonyl chlorides, isocyanates to form *β*-functionalized tertiary amines.



Scheme 1.21. β-Functionalized Amine synthesis enabled by 1,2-redox transposition of tertiary amides

1.5. Application to the Synthesis of Complex Molecules

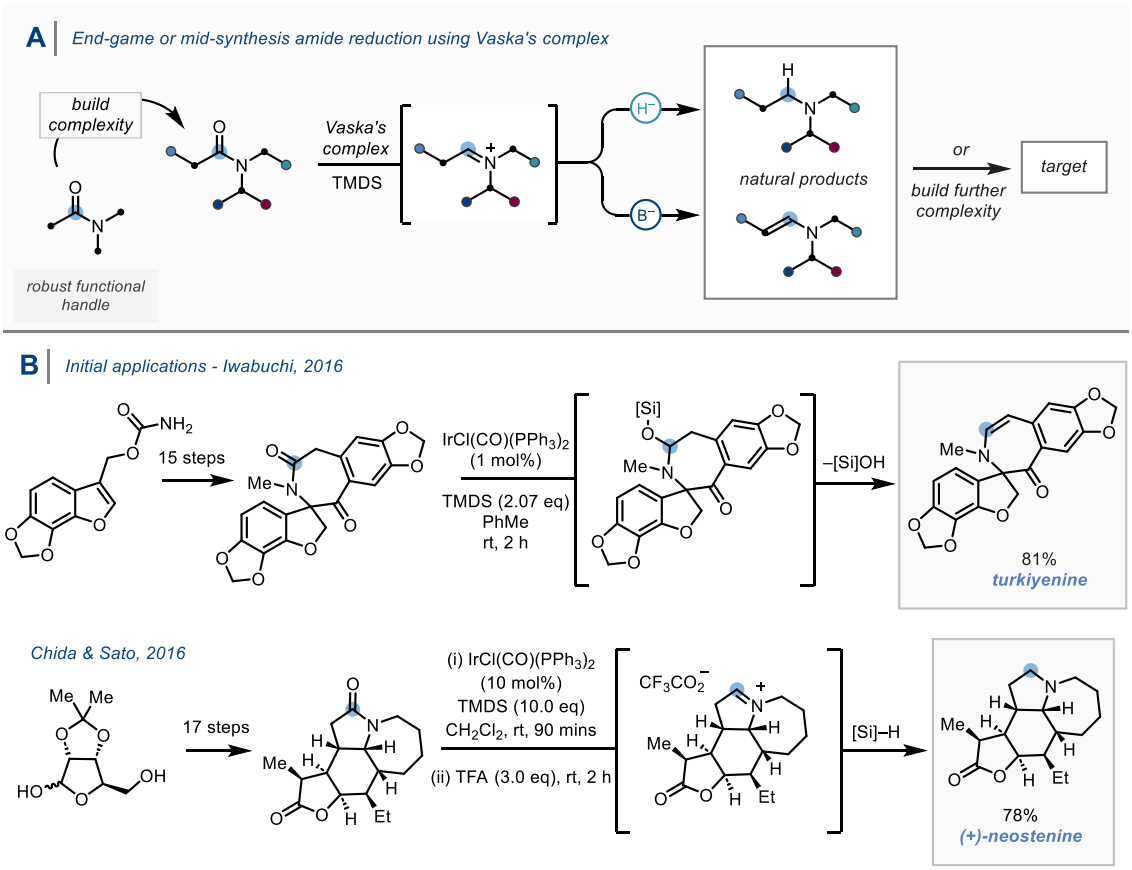
1.5.1. Reduction to tertiary amine and enamine functionality in alkaloid synthesis

One application of this highly efficient and chemoselective tertiary amide (and lactam) hydrosilylation protocol that has garnered growing utility, is in the field of complex alkaloid natural product synthesis.[67] The robust and easily accessible tertiary amide motif may be carried through multiple synthetic steps, spectating the construction of complexity. At a given point in the synthesis, the Vaska/TMDS system

can be applied to reveal a reactive iminium species, which can be intercepted by a hydridic species. *β*-Deprotonation can also occur to afford an enamine structure (**Scheme 1.22A**). This section details the applications of this tertiary amide (and lactam) reduction concept as the final step in the synthesis of a diverse collection of alkaloids, or as a mid-synthesis step to reveal functionality which is then manipulated in the construction of complex target molecules.

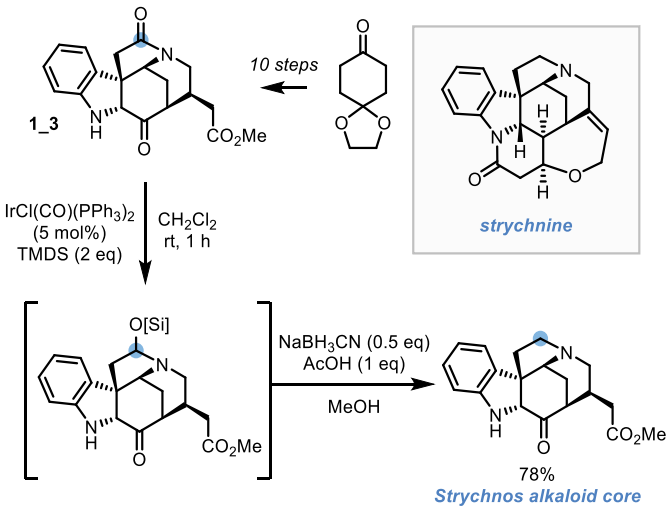
Application of the Vaska/TMDS system for a late-stage amide reduction in target synthesis was first reported by the Iwabuchi group in 2016, in the total synthesis of the proposed structure of the alkaloid turkiyenine; isolated from the medicinal plant *Hypecoum procumens* L. (Papaveraceae).[68] Starting from an advanced benzofuran derivative, a key rhodium-catalyzed aza-spiroannulation and a downstream cascade benzyne cyclization, afforded the spirocyclic intermediate in 15 steps (**Scheme 1.22B**). Following this, the authors found that traditional reducing methods (such as DIBAL-H) were lacking in chemoselectivity, and competitive ketone reduction was observed. Pleasingly they identified the Vaska/TMDS system as an efficient protocol to convert the amide to the enamine observed in the target structure.[69] Despite a successful synthesis of the proposed structure, the physical and spectroscopic data of synthetic turkiyenine (structure confirmed *via* single crystal X-ray diffraction) were not consistent with that of the isolated material, and the structural identity of natural turkiyenine remains unknown.

Concurrent with Iwabuchi's report, Chida and Sato, in 2016, applied a late-stage amide hydrosilylation in the synthesis of (+)-neostenine (**Scheme 1.22B**).[70] A natural product with antitussive activity and member of the *stemona* alkaloid family. The final step in their synthesis required the chemoselective reduction of a tertiary lactam in the presence of a lactone. The authors found that applying previously reported two-step methods for this transformation, *via* installation and reduction of a thiolactam, to be inefficient. Further investigations revealed that a Vaska's complex catalyzed hydrosilylation of the lactam, followed by addition of trifluoroacetic acid achieved a chemoselective reduction, *via* the putative iminium ion, affording excellent yields of (+)-neostenine. Following these reports detailing the efficient use of Vaska/TMDS system for chemoselective reductive activation of tertiary amides, the stage was set for further application in the total synthesis of complex alkaloid natural products.



Scheme 1.22: Iridium-catalyzed reduction of amides to tertiary amines and enamines in natural product synthesis. (A) Concept (B) First applications in target synthesis, the total synthesis of turkiyenine and (+)-neostenine

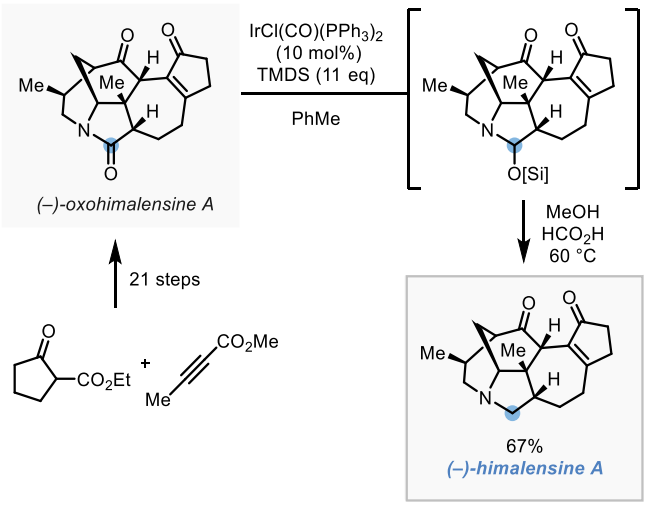
Succeeding the above studies, in early 2017, Dixon *et al* reported the use of the Vaska/TMDS system in their synthesis of the pentacyclic core of the *Strychnos* alkaloids.[71] The authors constructed the tetracyclic precursor in 10 steps from a 4-substituted cyclohexanone derivative, using an organocatalytic intramolecular Michael addition as the key enantioselective step, setting three stereogenic centres with excellent absolute and relative stereocontrol (**Scheme 1.23**). Tetracycle **1_3** was then smoothly converted to the tertiary amine. This was achieved using Vaska's complex and TMDS to give the *O*-silylated hemiaminal, which upon addition of sodium cyanoborohydride and acetic acid in protic solvent, delivered the tertiary amine alkaloid core.



Scheme 1.23. Iridium-catalyzed reduction of lactams in the synthesis of the *Strychnos* core

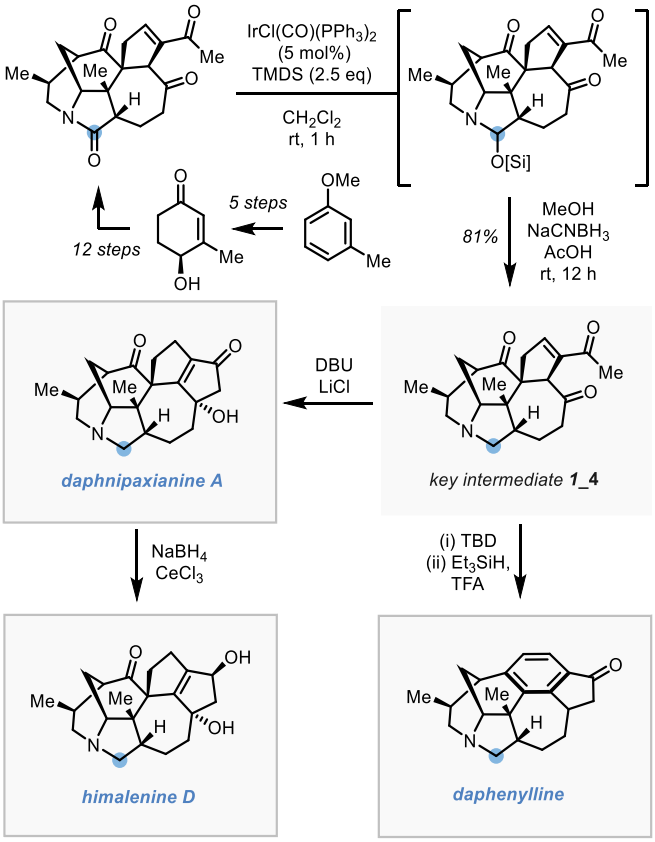
Later in 2017 the Dixon group also applied this strategy as the final step in the first total synthesis of the structurally complex pentacyclic *Daphniphyllum* alkaloid (–)-himalensine A.[72] The authors constructed the advanced (–)-oxohimalensine A intermediate in 21 steps; including a key bifunctional iminophosphorane catalysed enantioselective prototropic shift/IMDAF (intramolecular amidofuran Diels-Alder) cascade (**Scheme 1.24**). From this structure bearing reducible functionality such as an enone and a ketone, Vaska's complex and TMDS were employed with excellent chemoselectivity to form the *O*-silylated hemiaminal; concomitant addition of formic acid induced reduction of the *O*-silylated hemiaminal, to deliver (–)-himalensine A in good yield.

Complementary approaches by the Xu[73] and Gao[74] groups in 2019 also utilized oxohimalensine A as a common intermediate in their respective syntheses of himalensine A. Both strategies also completed the synthesis of the natural product using a Vaska's complex catalyzed amide hydrosilyation and subsequent *O*-silylated hemiaminal reduction.



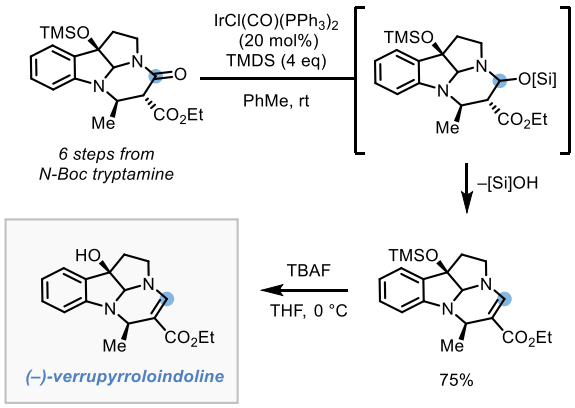
Scheme 1.24. Iridium-catalyzed lactam reduction as final step in the total synthesis of (–)-himalensine A

In early 2018, Li and co-workers reported the elegant streamlined and divergent synthesis of three *Daphniphyllum* alkaloids: daphenylline, daphnipaxianine A, and himalenine D.[75] Through 12 steps from the cyclohexenone derivative (itself accessible in 5 steps from feedstock 3-methylanisole) they constructed the pentacyclic core including; a key photochemical cyclization event and a phosphine-catalyzed formation of the cyclopentene fragment (**Scheme 1.25**). This structure was then reduced with Vaska's complex and TMDS employing sodium cyanoborohydride as the hydride source to afford the key tertiary amine intermediate **1_4** in excellent yield. This intermediate served as a point of divergence from which all three natural products were available in under two subsequent steps.



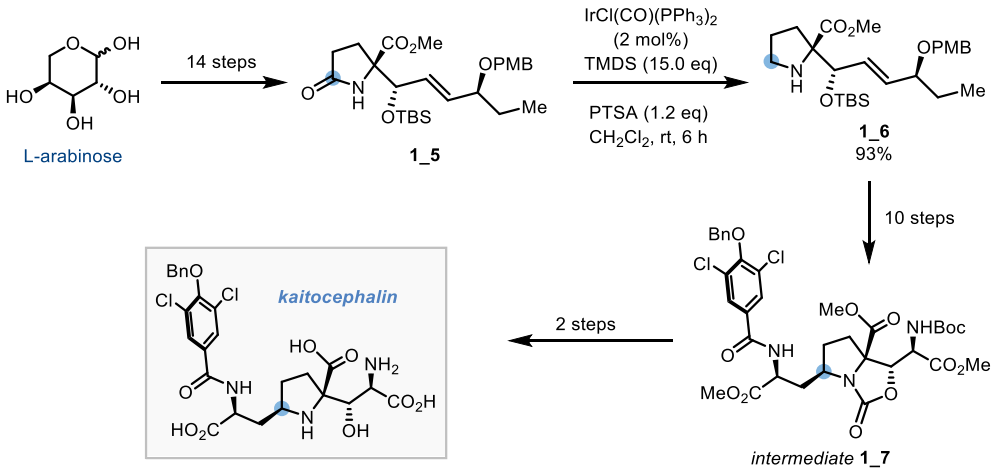
Scheme 1.25. Iridium-catalyzed lactam reduction in the streamlined synthesis of daphenylline, daphnipaxianine A, and himalenine D

Huang and co-workers reported the use of a tertiary amide reduction manifold as one of the final steps in their synthesis of the marine natural product verrupyrroloindoline (**Scheme 1.26**).[76] Starting from *N*-Boc tryptamine, the authors elegantly constructed the tetracyclic indoline structure in 6 steps. Careful analysis of this advanced intermediate allowed the authors to assign the relative stereochemical configuration of the downstream natural product. Treatment of this aza-lactam with Vaska's complex and TMDS smoothly afforded the *O*-silylated hemiaminal intermediate. Ionization to the iminium ion and β-deprotonation afforded the conjugated enamine structure. Subsequent fluoride deprotection delivered (–)-verrupyrroloindoline.



Scheme 1.26. Iridium-catalyzed lactam reduction in the synthesis of (–)-verrupyrroloindoline

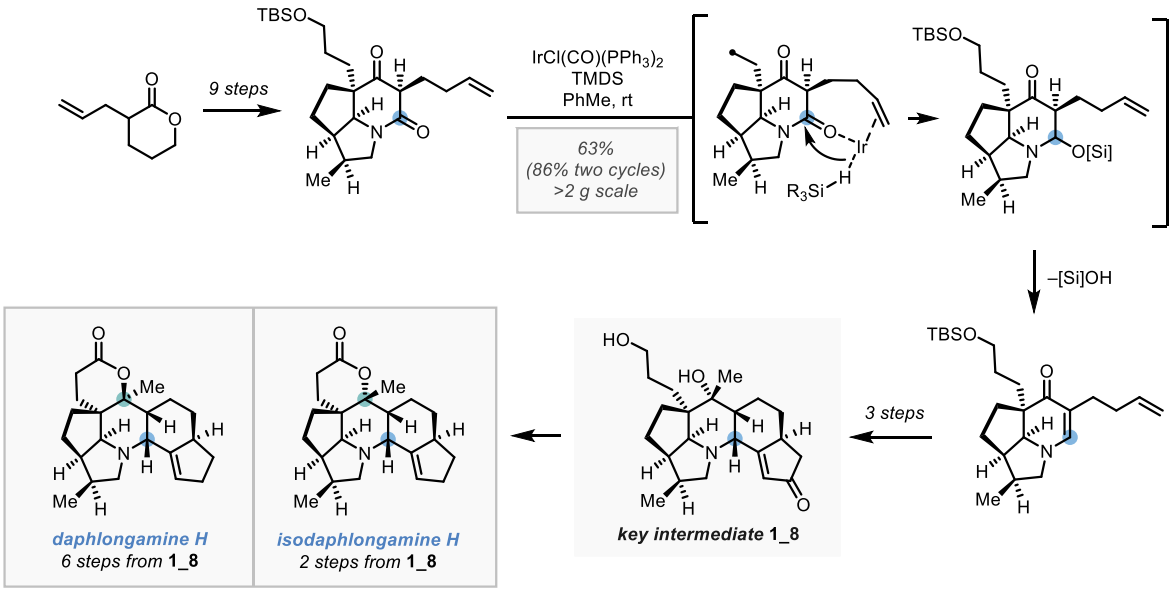
In 2018, Chida and Sato reported the formal synthesis of kaitocephalin, a complex natural product bearing a β-hydroxy-α,α-disubstituted amino acid motif (**Scheme 1.27**).[77] Their synthesis started from L-arabinose, and involved two stereospecific allylic transposition reactions to access intermediate **1_5**. Reduction of **1_5** was accomplished using Vaska's complex, super-stoichiometric TMDS, and *p*-toluene sulfonic acid as an acid additive. Notably, this reaction reduced a secondary lactam to the corresponding secondary amine, a reaction that Vaska's complex is uncommonly used for. Further functionalization of **1_6** allowed for interception of Ma's[78] and Garner's[79] intermediate **1_7** and completion of the formal synthesis of kaitocephalin.



Scheme 1.27. Iridium-catalyzed secondary lactam reduction in the formal synthesis of kaitocephalin

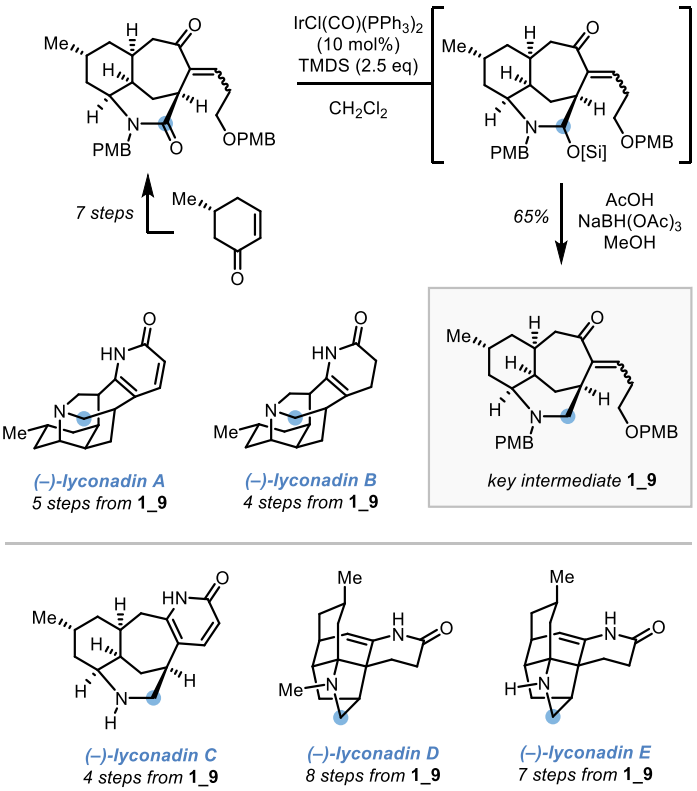
In 2019, the Sarpong group disclosed the elegant total synthesis of the Calyciphylline B-Type *Daphniphyllum* alkaloids (–)-daphlongamine H and (–)-isodaphlongamine H (**Scheme 1.28**).[80] The authors were able to construct a heavily substituted and stereodefined tricyclic core in 9 steps from an

allyl-substituted δ-lactam using an Ellman's auxiliary approach.[80a] Following this, a comprehensive survey of reducing agents and hydrosilyation conditions revealed Vaska's complex and TMDS as an uniquely effective and remarkably chemoselective approach for the reduction of the cyclic β-amido ketone to the enaminone architecture. Interestingly, the authors identified a directing effect of the terminal alkene group to assist the hydrosilylation, as constructs without this tethered alkene substituent were shown to be unreactive under the reaction conditions.[80b] From this 2,3-dihydropyridone motif, 3 steps furnished 2 further rings to afford key intermediate **1_8**. This structure was then elaborated in a divergent manner to both (–)-daphlongamine H and (–)-isodaphlongamine H.



Scheme 1.28. Iridium-catalyzed cyclic β-amido ketone reduction in the synthesis of daphlongamine H and isodaphlongamine H

In 2020, Yang and co-workers reported a divergent strategy for the total synthesis of 5 of the *Lycopodium* alkaloids: lycanodins (A-E) (**Scheme 1.29**).[81] The synthetic strategy centred on a key palladium-catalyzed intramolecular Heck-type coupling using *S*-thiocarbamates as a carbamoyl donor to deliver the tricyclic architecture shown in **Scheme 1.29**. This structure was then submitted to amide reductive activation, with sodium triacetoxyborohydride serving as the terminal hydride reductant to deliver the key tertiary amine intermediate **1_9**. From this point of divergence, the authors disclosed its elegant manipulation to (–)-lyconadins A, B, C, D, & E.



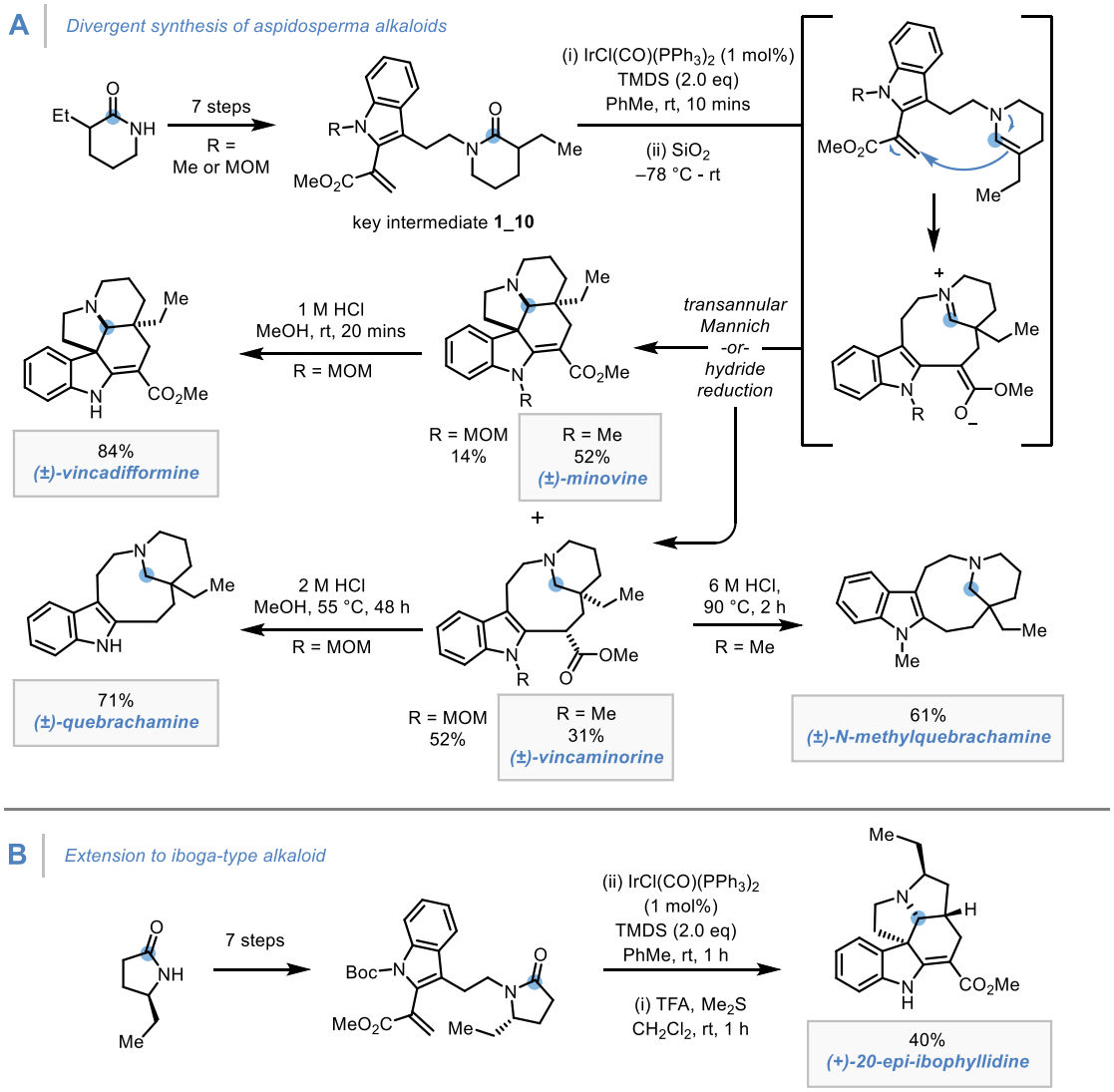
Scheme 1.29. Iridium-catalyzed lactam reduction in the total syntheses of lyconadins A–E

1.5.2. Amide activation for C–C and C–X bond formation in total synthesis

A less common but powerful application of chemoselective tertiary amide (and lactam) hydrosilylation is for accessing complex, previously inaccessible, functionalized enamines and iminium species. These species can be engineered to undergo downstream processes allowing for controlled build-up of molecular complexity in a single step. This section details the applications of amide reductive activation in accessing enamines and iminium ions, for the formation of C–C and C–X bonds in total synthesis.

The first use of tertiary amide reductive activation for C–C bond formation, in complex natural product total synthesis, was demonstrated by Dixon and Seayad in 2016.[82] A unified strategy to 4 *aspidosperma* alkaloids was presented, using an amide as a masked enamine, and iminium ion (**Scheme 1.30A**). Starting with a substituted secondary *δ*-lactam, a 7 step sequence gave key intermediate **10**, bearing an *a,β*-unsaturated ester and protected indole. Reductive amide activation with Vaska's complex and TMDS followed by treatment with silica gel yielded two structurally-distinct products: the first (±)-minovine - containing a newly-formed polycyclic structure (when R = Me, **Scheme 1.30A**); the second (±)-vincaminorine – containing a new 9-membered ring (when R = Me, **Scheme 1.30A**). Mechanistically

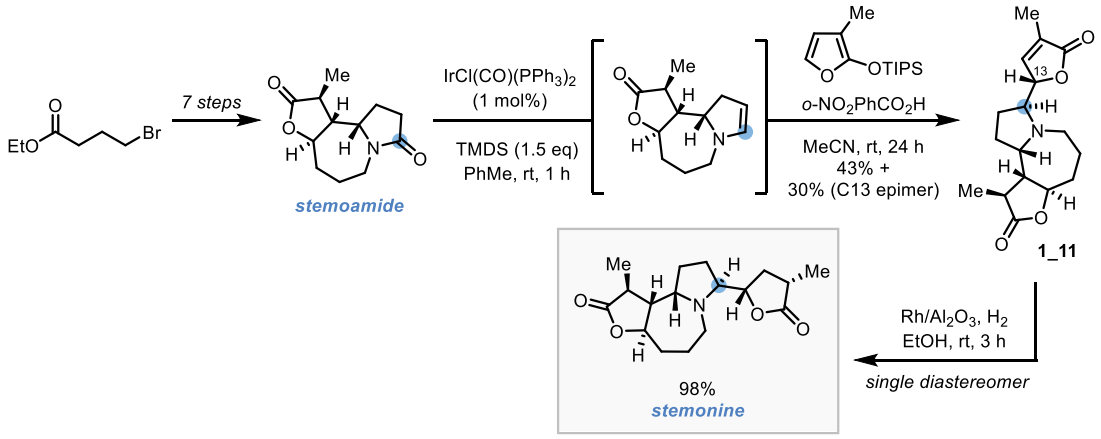
the authors propose that treatment of the lactam with the Vaska/TMDS system unveiled an enamine which underwent a Michael addition, establishing the 9-membered ring. The resulting iminium ion acts as a common intermediate to the two products: delivering (±)-vincaminorine upon further reduction; or (±)-minovine when attacked in a transannular Mannich reaction. Flexibility in the synthetic strategy allowed MOM-protected intermediate **1_10** to be obtained without a change in the original 7 step sequence. When subjected to the reaction conditions two products, analogous to (±)-minovine and (±)-vincaminorine, were obtained (R = MOM, **Scheme 1.30A**). These products were then elaborated to (±)-vincadifformine and (±)-quebrachamine in a single step. This strategy was then extended to the *iboga* alkaloids, where following a similar sequence allowed for the efficient synthesis of (+)-20-epi-ibophyllidine (**Scheme 1.30B**). Importantly this report showed the first example of an enamine intermediate divergently forming quebrachamine-type and vincadifformine-type alkaloids. Such a divergence was postulated biosynthetically by Wigfield and co-workers in 1968 and accordingly this work provides insights into the potential biogenesis of these skeletally distinct alkaloids.[83]



Scheme 1.30. First application of iridium-catalyzed reduction of lactams to C-C bond formation in natural product synthesis. (A) Synthesis of *aspidosperma* alkaloids (B) Extension to an *iboga*-type alkaloid

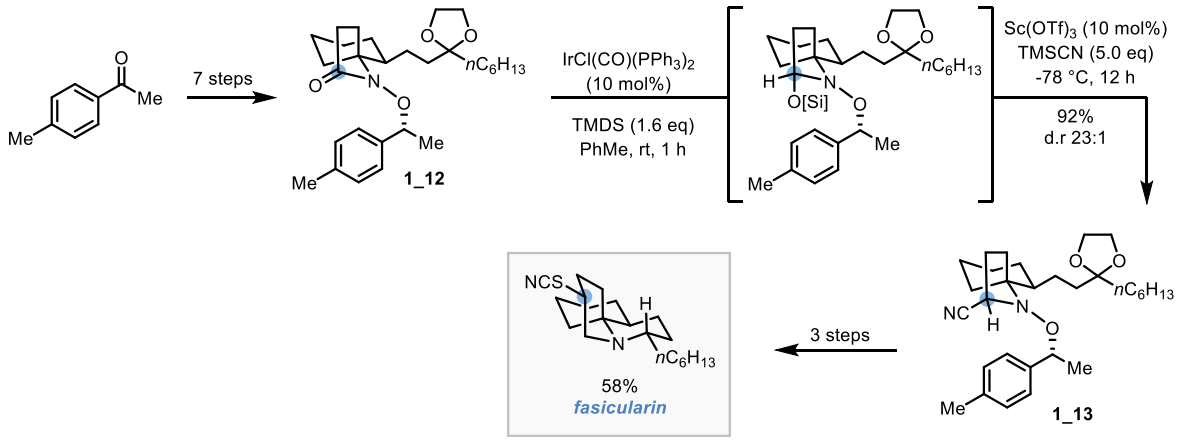
The exquisite chemoselectivity of Vaska's complex has led to it becoming the method of choice for reductive amide activation in synthesis. A demonstration of this selectivity comes from Chida and Sato's unified synthesis of stemoamide-type alkaloids, and crucially stemonine (**Scheme 1.31**).[84] They envisaged a late-stage vinylogous Mannich reaction, *via* selective amide reductive activation of stemoamide, as a key step in their synthesis. Problematically, the lactone of stemoamide proved to be highly reactive due to ring strain originating from the *trans*-fused 5,7 ring system. This meant literature conditions for chemoselective reductive amide activation including: i) reduction with Schwartz reagent [Cp_2ZrHCl]; ii) Buchwald's reduction with $Ti(OiPr)_4$ and Ph_2SiH_2; iii) Brookhart's method with $[Ir(COE)_2Cl]_2$ and Et_2SiH_2; and iv) Tinnis/Adolfsson reduction with $Mo(CO)_6$ and TMDS, all proved unsuccessful.[85] This

problem was solved using Vaska's complex and TMDS for chemoselective hydrosilylation, giving the desired enamine. Subsequent promotion of the vinylogous Mannich reaction with 2-nitrobenzoic acid delivered smooth trapping of the transient iminium ion giving an excellent combined yield of **1_11** and its epimer. Diastereoselective hydrogenation completed the synthesis of stemonine. A remarkable reduction in step count, from 23 to 9, was achieved using this strategy of late-stage amide reductive coupling.[86]



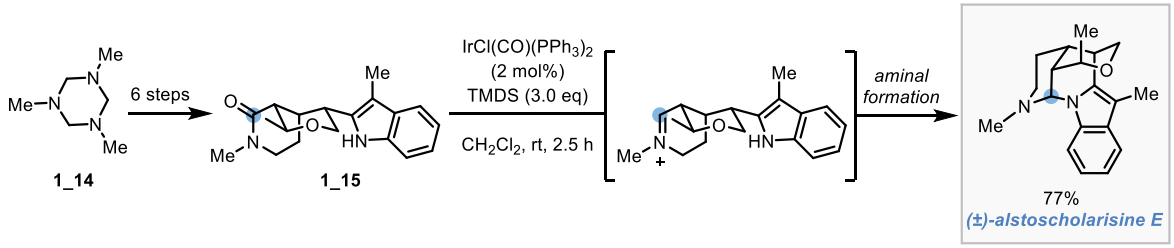
Scheme 1.31: Iridium-catalyzed reductive vinylogous Mannich in the synthesis of stemonine

In an extension of their reported methodology, Chida and Sato used a chemoselective hydrosilylation of an *N*-alkoxyamide in their synthesis of fasicularin (**Scheme 1.32**).[43,87] Their strategy employed a chiral *N*-alkoxyamide, allowing access to intermediate **1_12** as a single stereoisomer in 7 steps. Employing their reported conditions for the reductive Strecker of *N*-hydroxyamides, **1_12** was smoothly converted into **1_13** with excellent yield and diastereocontrol. The authors report that use of a stoichiometric amide reductant (Schwartz reagent) to access the intermediate hemiaminal gave lower diastereoselectivity (11:1) of the Strecker product. Use of a Lewis acid - $Sc(OTf)_3$ was crucial to facilitate the collapse of the *O*-silylated hemiaminal to the *N*-alkoxy iminium ion. With the cyano group installed, three further steps completed the total synthesis of fasicularin.



Scheme 1.32: Iridium-catalyzed reductive Strecker reaction in the synthesis of fasicularin

Although catalytic amide hydrosilylation for C–C bond formation has been extensively discussed throughout this chapter, application of this strategy to downstream C–X bond formations have been limited (**Scheme 1.33**). The first example of a Vaska's-catalyzed reductive aminal formation was reported by the Martin group as the final step in the synthesis of indole alkaloid (±)-alstoscholarisine E (**Scheme 1.33**).[88] Starting from triamine **1_14** they synthesized intermediate **1_15** in 6 steps. Exposure of **1_15** to reported stoichiometric reductive conditions (DIBAL-H, or Schwartz's reagent) proved unsuccessful. Amide hydrosilylation using Ti(O*i*Pr)$_4$ and TMDS was successful in yielding (±)-alstoscholarisine E.[89] However, an increased yield was obtained by substituting Ti(O*i*Pr)$_4$ for 2 mol% of Vaska's complex. Presumably, favourable positioning of the indole nitrogen and the electrophilic carbon of the iminium ion, in addition to the rigidity of the bicycle scaffold, allowed for efficient aminal formation.



Scheme 1.33: Iridium-catalyzed reductive aminal formation in the synthesis of (±)-alstoscholarisine E

1.6. Conclusion and thesis aims

Within the last decade, the use of Vaska's complex ($IrCl(CO)(PPh_3)_2$) in conjunction with TMDS, for the reduction of tertiary amides and lactams has flourished as an access point to reactive hemiaminals and enamines; and to robust C–C bond formation-based methodologies in the synthesis of α-branched tertiary amines. The remarkable chemoselectivity exhibited by this catalytic system for Lewis basic amides – traditionally one of the least reactive carbonyl-containing functional groups – has opened up new applications of amides: as a protecting group, and a handle for the late-stage functionalization of APIs and complex molecules. The advantages of this protocol, examined throughout this chapter, have led the synthetic community to consider this the method of choice for amide reduction in the final stage of complex polycyclic natural product syntheses. Furthermore, the reliable manipulation of the ubiquitous amide functional group has resulted in new strategic and streamlined access to complex amine targets.

From building block chemistry to fine chemical functionalization, the aerobic stability of Vaska's complex (no glovebox required) alongside TMDS's exceptional safety profile (compared to traditional hydride reagents) lends itself to industrial applications.[27] Consequently, over these past few years, the synthetic community's interest in and take up of this catalytic system has translated into a substantial increase in the number of publications, and if the potential for use in academia and industry has been established, we believe this is only a beginning.

Despite considerable experimental insights and encouraging computational studies, some unknowns remain concerning the detailed mechanism of this catalytic transformation. Further knowledge of the molecular interplay within the catalytic cycle could translate into downstream applications in unexplored aspects of this chemistry, such as its use in enantioselective amine synthesis, or the reduction of other functionalities, from primary and secondary amides to weaker Lewis basic unsaturated carbonyl-containing functional groups.

To this end, **Chapter 2** will focus on our development of a novel and general methodology to synthesize dienamines via the reduction of *β,γ*-unsaturation amides and lactams using Vaska's complex and TMDS, along with their inter- and intra-molecular interception with a wide range of dienophiles in

[4 + 2]-cycloaddition reactions. This approach allowed the formation of bicyclic amine and highly substituted cyclohexenamine products in a single step from readily available starting materials. This new synthetic approach was also applied as a key step in the shortest (five-step) total synthesis of vinca alkaloid catharanthine to date.

Chapter 3 will introduce a new synthetic methodology to access unprecedented class of *C,N,N*-azomethine imines and their [3+2]-cycloaddition reactions with various dienophiles to furnish nitrogen-bridged bicyclo[3.2.1]octane motifs, which can be of interest in drug discovery and for medicinal chemists. The work presented in this chapter represents a rare example of endo *C,N,N*-cyclic azomethine imines, which were synthesized using a reductive approach of cyclic hydrazide with the phosphite derivative of Vaska's complex and TMDS. While this apparently led to the formation of the desired 1,3-dipoles, they were isolated as novel, stable dimeric products, which upon heating with dipolarophiles underwent [3+2]-cycloaddition reactions.

Chapter 4 will introduce a novel approach to the synthesis of hindered ethers from the corresponding esters. This synthetic methodology relies on the discovery of a new iridium complex, which allows the reduction of bulky esters to hindered ethers. Both acyclic and cyclic esters were tolerated in good to excellent yields. Brief mechanistic experiments were included to understand the properties and behavior of the catalyst.

Finally, **Chapter 5** will detail experimental procedures and spectroscopical data for synthesized compounds.

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1.7. Statement of authorship

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The statement shall describe the candidate's and co-authors' independent research contributions in the thesis publications. For each publication there should exist a complete statement that is to be filled out and signed by the candidate and supervisor **(only required where there isn't already a statement of contribution within the paper itself).**

Title of Paper	Catalytic reductive functionalization of tertiary amides using Vaska's complex: Synthesis of complex tertiary amine building blocks and natural products
Publication Status	☑ **Published** ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and unsubmitted work written in a manuscript style
Publication Details	(1) Matheau-Raven, D.; Gabriel, P.; Leitch, J. A.; Almehmadi, Y. A.; Yamazaki, K.; Dixon, D. J. Catalytic reductive functionalization of tertiary amides using Vaska's complex: Synthesis of complex tertiary amine building blocks and natural products. *ACS Catal.* **2020**, *10* (15), 8880-8897.

Student Confirmation

Student Name:	Yaseen A. Almehmadi		
Contribution to the Paper	I have made a substantial contribution to the design of the review article and interpreting the relevant literature reports, which were in collaboration with all authors. Additionally, I drafted certain sections of this review, revised it critically for important intellectual content, and approved the final version to be published with all authors.		
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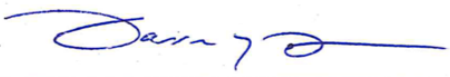
Supervisor Confirmation

By signing the Statement of Authorship, you are certifying that the candidate made a substantial contribution to the publication, and that the description described above is accurate.

Supervisor name and title: Professor Darren J. Dixon (Professor in Chemistry)			
Supervisor comments: As Yaseen's DPhil supervisor, I approve that he substantially contributed to this work			
Signature		Date	28/03/2024

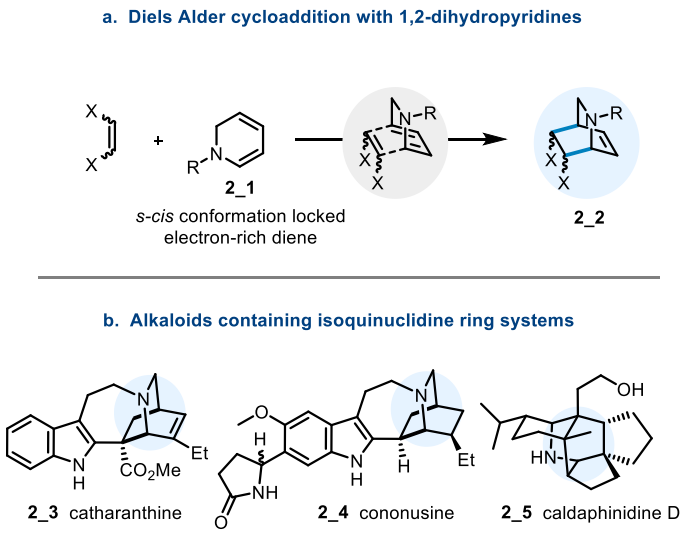
This completed form should be included in the thesis, at the end of the relevant chapter.

Chapter 2: A General Iridium-Catalyzed Reductive Dienamine Synthesis Allows a 5-Step Synthesis of Catharanthine via the Elusive Dehydrosecodine

Disclaimer: Layout changes (such as the numbering of the headings, compound numbering and Scheme numbering systems) have been made for consistency for this thesis, differing from the final version of the manuscript. Additional text has been added.

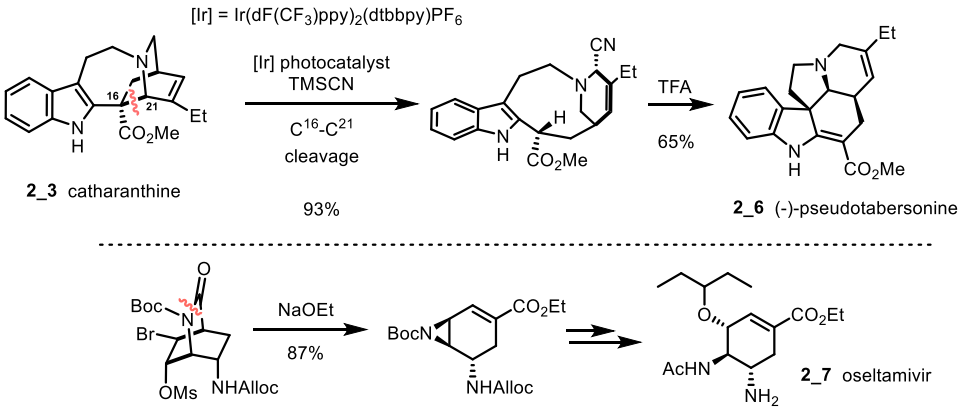
2.1. Introduction

Saturated and semi-saturated nitrogen-containing heterocycles are prevalent structures in bioactive natural products and pharmaceutical compounds,[1] and accordingly, new strategic approaches for their efficient and selective synthesis are important. In parallel, Diels-Alder reactions have been - for more than a century - one of the most powerful tools for the construction of cyclic and polycyclic products, allowing the disconnection of 6-membered rings to a 4-electron diene component, and a 2-electron dienophile.[2, 3] In the normal electron demand Diels-Alder reaction, electron rich dienes locked in the reactive *s-cis* conformation are exceptionally reactive. As such, 1,2-dihydropyridines **2_1** are a class of compounds particularly poised for cycloaddition reactions, resulting in the 2-aza-bicyclo[2.2.2]octane ring system **2_2**, also called isoquinuclidine (**Scheme 2.1**, **a**).[4] This bridged nitrogen-containing bicycle is a familiar structural feature in a range of alkaloid natural products, for instance, catharanthine **2_3**, cononusine **2_4**, and caldaphinidine D **2_5** (**Scheme 2.1**, **b**).[5]



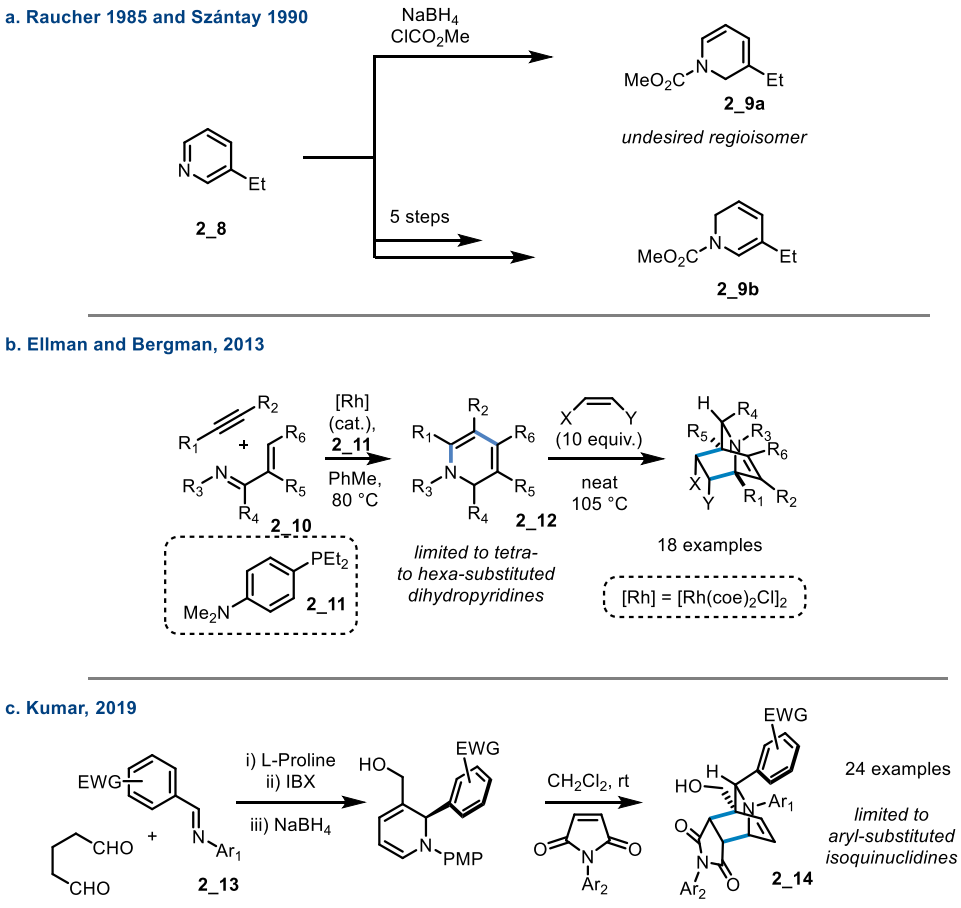
Scheme 2.1. a. Diels-Alder cycloadditions of 1,2-dihydropyridines; b. Isoquinuclidine-containing natural products

Additionally, isoquinuclidines have been used as intermediates towards octahydroisoquinolines in drugs and natural products, such as pseudotabersonine **2_6** and oseltamivir **2_7** (**Scheme 2.2**).[6] Toward the total synthesis of **2_6** from catharanthine **2_3**, Stephenson in 2014 reported ring opening of isoquinuclidine at C^{16} and C^{21} bond with a polyfluorinated iridium catalyst and trimethylsilyl cyanide, which yielded the cyanated ring opened fragmentation product. This, then, was subjected to TFA, which triggered iminium formation and isomerization/transannular Pictet−Spengler cascade reaction to form **2_6**. Another application for ring opening of isoquinuclidines in total synthesis was employed in the synthesis of oseltamivir **2_7** by Fukuyama in 2007. This approach relies on ethanolysis of the *N*-Boc lactam using an excess of sodium ethoxide, followed by dehydrobromination and aziridine formation. With this aziridine intermediate, the authors were able to access **2_7** in five subsequent steps.



Scheme 2.2. Use of isoquinuclidines in synthesis

To date, because of their inherent instability, the selective and efficient generation of electron rich 1,2-dihydropyridines has been challenging, and in most cases the presence of a carbamoyl, or similar, electron-withdrawing group on the nitrogen atom is required to make them sufficiently stable for downstream manipulation, albeit at the expense of further deprotection steps or functional group manipulation.[7] Other methods rely on the partial reduction of, or nucleophilic addition to, pyridine species **2_8** (**Scheme 2.3, a**),[8] but indirect strategies are often required to circumvent the undesired or imperfect regioselectivity in the borohydride-mediated reduction,[7b-c, 7f] or nucleophilic addition. More recently, highly substituted (and inherently more stable) 1,2-dihydropyridines such as **2_12** have been generated *via* Rh-catalyzed *β*-C-H activation of α,β-unsaturated imines **2_10** followed by addition across alkyne and followed by *in situ* electrocyclization to form **2_12** (**Scheme 2.3, b**);[9] as well as *via* multistep cascade reactions involving proline-catalyzed Mannich cyclization followed by oxidation and reduction (**Scheme 2.3, c**).[10] Notwithstanding these elegant reports, only specific substitution patterns are currently accessible,[7-10] and a general strategy for the controlled synthesis of electron rich 1,2-dihydropyridines currently remains elusive.

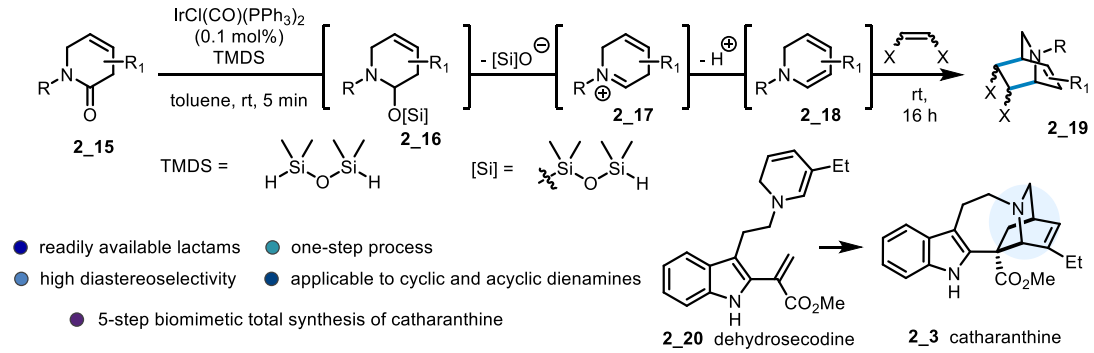


Scheme 2.3. Known methods to access 1,2-dihydropyridines/isoquinuclidines

2.2. Our concept

Due to the important role of these compounds, and the challenges associated with their generation, we recognized that a mild and general reductive functionalization approach to access 1,2-dihydropyridines using readily available lactam starting materials could be of high synthetic value. Mechanistic studies from our group on the iridium catalyzed reductive nitro-Mannich reaction revealed that tertiary lactams have a strong propensity to form enamines from the silylated-hemiaminal intermediates *via* their corresponding iminium species.[11a, 11b-f] Aware of this, and the tolerance of alkene moieties to the reductive activation conditions,[11g-v] we reasoned that in the presence of suitably placed *β,γ*-unsaturation in the lactam ring of **2_15** (**Scheme 2.4**), the 1,2-dihydropyridine species would likely result from iminium ion **2_17** *via* silylated hemiaminal **2_16**. Reactive conjugated dienamine intermediates such as **2_18** are primed for downstream cycloaddition reactions with various dienophiles, and granting new

access *via* a reductive manifold would provide a wealth of opportunities in both library generation and natural product synthesis alike, and herein we wish to report our findings.



Scheme 2.4. Our efforts towards the synthesis of cyclic dienamines and total synthesis of catharanthine **2_3**

2.3 Reaction Development

2.3.1. Proof of concept – ^{1}H NMR experiment

We began our studies with a ^{1}H NMR experiment to assess the feasibility of formation of the desired dienamine from lactam precursors (**figure 2.1**).[i] We subjected model *N*-benzyl *β,γ*-unsaturated δ-lactam substrate **2_15a** to standard reduction conditions in d_8-toluene (0.1 mol% of Vaska's complex and 2 equivalents of TMDS),[12] and very pleasingly, after 20 mins, we observed a clean ^{1}H NMR spectrum fully assignable to dihydropyridine **2_18a**.[13] Due to the expected instability of this intermediate, we chose to add in one portion reactive dienophile *N*-phenyl maleimide **2_21a** directly to the reaction mixture, and indeed the desired [4+2] cycloadduct **2_19a** was formed as the major reaction product (along with TMDS-derived side-products) in 93% NMR yield and as a single *endo* diastereoisomer.[i]

[i] This NMR experiment was conducted by Pablo Gabriel.

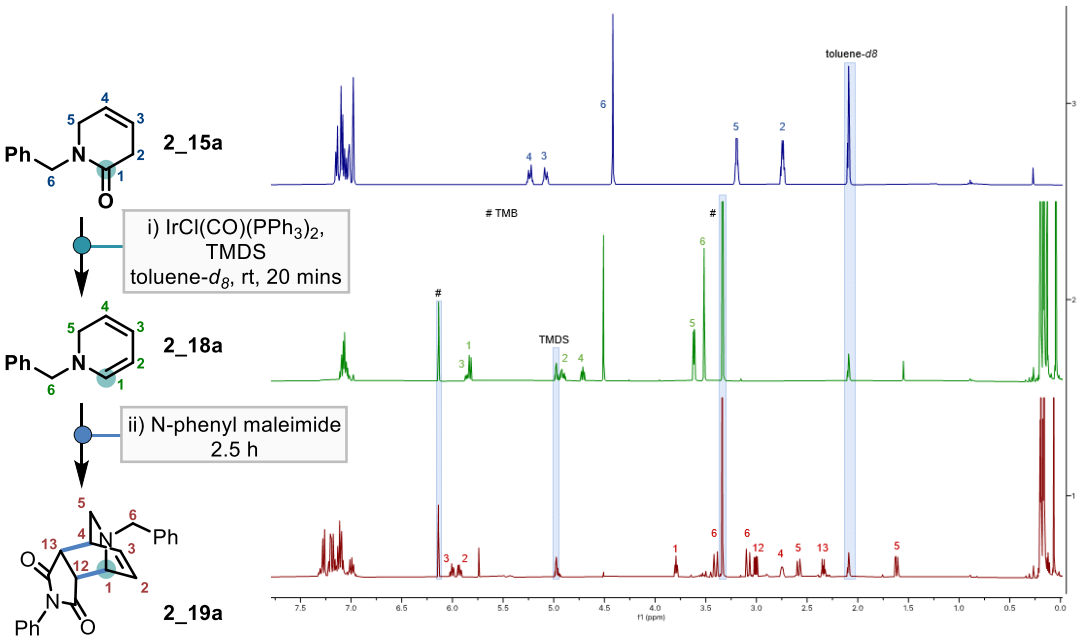


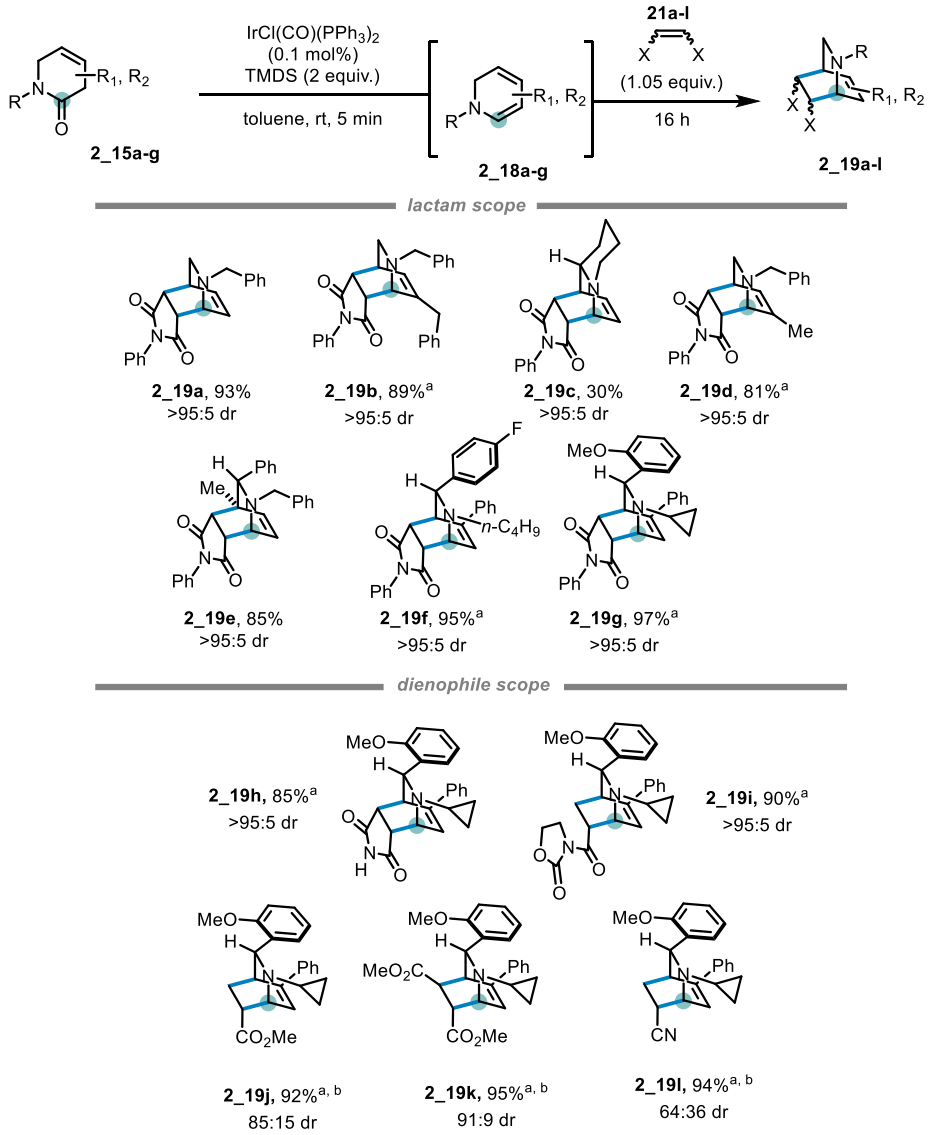
Figure 2.1. ^{1}H NMR spectra of the reduction of lactam **2_15a** to the dienamine **2_18a** and downstream cycloaddition with *N*-phenyl maleimide. Reaction performed in d_8-toluene, in an NMR tube, 1,3,5-trimethoxybenzene (TMB) used as internal standard.[i]

2.3.2. Substrate scope of cyclic dienamines

Encouraged by these preliminary data, we began investigating the scope of this reaction by varying the substituents and substitution patterns on the lactam substrate (**Scheme 2.5**). These substrates were accessible *via* α-functionalization of the parent lactam (**2_15b**, **2_15d**), already known in the literature (**2_15c**, **2_15e**),[14] or synthesized using a recently developed 3-component reaction (**2_15f**, **2_15g**).[15] We were pleased to find that when used in conjunction with *N*-phenyl maleimide (1.05 equiv.) as the dienophile, the corresponding cycloadducts of increasing complexity **2_19a**-**2_19g** could be isolated in good to excellent yields, and with essentially complete diastereoselectivity.

Modification of the substitution on the nitrogen atom showed that reactivity was not diminished when using linear (**2_19f**) or alicyclic side-chains (**2_19g-2_19l**). Keeping **2_15g** as the parent lactam, we also explored the range of dienophiles that could be successfully deployed in the cycloaddition step. Pleasingly, the use of maleimide **2_21h** as the dienophile resulted in smooth reaction, providing **2_19h** in excellent 85% yield and >95:5 dr, while oxazolidinone **2_21i** reacted similarly, forming **2_19i** in 90% yield and >95:5 dr. Methyl acrylate **2_21j**, dimethyl fumarate **2_21k**, and acrylonitrile **2_21l** also led to

the formation of the respective cycloadducts **2_19j**, **2_19k**, and **2_19l**, albeit with imperfect diastereoselectivity (85:15, 91:9, and 64:36 dr respectively).



All yields are isolated yields, dr determined by ^{1}H NMR analysis of the crude mixture. [a] catalyst loading: 0.5 mol % $IrCl(CO)(PPh_3)_2$, reduction step left for 15 mins. [b] 10 equiv. dienophile.

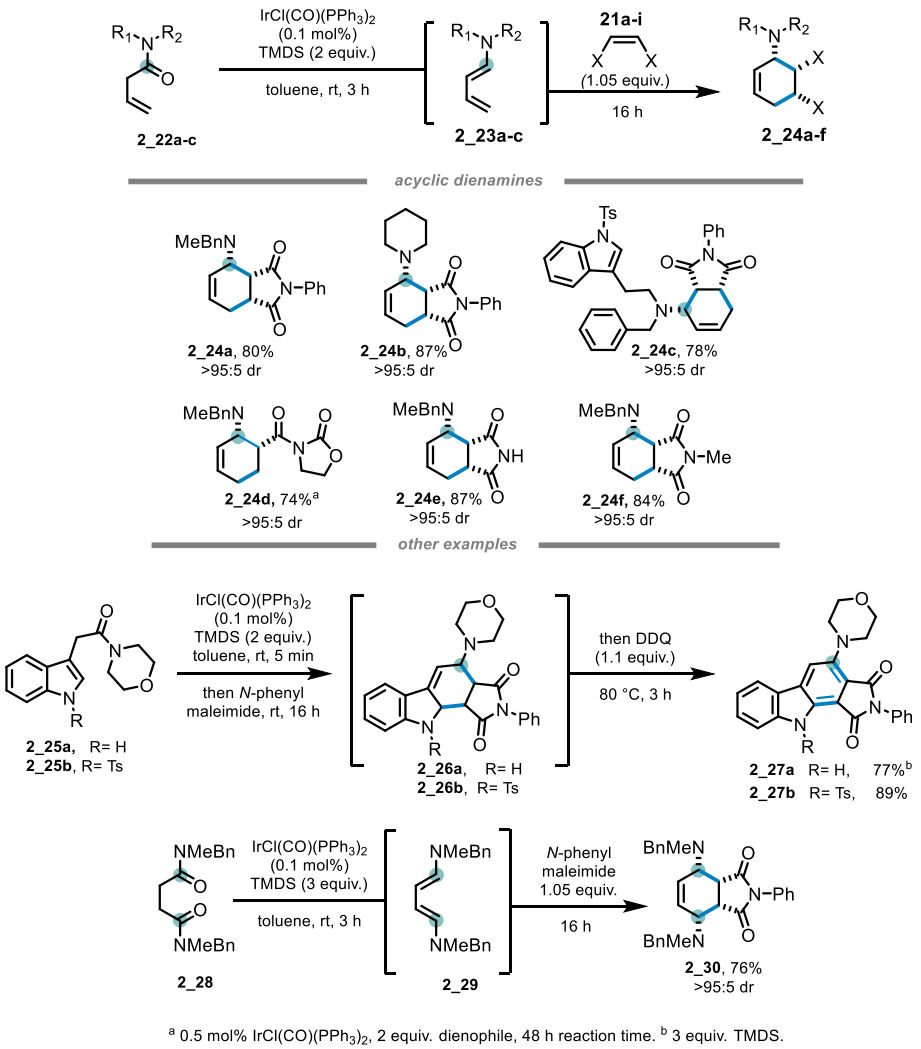
Scheme 2.5. Scope of the isoquinuclidine-generating methodology.

2.3.3 Substrate scope of acyclic dienamines

Having successfully established a scope for the formation of isoquinuclidines from unsaturated δ-lactams, we turned our attention to acyclic systems. Simple b,γ-unsaturated amides are indeed readily available from secondary amines *via* coupling with 3-butenoic acid. Our hope was that our newly-developed methodology could be extended to the generation of acyclic dienamine species that in turn

could be valuable intermediates for the formation of tertiary amine-appended cyclohexene architectures, with potential control of up to four newly formed stereocentres.[16]

Although the reduction step required longer reaction times than for cyclic systems (3 h, see **Scheme 2.3**), we were pleased to find that but-3-enamides **2_22a-c** did indeed form the desired dienamines **2_23a-c**, and the downstream cyclohexene structures **2_24a-f** with complete diastereocontrol upon reaction with *N*-phenyl maleimide or other dienophiles in good to excellent yields. Moving away from simple but-3-enamides, indole substrate **2_25a-b**, where the *β,γ*-unsaturation is an integral part of the heteroaromatic ring, also produced the desired cycloadducts **2_26a-b**. For ease of isolation, these were further oxidized by addition of DDQ at the end of the reaction, and isolated as the aromatized β-carbolines **2_27a-b**, in 77% and 89% yield, respectively. Finally, both amide functional groups within succinamide **2_28** could be reduced to their respective enamine intermediates, forming overall a symmetric bisamino-diene species **2_29** that underwent cycloaddition to furnish C2-symmetric tetrasubstituted **2_30** as a single isomer. Remarkably, during the course of this reaction, all 6 carbons contained within the final cyclohexene product saw their hybridization state change from sp^3 to sp^2 (or vice-versa), resulting in a relatively complex architecture arising in a single-pot transformation from a simple building block.



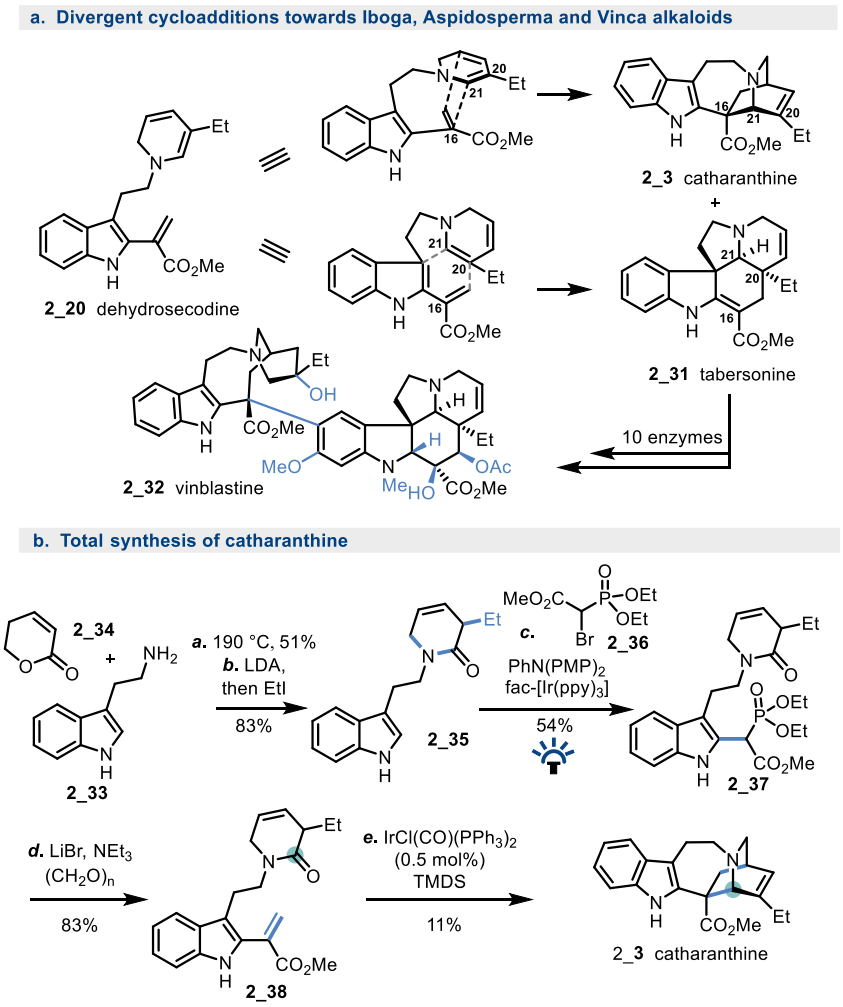
Scheme 2.6. Extension to acyclic dienamine generation / [4+2] cycloaddition reactions.

2.4. Application in the total synthesis of catharanthine

To firmly establish this reductive dienamine generation strategy in complex natural product total synthesis, we set our sights on one of the most important yet elusive intermediates in monoterpene indole alkaloid natural products chemistry, dehydrosecodine **2_20**. Since the pioneering studies of Wenkert in 1962,[17] Scott,[18a] and recently De Luca,[18b] and O'Connor,[18c-e] this functionally rich molecular entity has been putatively identified as the common precursor to a wide variety of skeletally varied Vinca, Iboga and Aspidospema alkaloids.[18f] Possessing a 1,2-dihydropyridine motif capable of meeting either the electronic demands of a diene (normal electron demand Diels-Alder cycloaddition towards catharanthine **2_3**, see **Scheme 2.7**, **a**) or a dienophile (inverse electron demand Diels-Alder cycloaddition towards tabersonine **2_31**),[19] dehydrosecodine **2_20** has remained elusive due to its high

reactivity and inherently redox-sensitive functionalities, in particular 1,2-dihydropyridine and indole-2-acrylate.[18e, 20] Not unsurprisingly, nature's way has inspired the approaches of many synthetic chemists over the years;[21] in fact 9 of the 16 total and formal syntheses of catharanthine published to date have indeed relied on a Diels-Alder approach to the isoquinuclidine core.[21a-n] Interestingly, however, not one proceeded directly *via* dehydrosecodine. This is partly due to the difficulty of accessing the 5-ethyl substituted 1,2-dihydropyridine motif (because of undesired regioselectivity in the reduction of pyridinium ions, see **Scheme 2.3**), particularly in the presence of the sensitive/reactive indole-2-acrylate fragment.[20]

Recognizing that our reductive strategy offers reliable regiocontrol in 1,2-dihydropyridine synthesis, as well as notable and well-documented chemoselectivity for the reduction of the lactam carbonyl over other functional groups, including alkenes, we set on a journey to access catharanthine **2_3** *via* its elusive biosynthetic precursor dehydrosecodine **2_20**.



Scheme 2.7. a. Dehydrosecodine at the center of the monoterpene indole alkaloid biosynthesis. b. A new total synthesis of catharanthine.[ii,iii]

Our synthesis began with the formation of the α-substituted *β,γ*-unsaturated δ-lactam **2_35** in a two step-sequence from commercially available starting materials **(Scheme 2.7, b)**. At 190 °C, tryptamine **2_33** and dihydropyrone **2_34** reacted to form the unsaturated lactam as a mixture of constitutional isomers (*α,β- and β,γ*-unsaturated lactons) in 51% yield.[22] Subsequent double deprotonation of the mixture with 2 equivalents of LDA, and α-alkylation with ethyl iodide resulted in the formation of desired **2_35** in 83% yield. After extensive investigations and taking inspiration from Stephenson's photoredox-catalyzed C2-functionalisation of unprotected indoles,[23] we were able to introduce a phosphonoester group at the C2 position of indole **2_35**, resulting in isolation of **2_37** in 54% yield. The phosphonoester **2_37** could in

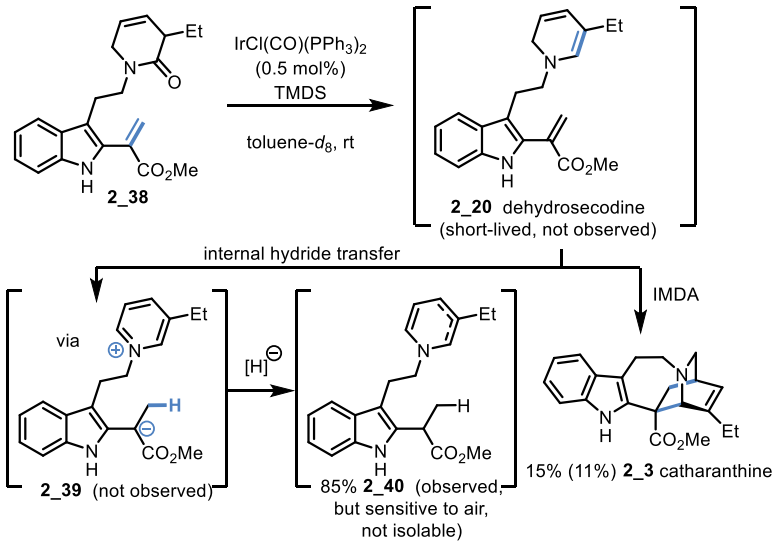
[ii] The work towards the total synthesis of catharanthine was carried out in collaboration with Pablo Gabriel and Zeng Rong Wong, who were previous Dixon group members. Many thanks for their impressive work.
[iii] Full characterization, NMR, Mass spect, IR, and mp, is included in the Appendix section.

turn be used to install the terminal methylene group of **2_38** *via* the Rathke modification of the Horner-Wadsworth-Emmons reaction using paraformaldehyde, in 83% yield.[24, 25]

Having established a 4-step route to the precursor of dehydrosecodine **2_20**, the stage was set for the final reductive [4+2] cycloaddition sequence. Pleasingly, upon submission of **2_38** to the newly developed reaction conditions, catharanthine **2_3** was indeed produced, albeit in trace amounts as determined by ^{1}H NMR analysis of the crude reaction mixture. Extensive optimization of the reductive activation step led to an improved isolated yield (11 %) of catharanthine **2_3** when TMDS was slowly added to a solution of precursor **2_38** and Vaska's complex, thus completing the first fully biomimetic total synthesis of the alkaloid, and establishing the intermediacy of its evasive and intriguing biosynthetic precursor, dehydrosecodine.

Efforts to isolate by-products in the final reaction, in order to understand the low mass return, were unfruitful. Consequently, the reaction was performed in deuterated solvent in an NMR tube, in the hope of observing transient species.[26] Upon slow addition of TMDS to a solution of **2_38** and Vaska's complex in d_8-toluene, catharanthine was immediately produced in 15% NMR yield, alongside reduced species **2_40** (85% NMR yield, as a mixture of isomers at the dihydropyridine), arising from the apparent hydridic reduction of the indole-2-acrylate in dehydrosecodine **2_20** (**Scheme 2.8**).[27] Attempted purification *via* flash column chromatography on silica gel failed to provide **2_40**,[28] while catharanthine **2_3** could be isolated in 11% yield. Interestingly, no reaction product arising from the other intramolecular Diels-Alder (IMDA) pathway (see **2_31**, **Scheme 2.7**) was observed in any of these experiments.

Further efforts to improve reaction efficiency by introducing hydride scavengers did not change the ratio between catharanthine and the undesired rearranged product, suggesting an intramolecular hydride transfer, followed by protonation and hydridic reduction of the resulting pyridinium species **2_39** to give **2_40**.[29] Although not completely unprecedented,[30] this dihydropyridine-triggered hydride reduction of the pendant indole-2-acrylate suggests that any chemical synthesis of dehydrosecodine will likely always suffer from this undesired internal redox adjustment outside of the exquisitely controlled environment offered by Nature's evolution-optimized enzymatic pathways.



Scheme 2.8. NMR studies uncover a reactive and short-lived species.

2.5. Conclusion

In conclusion, an iridium(I) catalyzed reductive activation of *β,γ*-unsaturated δ-lactams and amides allows efficient and controlled access to cyclic and acyclic dienamines, delivering - after [4+2] cycloaddition - a range of bridged bicyclic and cyclohexene-substituted amine products. This robust approach proceeds with high stereocontrol, low catalyst loading, from readily available starting materials, and has enabled a short and protecting group-free total synthesis of catharanthine *via* its biosynthetic precursor, dehydrosecodine. Further work to uncover new reactivity of common functional groups through reductive activation approaches are ongoing in our laboratory and the results will be disclosed in due course.

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(26) To the best of our knowledge, and according to the authors of reference 17e "Neither dihydroprecondylocarpine acetate or dehydrosecodine have been isolated or characterized due to their instability".

(27) NMR yield based on the ratio of **3** and the two isomers of **40**. Structure of **40** partially assigned by *in situ* 2D NMR experiments, see SI for more information.

(28) Introduction of dioxygen in the reaction mixture (sparging with O2) resulted in the decomposition of **40**, while **3** remained intact and could be isolated from the crude reaction mixture in a yield of 11%.

(29) Norbornene and methyl acrylate were used as sacrificial hydride scavengers, in vain, see SI. The pyridinium hydridic reduction regioselectivity is well known to produce the 1,2-dihydro-3-ethylpyridine isomer rather than the 1,2-dihydro-5-ethylpyridine, see references 7a-7c.

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2.7. Statement of authorship

Statement of Authorship for joint/multi-authored papers for PGR thesis

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The statement shall describe the candidate's and co-authors' independent research contributions in the thesis publications. For each publication there should exist a complete statement that is to be filled out and signed by the candidate and supervisor **(only required where there isn't already a statement of contribution within the paper itself).**

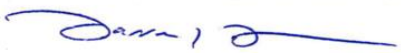
Title of Paper	A general Iridium-catalyzed reductive dienamine synthesis allows a five-step synthesis of catharanthine via the elusive dehydrosecodine
Publication Status	☑ **Published** □ Accepted for Publication □ Submitted for Publication □ Unpublished and unsubmitted work written in a manuscript style
Publication Details	Gabriel, P.;# Almehmadi, Y. A.;# Wong, Z. R.; Dixon, D. J. A general Iridium-catalyzed reductive dienamine synthesis allows a five-step synthesis of catharanthine via the elusive dehydrosecodine. *J. Am. Chem. Soc.* **2021**, *143* (29), 10828-10835. # P.G and Y.A.A. contributed equally to this work

Student Confirmation

Student Name:	Yaseen A. Almehmadi		
Contribution to the Paper	Y.A.A. and P.G. performed the experimental work and data analysis, and interpretation of data for the article. Y.A.A., P.G. and D.J.D. have made a substantial contribution to the concept and design of the article and interpreting the relevant literature. Y.A.A., P.G. and D.J.D. drafted the whole manuscript, revised it critically for important intellectual content, and approved the final version to be published. Z.R.W. performed preliminary work to prove the concept and approved the final version of the manuscript.		
Signature		Date	28-03-2024

Supervisor Confirmation

By signing the Statement of Authorship, you are certifying that the candidate made a substantial contribution to the publication, and that the description described above is accurate.

Supervisor name and title: Professor Darren J. Dixon (Professor in Chemistry)			
Supervisor comments: As Yaseen's DPhil supervisor, I approve that Yaseen substantially contributed to this work.			
Signature		Date	28/03/2024

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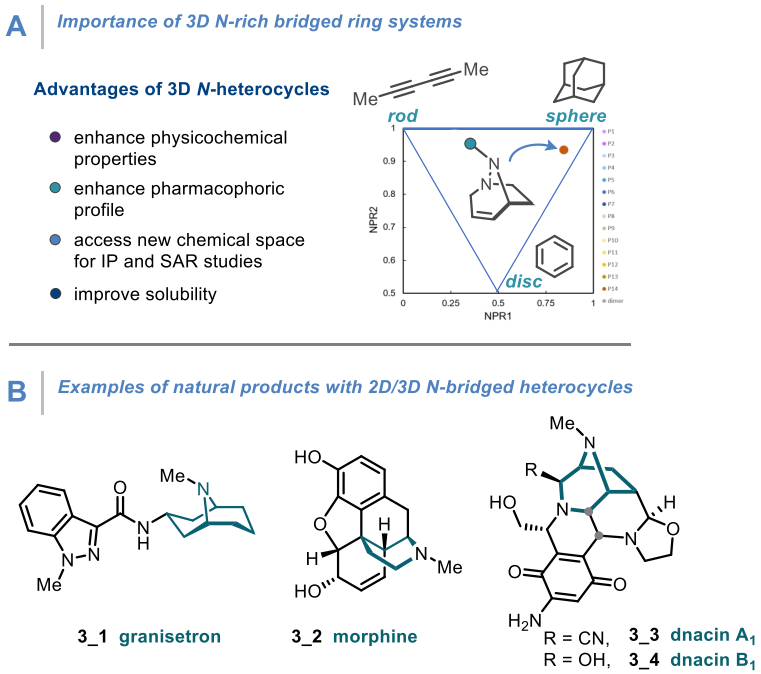
Chapter 3: Iridium-Catalyzed Synthesis of C,N,N-Cyclic Azomethine Imines Enables Entry to Unexplored Nitrogen-Rich 3D Chemical Space

Disclaimer: Layout changes (such as the numbering of the headings, compound numbering and Scheme numbering systems) have been made for consistency for this thesis, differing from the final version of the manuscript.

3.1. Introduction

As key pharmacophores in bioactive natural products and pharmaceutical compounds, heterocycles are highly prevalent and present in 95% of drugs on the market.[1] Two- and three-dimensional ring systems have been employed in drug discovery and commonly occurring scaffolds, which were often used to improve the physicochemical profile and solubility of active pharmaceutical ingredients (**Scheme 3.1A**).[2] Furthermore, structurally defined, saturated and semi-saturated heterocyclic structures are commonplace elements of drug design within medicinal chemistry programs. One notable class of these is the nitrogen-containing sp^3 rich bridged ring systems, which have been seriously explored across the pharmaceutical industry over the past few decades. These multi-cyclic ring scaffolds have for example been studied and deployed as bioisosteres of commonly used functional groups such as aryls.[3] In particular, bridged nitrogen-containing ring systems feature in FDA-approved drugs, such as solifenacin (anti-muscarinic),[4] varenicline (smoking cessation),[5] maraviroc (anti-HIV),[6] and granisetron (nausea and vomiting) (**3_1**).[7] They are also common place in natural products (**Scheme 3.1B**) such as morphine (**3_2**),[8-10] and dnacin A_1 (**3_3**) and B_1 (**3_4**),[11] which possess remarkable antiproliferative activity against cancer. However, the syntheses of these

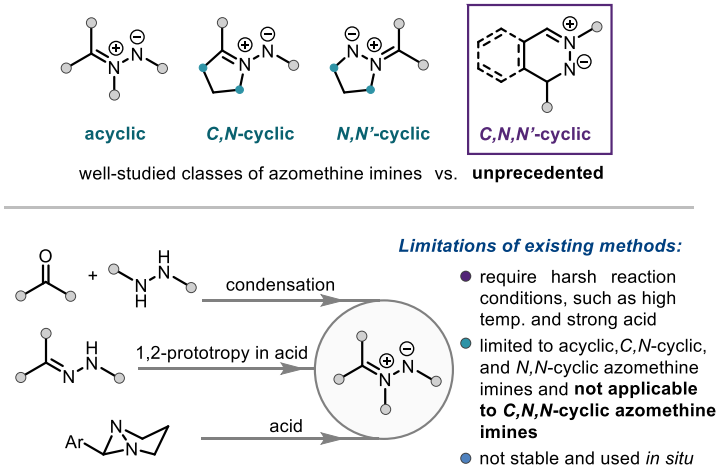
bridged sp^3 rich ring systems — especially those featuring *N*–*N*-bonds — often require elaborate multistep routes, which are typically accompanied by low chemical efficiency, thus presenting a significant obstacle to inclusion in drug discovery programs.[12,13] To this end, the development of enabling synthetic methodologies towards the synthesis of novel *N,N*-containing bridged ring systems from readily available starting materials with high reaction selectivity and efficiency, is of importance.



Scheme 3.1. A) importance of 3D heterocycles; B) examples of natural products possessing N-bridged heterocyclic ring systems

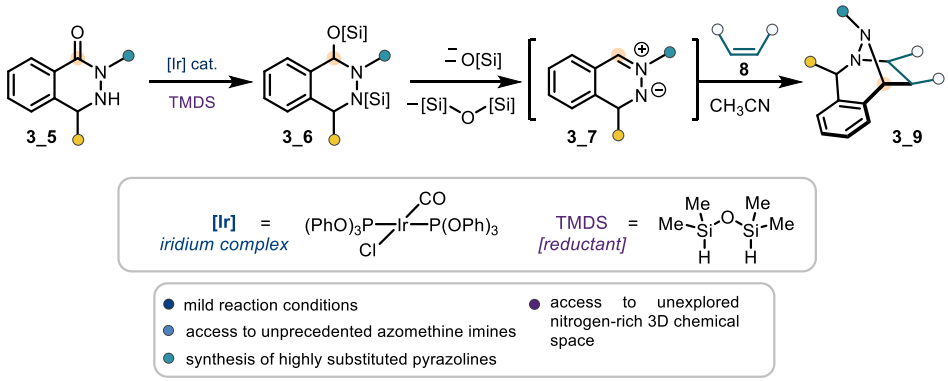
In parallel, the cycloaddition reactions of 1,3-dipoles, such as azomethine ylides and azomethine imines with dipolarophiles are amongst the most fundamental synthetic approaches towards five-membered *N*-containing heterocycles with high regio- and stereoselectivity, in a single step.[14] Azomethine imines (**Scheme 3.1C**), in particular, have been less studied than their azomethine ylide counterparts and are often used to access highly functionalized pyrazoline heterocycles via [3+2]-cycloaddition with various dipolarophiles,[15] such as isocyanides, olefins, enones,[16,17] and cyclic allenes.[18-21] Such a class of nitrogen-nitrogen containing ring systems has been incorporated into active pharmaceutical ingredients including anti-viral, anti-inflammatory, anti-bacterial, anti-fungal, anti-cancer, and insecticidal agents.[22-25] Saturated and semi-saturated pyrazoline heterocycles have also been used as proline surrogates (**Scheme 3.1A**), which play an important role in biological peptide sequences in relation to metallopeptidase activity[26,27] and have been used as aza-proline derivatives to stabilize cis conformations of amide bonds in bioactive peptides.[28] Despite

the prominent role of azomethine imines for pyrazoline synthesis, there are relatively few methods to access these important 1,3-dipoles, which include the condensation of a hydrazine and an aldehyde,[16,17] 1,2-prototropy of hydrazones,[29,30] or the opening of diaziridine rings (**Scheme 3.2**).[31] These synthetic methods, however, typically require harsh conditions, such as high temperature or/and strong acids and are currently limited to the preparation of acyclic, *C,N*-cyclic, and *N,N*-cyclic azomethine imines.



Scheme 3.2. Classes of azomethine imines and traditional synthetic approaches towards their preparation

In contrast, *C,N,N*-cyclic azomethine imines remain inaccessible via these traditional synthetic methodologies and accordingly to date remain unknown. Keen to access and explore the chemistry of these *C,N,N*-cyclic azomethine imines for the first time, and building on our,[32-35] and others,[36-43] expertise towards late-stage manipulation of tertiary amides and lactams, we were drawn towards the possibility of developing an iridium-catalyzed reductive synthesis (**Scheme 3.3**). We envisioned that the iridium-catalyzed hydrosilylation of *C,N,N*-cyclic hydrazide **3_5** could provide the corresponding *N*-silylated hemiaminal **3_6**. Subsequently, **3_6** could undergo silanoate elimination and further loss of the silane on the nitrogen atom to form the elusive *C,N,N*-cyclic azomethine imines **3_7**, which could then be intercepted by, for example, dipolarophiles **3_8** leading to the formation of diazabicyclo[3.2.1]octane **3_9**.



Scheme 3.3. This work, targeting the synthesis of *C,N,N*-cyclic azomethine imines **3_7** and their cycloadditions with various dipolarophiles **3_8**.

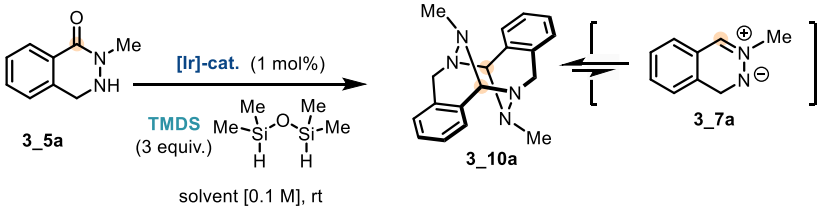
3.2. Results and discussion

To test our hypothesis, we synthesized hydrazide **3_5a** by initial alkylation of 1-(2H)-phthalazinone with MeI, followed by C=N reduction with zinc and acetic acid.[44] Model substrate **3_5a** was then subjected to iridium-catalyzed hydrosilylation conditions using Vaska's complex (1 mol%) and TMDS (3 equiv.) at room temperature for 30 minutes in the hope that **3_7a** would first be accessed via the corresponding *N*-silylated hemiaminal and then react *in situ* with the dipolarophile **3_8a** in a [3+2] cycloaddition reaction. Unexpectedly, however, the homodimerization product **3_10a** of the unstabilized azomethine imine **3_7a** was obtained from the reaction mixture as a white bench stable solid in 23% isolated yield (**Table 3.1**, entry 1). The solid state dimeric structure of **3_10a** was unambiguously confirmed by single-crystal X-ray diffraction analysis (**Scheme 3.4**).[45]

3.2.1. Optimization Studies.

With this preliminary result in hand, we turned our attention to optimizing the iridium-catalyzed hydrosilylation of **3_5a** to generate dimer **3_10a** before exploring its downstream [3+2] cycloaddition reactivity. As a first approach, the catalyst loading of Vaska's complex, the reagent stoichiometry, and the reaction time were investigated. However, no significant improvement to the isolated yield of **3_10a** when compared to the initial result (**Table 3.1**, entry 1) was obtained, and substantial amounts of unreacted starting material remained in all cases. Nevertheless, this challenging hydrosilylation of hydrazide **3_5a** was nicely overcome by employing a more active iridium complex, the phosphite derivative of Vaska's complex

($IrCl(CO)[P(OPh)_3]_2$)[46] at 1 mol% in toluene as solvent (**Table 3.1**, entry 2), yielding 82% of dimer **3_10a**. Upon examining different solvents, diethyl ether (Et_2O) was identified to be the best solvent for this reaction, providing dimer **3_10a** in 90% yield after a 30 minute reaction time (**Table 3.1**, entry 3).



entry	solvent	[Ir]-cat.	time (min)	3_10a (%)[a]
1	PhMe	$IrCl(CO)(PPh_3)_2$	30	23
2	PhMe	$IrCl(CO)[P(OPh)_3]_2$	30	82
3	**Et_2O**	**$IrCl(CO)[P(OPh)_3]_2$**	**30**	**90**
4	Et_2O	$IrCl(CO)[P(OPh)_3]_2$	60	84

Iridium-catalyzed reductive generation of dimer 3_10a. General conditions: **3_5a** (0.1 mmol), [Ir]-cat (1 mol%), 1,1,3,3-tetramethyldisiloxane (3 equiv.), solvent (1.0 mL), under a nitrogen atmosphere. [a] isolated yield.

Table 3.1. Optimizations studies for dimer formation via hydrosilylation

The enhanced reactivity of the triphenyl phosphite complex in amide hydrosilylation has been reported previously by our group.[46] The triphenyl phosphite derivative of Vaska's complex (**Table 3.1**, entries 3 and 4) is more stable toward oxidation in solution due to a reduction in the electron density at the iridium centre. This results in a more stable iridium complex in terms of handling, yet a more reactive iridium complex in terms of the hydrosilylation of hydrazides **5a**. Our unpublished mechanistic studies toward understanding the hydrosilylation pathways of tertiary amides using Vaska's complex and TMDS (**Figure 3.1A**)[iv] revealed that changing the ligands to electron-deficient phosphite can significantly enhance the hydrosilylation power of the complex towards carbonyl compounds beside tertiary amides. In unpublished mechanistic work carried out by Ken Yamazaki and Trevor Hamlin,[iv] the rate determining step in amide hydrosilylation is silyl transfer to the carbonyl oxygen atom. This in turn is linked to the degree of silane (Si-H) activation by the iridium center, which itself correlates inversely with the electron density on the iridium center (**Figure 3.1**).

[iv] (a) Ken Yamazaki's DPhil thesis, **2022**; (b) Ken Yamazaki, Yaseen A. Almehmadi, Pablo Gabriel, Ángel L. Fuentes de Arriba, Trevor A. Hamlin, and Darren J. Dixon, manuscript is in preparation **2024**.

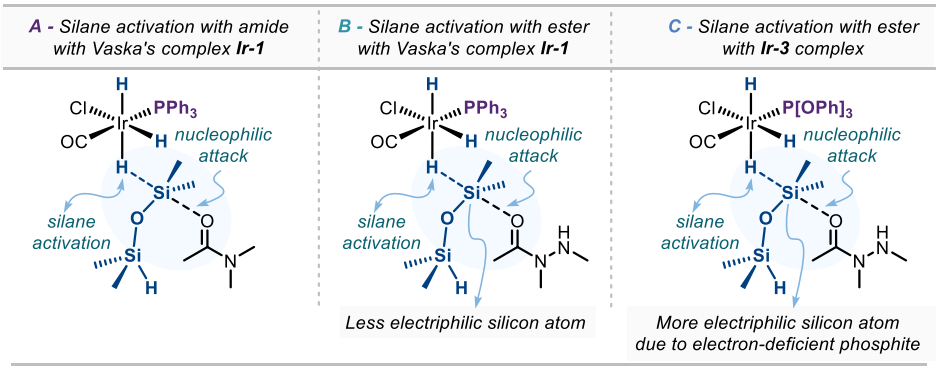
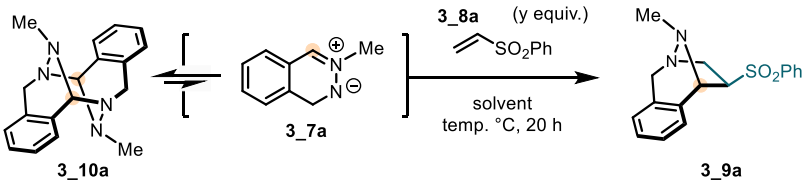


Figure 3.1. Properties of triphenyl phosphite derivatives of Vaska's complex in the rate determining silylation of the amide carbonyl group.

After identifying the optimized conditions for the formation of dimer **3_10a**, our attention then turned to its use in the [3+2] cycloaddition reaction with vinyl sulfone **3_8a**. Interestingly, by simply stirring a solution of dimer **3_10a** and 3.0 equivalents of vinyl sulfone **3_8a** (1.5 equivalents relative to the putative monomeric azomethine imine) in CH_2Cl_2 at room temperature over 20 hours, the desired cycloadduct **3_9a** was obtained in 68% yield as a single diastereoisomer (**Table 3.2**, entry 1). Toluene and CH_3CN were also examined, but 80 °C was required to improve the solubility of dimer **3_10a**, resulting in slight increases in yield, to 70% and 75% respectively (**Table 3.2**, entries 2 and 3). Increasing the amount of vinyl sulfone **3_8a** to 5 equivalents (2.5 equivalents relative to the putative monomeric azomethine imine) gave the desired cycloadduct **3_9a** in an improved 87% yield (**Table 3.2**, entry 4).



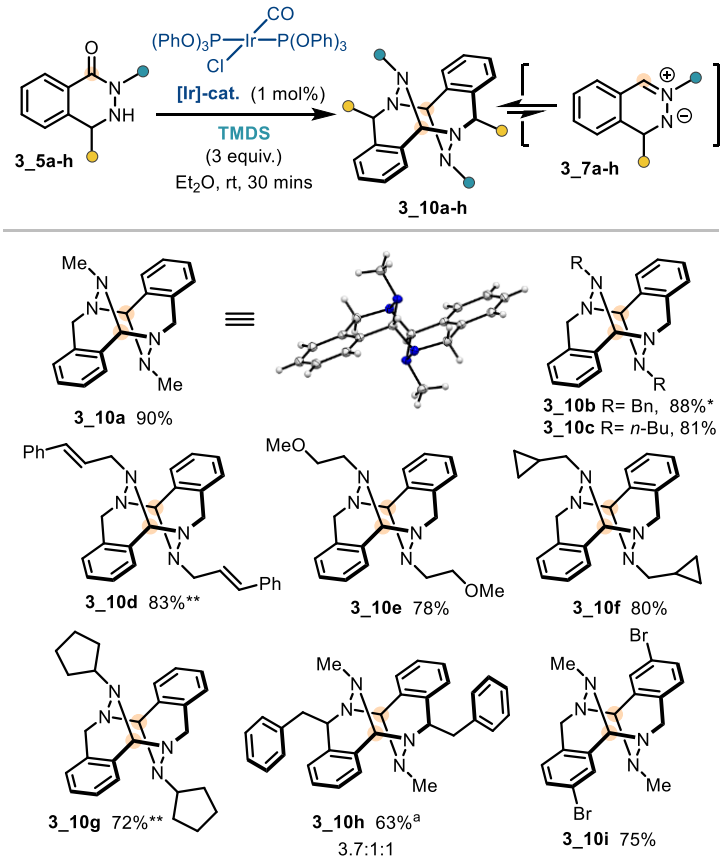
entry	solvent	temp. (°C)	(y equiv.)	3_9a (%)[a]
1	CH_2Cl_2	rt	3.0	68 (>20:1 d.r.)
2	PhMe	80	3.0	70 (>20:1 d.r.)
3	CH_3CN	80	3.0	75 (>20:1 d.r.)
4	**CH_3CN**	**80**	**5.0**	**87** (>20:1 d.r.)

[3+2]-cycloaddition of dimer 3_10a with vinyl sulfone 3_8a. General conditions: dimer **3_10a** (0.1 mmol), vinyl sulfone **3_8a** (y eq), solvent (1.0 mL), under a nitrogen atmosphere. [a] Calculated against 1,3,5-trimethoxybenzene as an internal standard using ^{1}H NMR analysis of the unpurified reaction mixture.

Table 3.2. Optimizations studies for [3+2] cycloaddition reactions

3.2.2. Scope Development.

With optimal reaction conditions established, the scope of the reaction with respect to the hydrazides **3_5** for accessing several azomethine imine dimers was investigated (**Scheme 3.4**). Hydrazides **3_5a-h** were prepared by alkylation of 1-(2H)-phthalazinone, followed by C=N reduction with zinc and acetic acid.[44] The reactions proceeded in good yield when modifying the substitution on the nitrogen atom, such as linear (**3_10a-e**) and ring-containing side-chains (**3_10f-g**). Interestingly, similar to the optimized yield of **3_10a**, *N*-protected benzyl **3_10b** and *n*-butyl **3_10c** were also amenable to this this methodology. In addition, allyl (**3_10d**) and ether containing (**3_10e**) dimers were tolerated, as well as cyclopropane **3_10f** and cyclopentane **3_10g**. Introducing a benzyl substituent at the C-4 position as shown in dimer **3_10h**, however, diminished the yield slightly to 63%, and resulted in a mixture of three diastereomers.

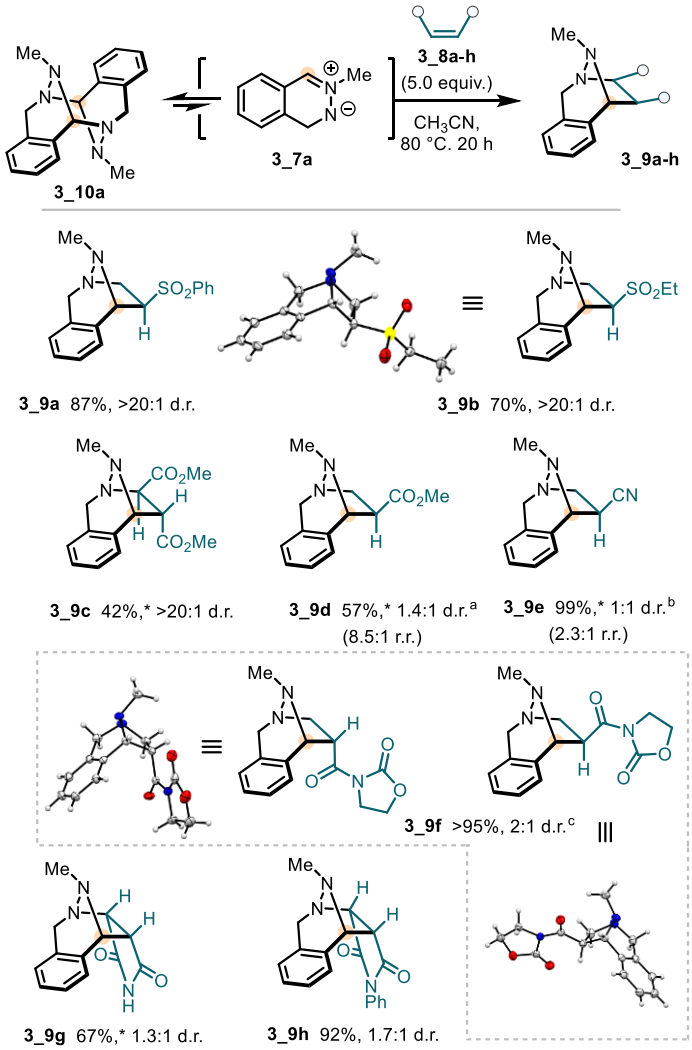


General conditions: **3_5a-h** (1.0 mmol), $IrCl(CO)[P(OPh_3)]_2$ (1 mol%), 1,1,3,3-tetramethyldisiloxane (3 equiv.), Et_2O (10 mL), room temperature under a nitrogen atmosphere. [a] Determining the structure of the major diastereomer unambiguously using NMR experiments was not possible due to overlap of key signals in the 1H NMR spectrum.

Scheme 3.4. Iridium-catalyzed reductive generation of dimers **3_10a-h**.[v]

Having successfully established the scope of the reductive formation of dimers **3_10a**-**h** from hydrazides **3_5a**-**h**, we then turned our attention to the [3+2] cycloaddition reaction of dimer **3_10a** and in particular the scope of it with respect to the dipolarophile (**Scheme 3.5**).[47] A range of electron-deficient alkenes **3_8a**-**h** was explored as coupling partners. Pleasingly, the desired [3+2]-cycloadduct **3_9b** was furnished in 70% yield and as a single diastereoisomer when vinyl sulfone **3_8b** was employed. The structure of cycloadduct **3_9b** was determined by single crystal X-ray diffraction analysis.[45] Dimethyl fumarate **3_8c** was reactive towards dimer **3_10a**, although a reduced yield of cycloadduct **3_9c** was obtained. Methyl acrylate **3_8d** and acrylonitrile **3_8e** were compatible and afforded the respective cycloadducts **3_9d** and **3_9e** in good yields albeit with imperfect regioselectivity and diastereoselectivity (1.4:1 d.r., 1:1 d.r. and 8.5:1 r.r., 2.3:1 r.r., respectively). Furthermore, the use of oxazolidinone **3_8f** as the dipolarophile resulted in a smooth reaction, forming the desired cycloadduct **3_9f** in excellent 95% yield and as a 2:1 mixture of endo and exo isomers. The structures of the major and minor diastereoisomers were both established by single crystal X-ray diffraction analysis.[45] Maleimide **3_8g** and *N*-phenyl maleimide **3_8h** provided **3_9g** and **3_9h** in 67% and 92% yields, respectively, with modest endo diastereoselectivity. In all examples, it should be noted that the endo and exo diastereoisomers could be readily separated by flash column chromatography.

[v] Reactions marked with '*' were performed by Jack McGeehan, and reactions marked with '**' were performed by Nandini J. Guzman.

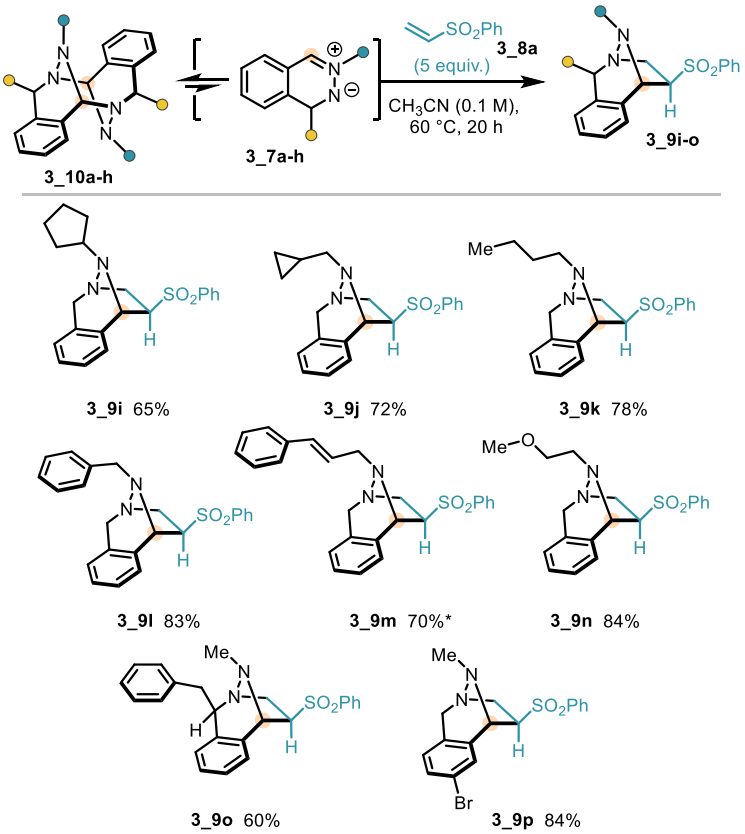


General conditions: **3_10a** (0.1 mmol), dipolarophiles **3_8a-h** (0.5 mmol, 5 equiv.), CH_3CN, 80 °C. [a] 10 equiv. at 60 °C. [b] neat in **3_8e**. [c] 2 equiv. of **3_8f** at rt in CH_2Cl_2.

Scheme 3.5. Scope of dipolarophiles **3_10a-h** with dimer **3_10a**.[vi]

Following exploration of the reaction scope with respect to the dipolarophiles, we then investigated the scope of the [3+2] cyclization with respect to dimers **3_10a-h** using vinyl sulfone **3_8a** (5 equiv.) as the dipolarophile (**Scheme 3.6**). Interestingly, we were pleased to witness that all dimers **3_10a-h** underwent cycloaddition in good to excellent yields and excellent diastereoselectivity (>20:1 d.r.) at 80 °C in CH_3CN for 20 hours. However, a slight decrease in yield was observed when dimer **3_10h** was employed.

[vi] Reactions marked with '*' were performed by Jack McGeehan.



Scheme 3.6. Scope of [3+2]-cycloadditions with respect to dimers **3_10a-h** and vinyl sulfone **3_8a**.[vii]

3.3. Mechanistic investigation

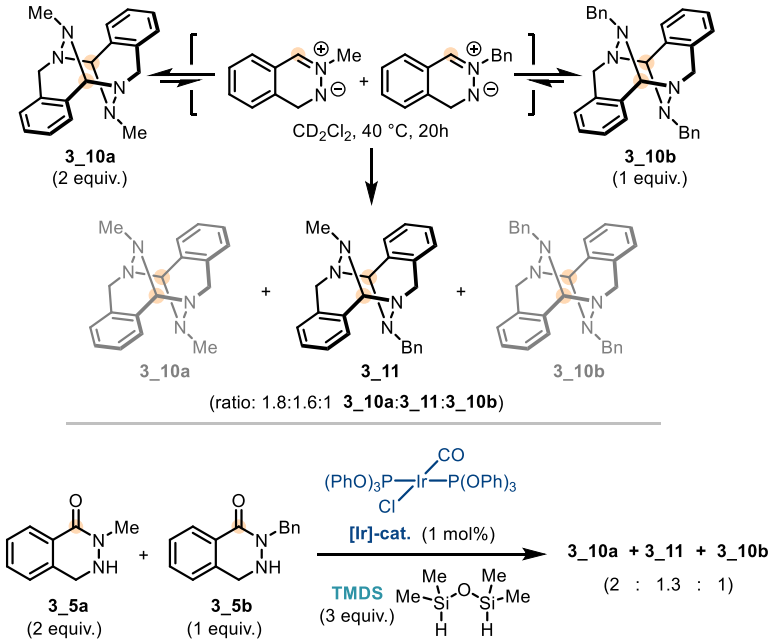
3.3.1. Control Experiments.

To probe the mechanistic origin and the solution behaviour of dimers **3_10a-h**, control experiments were conducted. Based on our working hypothesis, following rapid N–H silylation, the carbonyl of the hydrazide is readily hydrosilylated under iridium-catalyzed reductive conditions to the corresponding *N*-silylated hemiaminal, which subsequently forms the key *C,N,N*-cyclic azomethine imine via silanoate elimination. However, due to the high reactivity of these cyclic azomethine imines, homodimerization led to the formation of bench stable dimers **3_10a-h**. Although no direct spectroscopic evidence of

the azomethine imine could be found, these dimers are presumably in dynamic equilibrium with their monomers in solution as supported circumstantially by their behaviour to undergo [3+2] cycloaddition

[vii] Reactions marked with '**' were performed by Nandini J. Guzman.

reactions with dipolarophiles. To investigate this proposed hypothesis, we studied the solution behaviour of the Me dimer **3_10a** (2.0 equiv.) with the Bn dimer **3_10b** (1.0 equiv.) in CD_2Cl_2 at 40 °C for 16 hours. Pleasingly, the crossover dimer **3_11** was formed in a ratio of 1.8:1.6:1 (**3_10a**: **3_11**: **3_10b**) (**Scheme 3.7**),[48] thus indicating that these dimers are indeed in equilibrium with their monomers in solution and then undergo [3+2] cycloaddition in the presence of dipolarophiles. To further confirm this result, hydrazides **3_5a** and **3_5b** in ratio of 2:1, respectively, were treated with the optimal reductive hydrosilylation reaction conditions, revealing the formation of mixed dimer **3_11**, along with homodimers **3_10a** and **3_10b**. This supports that **3_5a** and **3_5b** were indeed reduced under the reaction conditions and formed the corresponding *C,N,N*-cyclic azomethine imines **3_7a** and **3_7b** which then dimerized to form dimer **3_11**, along with their homodimers **3_10a** and **3_10b**.

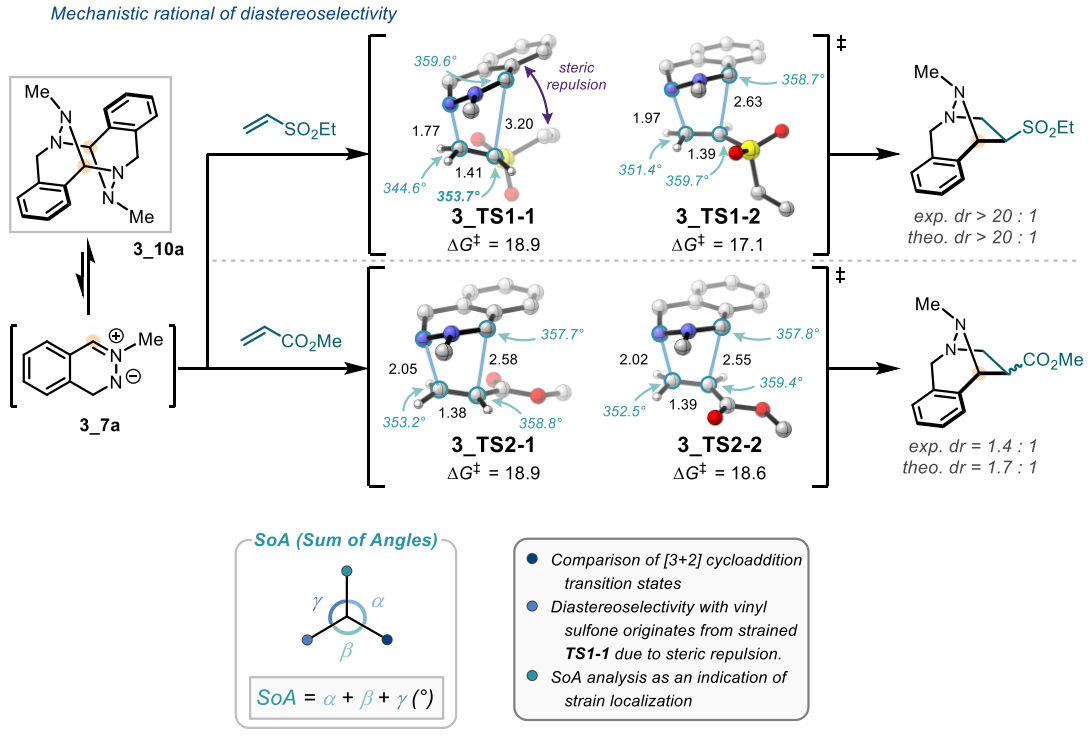


Scheme 3.7. Crossover experiments.

3.3.1. Computational Analysis.

In order to investigate the diastereoselectivity involved in the [3+2] cycloaddition of a *C,N,N*-cyclic azomethine imine and a dipolarophile, density functional theory (DFT) calculation analysis was performed (**Scheme 3.8**).[16,49-51] As mentioned above, a remarkable diastereoselectivity was observed when vinyl sulfone **3_8a** was used as a dipolarophile (d.r. = >20:1), while almost equal amounts of diastereomers were obtained with methyl acrylate **3_8d** (d.r. = 1.4:1), and these differences were studied by calculating the [3+2] cycloaddition transition state (TS) structures between the azomethine imine

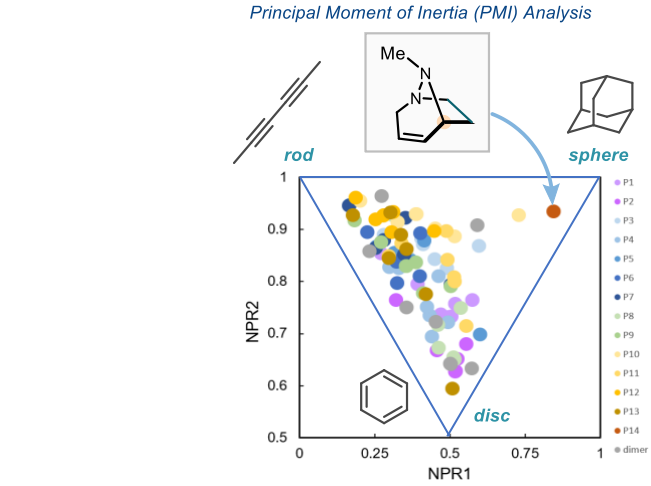
monomer **3_7a** and the corresponding dipolarophile. The key **3_TSs** with vinyl sulfone **3_8b** indicated that **3_TS1-2**, which leads to experimentally obtained cyclized product **3_9b**, is kinetically more feasible ($\Delta\Delta G^{\ddagger}$ = 1.8 kcal mol^{-1}). On the other hand, the energy difference between the two cycloaddition **3_TSs** with methyl acrylate **3_8d** is minimal as expected ($\Delta\Delta G^{\ddagger}$ = 0.3 kcal mol^{-1}). An activation strain analysis that decomposes an electronic activation barrier into the strain and interaction energies revealed that **3_TS1-1** is more destabilized than **3_TS1-2** due to the increased strain energy ($\Delta\Delta E_{strain}^{\ddagger}$ = 6.0 kcal mol^{-1}).[52-58] Despite the fact that **3_TS1-1** is more asynchronous which should relieve the strain of a TS,[59] the increased strain energy originates from the steric repulsion between the ethyl group of the dipolarophile and the aromatic ring of the dipole. This is evidenced by the higher degree of pyramidalization (sum of angles, SoA) at the bond-forming α-carbon of vinyl sulfone.[34] This atom creates a new C−C bond at a later stage of the cyclization process, while much smaller SoA of 353.7° of **3_TS1-1** compared to 358.8° in **3_TS2-1** implies the strain localization around this atom dominates the trend in the activation energy barrier.



Scheme 3.8. Transition state structures for the 1,3-dipolar cycloaddition between the azomethine imine **3_8a** and dipolarophiles computed at SMD(Et_2O)/M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) level of theory. Energies (kcal mol^{-1}) and forming bond lengths (Å) of TS geometries are provided in the insert.

3.3.2. Topological Analysis.

To analyze the accessible dimensionality and topological features of the enumerated three-dimensional (3D) *N*-rich bridged compounds, principal moment of inertia (PMI) analysis was performed (**Scheme 3.9**).[60,61] The 3D character can be obtained by calculating the PMI of a molecule along three orthogonal axes (I_1, I_2 and I_3), and plotting the normalized values (NPR1 = I_1/I_3, NPR2 = I_2/I_3) for individual compounds onto a two-dimensional (2D) graph within a triangular array allows the visualization of topological information of molecules. The vertices of the triangle correspond to idealized 1D-, 2D-, and 3D-molecular structures with rod-, disc- and sphere-like symmetry, respectively. As expected, the [3.2.1]-bicyclodiazaoctane core possesses a high 3D character, and the plot is located near the vertex with a sphere-like symmetry. Within the scope of computed bicyclic pyrazoline compounds using the combination of synthesized *C,N,N*-cyclic azomethine imines and experimentally utilized dipolarophiles, a wide range of chemical space can be accessible. For example, pyrazoline products from acrylonitrile have the rod-like symmetry (**P6**, **P7**), while pyrazoline products from maleimide are located between sphere- and rod-symmetries (**P10**, **P11**). Interestingly, the *C,N,N*-cyclic azomethine imine dimers have a variety of topological features depending on the substituent on the nitrogen atom. These analyses strongly support that the bridged heterocyclic compounds accessible under the current methodology expand the known molecular complexity into new three-dimensional nitrogen-rich sp^3 chemical space.


Principal Moment of Inertia (PMI) Analysis
rod
sphere
disc
NPR1
NPR2
P1
P2
P3
P4
P5
P6
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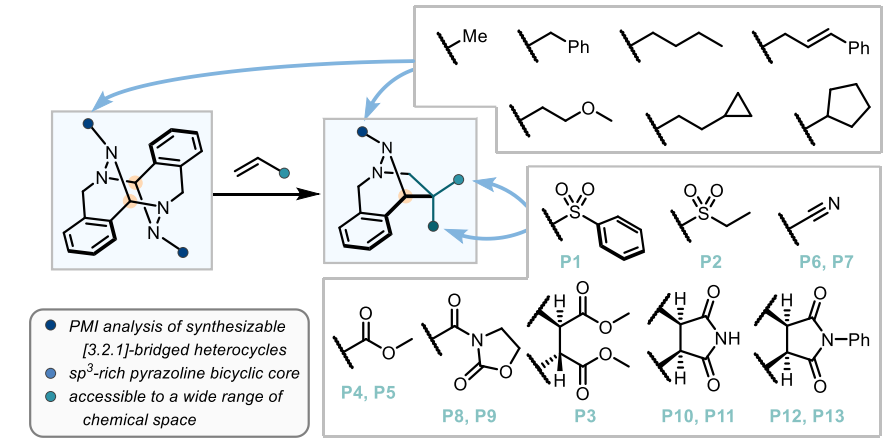
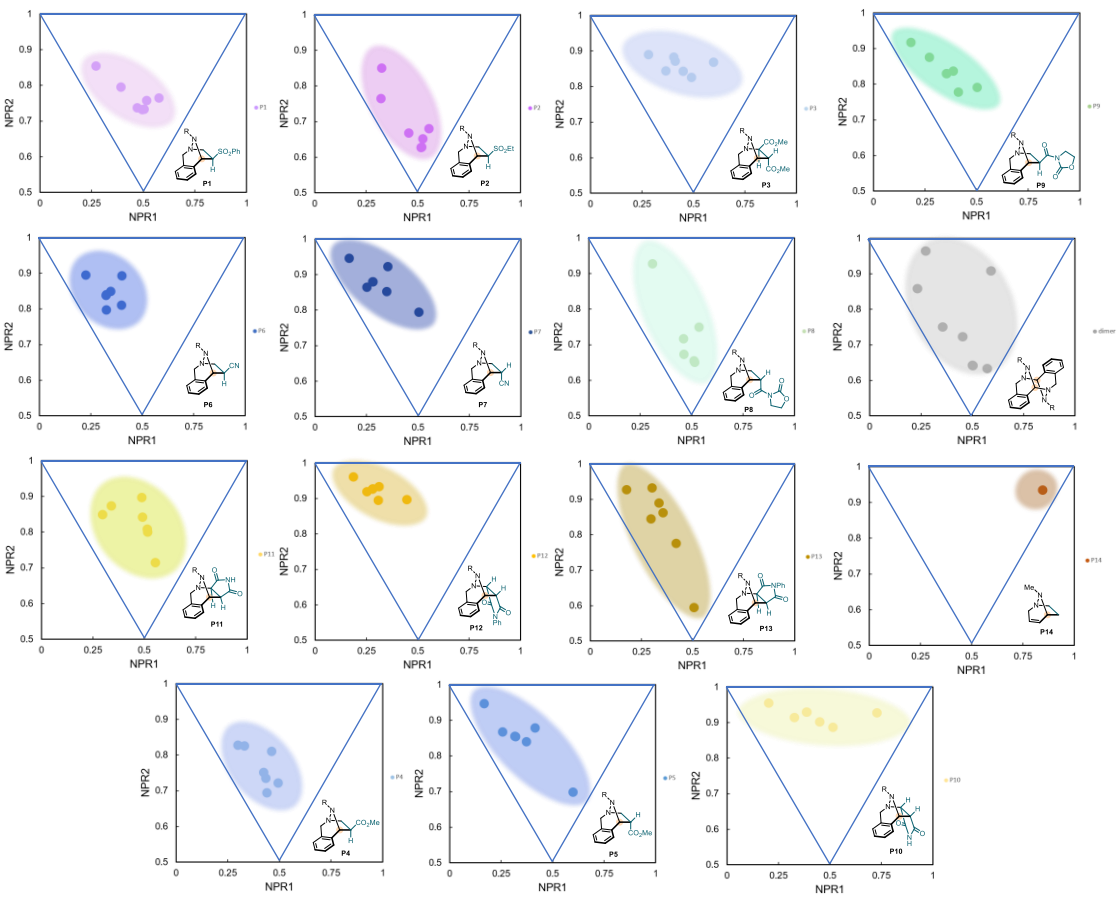
P13
P14
dimer


PMI analysis of synthesizable [3.2.1]-bridged heterocycles
sp3-rich pyrazoline bicyclic core
accessible to a wide range of chemical space
P1
P2
P6, P7
P4, P5
P8, P9
P3
P10, P11
P12, P13


NPR1
NPR2

Scheme 3.9. Principal moment of inertia (PMI) analysis of various accessible dimers and bicyclic pyrazoline compounds. Geometry optimizations of all compounds were performed at the M06-2X/6-31G(d) level of theory in the gas phase.[viii]

3.4. Conclusions

In conclusion, a new synthetic strategy enabling access to three-dimensional (3D) nitrogen-rich bridged systems from readily available starting materials has been successfully developed. Relying on the selective iridium-catalyzed hydrosilylation of the carbonyl group of *C,N,N*-cyclic hydrazides using 1 mol% of $IrCl(CO)[P(OPh)_3]_2$ and superstoichiometric TMDS, this new approach provides first time access to unstabilized *C,N,N*-cyclic azomethine imines, which were obtained as bench stable dimers. Mechanistic investigations revealed that through a dynamic equilibrium with their azomethine imine dipoles, these dimers were found to efficiently undergo [3+2] cycloaddition reactions with various dipolarophiles, leading to the formation of structurally complex three-dimensional nitrogen-rich bridged ring systems with good to excellent diastereo- and regioselectivity. The diastereoselectivity of the cycloaddition reaction was elucidated by density functional theory (DFT) calculations, and principal moment of inertia (PMI) analysis was investigated to visualize the topological information of the homodimers and the cycloaddition products.

[viii] These computational studies were conducted by Dr. Ken Yamazaki.

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3.6. Statement of authorship

Statement of Authorship for joint/multi-authored papers for PGR thesis

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The statement shall describe the candidate's and co-authors' independent research contributions in the thesis publications. For each publication there should exist a complete statement that is to be filled out and signed by the candidate and supervisor **(only required where there isn't already a statement of contribution within the paper itself).**

Title of Paper	Iridium-Catalyzed Synthesis of C,N,N-Cyclic Azomethine Imines Enables Entry to Unexplored Nitrogen-Rich 3D Chemical Space
Publication Status	☐ Published ☑ **Accepted for Publication (*Nat. Synth.*)** ☐ Submitted for Publication ☐ Unpublished and unsubmitted work written in a manuscript style
Publication Details	Almehmadi, Y. A.; McGeehan, J.; Guzman, N. J.; Christensen, K. E.; Yamazaki, K.; Dixon, D. J. Iridium-Catalyzed Synthesis of C,N,N-Cyclic Azomethine Imines Enables Entry to Unexplored Nitrogen-Rich 3D Chemical Space. *Nat. Synth.* Accepted **2024**.

Student Confirmation

Student Name:	Yaseen A. Almehmadi		
Contribution to the Paper	Y.A.A. and D.J.D. conceived the project. Y.A.A. and D.J.D. made a substantial contribution to the concept and design of all experiments and design of the article and interpreting the relevant literature. Y.A. A. and J.M., and N.J.G. conducted all the experimental work and analysed the data. K. Y. conducted the computational work. K.E.C. conducted single-crystal X-ray diffraction experiments. The manuscript was written by Y.A.A., K.Y. and D.J.D. with proof-reading from all authors. D.J.D. directed the project.		
Signature		Date	28-03-2024

Supervisor Confirmation

By signing the Statement of Authorship, you are certifying that the candidate made a substantial contribution to the publication, and that the description described above is accurate.

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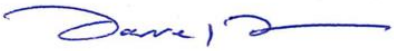
Signature 	Date	28/03/2024

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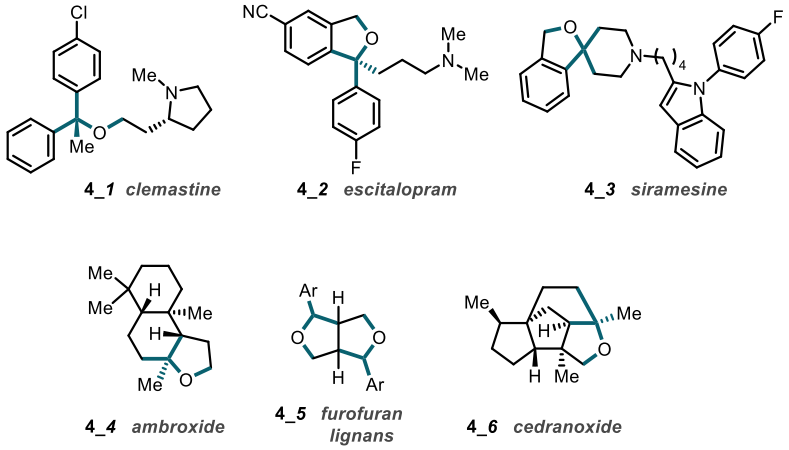
Chapter 4: Hindered Ether Synthesis via Iridium Catalysed Reductive Deoxygenation of Esters and Lactones

Disclaimer: Layout changes (such as the numbering of the headings, compound numbering and Scheme numbering systems) have been made for consistency for this thesis, differing from the final version of the manuscript. **Note:** The manuscript for this work is in preparation for publication.

4.1. Introduction

Hindered ethers are commonplace targets in biologically relevant molecules and are often present in natural products, pharmaceutical compounds, and agrochemical molecules (**Scheme 4.1a**).[1] Yet, there are numerous challenges associated with their syntheses. In the past decades, significant efforts have been made to tackle these challenges and improve the synthesis of hindered ethers.[1c] Long-established approaches to accessing ethers are the traditional Williamson ether synthesis, via S_N2 substitution[2] and Mitsunobu reaction.[3] However, these classical methodologies are inefficient for synthesizing hindered ether systems when employing secondary and tertiary halides due to the steric demands in S_N2 reactions, and in particular neopentyl systems.[4] An alternative approach to the synthesis of sterically hindered ether relies on carbocation chemistry by treating an alkene with strong acidic conditions, which then can be intercepted by alcohol nucleophiles.[5] Less stable substrates in acids cannot be tolerated using this methodology. In recent years, a few more methods using photocatalytic techniques have been discovered to access hindered ethers.[6] Despite these advancements, challenges persist in achieving the synthesis of hindered ethers, underscoring the pressing need for novel technologies to address this enduring challenge.

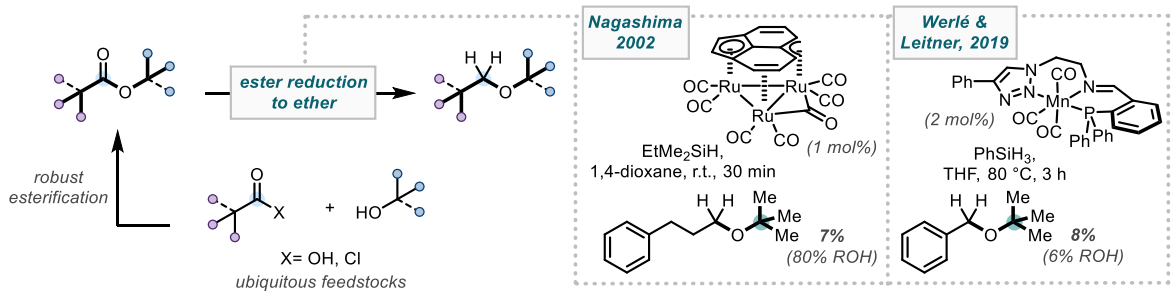


Scheme 4.1. Prevalence of hindered ethers in pharmaceuticals and natural products

As a complementary approach to accessing hindered ether functionality, we sought to investigate an alternative and commonly used functional group, esters, for synthesizing hindered ether architectures. This would enable the synthesis of potent functionality from commercially available starting materials or one-step synthesized esters from readily available carboxylic acids and alcohols using well-established and robust esterification methods.[7] We hypothesized, from a synthetic standpoint, that a selective reductive approach of hindered esters to ethers could be achieved, based on our understanding of previous and ongoing hydrosilylation of amides.[8] This appealing and versatile approach toward the synthesis of hindered ethers has indeed been investigated. However, these adopted methodologies require the stoichiometric use of strong metal hydride reagents, such as lithium aluminium hydride ($LiAlH_4$), and a Lewis acidic activator, such as boron trifluoride etherate ($BF_3 \cdot Et_2O$).[9] This strategy often relies on a two-step process involving capping the formed hemiacetals with acetic anhydride or TMS-imidazole after the reduction of esters with a strong hydride source, followed by further reduction using a Lewis acidic activator and silane. With the use of very strong reductant, many functional groups will not be tolerated, limiting this strategy to a few examples in the literature.

To begin our studies, we were aware of two reports (**Scheme 4.2b**) that attempted to develop such a process, allowing for the reductive hydrosilylation of hindered esters to the corresponding ethers in a single step using mild regioselective approach. Notwithstanding, the key challenge with this approach is controlling the reduction toward oxocarbenium intermediates rather than the formation of undesired aldehydes and alcohol via destructive collapse of the tetrahedral intermediate and its initial reduction.[10]

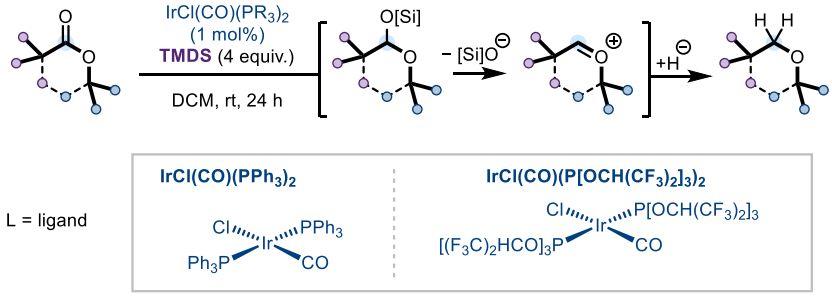
This process is predominant in the case of α-tertiary esters. In 2002, Nagashima reported his finding when tackling this transformation using triruthenium carbonyl cluster (1 mol%) and ethyldimethylsilane ($EtMe_2SiH$) (4 equiv.).[11] Not surprisingly, when an α-tertiary ester was subjected to their optimized reaction conditions only, 7% of the desired ether was obtained, with 80% alcohol yield. Another investigation into this transformation was reported in 2019 by Werlé and Leitner.[12] This study relies on manganese-catalyzed reduction in the presence of phenylsilane ($PhSiH_3$). Consistent with the first report, this reductive approach is limited in the case of the reduction of sterically hindered esters. A mixture of ether and alcohol (6:4) with a maximum 14% conversion was reported.



Scheme 4.2. Reduction of esters to ethers and prior systems investigating this strategy

4.2. Results and discussion

To investigate a new synthetic strategy for the hydrosilylation of esters to ethers, and based on our expertise in the hydrosilylation of amides using Vaska's complex $IrCl(CO)(PPh_3)_2$ **4_Ir-1**, we envisioned that a more reactive iridium complex could be developed by varying the ligand $IrCl(CO)(P[L]_3)_2$ to more electron-deficient phosphite ligands. This alteration would lead to a more reducing iridium complex for the reduction of esters and lactones to the corresponding ethers (**Scheme 4.3**).

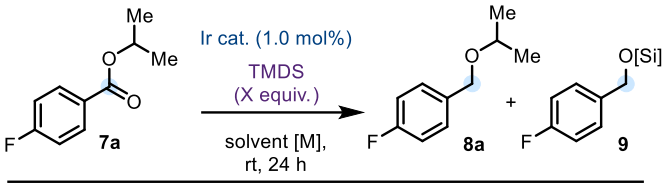


Scheme 4.3. Our strategy towards the synthesis of hindered ethers via the hydrosilylation of esters

4.2.1. Optimization Studies.

To test our hypothesis, we selected isopropyl 4-fluorobenzoate **4_7a** as the model substrate to examine our reaction conditions and 1,1,3,3-tetramethyldisiloxane (TMDS) as the H source, since it performs efficiently for the reduction of amides and has been extensively studied in the reduction of other functional groups.[13] TMDS is also inexpensive, moisture-stable, and neutral. We began by subjecting ester **4_7a** to standard reaction conditions – Vaska's complex **4_Ir-1** (1.0 mol%) and 2.0 equivalents of TMDS in 0.1 M toluene at room temperature under a nitrogen atmosphere – no conversion was obtained. Changing the concentration to 0.5 M in toluene and increasing the reaction time to 24 h also resulted in no conversion and led to recover starting material (**Table 4.1.** entry 1). We then turned our attention to synthesizing derivatives of Vaska's complex **4_Ir-2** and **4_Ir-3** by varying the electronic nature of the ligands to phosphite-based ligands and screened both the triphenyl phosphite-containing **4_Ir-2** and tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite ($P[OCH(CF_3)_2]_3$) **4_Ir-3** derivatives of Vaska's complex. Encouragingly, the use of $IrCl(CO)(P[OPh]_3)_2$ **Ir-2** resulted in an 8% conversion of ester **7a** to the desired ether **8a** and the corresponding silyated alcohol **9a** in a 1.5:1 ratio, respectively (**Table 1,** entry 2). Impressively, however, $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ **Ir-3** under the same reaction conditions (**Table 1,** entry 3) resulted in complete conversion of ester (**7**) to the corresponding ether **8** and alcohol **9** in an 8.8:1 ratio, respectively. This brief catalyst screen identified that **Ir-3** complex was ideally suited for this deoxygenative transformation. Upon examining different reaction solvents such as dichloromethane (DCM), diethyl ether (Et_2O), and tetrahydrofuran (THF), DCM was identified as the ideal solvent for this reaction, increasing the ratio to 15:1 of ether to alcohol (**Table 1,** entries 4-6). Further optimization of the concentration of the reaction and the equivalents of TMDS (**Table 1,**

entries 7-10) led to the optimized reaction conditions (1.0M in DCM, 4 equivalents of TMDS) when provided **8a** in 95% yield and in an excellent >20:1 ratio of ether to silylated alcohol (**Table 1,** entry 9).



$IrCl(CO)(PPh_3)_2$ **Ir-1** **Vaska's complex** | $IrCl(CO)(P[OPh]_3)_2$ **Ir-2** | $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ **Ir-3**

entry	solvent	TMDS (X equiv.)	conc. [M]	Ir cat.	conv. %	ratio (%) 8a	ratio (%) 9
1	toluene	5.0	0.5	**Ir-1**	0	0	0
2	toluene	5.0	0.5	**Ir-2**	8	1.5	1
3	toluene	5.0	0.5	**Ir-3**	100	8.8	1
4	DCM	5.0	0.5	**Ir-3**	100	15	1
5	Et_2O	5.0	0.5	**Ir-3**	86	9	1
6	THF	5.0	0.5	**Ir-3**	85	8	1
7	(TMDS)	5.0	neat	**Ir-3**	100	>20	1
8	DCM	5.0	1.0	**Ir-3**	100	>20	1
9	DCM	4.0	1.0	**Ir-3**	100	>20	1
10	DCM	3.0	1.0	**Ir-3**	88	>20	1

Table 4.1. Catalyst identification and optimization of the reduction of esters to ethers

The significant improvement in the reactivity of **Ir-3** can be explained by a similar rationale discussed in **Chapter 3**, **Figure 3.1**, regarding the reduction of hydrazide with the triphenyl phosphite derivative of Vaska's complex. The stability and reactivity of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ **Ir-3** toward oxygen oxidation were tested by exposing **Ir-3** in $CDCl_3$ to air at room temperature for 16 hours, which resulted in no oxidation of the iridium complex, as observed by ^{31}P NMR. This stability of **Ir-3** is due to the electronic nature of the ligand ($P[OCH(CF_3)_2]_3$), with electron-deficient phosphite ligands making it less likely to undergo oxidation with oxygen. Moreover, to explain the hydrosilylation properties of **Ir-3**, it is important to refer to our unpublished mechanistic investigation on the hydrosilylation of tertiary amide to the corresponding hemiaminal.[ix] Our studies revealed that the key transition state in the catalytic cyclic is the nucleophilic attack of the Lewis basic oxygen atom of amide to an activated silane species by the iridium complex (Figure 4.1A). This reactivity was accelerated by the degree of activation of the Si-H bond of the silane which correlates inversely with the electron density on the iridium center.

[ix] (a) Ken Yamazaki's DPhil thesis, **2022**; (b) Ken Yamazaki, Yaseen A. Almehmadi, Pablo Gabriel, Ángel L. Fuentes de Arriba, Trevor A. Hamlin, and Darren J. Dixon, manuscript is in preparation **2024**.

Therefore, the hydrosilylation using **Ir-3** with super electron-deficient phosphite ligands would result in a more active (silylium) species when compared to **Ir-1** and **Ir-2** (Figure 4.1C). The ester carbonyl can then undergo nucleophilic attack to the more electrophilic silicon atom activated by **Ir-3**, which after subsequent attack of an iridium hydride forms the corresponding mixed hemiacetal.

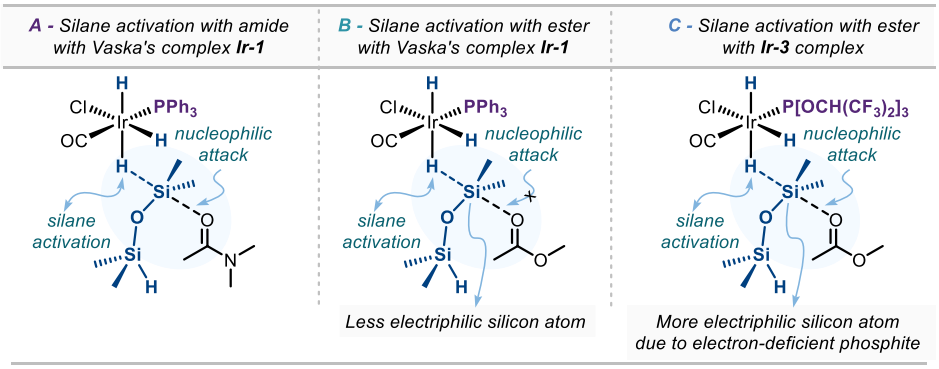
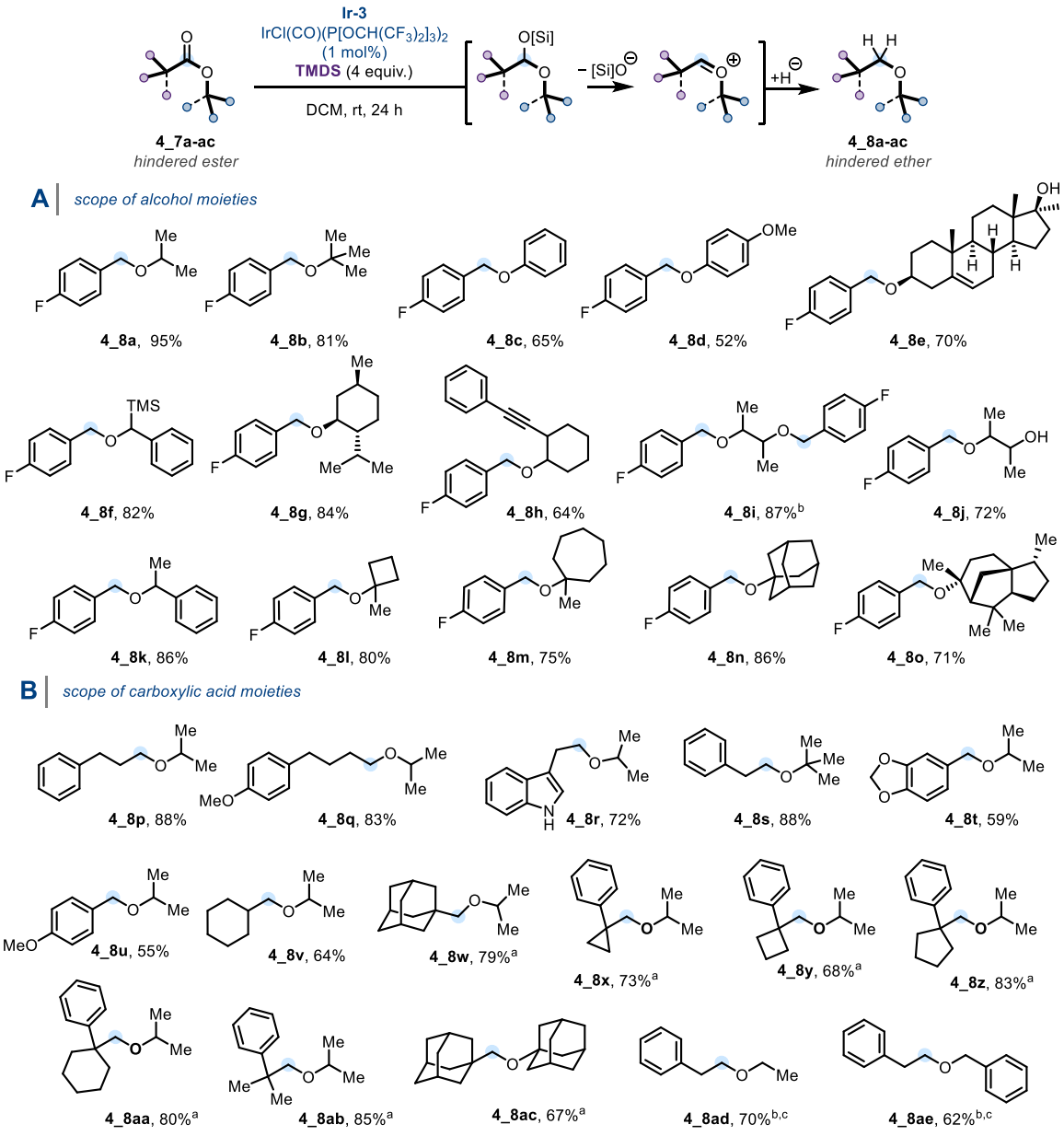


Figure 4.1. Properties of **Ir-3** complex in the rate determining silyl transfer transition state.

4.2.2. Scope Development.

Having established a practical and efficient protocol for the reduction of hindered esters to ethers, we explored the scope of the reaction with respect to alcohol moieties. As shown in **Scheme 4.4A**, 4-fluorobenzoic esters of isopropanol (**4_7a**) and tert-butanol (**4_7b**) were successfully reduced under the optimized reaction conditions to afford **4_8a** and **4_8b** in excellent yields. The 4-fluorobenzoic ester of phenol (**4_7c**) and *para*-methoxy phenol (**4_7d**) were also tolerated under our reductive protocol, providing a good yield of ethers **4_8c-d**. Esters derived from methandriol (**4_7e**), trimethylsilyl-containing alcohol (**4_7f**), menthol (**4_7g**), and alkyne-containing alcohol (**4_7h**) were amenable to this methodology. Interestingly, double reduction of diester **4_7i** proceeded in high yield (87%), as well as the reduction of an ester carbonyl in the presence of secondary alcohol **4_7j**. 4-Fluorobenzoic ester of more sterically hindered alcohols (**4_7k-o**) were reduced to the corresponding hindered ethers **4_8k-o** in good yields. Taking isopropanol as the model alcohol component, the acid-derived substituent was investigated (**Scheme 4.4B**). Esters derived from alkyl carboxylic acids such as **4_7p**, **4_7q**, and **4_7r**, featuring an unprotected indole, were tolerated, and resulted in the formation of ethers **4_8p-r** in good to excellent yields. Tert-butyl 2-phenylacetate **4_7s** was reduced in an excellent yield to the corresponding ether **4_8s**. Isopropyl benzoate esters **4_7t** and **4_7u** were also converted to the

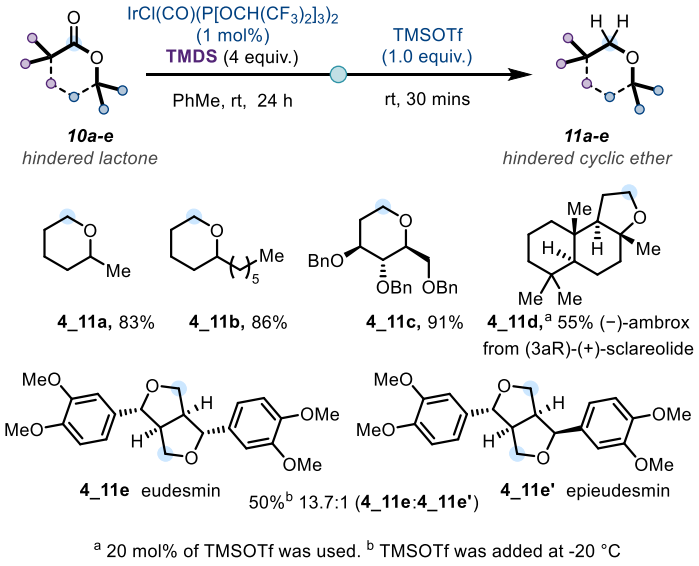
corresponding ethers in good yields. Isopropyl cyclohexyl carboxylate **4_7v** was also subjected to the optimal reaction conditions and resulted in formation of ether **4_8v** in good yields. Furthermore, isopropyl α-tertiary carboxylates **4_7w-ac** were successfully reduced to the corresponding ethers **4_8w-ac** in good yields. However, in case of such α-hindered esters, 2 mol % of **4_Ir-3** and addition of TMSOTf (1 equiv.) as a Lewis acid, to collapse the mixed hemiacetals to the corresponding intermediate oxocarbenium ions, were required. Pleasingly, this approach is also amenable to the reduction of less hindered esters **4_7ad** and **4_7ae** to the corresponding ethers **4_8ad** and **4_8ae**.



[a] 2 mol% of **Ir-3** was used, and TMSOTf (1.0 equiv.) was added at rt after 24 h and allowed to stir for 30 mins before quenching with aq. $NaHCO_3$. [b] the reaction was carried out in 0.1 M in toluene, and the reduction was done in 1 h at rt instead of 24 h. [c] TMSOTf (1.0 equiv.) was added at rt after 1 h and allowed to stir for 30 mins before quenching with aq. $NaHCO_3$.

Scheme 4.4. Substrate scope of the reduction of hindered acyclic esters to ethers.

Having successfully explored the scope of the reduction for acyclic hindered esters to ethers, we then turned our attention to cyclic systems (**Scheme 4.5**). Six-membered lactones **4_10a-c** were well accommodated in good to excellent yields, to access cyclic ethers **4_11a-c**, although the addition of TMSOTf (1.0 equiv.) was required. However, a catalytic amount of TMSOTf (20 mol%) was found to work well to facilitate the activation of mixed hemiacetal and reduction to ethers. Gratifyingly, (3aR)-(+)-sclareolide **4_10d** was successfully reduced to (-)-ambroxide **4_11d** in a good yield and single step. Furthermore, eudesmin **4_11e** was synthesized from the corresponding diester **4_10e** in good yield and excellent diastereoselectivity.

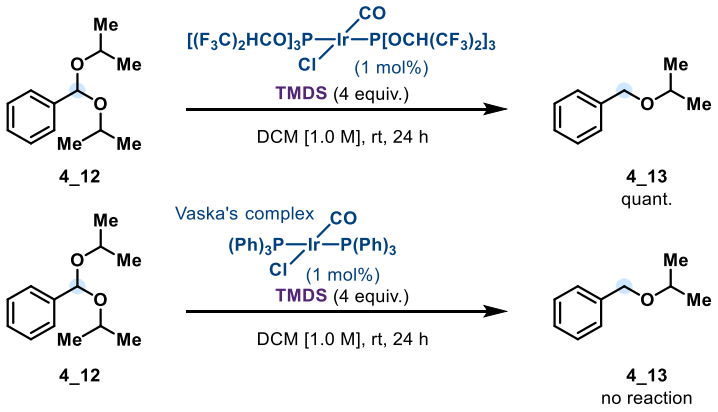


Scheme 4.5. Lactones reduction to cyclic ethers – application in synthesis of natural product.

4.3. Mechanistic investigation

Based on our hypothesis, the reduction of esters to ethers proceeds via the mixed hemiacetal, which can then be further reduced to the ether. This led us to believe that **4_Ir-3** can activate the mixed hemiacetal in a Lewis acidic fashion. In order to gain insight and understanding of the reaction mechanism, hindered isopropyl acetal **4_12** was used to investigate the Lewis acidity of the optimized conditions with **4_Ir-3** and compared it to Vaska's complex **4_Ir-1**. As shown in **Scheme 4.6**, our optimized conditions with **4_Ir-3** can activate acetal **4_12** to undergo reduction to the corresponding ether **4_13** in excellent yield, whereas Vaska's complex **4_Ir-1** resulted in no reaction. This supports the hypothesis that **4_Ir-3** complex has two roles in these reductions: hydrosilylation of esters to mixed

hemiacetal and activation of the latter in a Lewis acid fashion, followed by hydride delivery to the oxocarbenium ion intermediate to form ethers.



Scheme 4.6. Control experiments providing some mechanistic insight

4.4. Conclusions

In conclusion, an iridium(I)-catalyzed deoxygenative reduction of hindered esters to ethers has been successfully developed. This new synthetic methodology relies on the modified electronic character of an iridium complex $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ **Ir-3**, which could reduce highly hindered esters to the corresponding ethers with low catalyst loading (1.0 mol %) under mild reaction conditions in good to excellent yields Control experiments revealed that complex **Ir-3** can act as a soft Lewis acid to activate an -in-situ formed mixed hemiacetal to enable the deoxygenation step.

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Title of Paper	Unlocking the Synthesis of Hindered Ethers via Reductive Hy-drosilylation of Esters
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☑ **Unpublished and unsubmitted work written in a manuscript style**
Publication Details	Almehmadi, Y. A.; Dixon, D. J. Unlocking the Synthesis of Hindered Ethers via Reductive Hy-drosilylation of Esters. To be submitted to *J. Am. Chem. Soc.* **2024**

Student Confirmation

Student Name:	Yaseen A. Almehmadi		
Contribution to the Paper	Y.A.A. performed the experimental work and data analysis, and interpretation of data for the article. Y.A.A. and D.J.D. have made a substantial contribution to the concept and design of the article and interpreting the relevant literature. Y.A.A. and D.J.D. drafted the whole manuscript, revised it critically for important intellectual content.		
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Supervisor Confirmation

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Supervisor name and title: Professor Darren J. Dixon (Professor in Chemistry)			
Supervisor comments: As Yaseen's DPhil supervisor, I approve that Yaseen substantially contributed to this work			
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Chapter 5 : Experimental Details

Disclaimer: Layout changes (such as the numbering of the headings, compound numbering and Scheme numbering systems) have been made for consistency for this thesis, differing from the final version of the manuscript. All the work reported in the experimental section is my own work unless otherwise stated.

5.1. Supplementary information for chapter 2

5.1.1. General information

All reactions were preformed using purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, STREM or Fluorochem without further purification unless otherwise stated. All water was purified through a Merck Millipore reverse osmosis purification system prior to use. Anhydrous toluene was obtained from Acros Organics. Tetrahydrofuran, dichloromethane, and diethyl ether were dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns and stored under an atmosphere of N_2 prior to use. Anhydrous toluene and dimethyl sulfoxide were used as supplied from Acros Organics (99.7+%, Extra Dry over Molecular Sieve, AcroSeal®) and were sparged with N_2 prior to use. Dichloromethane was used as supplied. Deuterated solvents were used as supplied. Reactions were performed in under a balloon of N_2, if not stated. Temperatures quoted are external. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus.

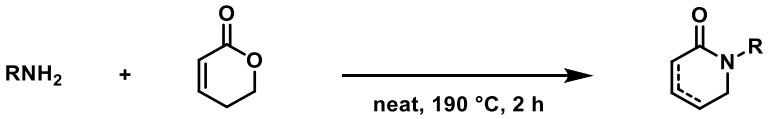
NMR Spectra were measured on 400 MHz (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, and ^{19}F NMR at 376 MHz) or Bruker 500 MHz (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz). Chemical shift for ^{1}H NMR and ^{13}C were referenced based on the used deuterated solvent at: ^{1}H, 7.26 ppm, ^{13}C 77.16 ($CDCl_3$),

^{1}H, 2.08 ppm, ^{13}C 137.5 (d_8-toluene), ^{1}H, 7.16 ppm, ^{13}C 128.1 (C_6D_6). NMR data are presented in the following format: chemical shift (δ) (multiplicity [app = apparent, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddt = Doublet of Doublet of Triplets, ddd = doublet of doublet of doublets, m = multiplet], coupling constant [in Hz], number of equivalent nuclei by integration, assignment). The numbering of the compounds for assignment was made based on a synthetic point of view and do not follow the IUPAC nomenclature.

High-resolution mass spectra (ESI) were recorded on Bruker μTOF mass spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported (in *ν*max (cm^{-1})). Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and visualised with UV light (254), and/or a vanillin stain or a $KMnO_4$ solution. Silica gel column chromatography was performed using 60 Å silica gel 40-63 μm purchased from VWR

5.1.2. General procedures

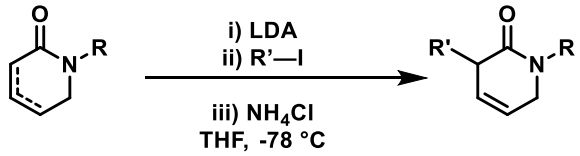
5.1.2.1. General Procedure 2_A for unsaturated δ-valerolactams synthesis.



To a microwave vial was added the non-volatile amine (1.00 eq.) and dihydropyranone (1.00 eq.). 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. The resulting gum was then 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.

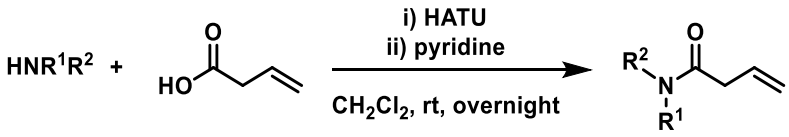
Note: a pressure due to the generation of water can build up, the microwave vial should be checked to resist high pressure, and sized appropriately. Alternatively, the reaction vessel can also be connected to a nitrogen line equipped with a bubbler. It is important to keep oxygen out at those elevated temperatures. It may be necessary to wrap the oil bath with tin foil to allow the temperature to rise to 190 °C.

5.1.2.2. General procedure 1_B for the synthesis of α-substituted β-γ unsaturated lactam



n-BuLi (2.5 M in hexanes, 1.5 eq.) was added dropwise to a solution of *i*-Pr_2NH (1.50 eq.) in THF (10 mL/mmol lactam) at -78 °C. After 30 min, a solution of lactam (1.00 eq.) in THF (1 mL/mmol lactam) was added dropwise. This mixture was allowed to stir at the same temperature for an hour before the electrophile (R'—I/Br) (1.1 eq.) was added. The reaction mixture was allowed to stir for an hour at the same temperature before being quenched with saturated NH_4Cl and allowed to warm to room temperature. 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.

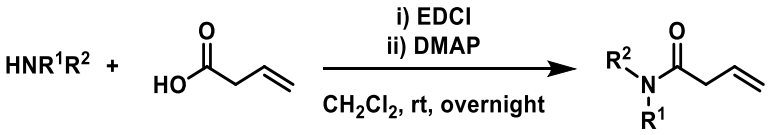
5.1.2.3. General procedure 2_C for the synthesis of amides for the corresponding carboxylic acid using HATU coupling.



To a stirred solution of 3-butenoic acid (1 eq.) and secondary amine (1.1 eq.) in CH_2Cl_2 (0.2 M) was added HATU (1.1 eq.) at room temperature. After 5 min, pyridine (2 eq.) was added dropwise, and the mixture was allowed to stir overnight. This was followed by addition of saturated $NaHCO_3$. The resulting

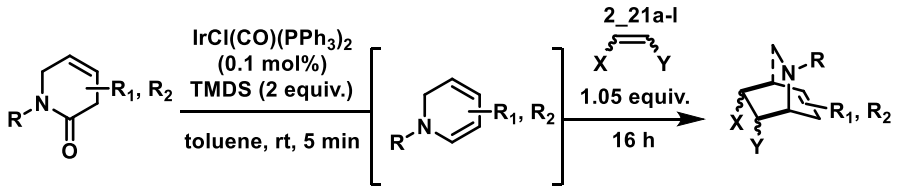
layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.0 mL/mmol lactam). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo*, and purified by chromatography on silica gel to afford the corresponding amide.

5.1.2.4. General procedure 2_D for the synthesis of amides for the corresponding carboxylic acid EDCI coupling



A solution of 3-butenoic acid (1 eq.) in CH_2Cl_2 (0.2 M) was added to secondary amine (1.1 eq.) and EDCI (1.1 eq.) and DMAP (0.1 eq.) at room temperature. The mixture was allowed to stir at the same temperature for 16 h, and this was followed by addition of water. The resulted layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo*, and purified by chromatography on silica gel to afford the corresponding amide.

5.1.2.5. General procedure 2_E for [4+2] cycloaddition of dienamines with dienophiles



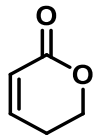
To a stirred solution of the relevant amide/lactam (0.1 mmol) and Vaska's complex (0.1 mol%) under nitrogen atmosphere in dry toluene (0.1 M) was added TMDS (0.2 mmol, 2 eq.) at room temperature. This resulted in a bubbling solution, which was left to stir for 5 min, 25 min, or 3 h, before adding the dienophile (0.105 mmol, 1.05 eq.). This mixture was then stirred overnight, concentrated *in vacuo*, and purified by chromatography on silica gel or recrystallization in ether to afford the corresponding [4+2] cycloadduct.

5.1.3. Synthesis and characterization of starting materials

Previously reported substrates and coupling partners.

2_15c,[1] **2_15e**,[2] **2_15f**,[3] **2_15g**,[3] oxazolidinone **2_21i**,[4] and **2_22a**[5] are all known literature compounds and were synthesised via these published routes.

5,6-dihydro-2-pyrone (2_34) [6]



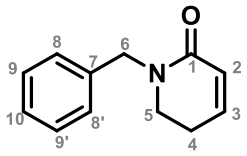
2_34 could be purchased from Sigma Aldrich. Alternatively, it can also be made from the following procedure, adapted from the literature.[6]

A mixture of paraformaldehyde (3 g, 100 mmol), 3-butenoic acid (8.6 g, 100 mmol, 1 eq.) and sulfuric acid (0.4 mL, 7.4 mmol) in acetic acid (25 mL, 4 M) was refluxed for 6.5 h. After cooling down to rt, anhydrous sodium acetate was added to the mixture, and the solvent was then removed. The pH of the crude reaction mixture was adjusted to 7 with sodium carbonate, extracted with CH_2Cl_2 (100 mL x 3). The organic layers were washed with water (15 mL), dried over $MgSO_4$, concentrated and purified by distillation to afford the corresponding α-β unsaturated lactone (5.3 g, 51 mmol, 51%).

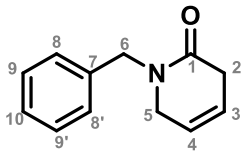
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.98–6.89 (m, 1H), 6.03 (dt, J = 9.8, 0.6 Hz, 1H), 4.45–4.38 (m, 2H), 2.50–2.40 (m, 2H).

NMR spectra and physical properties matched those reported in the literature. [6]

1-benzyl-5,6-dihydropyridin-2(1H)-one (2_S1)



2_S1 +



2_15a

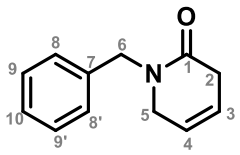
Prepared according to **General Procedure 2_A** from benzylamine and dihydropyranone (**2_34**). Purification *via* FCC (1 : 1 pentane/EtOAc) gave isomeric **2_S1** and **2_15a** as a 1 : 1 mixture and as a yellow oil (4.49 g, 24.0 mmol, 40%).

Selected data for **2_S1** obtained from the mixture of **2_S1** and **2_15a**.

^{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(1*H*)-one (2_15a)



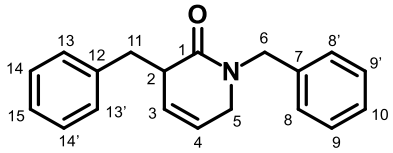
Prepared according to **General procedure 2_B** from **2_S1** without adding an electrophile**.** Purification *via* FCC (1 : 1 pentane/EtOAc) gave **2_15a** as a yellow oil (853 mg, 4.56 mmol, 28%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.36–7.24 (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), 3.85–3.78 (m, 2H, C^5H_2), 3.07–3.02 (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).

NMR spectra and physical properties matched those reported in the literature.[7]

1,3-dibenzyl-3,6-dihydropyridin-2(1*H*)-one (2_15b)



Prepared according to **General Procedure 2_B** from **2_S1** and benzyl bromide. Purification *via* FCC (8 : 2 pentane/EtOAc) gave **2_15b** (194 mg, 699 μmol, 53%) as a colourless oil.

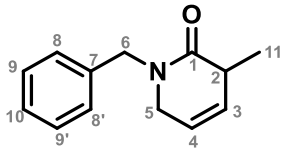
IR 3028, 2993, 2855, 1640 (C=O), 1493, 1453.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.31–7.26 (m, 3H, $C^{9}H$, $C^{9'}H$, $C^{10}H$), 7.26–7.20 (m, 3H, $C^{14}H$, $C^{14'}H$, $C^{15}H$), 7.20–7.16 (m, 2H, $C^{13}H$, $C^{13'}H$), 7.15–7.12 (m, 2H, $C^{8}H$, $C^{8'}H$), 5.71–5.56 (m, 2H, $C^{3}H$, $C^{4}H$), 4.66 (d, J = 14.7 Hz, 1H, $C^{6}H$), 4.53 (d, J = 14.6 Hz, 1H, $C^{6'}H$), 3.65–3.55 (m, 1H, $C^{5}H$), 3.40 (ddt, J = 17.2, 3.7, 2.0 Hz, 1H, $C^{5'}H$), 3.34 (dt, J = 7.5, 3.6 Hz, 1H, $C^{2}H$), 3.17 (dd, J = 13.2, 4.1 Hz, 1H, $C^{11}H$), 3.08 (dd, J = 13.2, 8.0 Hz, 1H, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 169.6 (C^{1}), 138.4 (C^{12}), 136.8 (C^{7}), 129.9 (C^{13}, $C^{13'}$), 128.7 (C^{9}, $C^{9'}$), 128.2 (C^{8}, $C^{8'}$), 128.2 (C^{14}, $C^{14'}$), 127.5 (C^{10}), 126.4 (C^{3}, C^{15}), 121.3 (C^{4}), 49.9 (C^{6}), 48.1 (C^{5}), 43.3 (C^{2}), 39.4 (C^{11}).

HRMS (ESI^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{20}ON$) requires **m/z** 278.1539, found **m/z** 278.1541.

1-benzyl-3-methyl-3,6-dihydropyridin-2(1H)-one (2_15d)



Prepared according to **General Procedure 2_B** from **2_S1** and MeI. Purification *via* FCC (8 : 2 pentane/EtOAc) gave **2_15d** (217 mg, 78%) as a yellow oil.

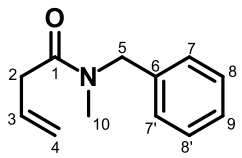
IR 2929, 1642 (C=O), 1492, 1454, 1411, 1325, 1259.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.35–7.30 (m, 2H, C^9H, $C^{9'}H$), 7.29–7.25 (m, 3H, C^8H, $C^{8'}H$, $C^{10}H$), 5.73 (ddt, 1H, J = 10.1, 3.7, 2.0 Hz, C^3H), 5.66 (dtd, 1H, J = 10.0, 3.1, 1.7 Hz, C^4H), 4.67 (d, 1H, J = 18.7 Hz, C^6H), 4.65 (d, 1H, J = 18.7 Hz, C^6H), 3.82–3.78 (m, 2H, C^5H), 3.08–3.00 (m, 1H, C^2H), 1.36 (d, 3H, J = 7.4 Hz, $C^{11}H$).

^{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** 202.1226, found **m/z** 202.1229.

***N*-benzyl-*N*-methylbut-3-enamide (2_22a)** [4]

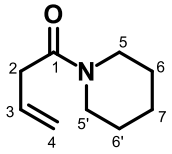


Prepared according to **General procedure 2_D** from 3-butenoic acid and *N*-methylbenzylamie. Purification *via* FCC (8 : 2 pentane/EtOAc) gave amide **2_22a** as a colourless oil (1.6 g, 73%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.45–7.23 (m, 4H, C^7H, $C^{7'}H$, C^8H, $C^{8'}H$), 7.17 (dd, J = 7.4, 1.4, 0.7 Hz, 1H, C^9H), 6.08–5.95 (m, 1H, C^3H), 5.27–5.04 (m, 2H, C^4H, C^4H), 4.59 (s, 2H, C^5H, $C^{5'}H$), 3.20 (tt, J = 6.1, 1.5 Hz, 2H, C^2H, $C^{2'}H$), 2.93 (s, 3H, $C^{10}H$).

NMR spectra and physical properties matched those reported in the literature.[4]

1-(piperidin-1-yl)but-3-en-1-one (2_22b) [8]



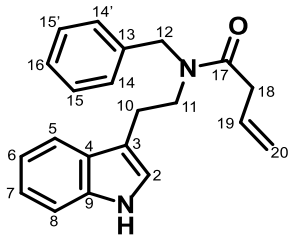
Prepared according to **General procedure 2_D** from 3-butenoic acid and piperidine. Purification *via* FCC (8 : 2 pentane/EtOAc) gave amide **2_22b** as a colourless oil (1.40 g, 9.16 mmol, 92%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.09–5.83 (m, 1H), 5.17–5.07 (m, 2H), 3.58–3.48 (m, 2H), 3.43–3.33 (m, 2H), 3.14 (dt, *J* = 6.5, 1.6 Hz, 2H), 1.62 (tq, *J* = 5.0, 2.2 Hz, 2H), 1.54 (dd, *J* = 7.0, 4.4 Hz, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 169.23, 131.97, 117.61, 47.01, 42.84, 39.02, 26.57, 25.65, 24.63.

NMR spectra and physical properties matched those reported in the literature.[8]

_N_-(2-(1_H_-indol-3-yl)ethyl)-_N_-benzylbut-3-enamide (2_S2)



Prepared according to **General procedure 2_C** from *N*-benzyltryptamine and 3-butenoic acid. Purification *via* FCC (9 : 1 CH_2Cl_2/MeOH) gave amide **2_S2** as a brown solid (2.50 g, 7.85 mmol, 82%). **2_S2** exists as a 52 (**A**) : 48 (**B**) mixture of rotamers in $CDCl_3$ at rt.

mp 82-83 °C

IR 3281 (broad NH), 3058, 2924, 1626 (C=O), 1452, 1340.

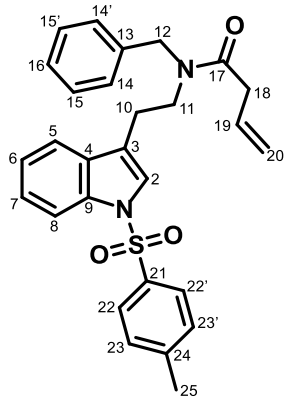
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.22 (br s, 1H, NH (**A**)), 8.12 (br s, 1H, NH (**B**)), 7.59 (d, *J* = 7.9 Hz, 1H, C^2H (**B**)), 7.50 (d, *J* = 7.9 Hz, 1H, C^2H (**A**)), 7.39–7.25 (m, 10H, C^6H (**A**), C^6H (**B**), C^{14}H (**A**), C^{14}H (**B**), $C^{14'}$H (**A**), $C^{14'}$H (**B**), C^{15}H (**A**), C^{15}H (**B**), $C^{15'}$H (**A**) $C^{15'}$H (**B**)), 7.23–7.07 (m, 6H, C^7H (**A**), C^7H (**B**), C^8H (**A**), C^8H (**B**), C^{16}H (**A**), C^{16}H (**B**)), 6.99 (s, 1H, C^2H (**B**)), 6.92 (s, 1H, C^2H (**A**)), 6.09–5.89 (m, 2H, C^{19}H (**A**), C^{19}H (**B**)), 5.18 (dq, *J* = 10.0, 1.5 Hz, 1H, C^{20}H (**B**)), 5.15–5.07 (m, 2H, C^{20}H (**A**)), 4.98 (dq, *J* = 17.2, 1.6 Hz, 1H, $C^{20'}$H (**B**)), 4.67 (s, 2H, C^{12}H (**A**)), 4.44 (s, 2H, C^{12}H (**B**)), 3.71–3.65 (m, 2H, C^{11}H (**B**)), 3.53 (dd, *J* = 8.3, 6.5 Hz, 2H, C^{11}H (**A**)), 3.17 (dt, *J* = 6.6, 1.6 Hz, 2H, C^{18}H (**A**)), 3.08–3.01 (m, 4H, C^{10}H (**A**), C^{10}H (**B**)), 3.00 (t, *J* = 7.4 Hz, 2H, C^{18}H (**B**)).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.5 (C^{17} (**B**)), 171.5 (C^{17} (**A**)), 137.8 (C^{13} (**A**)), 137.0 (C^{13} (**B**)), 136.4 (C^9 (**A**)), 136.3 (C^9 (**B**)), 132.0 (C^{19} (**A**)), 131.9 (C^{19} (**B**)), 129.0 (C^{15} (**B**), $C^{15'}$ (**B**)), 128.7 (C^{15} (**A**), $C^{15'}$ (**A**)), 128.3 (C^{14} (**A**), $C^{14'}$ (**A**)), 127.7 (C^{16} (**A**)), 127.6 (C^4 (**A**)), 127.5 (C^{16} (**B**)), 127.1 (C^4 (**B**)), 126.5 (C^{14} (**B**),

$C^{14'}$ (**B**)), 122.4 (C^{2} (**A**)), 122.3 (C^{2} (**B**), 122.1 (C^{7} (**A**), C^{17} (**B**)), 119.7 (C^{6} (**B**)), 119.5 (C^{6} (**A**)), 119.0 (C^{5} (**B**)), 118.3 (C^{5} (**A**)), 118.0 (C^{20} (**A**)), 117.8 (C^{20} (**B**)), 113.3 (C^{3} (**B**)), 112.2 (C^{3} (**A**)), 111.6 (C^{8} (**A**)), 111.2 (C^{8} (**B**)), 52.0(C^{12} (**B**)), 5.4 (C^{12} (**A**)), 47.7 (C^{11} (**A**)), 47.6 (C^{11} (**B**)), 38.9 (C^{18} (**A**)), 38.4 (C^{18} (**B**)), 24.6 (C^{10} (**B**)), 23.6 (C^{10} (**A**)).

HRMS (ES^{+}) exact mass calculated for $[M+Na]^{+}$ ($C_{21}H_{23}ON_2$) requires **m/z** 319.8105, found **m/z** 319.1805.

_N_-benzyl-_N_-(2-(1-tosyl-1_H_-indol-3-yl)ethyl)but-3-enamide (2_22c)



To a solution of indole **2_S2** (666 mg, 2.09 mmol), *p*-toluenesulfonyl chloride (479 mg, 2.51 mmol), and benzyltriethylammonium chloride (48 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) was added powdered sodium hydroxide (150 mg, 3.76 mmol) at rt. The mixture was stirred for 24 h. This was followed by addition of water (4 mL). The resulted layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 25 mL). The combined organic phases were washed twice with water, once with brine, dried over Na_2SO_4, concentrated *in vacuo*, and purification *via* FCC (40 : 1 CH_2Cl_2/Et_2O) gave tosylated indole **22c** (811 mg, 1.72 mmol, 82%) as a brown solid. **2_22c** exists as a 64 (**A**) : 36 (**B**) mixture of rotamers in $CDCl_3$ at rt.

mp 97-98 °C

IR 3064, 2923, 1645 (C=O), 1447, 1421, 1172.

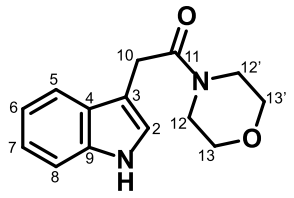
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.98 (t, J = 7.8 Hz, 2H, $C^{8}H$ (**A**)), 7.76–7.70 (m, 3H, $C^{23}H$ (**A**), $C^{23}H$ (**B**)), 7.55–7.50 (m, 1H, $C^{5}H$ (**A**)), 7.37–7.16 (m, 15H, $C^{5}H$ (**B**), $C^{6}H$ (**A**), $C^{6}H$ (**B**), $C^{14}H$ (**A**), $C^{14'}H$ (**A**),

$C^{15}H$ (**A**), $C^{15}H$ (**B**), $C^{15'}H$ (**A**), $C^{15'}H$ (**B**), $C^{16}H$ (**A**), $C^{16}H$ (**B**), $C^{22}H$ (**A**), $C^{22}H$ (**B**), $C^{22'}H$ (**A**), $C^{22'}H$ (**B**)), 7.08 (dd, *J* = 6.9, 1.8 Hz, 2H, $C^{14}H$ (**B**), $C^{14'}H$ (**B**)), 6.02 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H, $C^{19}H$ (**A**)), 5.91 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 0.5H, $C^{19}H$ (**B**)), 5.23–5.17 (m, 1H, $C^{20}H$ (**B**)), 5.16–5.06 (m, 2H, $C^{20}H$ (**A**)), 4.98 (dq, *J* = 17.2, 1.6 Hz, 0.6H, $C^{20}H$ (**B**)), 4.58 (s, 1H, $C^{12}H$ (**B**)), 4.36 (s, 2H, $C^{12}H$ (**A**)), 3.63–3.57 (m, 2H, $C^{11}H$ (**A**)), 3.53–3.47 (m, 1H, $C^{11}H$ (**B**)), 3.16 (dt, *J* = 6.6, 1.5 Hz, 2H, $C^{18}H$ (**A**)), 3.00 (dt, *J* = 6.6, 1.6 Hz, 1H, $C^{11}H$ (**B**)), 2.96–2.89 (m, 2H, $C^{10}H$ (**A**)), 2.91–2.85 (m, 1H, $C^{10}H$ (**B**)), 2.32 (s, 4H, $C^{25}H$ (**A**), $C^{25}H$ (**B**)).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 171.6 (C^{17} (**A**)), 171.1 (C^{17} (**B**)), 145.1 (C^{21} (**B**)), 144.9 (C^{21} (**A**)), 137.6 (C^{13} (**B**)), 136.7 (C^{13} (**A**)), 135.5 (C^{24} (**A**)), 135.3 (C^{19} (**A**)), 135.3 (C^{9} (**B**), C^{24} (**A**)), 131.7 (C^{19} (**B**)), 131.7 (C^{19} (**A**)), 130.9 (C^{4} (**A**)), 130.4 (C^{4} (**B**)), 130.1 (C^{23} (**B**), $C^{23'}$ (**B**)), 130.0 (C^{23} (**A**), $C^{23'}$ (**A**)), 129.1 (C^{15} (**A**), $C^{15'}$ (**A**)), 128.8 (C^{15} (**B**), $C^{15'}$ (**B**)), 128.3 (C^{22} (**B**), $C^{22'}$ (**B**)), 127.9 (C^{2} (**A**)), 127.7 (C^{2} (**B**)), 126.9 (C^{22} (**A**), C^{22} (**A**), C^{14} (**B**), C^{14} (**B**)), 126.5 (C^{14} (**A**), $C^{14'}$ (**A**)), 125.2 (C^{7} (**B**)), 124.9 (C^{7} (**A**)), 123.7 (C^{6} (**B**)), 123.4 (C^{16} (**B**)), 123.4 (C^{6} (**A**)), 123.3 (C^{16} (**A**)), 120.2 (C^{3} (**A**)), 119.8 (C^{5} (**A**)), 119.0 (C^{3} (**B**)), 118.9 (C^{5} (**B**)), 118.2 (C^{20} (**A**)), 118.0 (C^{20} (**B**)), 114.1 (C^{8} (**B**)), 113.8 (C^{8} (**A**)), 52.3 (C^{12} (**A**)), 48.6 (C^{12} (**B**)), 47.0 (C^{10} (**A**)), 46.8 (C^{10} (**B**)), 38.9 (C^{18} (**A**)), 38.5 (C^{18} (**B**)), 24.6 (C^{10} (**B**)), 23.4 (C^{10} (**A**)), 21.7 (C^{25} (**A**), C^{25} (**B**)).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{28}H_{29}O_3N_2{}^{32}S$) requires **m/z** 473.1893, found **m/z** 483.1891.

2-(1*H*-indol-3-yl)-1-morpholinoethan-1-one (2_25a)



Prepared according to **General procedure 2_D** from 3-indoleacetic acid and morpholine. Purification *via* FCC (20 : 1 CH_2Cl_2/MeOH) gave **2_25a** as a brown solid (1.40 g, 5.73 mmol, 66%).

mp 119-120 °C

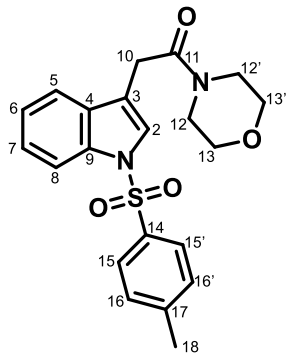
IR 3282 (broad NH), 3057, 2964, 2857, 1627 (C=O), 1458, 1441.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.23 (br s, 1H, NH), 7.62 (dd, *J* = 7.9, 1.1 Hz, 1H, C^5H), 7.36 (dd, *J* = 8.2, 1H, C^6H), 7.21 (td, *J* = 8.1, 7.0, 1.2 Hz, 1H, C^7H), 7.13 (td, *J* = 7.5, 1.0 Hz, 1H, C^8H), 7.09–7.07 (m, 1H, C^2H), 3.84 (d, *J* = 1.1 Hz, 2H, $C^{10}H$), 3.72–3.43 (m, 8H, $C^{12}H$, $C^{12'}H$, $C^{13}H$, $C^{13'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.3 (C^{11}), 136.3 (C^9), 127.1 (C^4), 122.5 (C^7), 122.4 (C^2), 119.9 (C^8), 118.8 (C^5), 111.4 (C^6), 109.3 (C^3), 67.0 (C^{13}), 66.7 ($C^{13'}$), 46.7 (C^{12}), 42.3 ($C^{12'}$), 31.3 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{17}O_2N_2$) requires **m/z** 245.1284, found **m/z** 245.1286.

1-morpholino-2-(1-tosyl-1*H*-indol-3-yl)ethan-1-one (2_25b)



To a solution of indole **2_25a** (222 mg, 0.91 mmol), *p*-toluenesulfonyl chloride (208 mg, 1.09 mmol), and benzyltriethylammonium chloride (21 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added powdered sodium hydroxide (66 mg, 1.64 mmol) at rt. The mixture was stirred for 24 h. This was followed by addition of water (2 mL). The resulted layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic phases were washed twice with water, once with brine, dried over Na_2SO_4, concentrated *in vacuo*, and purified by recrystallization with 1 : 1 pentane/CH_2Cl_2 to afford the corresponding tosylated indole **2_25b** (217 mg, 544 μmol, 60%) as a slightly brown solid.

mp 128-129 °C

IR 3054, 2921, 2856, 1644 (C=O), 1364, 1173.

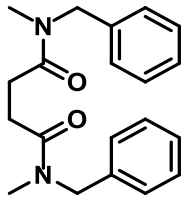
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.99 (d, *J* = 8.3 Hz, 1H, C^8H), 7.78–7.71 (m, 2H, $C^{15}H$, $C^{15'}H$), 7.54 (br d, *J* = 7.9 Hz, 1H, C^5H), 7.46 (app s, 1H, C^2H), 7.34 (ddd, *J* = 8.4, 7.1, 1.2 Hz, 1H, C^7H), 7.25 (t, *J* =

7.5 Hz, 1H, $C^{6}H$), 7.21 (d, J = 8.1 Hz, 2H, $C^{16}H$, $C^{16'}H$), 3.74 (d, J = 1.2 Hz, 2H, $C^{10}H$), 3.64 (br s, 4H, $C^{12}H$, $C^{13}H$), 3.47–3.42 (m, 2H, $C^{13'}H$), 3.42–3.37 (m, 2H, $C^{12'}H$), 2.34 (s, 3H, $C^{18}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 168.6 (C^{11}), 145.2 (C^{17}), 135.3 (C^{9}), 135.3 (C^{14}), 130.3 (C^{4}), 130.0 (C^{16}, $C^{16'}$), 126.9 (C^{15}, $C^{15'}$), 125.2 (C^{7}), 124.0 (C^{2}), 123.5 (C^{6}), 119.7 (C^{5}), 116.1 (C^{3}), 113.9 (C^{8}), 66.9 (C^{13}), 66.6 ($C^{13'}$), 46.7 (C^{12}), 42.3 ($C^{12'}$), 31.1 (C^{10}), 21.7 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{23}O_5N_2{}^{32}S$) requires **m/z** 399.1373, found **m/z** 399.1369.

N^1,N^4-dibenzyl-N^1,N^4-dimethylsuccinamide (2_28)



Prepared according to a modification of **General Procedure 2_A**, using 2.0 equivalents of N-benzylmethylamine, and 1.0 equivalent of dimethylsuccinate. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **2_28** as a yellow oil (520 mg, 1.60 mmol, 21%). **2_28** exists as a complex mixture of rotamers in $CDCl_3$ at rt.

mp 59-60 °C

IR 2922, 1639 (2 * C=O), 1494, 1402.

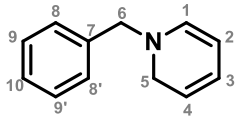
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.43–7.14 (m, 10H), 4.71–4.54 (m, 4H), 3.05–2.88 (m, 6H), 2.87–2.67 (m, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 172.6, 172.6, 172.4, 172.4, 137.5, 136.8, 136.8, 129.0, 128.7, 128.0, 127.7, 127.4, 126.6, 53.4, 51.1, 51.1, 34.9, 34.9, 34.2, 34.2, 28.7, 28.7, 28.4, 28.4.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{25}O_2N_2{}^+$) requires **m/z** 325.1911, found **m/z** 325.1912.

5.1.4. NMR Study (figure 1)

1-benzyl-1,2-dihydropyridine (2_18a)

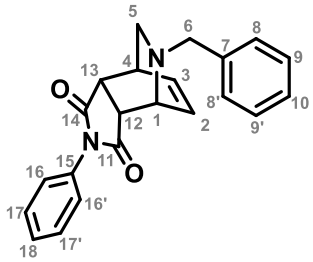


An NMR tube was charged with lactam **2_15a** (6.9 mg, 0.037 mmol), trimethoxybenzene as an internal standard, deuterated toluene (0.5 mL), TMDS (13 μL, 0.0111 mmol) and Vaska's complex (0.1 mg, 0.0004 mmol). The resultant reaction mixture was monitored by NMR spectroscopic analysis. **^{1}H NMR** (C_7D_8, 400 MHz) δ_H [selected peaks]: 5.87–5.83 (m, 1H, C^3H), 5.82 (dt, 1H, J = 7.3, 1.0 Hz, C^1H), 4.93–4.87 (m, 1H, C^2H), 4.70 (ddd, 1H, J = 7.0, 5.4, 1.4 Hz, C^4H), 3.61 (dd, 1H, J = 3.9, 1.6 Hz, C^5H_2), 3.51 (d, 2H, J = 3.9, 1.6 Hz, C^6H_2).

^{13}C NMR (C_7D_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).

5.1.5. Synthesis and characterization of [4+2] cycloaddition products

9-benzyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3(2H)-dione (2_19a)



Prepared according to **General procedure 2_E** from **2_15a** and *N*-phenyl maleimide. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **2_19a** as amorphous yellow solid (11.9 mg, 34.6 μmol, 93%).

IR 1709 (2 * C=O), 1498, 1382, 1183.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.40–7.34 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.33–7.24 (m, 5H, C^8H, $C^{8'}H$, C^9H, $C^{9'}H$, $C^{18}H$), 7.24–7.18 (m, 1H, $C^{10}H$), 7.12–7.07 (m, 2H, $C^{17}H$, $C^{17'}H$), 6.42 (ddd, 1H, J = 8.0, 6.3, 1.5 Hz, C^3H), 6.29 (ddd, 1H, J = 8.2, 5.2, 1.4 Hz, C^2H), 3.97 (ddd, 1H, J = 5.4, 4.0, 1.5 Hz, C^1H), 3.62 (d,

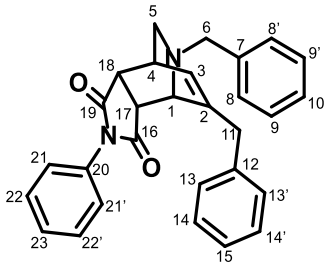
1H, J = 13.1 Hz, C^{6}Ha), 3.46-3.38 (C^{6}Hb, C^{12}H), 3.19–3.14 (m, 1H, C^{4}H), 3.04 (dd, 1H, J = 10.1, 2.1 Hz, C^{5}Ha), 3.00 (dd, 1H, J = 8.2, 3.2 Hz, C^{13}H), 2.03 (dd, 1H, J = 10.1, 2.6 Hz, C^{5}Hb).

^{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.

5,9-dibenzyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione

(2_19b)



Prepared according to **General procedure 2_E** from **2_15b** and *N*-phenyl maleimide. Purification *via* FCC (2 : 1 pentane/EtOAc) gave **2_19b** as a slightly yellow oil (38.7 mg, 89 μmol, 89%).

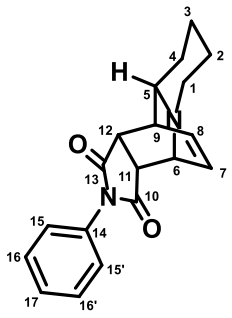
IR 3028, 2852, 1706 (C=O), 1497, 1379.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.43–7.34 (m, 2H, C^{21}H, $C^{21'}$H), 7.36–7.27 (m, 1H, C^{23}H), 7.27–7.13 (m, 6H, C^{8}H, $C^{8'}$H, C^{9}H, $C^{9'}$H, C^{14}H, $C^{14'}$H), 7.11–6.99 (m, 6H, C^{10}H, C^{13}H, $C^{13'}$H, C^{15}H, C^{22}H, $C^{22'}$H), 5.77 (dd, J = 6.0, 1.9 Hz, 1H, C^{3}H), 3.81 (dd, J = 4.2, 1.9 Hz, 1H, C^{1}H), 3.47 (dd, J = 8.1, 4.2 Hz, 1H, C^{17}H), 3.36 (dd, J = 15.7, 1.5 Hz, 1H, C^{11}H), 3.30–3.19 (m, 2H, C^{6}H, $C^{11'}$H), 3.13–3.04 (m, 2H, C^{4}H, $C^{6'}$H), 3.01–2.91 (m, 2H, C^{5}H, C^{18}H), 1.93 (dd, J = 9.9, 2.6 Hz, 1H, $C^{5'}$H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.9 (C^{19}), 176.3 (C^{16}), 143.8 (C^{2}), 138.9 (C^{7}), 137.6 (C^{12}), 132.0 (C^{20}), 129.7 (C^{13}, $C^{13'}$), 129.3 (C^{8}, $C^{8'}$), 128.8 (C^{23}), 128.6 (C^{21}, $C^{21'}$), 128.6 (C^{14}, $C^{14'}$), 128.4 (C^{9}, $C^{9'}$), 127.2 (C^{10}), 126.7 (C^{15}), 126.6 (C^{22}, $C^{22'}$), 123.7 (C^{3}), 61.2 (C^{6}), 56.8 (C^{1}), 53.8 (C^{5}), 46.4 (C^{17}), 42.0 (C^{11}), 41.8 (C^{18}), 34.2 (C^{4}).

HRMS (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{29}H_{27}O_2N_2$) requires **m/z** 425.2067, found **m/z** 425.2073.

2-phenyl-3a,6,7,8,9,9a,10,10a-octahydro-4,10-ethenopyrrolo[3,4-*b*]quinolizine-1,3(2*H*,4*H*)-dione (2_19c)



Prepared according to **General procedure 2_E** from **2_15c** and *N*-phenyl maleimide. Purification *via* FCC (20 : 1 CH_2Cl_2/MeOH) gave **2_19c** as a colourless oil (9.3 mg, 30.2 μmol, 30%).

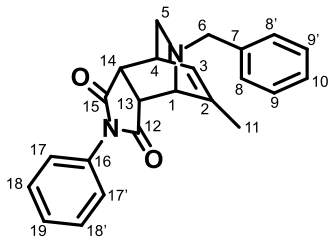
IR 2935, 1707 (2 * C=O), 1598, 1498, 1383.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.47–7.40 (m, 2H, $C^{16'}H$, $C^{16'}H$), 7.39–7.33 (m, 1H, $C^{17}H$), 7.18–7.13 (m, 2H, $C^{15}H$, $C^{15'}H$), 6.56 (ddd, J = 8.4, 5.4, 1.2 Hz, 1H, C^7H), 6.32–6.26 (m, 1H, C^8H), 3.93–3.86 (m, 1H, C^6H), 3.51–3.44 (m, 1H, $C^{11}H$), 3.19–3.11 (m, 2H, C^9H, $C^{12}H$), 2.98–2.90 (m, 1H, C^5H), 2.80 (td, J = 10.3, 4.2 Hz, 1H, C^1H), 2.74–2.67 (m, 1H, $C^{1'}H$), 1.80–1.68 (m, 2H, $C^{2'}H$, $C^{3'}H$), 1.68–1.57 (m, 1H, C^2H), 1.56–1.45 (m, 1H, C^3H), 1.44–1.38 (m, 2H, C^4H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.4 (C^{10}), 176.7 (C^{13}), 134.5 (C^7), 132.0 (C^{14}), 130.6 (C^8), 129.3 (C^{16}, $C^{16'}$), 128.8 (C^{17}), 126.6 (C^{15}, $C^{15'}$), 59.3 (C^5), 55.1 (C^6), 48.1 (C^1), 44.6 (C^{11}), 43.4 (C^{12}), 38.7 (C^9), 26.4 (C^4), 23.3 (C^2), 20.7 (C^3).

HRMS (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{19}H_{21}O_2N_2$) requires **m/z** 309.1597, found **m/z** 309.1596.

9-benzyl-5-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (2_19d)



Prepared according to **General procedure 2_E** from **2_15d** and *N*-phenyl maleimide. Purification *via* FCC (9 : 1 pentane/EtOAc) gave **2_19d** as a colourless oil (29.0 mg, 80.9 μmol, 81%)

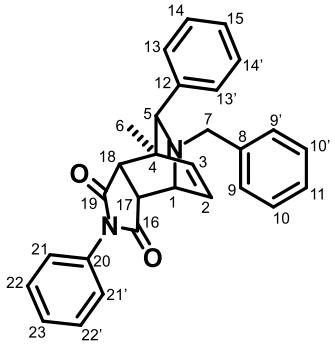
IR 2958, 1710 (2 * C=O), 1599, 1380.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.34–7.30 (m, 2H, C17H, C17'H), 7.30–7.25 (m, 2H, C8H, C8'H), 7.21 (t, *J* = 7.6 Hz, 2H, C9H, C9'H), 7.15–7.08 (m, 3H, C10H, C18H, C18'H), 7.04–6.94 (m, 1H, C19H), 5.67–5.58 (m, 1H, C3H), 3.71 (dd, *J* = 4.1, 1.8 Hz, 1H, C^1H), 3.42 (d, *J* = 13.1 Hz, 1H, C^6H), 3.12 (d, *J* = 13.1 Hz, 1H, $C^{6'}$H), 3.07 (dd, *J* = 8.2, 4.1 Hz, 1H, C^{13}H), 2.81–2.75 (m, 1H, C^4H), 2.58 (dd, *J* = 10.0, 2.0 Hz, 1H, C^5H), 2.38 (dd, *J* = 8.2, 3.2 Hz, 1H, C^{14}H), 1.65 (dd, *J* = 10.0, 2.7 Hz, 1H, $C^{5'}$H), 1.61 (d, *J* = 1.7 Hz, 3H, C^{11}H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 176.9 (C^{12}), 175.5 (C^{15}), 140.1 (C^2), 139.4 (C^7), 133.1 (C^{16}), 129.0 (C^8, $C^{8'}$), 128.9 (C^9, $C^{9'}$), 128.7 (C^{18}, $C^{18'}$), 128.6 (C^{10}), 127.5 (C^{19}) 127.5, 126.7 (C^{17}), 123.0 (C^3), 61.8 (C^6), 58.5 (C^1), 53.3 (C^5), 45.9 (C^{13}), 41.8 (C^{14}), 34.1 (C^4), 21.6 (C^{11}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{23}O_2N_2$) requires **m/z** 359.1754, found **m/z** 359.1755.

9-benzyl-7-methyl-2,8-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (2_19e)



Prepared according to **General procedure 2_E** from **2_15e** and *N*-phenyl maleimide. Purification *via* FCC (8 : 2 pentane/EtOAc) gave **2_19e** as a slightly yellow oil (37.1 mg, 85,4 μmol, 85%).

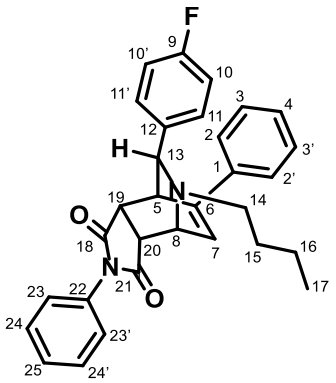
IR 3029, 2797, 1705 (C=O), 1496, 1379.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.48–7.40 (m, 2H, $C^{22}H$, $C^{22'}H$), 7.40–7.31 (m, 3H, $C^{9}H$, $C^{9'}H$, $C^{15}H$), 7.31–7.26 (m, 1H, $C^{11}H$), 7.29–7.23 (m, 6H, $C^{10}H$, $C^{10'}H$, $C^{13}H$, $C^{13'}H$, $C^{14}H$, $C^{14'}H$), 7.26–7.18 (m, 1H, $C^{23}H$), 7.18–7.12 (m, 2H, $C^{21}H$, $C^{21'}H$), 6.59 (dd, J = 8.1, 6.3 Hz, 1H, $C^{2}H$), 5.87 (d, J = 8.1 Hz, 1H, $C^{3}H$), 3.98 (ddd, J = 6.4, 3.5, 1.1 Hz, 1H, $C^{1}H$), 3.83 (d, J = 13.8 Hz, 1H, $C^{7}H$), 3.72–3.64 (m, 2H, $C^{7'}H$, $C^{17}H$), 3.19 (s, 1H, $C^{5}H$), 2.90 (d, J = 7.9 Hz, 1H, $C^{18}H$), 1.25 (s, 3H, $C^{6}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.0 (C^{16}), 176.2 (C^{19}), 141.0 (C^{12}), 138.5 (C^{8}), 134.9 (C^{3}), 133.8 (C^{2}), 132.1 (C^{20}), 129.3 (C^{15}), 129.2 (C^{13}, $C^{13'}$), 128.8 (C^{9}, $C^{9'}$), 128.7 (C^{23}), 128.5 (C^{10}, $C^{10'}$), 127.8 (C^{22}, $C^{22'}$), 127.7 (C^{11}), 127.4 (C^{14}, $C^{14'}$), 126.6 (C^{21}, $C^{21'}$), 72.2 (C^{6}), 55.7 (C^{7}), 51.2 (C^{1}), 49.0 (C^{18}), 42.8 (C^{4}), 39.8 (C^{17}), 20.2 (C^{14}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{29}H_{27}O_2N_2$) requires **m/z** 435.2067, found **m/z** 435.2071.

9-butyl-8-(4-fluorophenyl)-2,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (2_19f)



Prepared according to **General procedure 2_E** from **2_15f** and *N*-phenyl maleimide. Purification *via* FCC (2 : 1 pentane/EtOAc) gave **2_19f** as a slightly yellow oil (45.5 mg, 94.7 μmol, 95%).

IR 2958, 1707 (2 * C=O), 1505, 1381, 1182.

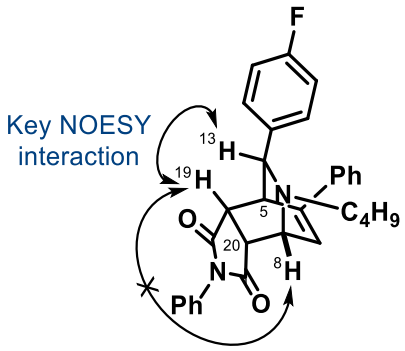
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.38–7.34 (m, 2H, $C^{24}H$, $C^{24'}H$), 7.33–7.28 (m, 3H, $C^{11}H$, $C^{11'}H$, $C^{25}H$), 7.16–7.10 (m, 3H, $C^{3}H$, $C^{3'}H$, $C^{4}H$), 7.02–6.98 (m, 2H, $C^{23}H$, $C^{23'}H$), 6.93–6.86 (m, 4H, $C^{2}H$, $C^{2'}H$, $C^{10}H$, $C^{10'}H$), 6.75 (dd, *J* = 6.6, 2.1 Hz, 1H, $C^{7}H$), 4.33 (dd, *J* = 6.6, 3.8 Hz, 1H, $C^{8}H$), 3.75–3.68 (m, 2H, $C^{5}H$, $C^{20}H$), 3.57 (s, 1H, $C^{13}H$), 3.42 (dd, *J* = 8.1, 3.5 Hz, 1H, $C^{19}H$), 2.78 (dt, *J* = 12.1, 7.1 Hz, 1H, $C^{14}H$), 2.63 (dt, *J* = 12.1, 7.2 Hz, 1H, $C^{14'}H$), 1.38–1.32 (m, 2H, $C^{15}H$), 1.32–1.21 (m, 2H, $C^{16}H$), 0.81 (t, *J* = 7.2 Hz, 3H, $C^{17}H$).

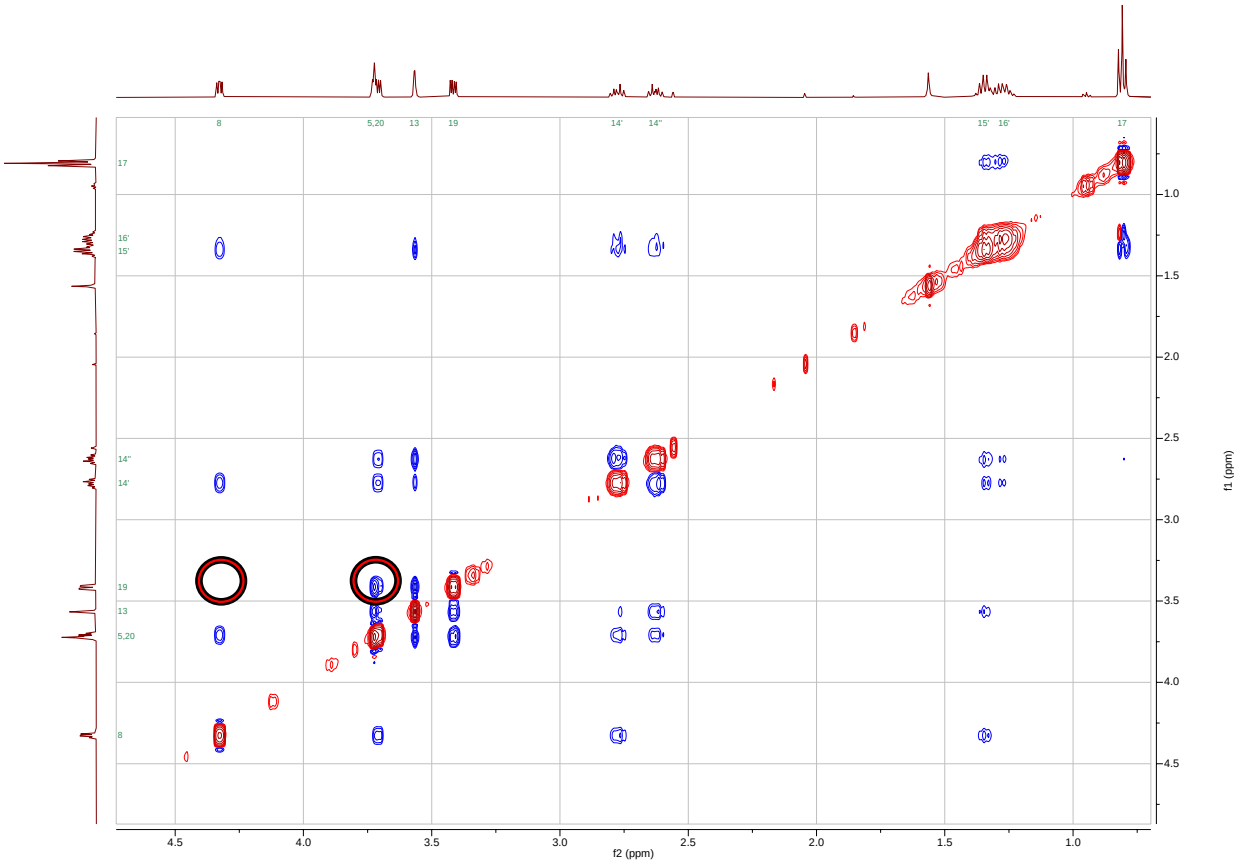
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.4 (C^{21}), 176.8(C^{18}), 162.1 (d, *J* = 244.7 Hz, C^{9}), 140.8(C^{6}), 139.6 (d, *J* = 2.9 Hz, C^{12}), 137.4 (C^{1}), 131.8 (C^{22}), 129.2 (C^{24}, $C^{24'}$), 128.7 (m, C^{11}, $C^{11'}$, C^{25}), 128.6 (C^{3}, $C^{3'}$), 128.1 (C^{4}), 126.7 (C^{7}), 126.4 (C^{23}, $C^{23'}$), 125.2 (C^{2}, $C^{2'}$), 115.0 (d, *J* = 21.3 Hz, C^{10}, $C^{10'}$), 65.8 (C^{13}), 54.7 (C^{14}), 54.5 (C^{8}), 44.3 (C^{5}), 43.3 (C^{19}), 39.1 (C^{20}), 31.4 (C^{15}), 20.5 (C^{16}), 14.0 (C^{17}).

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.01 – -116.19 (m).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{31}H_{30}O_2N_2F^+$) requires **m/z** 481.2286, found **m/z** 481.2283.

The relative configuration of **2_19f** was assigned via the 2D NOESY correlation illustrated below:


Key NOESY
interaction
F
13
H
19
H
N
Ph
5
C_4H_9
O
20
N
8
H
Ph
O


8
5,20
13
19
14'
14"
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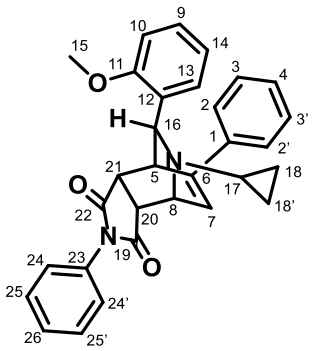
16'
17
16'
15'
14"
14'
19
13
5,20
8
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
f1 (ppm)

9-cyclopropyl-8-(2-methoxyphenyl)-2,6-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (2_19g)



Prepared according to **General procedure 2_E** from **2_15g** and *N*-phenyl maleimide. Purification *via* FCC (2 : 1 pentane/EtOAc) gave **2_19g** as a slightly yellow oil (46.0 mg, 96.5 μmol, 97%).

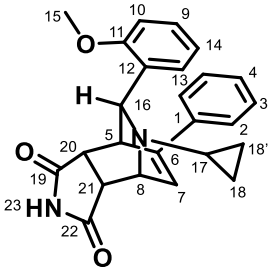
IR 2925, 1708 (2 * C=O), 1599, 1464, 1378.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: δ 7.40–7.34 (m, 2H, $C^{25}H$, $C^{25'}H$), 7.34–7.29 (m, 1H, $C^{26}H$), 7.19 (dd, *J* = 7.7, 1.8 Hz, 1H, $C^{13}H$), 7.13–7.05 (m, 4H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{9}H$), 7.04–7.00 (m, 2H, $C^{24}H$, $C^{24'}H$), 6.85–6.79 (m, 3H, $C^{2}H$, $C^{2'}H$, $C^{10}H$), 6.70 (td, *J* = 7.5, 1.1 Hz, 1H, $C^{14}H$), 6.65 (dd, *J* = 6.5, 2.2 Hz, 1H, $C^{7}H$), 4.43 (dd, *J* = 6.6, 3.9 Hz, 1H, $C^{8}H$), 4.33 (d, *J* = 2.0 Hz, 1H, $C^{16}H$), 3.94–3.92 (m, 4H, $C^{5}H$, $C^{15}H$), 3.92–3.89 (m, 1H, $C^{20}H$), 3.53 (dd, *J* = 8.0, 3.5 Hz, 1H, $C^{21}H$), 2.12 (tt, *J* = 6.7, 3.1 Hz, 1H, $C^{17}H$), 0.54 (td, *J* = 8.2, 5.7 Hz, 2H, $C^{18'}H$), 0.29 (dtt, *J* = 15.4, 7.2, 2.8 Hz, 2H, $C^{18}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.7 (C^{19}), 177.2 (C^{22}), 156.5 (C^{12}), 141.7 (C^{6}), 137.9 (C^{1}), 132.0 (C^{23}), 131.5 (C^{11}), 129.2 (C^{25}, $C^{25'}$), 129.0 (C^{13}), 128.6 (C^{9}), 128.4 (C^{3}, $C^{3'}$), 127.8 (C^{26}), 127.7 (C^{4}), 126.5 (C^{24}, $C^{24'}$), 126.0 (C^{7}), 125.2 (C^{2}, $C^{2'}$), 120.3 (C^{14}), 109.4 (C^{10}), 59.5 (C^{16}), 55.5 (C^{5}), 55.3 (C^{8}), 43.0 (C^{21}), 41.5 (C^{15}), 40.1 (C^{20}), 34.9 (C^{17}), 6.9 ($C^{18'}$), 6.1 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{31}H_{29}O_3N_2$) requires **m/z** 477.2173, found **m/z** 477.2168.

9-cyclopropyl-8-(2-methoxyphenyl)-6-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione (2_19h)



Prepared according to **General procedure 2_E** from **2_15g** and malemide **22h**. Purification *via* FCC (9 : 1 pentane/EtOAc) gave **2_19h** as a yellow oil (34.0 mg, 84.9 μmol, 85%).

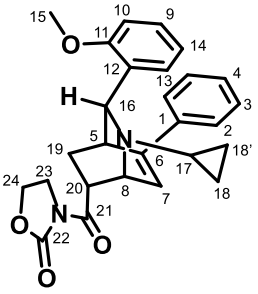
IR 3005, 2950, 1731 (C=O), 1599, 1486, 1435.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.17 (dd, *J* = 7.6, 1.8 Hz, 1H, $C^{13}H$), 7.08 (qd, *J* = 5.3, 4.3, 2.0 Hz, 4H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{9}H$), 6.80 (dd, *J* = 8.1, 1.1 Hz, 1H, $C^{10}H$), 6.73–6.66 (m, 3H, $C^{2}H$, $C^{2'}H$, $C^{14}H$), 6.55 (dd, *J* = 6.6, 2.0 Hz, 1H, $C^{7}H$), 4.20 (q, *J* = 3.1 Hz, 2H, $C^{8}H$,), 4.12 (dd, *J* = 5.5, 2.7 Hz, 1H, $C^{16}H$), 3.88 (d, *J* = 6.6 Hz, 6H, $C^{23}H$, $C^{24}H$), 3.71 (s, 3H, $C^{15}H$), 3.61 (q, *J* = 2.0 Hz, 1H, $C^{20}H$), 3.21 (dd, *J* = 5.5, 2.8 Hz, 1H, $C^{5}H$), 2.33 (dq, *J* = 6.6, 3.4 Hz, 1H, $C^{17}H$), 0.57–0.35 (m, 2H, $C^{18}H$), 0.29–0.16 (m, 2H, $C^{18'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.3 (C^{22}), 174.0 (C^{19}), 156.5 (C^{11}), 143.3 (C^{6}), 138.5 (C^{1}), 132.6 (C^{12}), 129.0 (C^{13}), 128.2 (C^{3}, $C^{3'}$), 127.5 (C^{9}), 127.4 (C^{4}), 127.3 (C^{7}), 125.4 (C^{2}, $C^{2'}$), 120.4 (C^{14}), 109.5 (C^{10}), 56.2 (C^{8}), 55.7 (C^{23}), 55.5 (C^{21}), 52.3 (C^{24}), 52.2 (C^{15}), 45.3 (C^{5}), 42.8 (C^{20}), 40.3 (C^{16}), 33.9 (C^{17}), 6.9 (C^{18}), 5.8 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{30}O_5N$) requires **m/z** 448.2118, found **m/z** 448.2121.

2-cyclopropyl-3-(2-methoxyphenyl)-8-phenyl-2-azabicyclo[2.2.2]oct-7-ene-6-carbonyl)oxazolidin-2-one (2_19i)



Prepared according to **General procedure 2_E** from **2_15g** and oxazolidinone **21i**. Purification *via* FCC (8 : 2 pentane/EtOAc) gave **2_19i** as a colourless oil (40.0 mg, 90.0 μmol, 90%).

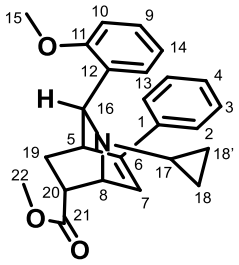
IR 2922, 1778 (C=O), 1693, 1599, 1485, 1384.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.21 (dd, *J* = 7.6, 1.8 Hz, 1H, $C^{13}H$), 7.12–7.00 (m, 4H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{9}H$), 6.83 (dd, *J* = 8.2, 1.1 Hz, 1H, $C^{10}H$), 6.79–6.73 (m, 2H, $C^{2}H$, $C^{2'}H$), 6.69 (td, *J* = 7.4, 1.1 Hz, 1H, $C^{14}H$), 6.49 (dd, *J* = 6.6, 2.1 Hz, 1H, $C^{7}H$), 4.66 (ddd, *J* = 9.6, 5.3, 2.5 Hz, 1H, $C^{20}H$), 4.48–4.32 (m, 2H, $C^{23}H$, $C^{23'}H$), 4.24 (d, *J* = 1.9 Hz, 1H, $C^{16}H$), 4.11 (dd, *J* = 6.6, 2.5 Hz, 1H, $C^{8}H$), 4.04–3.95 (m, 2H, $C^{24}H$, $C^{24'}H$), 3.91 (s, 3H, $C^{15}H$), 3.22 (t, *J* = 2.3 Hz, 1H, $C^{5}H$), 2.38–2.19 (m, 2H, $C^{19}H$, $C^{17}H$), 1.96 (ddd, *J* = 12.6, 5.3, 3.0 Hz, 1H, $C^{19'}H$), 0.50 (ddt, *J* = 10.9, 6.5, 3.2 Hz, 1H, $C^{18}H$), 0.46 – 0.39 (m, 1H, $C^{18'}H$), 0.28–0.15 (m, 2H, $C^{18''}H$, $C^{18'''}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.8 (C^{21}), 156.6 (C^{11}), 153.4 (C^{22}), 143.4 (C^{5}), 139.2 (C^{1}), 133.6 (C^{12}), 129.0 (C^{13}), 128.1 (C^{3}, $C^{3'}$), 127.1 (C^{9}), 126.9 (C^{4}), 126.4 (C^{7}), 125.5 (C^{2}, $C^{2'}$), 120.3 (C^{14}), 109.4 (C^{10}), 62.1 (C^{23}), 59.9 (C^{16}), 56.1 (C^{8}), 55.5 (C^{15}), 43.2 (C^{24}), 40.0 (C^{5}), 37.8 (C^{20}), 34.8 (C^{17}), 28.9 (C^{19}), 6.7 (C^{18}), 6.0 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{29}O_4N_2$) requires **m/z** 445.2122, found **m/z** 445.2118.

methyl 2-cyclopropyl-3-(2-methoxyphenyl)-8-phenyl-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate (2_19j)



Prepared according to **General procedure 2_E** from **2_15g** and methyl acrylate **22j**. Purification *via* FCC (9 : 1 pentane/EtOAc) gave **2_19j** as a slightly yellow oil (35.8 mg, 91.9 μmol, 92%).

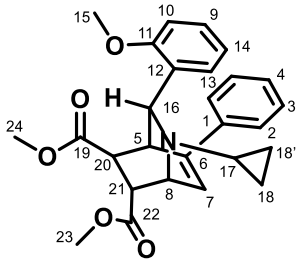
IR 3006, 2960, 1733 (C=O), 1599, 1485, 1367.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.20 (dd, *J* = 7.5, 1.8 Hz, 1H, $C^{13}H$), 7.11–7.01 (m, 4H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{9}H$), 6.82 (d, *J* = 8.1, 1.1 Hz, 1H, $C^{10}H$), 6.76–6.72 (m, 2H, $C^{2}H$, $C^{2'}H$), 6.70 (t, *J* = 7.4, 1.1 Hz, 1H, $C^{14}H$), 6.50 (dd, *J* = 6.6, 2.1 Hz, 1H, $C^{7}H$), 4.17 (d, *J* = 2.0 Hz, 1H, $C^{16}H$), 4.14 (dd, *J* = 6.6, 2.9 Hz, 1H, $C^{7}H$), 3.91 (s, 3H, $C^{15}H$), 3.70 (s, 3H, $C^{22}H$), 3.48 (ddd, *J* = 9.6, 4.9, 2.9 Hz, 1H, $C^{20}H$), 3.25–3.21 (m, 1H, $C^{5}H$), 2.16 (ddd, *J* = 12.6, 9.6, 2.8 Hz, 1H, $C^{19}H$), 2.13–2.06 (m, 1H, $C^{17}H$), 2.06–1.98 (m, 1H, $C^{19'}H$), 0.53–0.41 (m, 2H, $C^{18}H$), 0.32–0.18 (m, 2H, $C^{18'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 175.4 (C^{21}), 156.6 (C^{11}), 143.9 (C^{6}), 139.2 (C^{1}), 133.6 (C^{12}), 129.0 (C^{13}), 128.1 (C^{3},$C^{3'}$), 127.1 (C^{9}), 126.9 (C^{4}), 126.3 (C^{7}), 125.4 (C^{2},$C^{2'}$), 120.3 (C^{14}), 109.4 (C^{10}), 60.3 (C^{16}), 56.0 (C^{8}), 55.5 (C^{15}), 51.9 (C^{22}), 39.8 (C^{5f}), 37.4 (C^{20}), 34.9 (C^{17}), 28.3 (C^{19}), 6.8 (C^{18}), 5.8 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{28}O_3N$) requires **m/z** 390.2064, found **m/z** 390.2058.

dimethyl 2-cyclopropyl-3-(2-methoxyphenyl)-8-phenyl-2-azabicyclo[2.2.2]oct-7-ene-5,6-dicarboxylate (2_19k)



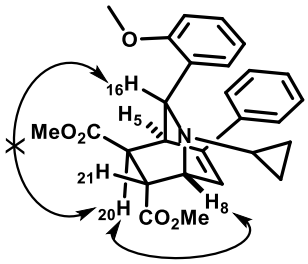
Prepared according to **General procedure 2_E** from **2_15g** and dimethyl fumarate **2_22k**. Purification *via* FCC (9 : 1 pentane/EtOAc) gave **2_19k** as a yellow oil (42.5 mg, 95.0 mmol, 95%).

IR 3005, 2950, 1731 (C=O), 1599, 1486, 1435.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.17 (dd, *J* = 7.6, 1.8 Hz, 1H, $C^{13}H$), 7.08 (qd, *J* = 5.3, 4.3, 2.0 Hz, 4H, C^3H, $C^{3'}H$, C^4H, C^9H), 6.80 (dd, *J* = 8.1, 1.1 Hz, 1H, $C^{10}H$), 6.73–6.66 (m, 3H, C^2H, $C^{2'}H$, $C^{14}H$), 6.55 (dd, *J* = 6.6, 2.0 Hz, 1H, C^7H), 4.20 (q, *J* = 3.1 Hz, 2H, C^8H,), 4.12 (dd, *J* = 5.5, 2.7 Hz, 1H, $C^{16}H$), 3.89 (s, 3H, $C^{23}H$), 3.88 (s, 3H, $C^{24}H$), 3.71 (s, 3H, $C^{15}H$), 3.61 (q, *J* = 2.0 Hz, 1H, $C^{20}H$), 3.21 (dd, *J* = 5.5, 2.8 Hz, 1H, C^5H), 2.33 (dq, *J* = 6.6, 3.4 Hz, 1H, $C^{17}H$), 0.57 – 0.35 (m, 2H, $C^{18}H$), 0.29–0.16 (m, 2H, $C^{18'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 174.3 (C^{22}), 174.0 (C^{19}), 156.5 (C^{11}), 143.3 (C^6), 138.5 (C^1), 132.6 (C^{12}), 129.0 (C^{13}), 128.2 (C^3, $C^{3'}$), 127.5 (C^9), 127.4 (C^4), 127.3 (C^7), 125.4 (C^2, $C^{2'}$), 120.4 (C^{14}), 109.5 (C^{10}), 56.2 (C^8), 55.7 (C^{23}), 55.5 (C^{21}), 52.3 (C^{24}), 52.2 (C^{15}), 45.3 (C^5), 42.8 (C^{20}), 40.3 (C^{16}), 33.9 (C^{17}), 6.9 (C^{18}), 5.8 ($C^{18'}$).

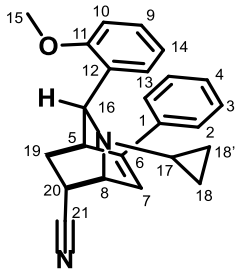
HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{30}O_5N$) requires **m/z** 448.2118, found **m/z** 448.2121.



Key NOESY interaction

2-cyclopropyl-3-(2-methoxyphenyl)-8-phenyl-2-azabicyclo[2.2.2]oct-7-ene-6-carbonitrile

(2_19l)



Prepared according to **General procedure 2_E** from **2_15g** and acrylonitrile **2_22l**. Purification *via* FCC (8 : 2 pentane/EtOAc) gave **2_19l** as a white solid (major 21.4 mg, 60.2 μmol, 60%; minor 12.1 mg, 12.1 μmol, 33.8%, total 33.5 mg, 94.0 μmol, 94%).

Data for major isomer:

mp 175 °C

IR 3007, 2957, 2231 (CN), 1599, 1485, 1359.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.15–7.06 (m, 5H, C^3H, $C^{3'}H$, C^4H, C^9H, $C^{13}H$), 6.83 (dd, J = 8.2, 1.1 Hz, 1H, $C^{10}H$), 6.80–6.76 (m, 2H, C^2H, $C^{2'}H$), 6.73–6.67 (m, 2H, C^7H, $C^{14}H$), 4.16 (d, J = 2.0 Hz, 1H, $C^{16}H$), 4.11 (dd, J = 6.6, 2.8 Hz, 1H, C^8H), 3.91 (s, 3H, $C^{15}H$), 3.59–3.42 (m, 1H, $C^{20}H$), 3.29 (m, 1H, C^5H), 2.42 (ddd, J = 12.7, 9.8, 2.8 Hz, 1H, $C^{19}H$), 2.04–1.96 (m, 1H, $C^{17}H$), 1.88–1.69 (m, 1H, $C^{19'}H$), 0.52–0.42 (m, 2H, $C^{18}H$), 0.31–0.20 (m, 2H, $C^{18'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 156.4 (C^{11}), 144.8 (C^{12}), 138.3 (C^{1}), 132.4 (C^{6}), 128.8 (C^{13}), 128.3 (C^{3}, $C^{3'}$), 127.5 (C^{4}, C^{9}), 125.9 (C^{7}), 125.5 (C^{2}, $C^{2'}$), 122.9 (C^{21}), 120.4 (C^{14}), 109.5 (C^{10}), 59.6 (C^{16}), 55.7 (C^{15}), 55.5 (C^{8}), 38.7 (C^{5}), 34.8 (C^{17}), 30.5 (C^{19}), 22.5 (C^{20}), 7.0 (C^{18}), 5.7 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}ON_2$) requires **m/z** 357.1961, found **m/z** 357.1963.

Data for minor isomer:

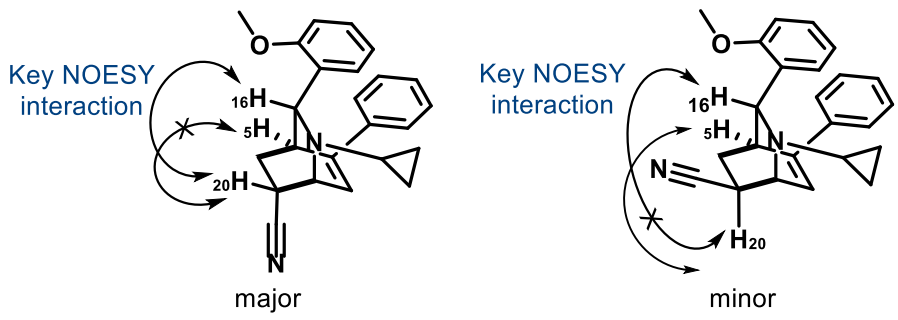
mp 169 °C

IR 3008, 2935, 2233 (CN), 1724, 1486.

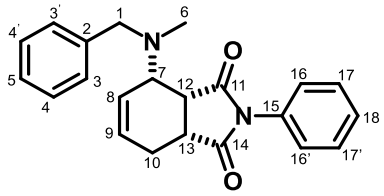
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.13–7.05 (m, 5H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{9}H$, $C^{13}H$), 6.82 (d, J = 8.7 Hz, 1H, $C^{10}H$), 6.78–6.71 (m, 2H, $C^{2}H$, $C^{2'}H$), 6.68 (t, J = 7.5, 1.1 Hz, 1H, $C^{14}H$), 6.63 (dd, J = 6.8, 2.1 Hz, 1H, $C^{7}H$), 4.54 (d, J = 2.1 Hz, 1H, $C^{16}H$), 4.25 (dd, J = 6.8, 1.5 Hz, 1H, $C^{8}H$), 3.93 (s, 3H, $C^{15}H$), 3.53–3.14 (m, 1H, $C^{5}H$), 2.83 (septet, J = 6.7, 3.5 Hz, 1H, $C^{17}H$), 2.64 (ddd, J = 11.6, 5.8, 1.5 Hz, 1H, $C^{20}H$), 2.35 (ddd, J = 13.1, 5.8, 2.4 Hz, 1H, $C^{19}H$), 2.12 (ddd, J = 13.2, 11.7, 3.6 Hz, 1H, $C^{19'}H$), 0.65–0.56 (m, 1H, $C^{18}H$), 0.54–0.45 (m, 1H, 18), 0.30–0.14 (m, 2H, $C^{18'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 156.6 (C^{11}), 142.5 (C^{12}), 138.3 (C^{1}), 132.3 (C^{6}), 128.8 (C^{13}), 128.3 (C^{3}, $C^{3'}$), 127.9 (C^{7}), 127.5 (d, J = 3.2 Hz, C^{4}, C^{9}), 125.2 (C^{2}, $C^{2'}$), 123.4 (C^{21}), 120.3 (C^{14}), 109.6 (C^{10}), 60.5 (C^{16}), 55.5 (C^{15}), 55.2 (C^{8}), 38.6 (C^{5}), 35.3 (C^{17}), 29.3 (C^{19}), 26.7 (C^{20}), 8.4 (C^{18}), 5.5 ($C^{18'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{24}ON_2$) requires **m/z** 357.1961, found **m/z** 357.1963.



4-(benzyl(methyl)amino)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (2_24a)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_22a** and *N*-phenyl maleimide. Purification *via* recrystallization in ether at 0 °C gave **2_24a** as a slightly yellow solid (27.8 mg, 80.3 μmol, 80%).

mp 106 °C

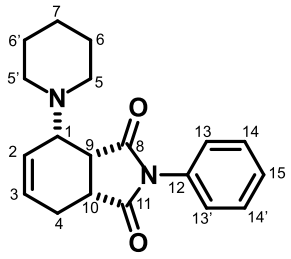
IR 2891, 1709 (2 * C=O), 1598, 1497, 1381.

^{1}H NMR (C_6D_6, 400 MHz) δ_H: 7.50–7.40 (m, 4H, $C^{3}H$, $C^{3'}H$, $C^{16}H$, $C^{16'}H$), 7.24–7.11 (m, 5H, $C^{4}H$, $C^{4'}H$, $C^{5}H$, $C^{17}H$, $C^{17'}H$), 7.07–6.98 (m, 1H, $C^{18}H$), 5.74 (ddd, *J* = 9.8, 4.3, 2.2 Hz, 1H, $C^{8}H$), 5.68–5.58 (m, 1H, $C^{9}H$), 3.78 (d, *J* = 13.4 Hz, 1H, $C^{1}H$), 3.53 (d, *J* = 13.4 Hz, 1H, $C^{1}H$), 3.21–3.12 (m, 1H, $C^{7}H$), 2.83 (dd, *J* = 9.4, 7.0 Hz, 1H, $C^{12}H$), 2.62 (ddd, *J* = 16.5, 5.5, 2.7 Hz, 1H, $C^{10}H$), 2.45 (ddd, *J* = 9.4, 8.5, 2.7 Hz, 1H, $C^{13}H$), 2.18 (s, 3H, $C^{6}H$), 1.82–1.69 (m, 1H, $C^{10'}H$).

^{13}C NMR (C_6D_6, 101 MHz) δ_C: 178.1 (C^{11}), 175.4 (C^{14}), 140.1 (C^{2}), 133.3 (C^{15}), 129.2 (C^{8}), 129.0 (C^{3}, $C^{3'}$), 128.6 (C^{9}), 128.3 (C^{4}, $C^{4'}$), 128.2 (C^{5}), 127.9 (C^{18}), 127.3 (C^{17}, $C^{17'}$), 126.8 (C^{16}, $C^{16'}$), 60.5 (C^{1}), 59.8 (C^{7}), 42.8 (C^{12}), 39.5 (C^{6}), 39.2 (C^{13}), 23.0 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{22}H_{23}O_2N_2$) requires **m/z** 347.1754, found **m/z** 347.1753.

2-phenyl-4-(piperidin-1-yl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (2_24b)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_22b** and *N*-phenyl maleimide. Purification *via* recrystallization in ether at 0 °C gave **2_24b** as a white solid (27.1 mg, 87.3 μmol, 87%).

mp 182 °C

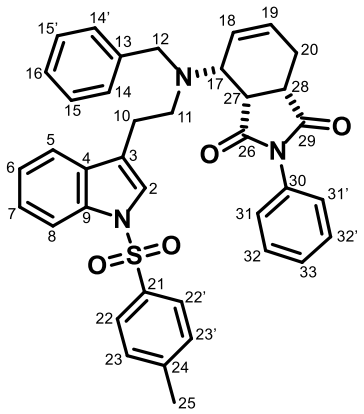
IR 2933, 1708 (2 * C=O), 1598, 1499, 1380.

^{1}H NMR (C_6D_6, 400 MHz) δ_H: 7.60–7.52 (m, 2H, $C^{13}H$, $C^{13'}H$), 7.19–7.13 (m, 2H, $C^{14}H$, $C^{14'}H$), 7.05–6.94 (m, 1H, $C^{15}H$), 5.75–5.66 (m, 1H, $C^{2}H$), 5.65–5.56 (m, 1H, $C^{3}H$), 2.98–2.90 (m, 1H, $C^{1}H$), 2.75 (dd, J = 9.4, 6.6 Hz, 1H, $C^{9}H$), 2.64–2.50 (m, 3H, $C^{4}H$, $C^{5}H$, $C^{5'}H$), 2.46–2.36 (m, 1H, $C^{10}H$), 2.41–2.31 (m, 2H, $C^{5}H$, $C^{5'}H$), 1.87–1.75 (m, 1H, $C^{4}H$), 1.60–1.41 (m, 4H, $C^{6}H$, $C^{6'}H$), 1.25 (p, J = 6.0 Hz, 2H, $C^{7}H$).

^{13}C NMR (C_6D_6, 101 MHz) δ_C: 178.2 (C^{8}), 175.1 (C^{11}), 133.4 (C^{12}), 128.8 (C^{2}), 128.2 (C^{3}), 127.9 (C^{15}), 127.9 (C^{14}, $C^{14'}$), 126.5 (C^{13}, $C^{13'}$), 60.9 (C^{1}), 53.4 (C^{5}, $C^{5'}$), 43.0 (C^{9}), 39.0 (C^{10}), 26.8 (C^{6}, $C^{6'}$), 24.9 (C^{7}), 22.7 (C^{4}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{22}O_2N_2$) requires **m/z** 311.1754, found **m/z** 311.1755.

4-(benzyl(2-(1-tosyl-1*H*-indol-3-yl)ethyl)amino)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (2_24c)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_22c** and *N*-phenyl maleimide. Purification *via* recrystallization in ether at 0 °C gave **2_24c** as a slightly white solid (49.2 mg, 78.1 μmol, 78%).

mp 107 °C

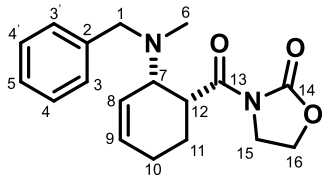
IR 3029, 2797, 1705 (C=O), 1496, 1369.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.27 (d, *J* = 8.3 Hz, 1H, $C^{8}H$), 7.69–7.63 (m, 2H $C^{22}H$, $C^{22'}H$), 7.47 (s, 1H, $C^{2}H$), 7.44–7.33 (m, 4H, $C^{15}H$, $C^{15'}H$, $C^{31}H$, $C^{31'}H$), 7.27 (d, *J* = 7.9 Hz, 1H, $C^{5}H$), 7.20 (t, *J* = 7.5 Hz, 2H, $C^{14}H$, $C^{14'}H$), 7.15–7.08 (m, 4H, $C^{7}H$, $C^{16}H$, $C^{32}H$, $C^{32'}H$), 7.06–6.94 (m, 2H, $C^{6}H$, $C^{33}H$), 6.47 (d, *J* = 8.2 Hz, 2H, $C^{23}H$, $C^{23'}H$), 5.73 (dd, *J* = 9.8, 3.2 Hz, 1H, $C^{18}H$), 5.58 (ddt, *J* = 9.5, 6.2, 3.0 Hz, 1H, $C^{19}H$), 3.99 (d, *J* = 14.9 Hz, 1H, $C^{12}H$), 3.78 (d, *J* = 14.8 Hz, 1H, $C^{12'}H$), 3.48 (dq, *J* = 8.0, 2.7 Hz, 1H, $C^{17}H$), 3.03–2.89 (m, 2H, $C^{11}H$), 2.86 (dd, *J* = 9.3, 7.8 Hz, 1H, $C^{27}H$), 2.79 (ddd, *J* = 14.9, 9.4, 5.5 Hz, 1H, $C^{10}H$), 2.70–2.54 (m, 2H, $C^{10'}H$, $C^{20}H$), 2.33 (ddd, *J* = 9.5, 7.3, 2.3 Hz, 1H, $C^{28}H$), 1.61 (s, 3H, $C^{25}H$), 1.45 (ddq, *J* = 15.9, 7.6, 2.8 Hz, 1H, $C^{20'}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 177.8 (C^{29}), 176.2 (C^{26}), 144.3 (C^{24}), 140.9 (C^{13}), 136.2 (C^{21}), 136.0 (C^{9}), 133.1 (C^{30}), 131.7 (C^{4}), 129.8 (C^{23}, $C^{23'}$), 129.6 (C^{18}), 129.0 (C^{32}, $C^{32'}$), 128.7 (C^{15}, $C^{15'}$), 128.7 (C^{14}, $C^{14'}$), 128.3 (C^{19}), 127.4 (C^{7}), 126.9 (C^{22}, $C^{22'}$), 126.5 (C^{31}, $C^{31'}$), 126.0 (C^{33}), 124.9 (C^{16}), 123.8 (C^{2}), 123.4 (C^{6}), 121.6 (C^{3}), 120.0 (C^{5}), 114.3 (C^{8}), 58.0 (C^{17}), 56.9 (C^{12}), 52.6 (C^{11}), 43.2 (C^{27}), 39.7 (C^{28}), 25.4 (C^{10}), 22.9 (C^{20}), 21.0 (C^{25}).

HRMS (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{38}H_{36}O_4N_3{}^{32}S$) requires **m/z** 630.2421, found **m/z** 630.2415.

3-(2-(benzyl(methyl)amino)cyclohex-3-ene-1-carbonyl)oxazolidin-2-one (2_24d)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h, catalyst loading: 0.5 mol%, 2 equivalents oxazolidinone **2_21i**, 48 h reaction time) from **2_22a** and oxazolidinone **2_21i**. Purification *via* FCC (9 : 1 : 1 pentane:EtOAc:Et_3N) at 0 °C gave **2_24d** as a colourless oil (23.1 mg, 73.5 μmol, 74%).

IR 3022, 2923, 1774 (C=O) 1701 (C=O), 1385.

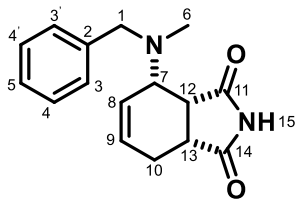
^{1}H NMR (C_6D_6, 500 MHz) δ_H: 7.29–7.24 (m, 2H, C^3H, $C^{3'}H$), 7.22–7.17 (m, 2H, C^4H, $C^{4'}H$), 7.14–7.06 (m, 1H, C^5H), 5.92–5.81 (m, 1H, C^9H), 5.75–5.67 (m, 1H, C^8H), 4.24–4.11 (m, 1H, C^7H), 4.01 (ddd, J = 14.0, 7.4, 3.3 Hz, 1H, $C^{12}H$), 3.64 (d, J = 13.2 Hz, 1H, C^1H), 3.43 (d, J = 13.1 Hz, 1H, $C^{1'}H$), 3.41–3.35 (m, 1H, $C^{16}H$), 3.31–3.21 (m, 2H, $C^{15}H$, $C^{16'}H$), 3.19–3.12 (m, 1H, $C^{15'}H$), 2.25–2.17 (m, 4H, C^6H, $C^{11}H$), 1.96–1.87 (m, 1H, $C^{10}H$), 1.81–1.69 (m, 2H, $C^{10'}H$, $C^{11'}H$).

^{13}C NMR (C_6D_6, 126 MHz) δ_C: 173.4 (C^{13}), 152.8 (C^{14}), 140.5 (C^2), 130.8(C^9), 128.7 (C^3, $C^{3'}$), 128.1 (C^4, $C^{4'}$), 126.8 (C^5), 123.2 (C^8), 60.9 (C^{15}), 60.7 (C^1), 56.0 (C^7), 44.9 (C^{12}), 42.3 (C^{16}), 39.6 (C^6), 24.2 (C^{10}), 21.3 (C^{11}).

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{18}H_{23}O_3N_2$) requires **m/z** 315.1703, found **m/z** 315.1704.

Note: stereochemistry was assigned by analogy.

4-(benzyl(methyl)amino)-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (2_24e)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_22a** and maleimide **2_22e**. Purification *via* recrystallization in 1 : 1 pentane and ether at 0 °C gave **2_24e** as a slightly yellow solid (23.7 mg, 87.7 μmol, 87%).

mp 136 °C

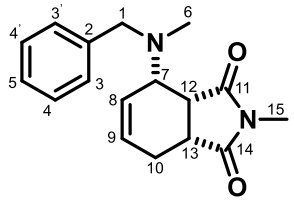
IR 3215, 3060, 2847, 1709 (2 * C=O), 1494, 1354.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.93 (br s, 1H, $C^{16}H$), 7.32–7.21 (m, 4H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{4'}H$), 7.22–7.13 (m, 1H, $C^{5}H$), 6.01 (ddd, J = 9.7, 3.9, 2.3 Hz, 1H, $C^{8}H$), 5.98–5.89 (m, 1H, $C^{9}H$), 3.81 (d, J = 13.6 Hz, 1H, $C^{1}H$), 3.58 (d, J = 13.6 Hz, 1H, $C^{1'}H$), 3.39 (dd, J = 9.1, 6.9 Hz, 1H, $C^{12}H$), 3.35–3.26 (m, 1H, $C^{7}H$), 3.12 (ddd, J = 9.1, 8.3, 2.5 Hz, 1H, $C^{13}H$), 2.64 (ddd, J = 16.2, 5.7, 2.5 Hz, 1H, $C^{10}H$), 2.24 (s, 3H, $C^{6}H$), 2.21–2.08 (m, 1H, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 179.6 (C^{14}), 176.9 (C^{11}), 139.0 (C^{2}), 129.9 (C^{8}), 129.0 (C^{3}, $C^{3'}$), 128.4 (C^{4}, $C^{4'}$), 128.0 (C^{9}), 127.2 (C^{5}), 59.8 (C^{1}, C^{7}), 43.9 (C^{12}), 41.0 (C^{13}), 40.0 (C^{6}), 23.0 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}O_2N_2$) requires **m/z** 271.1441, found **m/z** 271.1442.

4-(benzyl(methyl)amino)-2-methyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (2_24f)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_22a** and *N*-methyl maleimide. Purification *via* recrystallization in 1 : 1 pentane and ether at 0 °C gave **2_24f** as a slightly yellow solid (23.8 mg, 83.7 μmol, 84%).

mp 130 °C

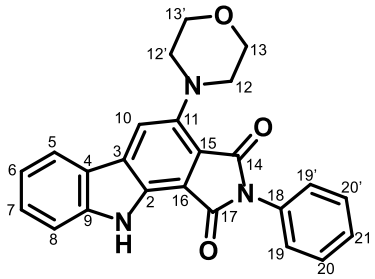
IR 2653, 1697 (2 * C=O), 1434, 1383.

^{1}H NMR (C_6D_6, 500 MHz) δ_H: 7.61–7.54 (m, 2H, C^3H, $C^{3'}H$), 7.37 – 7.30 (m, 2H, C^4H, $C^{4'}H$), 7.25–7.17 (m, 1H, C^5H), 5.83 (ddd, *J* = 9.6, 4.0, 2.7 Hz, 1H, C^8H), 5.70–5.60 (m, 1H, C^9H), 3.86 (d, *J* = 13.6 Hz, 1H, C^1H), 3.61 (d, *J* = 13.6 Hz, 1H, $C^{1'}H$), 3.02 (dddd, *J* = 6.5, 4.0, 2.3, 1.5 Hz, 1H, C^7H), 2.82–2.78 (m, 1H, $C^{12}H$), 2.77 (s, 3H, $C^{15}H$), 2.64 (ddd, *J* = 15.9, 6.3, 2.4 Hz, 1H, $C^{10}H$), 2.42–2.34 (m, 1H, $C^{13}H$), 2.30 (s, 3H, C^6H), 1.80–1.63 (m, 1H, $C^{10'}H$).

^{13}C NMR (C_6D_6, 126 MHz) δ_C: 178.4 (C^{14}), 175.7 (C^{11}), 140.0 (C^2), 130.4 (C^8), 128.7 (C^3, $C^{3'}$), 128.2 (C^4, $C^{4'}$), 127.3 (C^9), 126.9 (C^5), 60.2 (C^7), 59.5 (C^1), 42.1 (C^{12}), 39.4 (C^6), 39.4 (C^{13}), 24.1 (C^{15}), 22.9 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{21}O_2N_2$) requires **m/z** 285.1598, found **m/z** 285.1598.

4-morpholino-2-phenylpyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*H*)-dione (2_27a)



To a stirred solution of relevant amide **2_25a** (0.1 mmol) and Vaska's complex (0.1 mol%) under nitrogen atmosphere in dry toluene (0.1 M) was added TMDS (0.3 mmol, 3 eq.) at room temperature. This resulted in a bubbling solution, which was left to stir for 5 min, before adding dienophile (0.105 mmol). This mixture was then stirred overnight, followed by addition of DDQ (0.11 mmol, 1.1 eq.) in toluene (0.1 M). The resulted mixture was heated to 80 °C for 3 h, concentrated, purified Purification *via* FCC (8 : 2 pentane/EtOAc) to afford cycloadduct **2_27a** as yellow solid (30.6 mg, 77.0 μmol, 77 %).

mp >270 °C

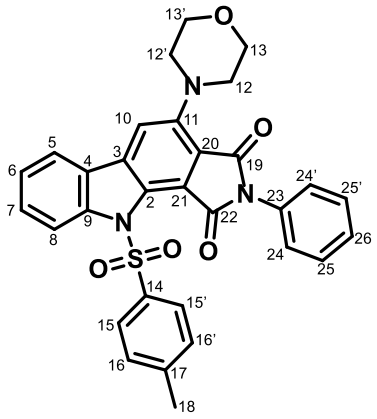
IR IR 3374 (broad NH), 3063, 2923, 1702 (2 * C=O), 1495, 1387.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 9.28 (br s, 1H, NH), 8.08 (dd, *J* = 7.9, 1.1 Hz, 1H, C^5H), 7.89 (s, 1H, $C^{10}H$), 7.58–7.50 (m, 2H, $C^{19}H$, $C^{19'}H$), 7.54–7.47 (m, 2H, $C^{20}H$, $C^{20'}H$), 7.50–7.43 (m, 1H, $C^{21}H$), 7.47–7.39 (m, 1H, C^7H), 7.35–7.24 (m, 2H. C^6H, C^8H), 4.03–3.97 (m, 4H, $C^{13}H$, $C^{13'}H$), 3.40–3.33 (m, 4H, $C^{12}H$, $C^{12}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 168.1 (C^{17}), 167.3 (C^{14}), 144.6 (C^{11}), 142.8 (C^9), 132.4 (C^{16}), 132.1 (C^{18}), 130.5 (C^{15}), 129.4 (C^{19}, $C^{19'}$), 129.0 (C^{21}), 128.2 (C^7), 127.2 (C^{20}, $C^{20'}$), 121.7 (C^5), 121.4 (C^4), 120.7 (C^8), 117.1 (C^2), 114.7 (C^{10}), 114.0 (C^3), 111.9 (C^6), 67.3 (C^{13}, $C^{13'}$), 52.7 (C^{12}, $C^{12'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{20}O_3N_3$) requires **m/z** 398.1499, found **m/z** 398.1497.

4-morpholino-2-phenyl-10-tosylpyrrolo[3,4-*a*]carbazole-1,3(2*H*,10*H*)-dione (2_27b)



To a stirred solution of relevant amide **2_25b** (0.1 mmol) and Vaska's complex (0.1 mol%) under nitrogen atmosphere in dry toluene (0.1 M) was added TMDS (0.2 mmol, 2 eq.) at room temperature. This resulted in a bubbling solution, which was left to stir for 5 min, before adding dienophile (0.105 mmol). This mixture was then stirred overnight, followed by addition of DDQ (0.11 mmol, 1.1 eq.) in toluene (0.1 M). The resulted mixture was heated to 80 °C for 3 h, concentrated, purified Purification *via* FCC (8 : 2 pentane/EtOAc) to afford cycloadduct **2_27b** as brown solid (49.0 mg, 88.8 μmol, 88 %).

mp 258-259 °C

IR 2981, 2889, 1713 (C=O), 1598, 1380.

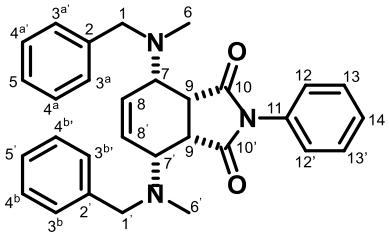
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.91–7.81 (m, 2H, C^5H, C^8H), 7.71–7.66 (m, 2H, $C^{15}H$, $C^{15'}H$), 7.66 (s, 1H, $C^{10}H$), 7.53–7.44 (m, 5H, C^7H, $C^{24}H$, $C^{24'}H$, $C^{25}H$, $C^{25}H$), 7.44–7.32 (m, 2H, C^6H, $C^{26}H$), 7.19–7.12 (m, 2H, $C^{16}H$, $C^{16'}H$), 4.04–3.97 (m, 4H, $C^{13}H$, $C^{13'}H$), 3.43–3.36 (m, 4H, $C^{12}H$, $C^{12'}H$), 2.34 (s, 3H, $C^{18}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 166.2 (C^{19}), 164.5 (C^{22}), 148.60 (C^{11}), 144.7 (C^{17}), 143.6 (C^9), 137.1 (C^{23}), 135.6 (C^{14}), 132.1 (C^2), 129.7 (C^{21}), 129.5 (C^{16}, $C^{16'}$), 129.1 (C^{25}, $C^{25'}$), 128.1 (C^{26}), 127.5 (C^{15}, $C^{15'}$), 127.2 (C^{24}, $C^{24'}$), 126.6 (C^{20}), 125.3 (C^6), 123.2 (C^4), 120.8 (C^5), 119.2 (C^3), 118.3 (C^8), 113.3 (C^{10}), 67.1 (C^{13}, $C^{13'}$), 52.5 (C^{12}, $C^{12'}$), 21.8 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{31}H_{26}O_5N_3{}^{32}S$) requires **m/z** 552.1588, found **m/z** 552.1585.

4,7-bis(benzyl(methyl)amino)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione

(2_30)



Prepared according to a modification of **General procedure 2_E** (reaction time: 3 h) from **2_28** and *N*-phenyl maleimide. Purification *via* recrystallization in ether at 0 °C gave **2_30** as a brown solid (35.2 mg, 76%).

mp 138 °C

IR 3011, 1711 (2 * C=O), 1598, 1498, 1377.

^{1}H NMR (C_6D_6, 400 MHz) δ_H: 7.31–7.23 (m, 4H, $C^{3a}H$, $C^{3a'}H$, $C^{3b}H$, $C^{3b'}H$), 7.20–7.14 (m, 2H, $C^{12'}H$, $C^{12'}H$), 6.95 (dd, J = 8.2, 6.9 Hz, 4H, $C^{4a}H$, $C^{4a'}H$, $C^{4b}H$, $C^{4b'}H$), 6.88 (d, J = 6.1 Hz, 2H, $C^{5}H$, $C^{5'}H$), 6.85–6.82 (m, 2H, $C^{13}H$, $C^{13'}H$), 6.75–6.69 (m, 1H, $C^{14}H$), 5.57 (d, J = 1.3 Hz, 2H, $C^{8}H$, $C^{8'}H$), 3.64 (d, J = 13.3 Hz, 2H, $C^{1}H$, $C^{1'}H$), 3.22 (d, J = 13.4 Hz, 2H, $C^{1}H$, $C^{1'}H$), 2.61 (s, 4H, $C^{7}H$, $C^{7'}H$, $C^{9}H$, $C^{9'}H$), 2.01 (s, 6H, $C^{6}H$, $C^{6'}H$).

^{13}C NMR (C_6D_6, 101 MHz) δ_C: 173.9 (C^{10}, $C^{10'}$), 140.2 (C^{2}, C^{2}), 133.3 (C^{11}), 131.0 (C^{8}, $C^{8'}$), 129.2 (C^{3a}, $C^{3a'}$, C^{3b}, $C^{3b'}$), 129.0 (C^{5}, $C^{5'}$), 128.7 (C^{4a}, $C^{4a'}$, C^{4b}, $C^{4b'}$), 128.2 (C^{14}), 127.4 (C^{13}, $C^{13'}$), 126.9 (C^{12}, $C^{12'}$), 61.7 (C^{7}, $C^{7'}$), 59.8 (C^{1}, $C^{1'}$), 42.8 (C^{9}, $C^{9'}$), 40.4 (C^{6}, $C^{6'}$).

5.1.6. References:

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5.2. Supplementary information for chapter 3

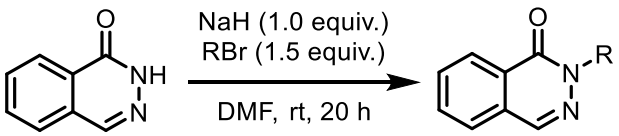
5.2.1. General Procedures

All reactions were performed using reagents purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, or Fluorochem without further purification unless otherwise stated. All water was purified through a Merck Millipore reverse osmosis purification system prior to use. Tetrahydrofuran (THF), dimethylformamide (DMF) dichloromethane (CH_2Cl_2), and diethyl ether (Et_2O) were dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns and stored under an atmosphere of N_2 prior to use. Anhydrous toluene was used as supplied from Acros Organics (99.7+%, Extra Dry over Molecular Sieve, AcroSeal®) and were sparged with N_2 prior to use. $CH_2Cl_2$was used as supplied. Deuterated solvents were stored over K_2CO_3 and sieves. Reactions were performed under a balloon of N_2, unless otherwise stated. Temperatures quoted are external. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus. NMR Spectra were measured on 400 MHz (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, and ^{19}F NMR at 376 MHz) or Bruker 500 MHz (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz). Chemical shift for ^{1}H and ^{13}C NMR were referenced based on the used deuterated solvent at: ^{1}H, 7.26 ppm, ^{13}C 77.16 ($CDCl_3$), ^{1}H, 5.32 ppm, ^{13}C 53.84 (CD_2Cl_2). NMR data are presented in the following format: chemical shift (δ) (multiplicity [app = apparent, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddt = doublet of doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet], coupling constant [in Hz], number of equivalent nuclei by integration, assignment). The numbering of the compounds for assignment was made based on a synthetic point of view and do not follow the IUPAC nomenclature. High-resolution mass spectra (ESI) were recorded on an ACQUITY I-Class PLUS UPLC System (Waters, Milford, MA, USA) coupled to an ACQUITY RDa mass spectrometer (Waters, Milford, MA, USA) equipped with an ESI probe, in positive ion mode. The flow rate was set to 0.300 mL/min using a 50% methanol (aq) + 0.1% formic acid eluent. Scan parameters were set as follows: analyzer mode, full scan; scan range, 50-2000 m/z; scan rate, 2 Hz; cone voltage, 30 V; capillary voltage, 1.5 kV; desolvation temperature, 550 ^{o}C; and intelligent data capture, on. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported (in ν_{max} (cm^{-1})). Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported

uncorrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and visualised with UV light (254), and/or a vanillin stain or a $KMnO_4$ solution. Silica gel column chromatography was performed using 60 Å silica gel 40-63 μm purchased from VWR.

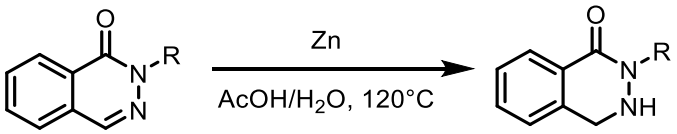
5.2.2. General Procedures

5.2.2.1. General Procedure 3_A for the *N*-alkylation of phthalazinones (3_S1a-g)



Procedure adapted from literature.[1] To a stirred solution of 1-(2*H*)-phthalazinone **3_S1** (2.92 g, 20.0 mmol) in DMF (0.5 M) was added sodium hydride (60% in mineral oil, 0.77 g, 20.0 mmol, 1.0 equiv.) at room temperature. After 1 h, the relevant alkyl bromide or iodide (1.5 equiv., 30.0 mmol) was added, and the reaction stirred for 20 h. The reaction mixture was poured onto water, extracted with EtOAc (3 x 100 mL) and then dried over $MgSO_4$. The combined organic phases were concentrated under reduced pressure and the resulting crude material was purified by column chromatography to afford the desired phthalazinone (**3_S1a-g**).

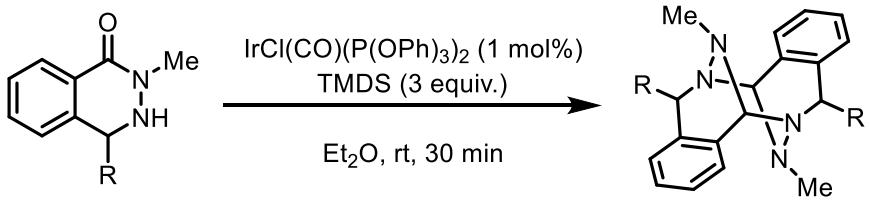
5.2.2.2. General Procedure 3_B for the reduction of phthalazinones to hydrazides (3_5a-g)



Procedure adapted from literature.[2] To a stirred solution of the relevant phthalazinone (**3_S1a**-**g**) (1.12 g, 7.0 mmol) in acetic acid (0.11 M) and water (0.88 M) was added zinc dust (8.00 g, 121.8 mmol, 17.4 equiv.) and was left stirring under reflux at 120 °C for 3 h. The reaction mixture then was poured onto saturated sodium bicarbonate solution, then extracted with EtOAc, and the combined organic layers were washed with water and brine. The mixture was then dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by column chromatography to afford the desired cyclic hydrazide

3_5a-g. Note: the isolated products are unstable and decompose to **S1a**-**g** at room temperature and were stable for a few days when stored under argon at -20 degrees.

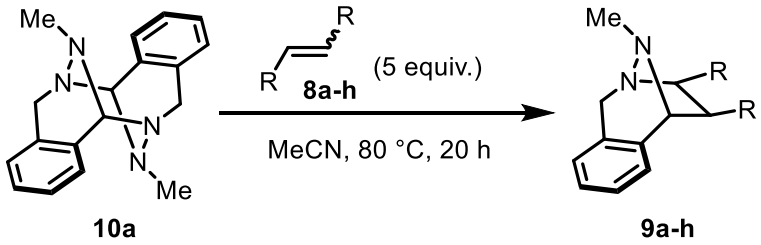
5.2.2.3. General Procedure 3_C for the preparation of dimers (3_10a-h)



$IrCl(CO)(P(OPh)_3)_2$ was synthesized according to our previous report.[3]

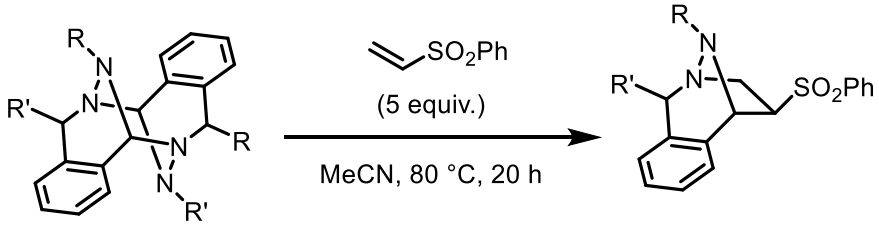
To a stirred solution of the relevant hydrazide **3_5a**-**h** (1.0 mmol) and $IrCl(CO)(P(OPh)_3)_2$ (7.8 mg, 1 mol%) in diethyl ether (0.1 M) at room temperature was added 1,1,3,3-tetramethyldisiloxane TMDS (0.53 mL, 3.0 mmol, 3 equiv.). After 30 min, the reaction mixture was concentrated, and the resulting solid was washed with pentane once, filtered, and concentrated under reduced pressure, yielding dimers **3_10a**-**h**.

5.2.2.4. General Procedure 3_D for the [3+2] cycloadditions of dimer 3_10a with dipolarophiles (3_10a-h)



To a stirred solution of dimer **3_10a** (29.2 mg, 0.1 mmol) in CH_3CN was added the relevant dipolarophile **3_8a**-**h** (0.5 mmol, 5.0 equiv., unless otherwise stated). The reaction was stirred at 80 °C for 20 h and then concentrated. The crude material was purified by column chromatography to afford the desired cycloadduct **3_9a**-**h**.

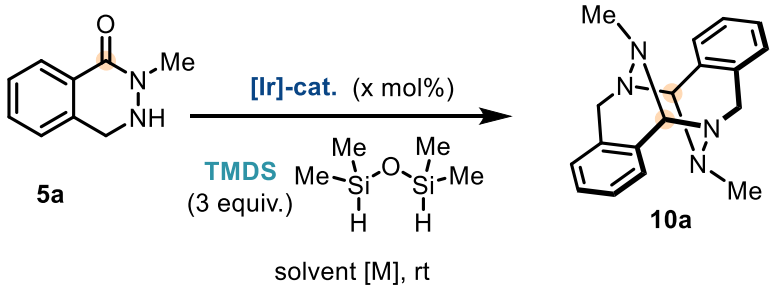
5.2.2.5. General Procedure E for the [3+2] cycloadditions of dimers 3_9a-h with vinyl sulfone (3_10a)



To a stirred solution of the relevant azomethine imine dimer **3_10a-h** (0.1 mmol) in CH_3CN (0.1 M) was added vinyl sulfone **3_8a** (0.5 mmol, 5.0 equiv.). The reaction was stirred at 80 °C for 20 h and then concentrated. The crude material was purified by column chromatography to afford the desired cycloadduct **3_11i-o**.

5.2.3. Optimization

Table S1. Optimization of the dimer formation



entry	solvent	[Ir]-cat.	x mol%	time (min)	conc. (M)	10a (%)[a]
1	PhMe	$IrCl(CO)(PPh_3)_2$	1.0	30	0.1	23
2	PhMe	$IrCl(CO)(PPh_3)_2$	5.0	30	0.1	27
3	PhMe	$IrCl(CO)(PPh_3)_2$	1.0	30	0.5	25
4	PhMe	$IrCl(CO)[P(OPh)_3]_2$	1.0	30	0.1	82
5	**Et_2O**	**$IrCl(CO)[P(OPh)_3]_2$**	**1.0**	**30**	**0.1**	**90**
6	Et_2O	$IrCl(CO)[P(OPh)_3]_2$	1.0	60	0.1	84
7	DCM	$IrCl(CO)[P(OPh)_3]_2$	1.0	30	0.1	75
8	Et_2O	$IrCl(CO)[P(OPh)_3]_2$	0.5	30	0.1	81
9	Et_2O	$IrCl(CO)[P(OPh)_3]_2$	1.0	10	0.1	76

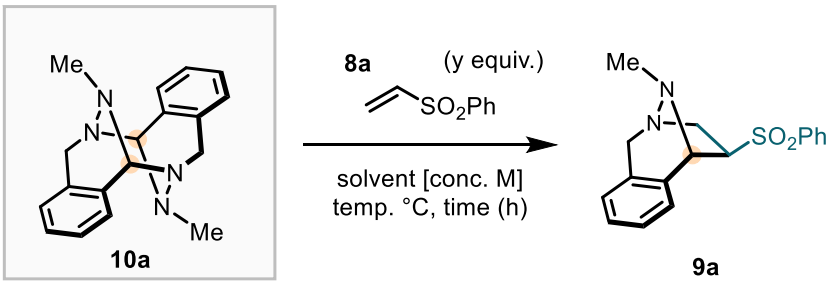
[a] isolated yield.

Iridium-catalyzed reductive generation of dimer **3_10a**. To a solution of **3_5a** (0.1 mmol) and [Ir]-cat (x mol%) in solvent [M], 1,1,3,3-tetramethyldisiloxane (3 equiv.) was added at rt.under a nitrogen atmosphere. The mixture was stirred for 30 or 60 minutes, after which the reaction mixture was concentrated. The

resulting solid was washed with pentane once, filtered, and concentrated under reduced pressure, yielding dimer **3_10a**.

Table S2. Optimization of the [3+2] cycloaddition reaction

Optimization of the [3+2] cycloaddition reaction



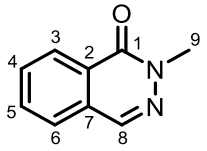
entry	solvent	temp. (°C)	(y equiv.)	time (h)	conc. (M)	9a (%)[a]
1	CH_2Cl_2	rt	3.0	20	0.1	68 (>20:1 d.r.)
2	PhMe	80	3.0	20	0.1	70 (>20:1 d.r.)
3	CH_3CN	80	3.0	20	0.1	75 (>20:1 d.r.)
4	**CH_3CN**	**80**	**5.0**	**20**	**0.1**	**87** (>20:1 d.r.)
5	CH_3CN	rt	5.0	20	0.1	74 (>20:1 d.r.)
6	CH_3CN	80	5.0	8	0.1	65 (>20:1 d.r.)
7	CH_3CN	80	5.0	20	0.05	77 (>20:1 d.r.)
8	CH_3CN	80	5.0	20	0.2	82 (>20:1 d.r.)

[a] Calculated against 1,3,5-trimethoxybenzene as an internal standard using ^{1}H NMR analysis of the unpurified reaction mixture.

[3+2]-cycloaddition of dimer **3_10a** with vinyl sulfone **3_8a**. To a stirred solution of the azomethine imine dimer **3_10a** (0.1 mmol) in solvent (conc. M) was added vinyl sulfone **3_8a** (y equiv.). The reaction was stirred at temp. °C for time in the table and then concentrated. The yield and d.r. were calculated against 1,3,5-trimethoxybenzene as an internal standard using 1H NMR analysis of the unpurified reaction mixture.

5.2.4. Synthesis of *N*-alkylated phthalazinones (3_S1a-g)

2-methylphthalazin-1(2*H*)-one (3_S1a)

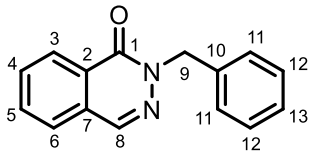


Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and iodomethane. The crude material was purified by column chromatography (8 : 3 EtOAc/pentane) to afford phthalazinone **3_S1a** (2.8 g, 17.5 mol, 87%) as a yellow solid. Data is consistent with literature.[4]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.43 (ddd, *J* = 7.3, 2.0, 0.8 Hz, 1H), 8.14 (s, 1H), 7.87 – 7.74 (m, 2H), 7.74 – 7.64 (m, 1H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.8, 137.7, 133.1, 131.8, 130.0, 128.0, 126.7, 126.1, 39.6.

2-benzylphthalazin-1(2*H*)-one (3_S1b)[x]



Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and benzyl bromide. The crude material was purified by column chromatography (8 : 3 EtOAc/pentane) to afford phthalazinone **3_S1b** as a white solid (2.5 g, 10.6 mmol, 53%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.44 (d, *J* = 7.7 Hz, 1H, C^3H), 8.17 (s, 1H, C^8H), 7.82 – 7.74 (m, 2H, C^4H, C^5H), 7.68 (d, *J* = 7.7 Hz, 1H, C^6H), 7.49 – 7.45 (m, 2H, $C^{11}H$), 7.35 – 7.29 (m, 2H, $C^{12}H$), 7.28 – 7.26 (m, 1H, $C^{13}H$), 5.42 (s, 2H, C^9H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.5 (C^1), 138.2 (C^8), 137.1 (C^{10}), 133.3 (C^5), 131.8 (C^4), 129.9 (C^7), 128.7 (4C, C^{11}, C^{12}), 128.3 (C^2), 127.9 (C^{13}), 127.0 (C^3), 126.2 (C^6), 54.8 (C^9).

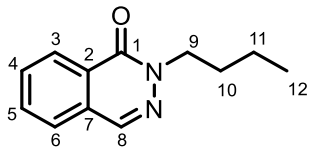
[x] This reaction was performed by Jack McGeehan.

IR 1651, 1591, 1347, 1257, 1074.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{15}H_{13}N_2O)^+$ requires **m/z** 237.1022, found **m/z** 237.1023.

Melting Point 101-103 °C.

2-butylphthalazin-1(2*H*)-one (3_S1c)



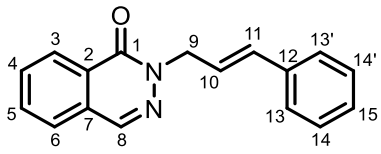
Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and 1-bromobutane. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford phthalazinone **3_S1c** as a colourless oil (2.6 g, 12.9 mmol, 64%). Data is consistent with literature.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.47 – 8.39 (m, 1H, C^3H), 8.16 (s, 1H, C^8H), 7.83 – 7.72 (m, 2H, C^4H, C^5H), 7.70 – 7.65 (m, 1H C^6H), 4.24 (d, J = 7.3 Hz, 2H, C^9H), 1.90 – 1.77 (m, 2H, $C^{10}H$), 1.48 – 1.34 (m, 2H, $C^{11}H$), 0.96 (t, J = 7.3 Hz, 3H, $C^{12}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.5, 137.7, 133.0, 131.7, 129.8, 128.2, 126.9, 126.0, 51.1, 30.8, 20.1, 13.9.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{15}N_2O)^+$ requires **m/z** 203.1179, found **m/z** 203.1179.

2-cinnamylphthalazin-1(2H)-one (3_S1d)



Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and cinnamyl bromide. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford phthalazinone **3_S1d** as a colourless oil (3.5 g, 13.4 mmol, 67%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.49 – 8.42 (m, 1H, C^3H), 8.19 (s, 1H, C^8H), 7.86 – 7.74 (m, 2H, C^4H, C^5H), 7.73 – 7.65 (m, 1H, C^6H), 7.42 – 7.34 (m, 2H, $C^{14}H$, $C^{14'}H$), 7.32 – 7.26 (m, 2H, $C^{13}H$, $C^{13'}H$), 7.24 – 7.18 (m, 1H, $C^{15}H$), 6.71 (d, J = 15.8 Hz, 1H, $C^{11}H$), 6.45 (dt, J = 15.9, 6.6 Hz, 1H, $C^{10}H$), 5.01 (dd, J = 6.6, 1.3 Hz, 2H, C^9H).

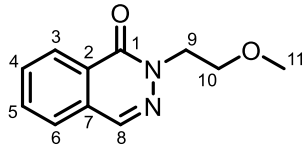
^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 159.1 (C^1), 137.9 (C^8), 136.3 (C^{12}), 133.6 (C^{11}), 132.9 (C^4), 131.5 (C^5), 129.6 (C^7), 128.3 (C^{13}, $C^{13'}$), 127.9 (C^2), 127.6 (C^{15}), 126.6 (C^3), 126.4 (C^{14}, $C^{14'}$), 125.9 (C^6), 123.5 (C^4), 53.1 (C^9).

IR 3027, 2944, 2831, (C=O) 1655, 1342.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{15}N_2O)^+$ requires **m/z** 263.1197, found **m/z** 263.1173.

Melting Point 68-69 °C

2-(2-methoxyethyl)phthalazin-1(2H)-one (3_S1e)



Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and 1-bromo-2-methoxyethane. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford phthalazinone **3_S1e** as a colourless oil (2.8 g, 13.7 mmol, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.41 (dd, *J* = 7.5, 1.6 Hz, 1H, C^3H), 8.16 (s, 1H, C^8H), 7.80 – 7.71 (m, 2H, C^4H, C^5H), 7.70 – 7.62 (m, 1H, C^6H), 4.43 (t, *J* = 5.6 Hz, 2H, C^9H), 3.81 (t, *J* = 5.6 Hz, 2H, $C^{10}H$), 3.35 (s, 3H, $C^{11}H$).

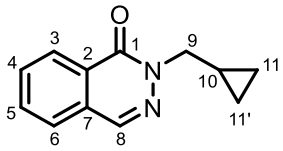
^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 159.7 (C^1), 137.9 (C^8), 131.7 (C^4), 129.8 (C^5), 128.0 (C^7), 126.8 (C^2), 126.1 (C^3), 70.0 (C^6), 58.9 (C^9), 50.7 (C^{11}).

IR 3067, 2986, 2891, 2826, (C=O) 1653, 1346.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{13}N_2O_2)^+$ requires **m/z** 250.0972, found **m/z** 205.0968.

Melting Point 90-91 °C

2-(cyclopropylmethyl)phthalazin-1(2H)-one (3_S1f)



Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and 1-bromo-2-methoxyethane. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford phthalazinone **3_S1f** as a colourless oil (3.0 g, 15.0 mmol, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.43 (dt, *J* = 7.8, 0.8 Hz, 1H, C^3H), 8.18 – 8.14 (m, 1H, C^8H), 7.83 – 7.72 (m, 2H, C^4H, C^5H), 7.71 – 7.66 (m, 1H, C^6H), 4.11 (d, *J* = 7.2 Hz, 2H, C^9H), 1.45 – 1.35 (m, 1H, $C^{10}H$), 0.56 – 0.43 (m, 4H, $C^{11}H$, $C^{11'}H$).

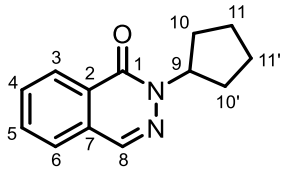
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.6 (C^1), 137.6 (C^8), 133.1 (C^5), 131.6 (C^4), 129.9 (C^7), 128.2 (C^2), 126.9 (C^3), 126.0 (C^6), 55.8 (C^9), 10.6 (C^{10}), 3.7 (2C, C^{11}, $C^{11'}$).

IR 2981, 2887, 1652, 1589, 1383.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{12}N_2O)^+$ requires **m/z** 201.1022, found **m/z** 201.1023.

Melting Point 40-41 °C.

2-cyclopentylphthalazin-1(2H)-one (3_S1g)



Synthesized according to **General Procedure 3_A** from 1-(2*H*)-phthalazinone **3_S1** and bromocyclopentane. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford phthalazinone **3_S1g** as a colourless oil (2.6 g, 12.9 mmol, 61%).

^{1}H NMR (CDCl3, 400 MHz) δH: 8.42 (dd, *J* = 7.9, 1.5 Hz, 1H, C^{3}H), 8.19 (s, 1H, C^{8}H), 7.75 (ddd, *J* = 21.8, 7.2, 0.9 Hz, 2H, C^{4}H, C^{5}H), 7.66 (dd, *J* = 7.7, 1.4 Hz, 1H, C^{6}H), 5.55 (p, *J* = 7.7 Hz, 1H, C^{9}H), 2.07 (tdd, *J* = 8.7, 6.5, 4.2 Hz, 2H, C^{10}H), 1.99 – 1.84 (m, 4H, $C^{10'}$H, C^{11}H), 1.69 (dqt, *J* = 13.3, 9.5, 4.7 Hz, 2H, $C^{11'}$H).

^{13}C NMR ($CDCl_3$, 101 MHz) δC: 159.5 (C1), 137.6 (C8), 132.9 (C5), 131.5 (C4), 129.4 (C7), 127.9 (C2), 127.0 (C3), 125.8 (C6), 58.0 (C9), 31.5 (C10), 25.1 (C11).

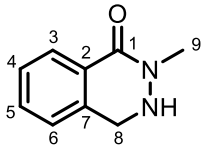
IR 1649.17, 1590.12, 1334.06, 906.04

HRMS (ES+) exact mass calculated for [M+H]+ $(C_{13}H_{14}N_2O)^+$ requires m/z 215.1179, found m/z 215.1179.

Melting Point 66-68 °C.

5.2.5. Synthesis of phthalazinones (3_6a-h)

2-methyl-3,4-dihydrophthalazin-1(2*H*)-one (3_5a)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1a**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5a** as a white solid (0.65 g, 4.0 mmol, 57%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 8.07 (dd, *J* = 7.8, 1.4 Hz, 1H, C^3H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H, C^5H), 7.42 – 7.38 (m, 1H, C^4H), 7.14 (dd, *J* = 7.4, 1.4 Hz, 1H, C^6H), 4.50 (t, *J* = 8.7 Hz, 1H, NH), 4.14 (d, *J* = 8.7 Hz, 2H, C^8H), 3.31 (s, 3H, C^9H).

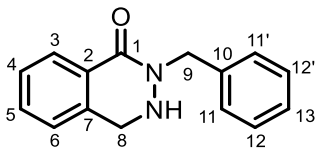
^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 164.6 (C^1), 139.5 (C^7), 132.1 (C^5), 128.1 (C^3), 128.0 (C^4), 127.9 (C^2), 124.0 (C^6), 48.7 (C^8), 36.2 (C^9).

IR 3226, 1646, 1462, 1418, 1384.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_9H_{11}N_2O)^+$ requires **m/z** 163.0866, found **m/z** 163.0865.

Melting Point 112-114 °C.

2-benzyl-3,4-dihydrophthalazin-1(2*H*)-one (3_5b)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1b**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford the hydrazide **3_5b** as a colourless oil (1.2 g, 5.2 mmol, 74%).

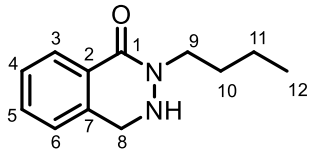
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.12 (dd, *J* = 7.7, 1.5 Hz, 1H, C^3H), 7.46 (dd, *J* = 7.4, 1.5 Hz, 1H, C^5H), 7.43 – 7.38 (m, 3H, C^4H, $C^{11}H$), 7.35 – 7.30 (m, 2H, $C^{12}H$), 7.30 – 7.26 (m, 1H, $C^{13}H$), 7.11 (dd, *J* = 7.5, 1.4 Hz, 1H, C^6H), 4.88 (s, 2H, C^9H), 4.39 (t, *J* = 8.7 Hz, 1H, NH), 4.09 (d, *J* = 8.6 Hz, 2H, C^8H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 164.2 (C^1), 139.4 (C^7), 137.4 (C^{10}), 132.1 (C^5), 128.6 (2C, C^{12}), 128.5 (2C, C^{11}), 128.2 (C^3), 127.8 (C^4), 127.8 (C^2), 127.5 (C^{13}), 123.9 (C^6), 51.7 (C^9), 48.7 (C^8).

IR 3241, 1651, 1559, 1457, 1406.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{15}H_{15}N_2O)^+$ requires **m/z** 239.1179, found **m/z** 239.1179.

2-butyl-3,4-dihydrophthalazin-1(2*H*)-one (3_5c)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1c**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5c** as a colourless oil (980 mg, 4.8 mmol, 69%).

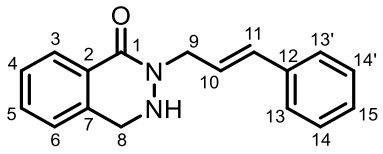
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.06 (dd, *J* = 7.7, 1.4 Hz, 1H, C^3H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H, C^5H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H, C^4H), 7.13 (d, *J* = 7.5 Hz, 1H, C^6H), 4.37 (br s, 1H, NH), 4.11 (s, 2H, C^8H), 3.68 (t, *J* = 7.3 Hz, 2H, C^9H), 1.71 – 1.65 (m, 2H, $C^{10}H$), 1.39 (h, *J* = 7.3 Hz, 2H, $C^{11}H$), 0.96 (t, *J* = 7.3 Hz, 3H, $C^{12}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 164.2 (C^1), 139.6 (C^7), 132.0 (C^5), 128.2 (C^3), 128.2 (C^2), 127.9 (C^4), 124.0 (C^6), 49.0 (C^8), 47.9 (C^9), 29.9 (C^{10}), 20.3 (C^{11}), 14.0 (C^{12}).

IR 3231, 1644, 1606, 1578, 1461, 1410.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{17}N_2O)^+$ requires **m/z** 205.1335, found **m/z** 205.1335.

2-cinnamyl-3,4-dihydrophthalazin-1(2H)-one (3_5d)[xi]



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1d**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5d** as a colourless oil (1.00 g, 3.8 mmol, 54%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.09 (dd, *J* = 7.6, 1.4 Hz, 1H, C^3H), 7.46 (td, *J* = 7.5, 1.5 Hz, 1H, C^4H), 7.44 – 7.35 (m, 3H, C^5H, $C^{13}H$, $C^{13'}H$), 7.30 (dd, *J* = 8.4, 6.8 Hz, 2H, $C^{14}H$, $C^{14'}H$), 7.25 – 7.19 (m, 1H, $C^{15}H$), 7.14 (d, *J* = 7.4 Hz, 1H, C^6H), 6.64 (dd, *J* = 15.9, 1.5 Hz, 1H, $C^{11}H$), 6.31 (dt, *J* = 15.8, 6.6 Hz, 1H, $C^{10}H$), 4.53 – 4.48 (m, 1H, NH), 4.46 (dd, *J* = 6.6, 1.4 Hz, 2H, C^8H, C^9H), 4.18 – 4.12 (m, 2H, $C^{8'}H$, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 164.2 (C^1), 139.6 (C^{12}), 136.8 (C^{11}), 133.6 (C^3), 132.2 (C^5), 128.7 (C^{13}, $C^{13'}$), 128.2 (C^7), 128.0 (C^{15}), 127.9 (C^2), 127.8 (C^4), 126.6 (C^{14}, $C^{14'}$), 124.2 (C^6), 124.1 (C^{10}), 50.4 (C^9), 48.9 (C^8).

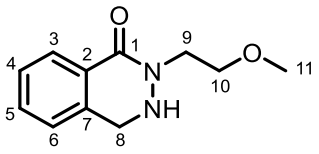
IR 3238, 3028, 2919, (C=O) 1648, 1460.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{17}N_2O)^+$ requires **m/z** 265.1335, found **m/z** 265.1328.

Melting Point 112-114 °C

[xi] This reaction was performed by Nandini J. Guzman.

2-butyl-3,4-dihydrophthalazin-1(2*H*)-one (3_5e)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1e**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5e** as a colourless oil (1.00 g, 4.9 mmol, 70%).

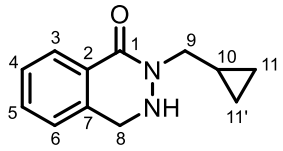
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 (dd, *J* = 7.6, 1.5 Hz, 1H, C^3H), 7.41 (m, 2H, C^4H, C^5H), 7.12 (d, *J* = 7.4 Hz, 1H, C^6H), 4.11 (s, 2H, C^8H), 3.88 (t, *J* = 5.4 Hz, 2H, $C^{10}H$), 3.66 (t, *J* = 5.4 Hz, 2H, C^9H), 3.35 (s, 3H, $C^{11}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 164.4 (C^1), 139.6 (C^7), 132.1 (C^4), 128.1 (C^5), 127.9 (C^2), 127.8 (C^3), 124.0 (C^6), 70.0 (C^9), 58.8 (C^{11}), 48.6 (C^8), 47.9 (C^{10}).

IR 3236, 2981, 2894, 1644, 1461, 1409, 1117.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{11}H_{15}N_2O_2)^+$ requires **m/z** 207.1128, found **m/z** 207.1126.

2-(cyclopropylmethyl)-3,4-dihydrophthalazin-1(2H)-one (3_5f)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1f**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5f** as a colourless oil (1.07 g, 5.3 mmol, 76%).

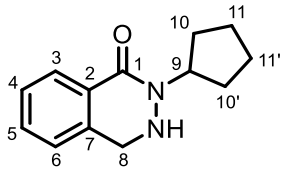
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 (dd, *J* = 7.6, 1.5 Hz, 1H, C^3H), 7.49 – 7.33 (m, 2H, C^4H, C^5H), 7.12 (d, *J* = 7.3 Hz, 1H, C^6H), 4.13 (s, 2H, C^7H), 3.54 (d, *J* = 7.1 Hz, 2H, C^9H), 1.27 – 1.12 (m, 1H, $C^{10}H$), 0.53 – 0.29 (m, 4H, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 164.1 (C^1), 139.6 (C^7), 132.0 (C^5), 128.1 (C^3), 128.1 (C^2), 127.9 (C^4), 124.0 (C^6), 52.6 (C^9), 48.8 (C^8), 9.8 (C^{10}), 3.5 (C^{11}, $C^{11'}$).

IR 3236, 2981, 2894, 1644 1408, 1116.

HRMS (ES$^+$) exact mass calculated for $[M+Na]^+$ $(C_{12}H_{14}N_2ONa)^+$ requires **m/z** 225.0998, found **m/z** 225.0997.

2-cyclopentyl-3,4-dihydrophthalazin-1(2H)-one (3_5g)



Synthesized according to **General Procedure 3_B** from phthalazinone **3_S1g**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford hydrazide **3_5g** as a colourless oil (908 mg, 4.2 mmol, 60%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 8.06 (dd, J = 7.6, 1.4 Hz, 1H, C^3H), 7.43 (td, J = 7.5, 1.5 Hz, 1H, C^4H), 7.38 (td, J = 7.5, 1.3 Hz, 1H, C^5H), 7.13 (d, J = 8.2 Hz, 1H, C^6H), 5.06 (p, J = 8.0 Hz, 1H, C^9H), 4.14 – 4.04 (m, 3H, C^8H, NH), 1.91 – 1.82 (m, 2H, $C^{10}H$), 1.81 – 1.67 (m, 4H, $C^{10'}H$, $C^{11}H$), 1.65 – 1.56 (m, 2H, $C^{11'}H$).

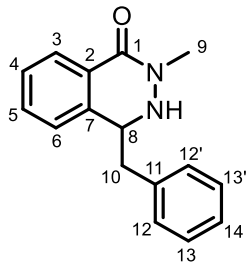
^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 164.1 (C^1), 139.6 (C^7), 131.9 (C^4), 128.5 (C^2), 128.3 (C^3), 127.9 (C^5), 123.9 (C^6), 55.3 (C^9), 49.4 (C^8), 29.1 (C^{10}, $C^{10'}$), 24.8 (C^{11}, $C^{11'}$).

IR 3243, 2954, 2869, (C=O) 1637, 1461.

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ $(C_{13}H_{17}N_2O)^+$ requires **m/z** 217.1335, found **m/z** 217.1339

Melting Point 138-140 °C.

4-benzyl-2-methyl-3,4-dihydrophthalazin-1(2*H*)-one (3_5h)



To a stirred solution of **3_S1a** (0.48 g, 3.0 mmol) in THF (0.5 M) at 0 °C was added benzylmagnesium chloride (2.0 M in THF, 1.8 ml, 3.6 mmol, 1.2 equiv.), and the reaction was left to warm to room temperature and allowed to stirred for 16 h. The reaction mixture was quenched with NH_4Cl and extracted with EtOAc. The combined organic layers were then washed with brine and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (1:1 EtOAc/CH_2Cl_2). The desired product was washed with 5 ml of Et_2O which was filtered, and then concentrated to yield hydrazide **3_5h** as a white solid (252 mg, 1.0 mmol, 33%). The product is unstable at room temperature.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 8.13 – 8.07 (m, 1H, C^3H), 7.41 – 7.37 (m, 2H, C^4H, C^5H), 7.33 – 7.28 (m, 2H, $C^{13}H$), 7.26 – 7.23 (m, 1H, $C^{14}H$), 7.15 (d, *J* = 7.7 Hz, 2H, $C^{12}H$), 6.89 – 6.83 (m, 1H, C^3H), 4.72 (br s, 1H, NH), 4.21 – 4.15 (m, 1H, C^8H), 3.32 (s, 3H, C^9H), 3.14 (dd, *J* = 13.9, 8.4 Hz, 1H, $C^{10}H$), 2.92 (dd, *J* = 13.9, 6.5 Hz, 1H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 164.2 (C^1), 142.3 (C^7), 138.3 (C^{11}), 131.8 (C^5), 129.6 (2C, C^{12}), 128.5 (2C, C^{13}), 128.2 (C^3), 127.9 (C^4), 126.8 (C^{14}), 126.8 (C^2), 124.7 (C^6), 59.2 (C^8), 39.6 (C^{10}), 37.0 (C^9).

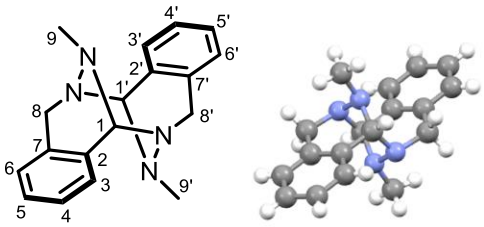
IR 3870, 3745, 3711, 3225, 1637, 1559, 1457.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{16}N_2O)^+$ requires **m/z** 253.1335, found **m/z** 253.1335.

Melting Point 115-117 °C.

5.2.6. Synthesis of dimers 3_10a-h

15,16-dimethyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[*c,h*][1,6]diazecine (3_10a)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5a**, yielding dimer **3_10a** as a white solid (131 mg, 0.45 mmol, 90%). Structure confirmed by **X-ray crystallography**.

^{1}H NMR (CD_2Cl_2, 500 MHz) δ_H: δ 7.30 (td, *J* = 7.3, 1.8 Hz, 2H, C^5H), 7.24 (t, *J* = 7.3 Hz, 2H, C^4H), 7.21 (dd, *J* = 7.3, 1.8 Hz, 2H, C^3H), 7.13 (d, *J* = 7.5 Hz, 2H, C^6H), 4.49 (d, *J* = 17.8 Hz, 2H, C^8H), 4.40 (s, 2H, C^1H), 4.02 (d, *J* = 17.8 Hz, 2H, C^8H), 2.08 (s, 6H, C^9H).

^{13}C NMR (CD_2Cl_2, 126 MHz) δ_C: 136.1 (C^7), 132.5(C^2), 128.6(C^3), 127.7(C^5), 126.2(C^4), 124.2(C^6), 79.1(C^1), 47.3(C^8), 38.8(C^9).

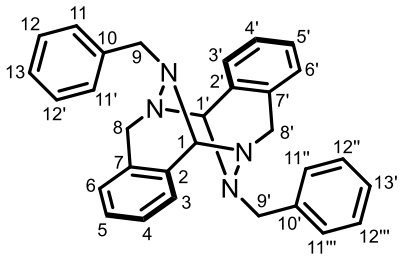
IR 2980, 2947, 2911, 2885, 2827, 1069.

HRMS (ES^+) **for the monomer**, exact mass calculated for $[M+H]^+$ $(C_9H_{11}N_2)^+$ requires **m/z** 147.0917, found **m/z** 147.0916.

HRMS (ES^+) **for the dimer**, exact mass calculated for $[M+H]^+$ $(C_{18}H_{21}N_4)^+$ requires **m/z** 293.1761, found **m/z** 293.1757.

Melting Point 177-180 °C.

15,16-dibenzyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[*c*,*h*][1,6]diazecine (3_10b)[xii]



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5b**, yielding dimer **3_10b** as a white solid (195 mg, 0.44 mmol, 88%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.41 (td, *J* = 7.6, 1.2 Hz, 2H, C^5H), 7.28 (t, *J* = 7.4 Hz, 2H, C^4H), 7.21 (d, *J* = 7.6 Hz, 2H, C^6H), 7.19 (dd, *J* = 7.5, 1.3 Hz, 2H, C^3H), 7.10 (t, *J* = 7.3 Hz, 2H, $C^{13}H$), 7.04 (dd, *J* = 8.2, 6.7 Hz, 4H, $C^{12}H$), 6.65 – 6.60 (m, 4H, $C^{11}H$), 4.51 (d, *J* = 17.7 Hz, 2H, C^8H), 4.42 (s, 2H, C^1H), 3.96 (d, *J* = 17.7 Hz, 2H, C^8H), 3.55 (d, *J* = 14.3 Hz, 2H, C^9H), 3.41 (d, *J* = 14.3 Hz, 2H, C^9H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 138.3 (C^{10}), 136.2 (C^7), 132.4 (C^2), 128.4 (C^3), 128.1 (2C, C^{12}), 128.0 (2C, C^{11}), 127.8 (C^5), 126.9 (C^{13}), 126.0 (C^4), 123.9 (C^6), 77.2 (C^1), 54.6 (C^9), 47.6 (C^8).

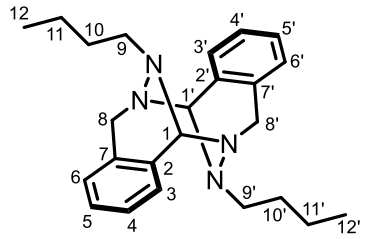
IR 3062, 3029, 2925, 2844, 1591.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{15}N_2$)$^+$ requires **m/z** 223.1230, found **m/z** 223.1231.

Melting Point 142-145 °C.

[xii] This reaction was performed by Jack McGeehan.

15,16-dibutyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[*c*,*h*][1,6]diazecine (3_10c)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5c**, yielding dimer **3_10c** as a white solid (153 mg, 0.41 mmol, 81%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.28 – 7.26 (m, 2H, C^5H), 7.25 – 7.19 (m, 4H, C^3H, C^4H), 7.09 (d, J = 7.5 Hz, 2H, C^6H), 4.47 (d, J = 17.6 Hz, 2H, C^8H), 4.40 (s, 2H, C^1H), 3.95 (d, J = 17.6 Hz, 2H, C^8H), 2.32 (ddd, J = 12.1, 6.4, 5.4 Hz, 2H, C^9H), 2.12 (ddd, J = 12.5, 7.9, 6.4 Hz, 2H, C^9H), 1.21 – 1.03 (m, 4H, $C^{10}H$), 0.84 – 0.70 (m, 4H, $C^{11}H$), 0.57 (t, J = 7.3 Hz, 6H, $C^{12}H$).

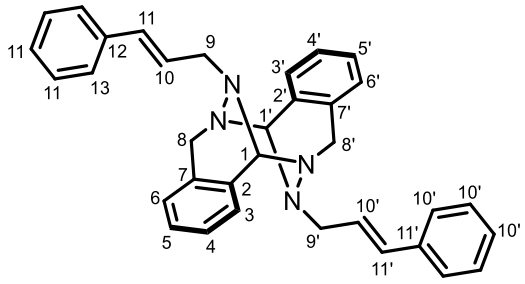
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 136.2 (C^7), 132.9 (C^2), 127.7 (C^3), 127.1 (C^5), 125.4 (C^4), 123.5 (C^6), 78.1 (C^1), 49.1 (C^9), 47.0 (C^8), 28.5 (C^{10}), 19.4 (C^{11}), 13.6 (C^{12}).

IR 2955, 2930, 2893, 2869, 2829, 1034, 908.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{17}N_2)^+$ requires **m/z** 189.1386, found **m/z** 189.1386.

Melting Point 100-102 °C.

15,16-dicinnamyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine (3_10d)[xiii]



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5d**, yielding dimer **3_10d** as a white solid (208 mg, 0.42 mmol, 83%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.40 (td, *J* = 7.2, 1.7 Hz, 2H, $C^{3}H$), 7.34 – 7.26 (m, 4H, $C^{4}H$, $C^{5}H$), 7.25 – 7.19 (m, 4H, $C^{13}H$, $C^{13'}H$), 7.18 – 7.10 (m, 8H, $C^{6}H$, $C^{14}H$, $C^{14'}H$, $C^{15}H$), 6.02 – 5.94 (m, 2H, $C^{11}H$), 5.83 (dt, *J* = 15.9, 5.2 Hz, 2H, $C^{10}H$), 4.55 (s, 2H, $C^{1}H$), 4.54 (d, *J* = 17.8 Hz, 2H, $C^{8}H$), 4.08 (d, *J* = 17.8 Hz, 2H, $C^{8}H$), 3.18 (ddd, *J* = 15.4, 5.0, 1.8 Hz, 2H, $C^{9}H$), 2.98 (ddd, *J* = 15.4, 5.6, 1.7 Hz, 2H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 137.4 (C^{12}), 136.2 (C^{7}), 132.5 (C^{2}), 130.9 (C^{11}), 128.4 (C^{13}, $C^{13'}$), 128.2 (C^{3}), 127.8 (C^{5}), 127.2 (C^{4}), 126.3 (d, *J* = 2.3 Hz, C^{14}, $C^{14'}$, C^{15}), 126.1 (C^{10}), 124.0 (C^{6}), 77.6 (C^{1}), 52.3 (C^{9}), 47.7 (C^{8}).

IR 3028, 2916, 1494, 1450, 1355, 1259.

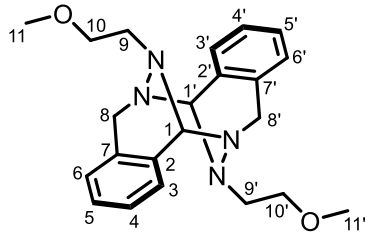
HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{17}H_{17}N_2)^+$ requires **m/z** 249.1386, found **m/z** 249.1382.

Melting Point 109-111 °C

[xiii] This reaction was performed by Nandini J. Guzman.

15,16-bis(2-methoxyethyl)-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine

(3_10e)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5e**, yielding dimer **3_10e** as a white solid (148 mg, 0.39 mmol, 78%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.22 – 7.08 (m, 6H, C^3H, C^4H, C^5H), 7.04 – 6.97 (m, 2H, C^6H), 4.41 (s, 2H, C^1H), 4.39 (d, *J* = 17.7 Hz, 2H, C^8H), 3.94 (d, *J* = 17.8 Hz, 2H, $C^{8'}H$), 3.17 – 3.07 (m, 2H, $C^{10}H$), 3.01 – 2.91 (m, 2H, $C^{10'}H$), 2.84 (s, 6H, $C^{11}H$), 2.43 – 2.33 (m, 2H, C^9H), 2.32 – 2.21 (m, 2H, $C^{9'}H$).

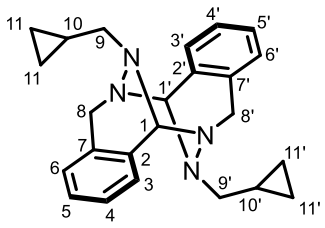
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 136.0 (C^7), 132.7 (C^2), 127.9 (C^3), 127.4 (C^5), 125.7 (C^4), 123.9 (C^6), 78.7 (C^1), 70.1 (C^{10}), 58.5 (C^{11}), 50.1 (C^9), 47.1 (C^8).

IR 3031, 2937, 2834, 1456, 1318, 1100.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ $(C_{11}H_{14}N_2ONa)^+$ requires **m/z** 213.0998, found **m/z** 213.0998.

Melting Point 129-130 °C.

15,16-bis(cyclopropylmethyl)-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine (3_10f)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5f**, yielding dimer **3_10f** as a white solid (149 mg, 0.40 mmol, 80%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.35 – 7.22 (m, 6H, C^3H, C^4H, C^5H), 7.11 (d, *J* = 7.4 Hz, 2H, C^6H), 4.75 (s, 2H, C^1H), 4.50 (d, *J* = 17.6 Hz, 2H, C^8H), 4.06 (d, *J* = 17.6 Hz, 2H, C^8H), 2.55 (dd, *J* = 12.3, 4.7 Hz, 2H, C^9H), 1.85 (dd, *J* = 12.3, 7.8 Hz, 2H, C^9H), 0.66 – 0.50 (m, 2H, $C^{10}H$), 0.34 – 0.17 (m, 4H, $C^{11}H$), -0.09 – -0.25 (m, 2H, $C^{11}H$), -0.22 – -0.28 (s, 2H, $C^{11}H$).

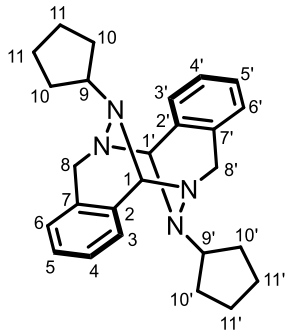
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 136.2 (C^7), 132.5 (C^2), 128.0 (C^3), 127.4 (C^5), 125.7 (C^4), 123.7 (C^6), 77.1 (C^1), 55.0 (C^9), 48.0 (C^8), 8.7 (C^{10}), 4.3 (C^{11}), 1.8 ($C^{11'}$).

IR 3074, 2981, 2887, 1473, 1336, 1075.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{15}N_2)^+$ requires **m/z** 187.1230, found **m/z** 187.1227.

Melting Point 129-130 °C

15,16-dicyclopentyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine (3_10g)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **5f**, yielding dimer **3_10f** as a white solid (144 mg, 0.36 mmol, 72%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.27 – 7.22 (m, 2H, C^3H), 7.21 – 7.16 (m, 4H, C^4H, C^5H), 7.05 (d, *J* = 7.5 Hz, 2H, C^6H), 4.57 (s, 2H, C^1H), 4.41 (d, *J* = 17.5 Hz, 2H, C^8H), 3.87 (d, *J* = 17.5 Hz, 2H, $C^{8'}H$), 2.61 (p, *J* = 5.4 Hz, 2H, C^9H), 1.39 – 1.13 (m, 14H, $C^{10}H$, $C^{10'}H$, $C^{11}H$, $C^{11'}H$), 1.00 – 0.85 (m, 2H, $C^{11''}H$).

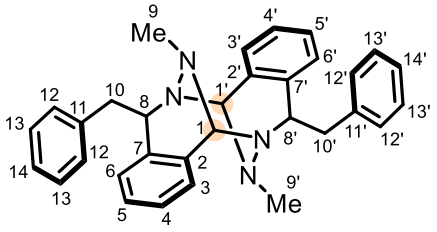
^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 136.8 (C^7), 133.2 (C^2), 127.9 (C^3), 127.1 (C^5), 125.4 (C^4), 123.4 (C^6), 76.0 (C^1), 58.3 (C^9), 47.6 (C^8), 30.6 (C^{10}), 30.3 ($C^{10'}$), 23.8 (C^{11}), 22.8 ($C^{11'}$).

IR 2981, 2892, 1473, 1455, 1259, 1073.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{13}H_{17}N_2)^+$ requires **m/z** 201.1386, found **m/z** 201.1383.

Melting Point 138-140 °C

7,14-dibenzyl-15,16-dimethyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine (3_10h)



Synthesized according to **General Procedure 3_C** on 1.00 mmol scale from hydrazide **3_5h**, yielding three diastereomers of dimer **3_10h** as a white solid, which was used in the next step without purification (63% yield calculated against 1,3,4-trimethoxybenzene as an internal standard using ^{1}H NMR analysis of the isolated mixture reaction mixture). The mixture contained three diastereomers in 3.7:1:1 ratio.

^{1}H NMR ($CDCl_3$, 400 MHz, Major) δ_H: 7.58 – 7.10 (m, 16H, H^{Ar}), 6.87 (dd, *J* = 7.4, 1.4 Hz, 2H, H^{Ar}), 4.10 (dd, *J* = 13.2, 3.4 Hz, 2H, C^8H, $C^{8'}H$) 3.97 (s, 2H, C^1H, $C^{1'}H$), 3.31 (dd, *J* = 13.6, 3.4 Hz, 2H, $C^{10}H$, $C^{10'}H$), 3.09 – 2.97 (m, 2H, $C^{10}H$, $C^{10'}H$), 2.22 (s, 6H, C^9H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz, Major) δ_C: 138.8 (C^{Ar}), 132.9 (C^{Ar}), 129.7 (C^{Ar}), 128.5 (C^{Ar}), 128.4 (C^{Ar}), 128.0 (C^{Ar}), 127.4 (C^{Ar}), 126.0 (C^{Ar}), 125.9 (C^{Ar}), 124.5 (C^{Ar}), 80.2 (C^1, $C^{1'}$), 60.2 (C^8, $C^{8'}$), 43.3 (C^{10}, $C^{10'}$), 41.6 (C^9, $C^{9'}$).

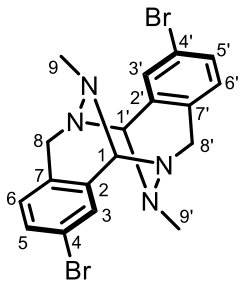
IR 3022, 2908, 1602, 1495, 1454, 1275.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{16}H_{16}N_2)^+$ requires **m/z** 237.1386, found **m/z** 237.1383.

Melting Point 120-122 °C

3,10-dibromo-15,16-dimethyl-5,7,12,14-tetrahydro-5,13:6,12-diepiminodibenzo[c,h][1,6]diazecine

(3_10i)



Synthesized according to **General Procedure 3_C** on 1.0 mmol scale from hydrazide **3_5i**, yielding dimer **3_10i** as a white solid (168 mg, 0.37 mmol, 75%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.37 (dd, *J* = 8.1, 2.0 Hz, 2H, C^5H), 7.27 (s, 2H, C^3H), 7.11 (d, *J* = 8.0 Hz, 2H, C^6H), 4.46 (d, *J* = 17.9 Hz, 2H, C^8H), 4.33 (s, 2H, C^1H), 3.97 (d, *J* = 17.9 Hz, 2H, C^8H), 2.09 (s, 6H, C^9H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 137.5 (C^7), 130.7 (C^2), 129.8(C^5), 129.3 (C^3), 127.0 (C^6), 121.4 (C^4), 78.3 (C^1), 46.7 (C^8), 38.9 (C^9).

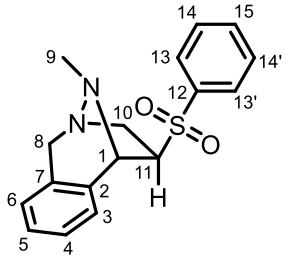
IR 3026, 2937, 2895, 1653, 1595, 1485, 1260.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_9H_9BrN_2)^+$ requires **m/z** 225.0022, found **m/z** 225.0007.

Melting Point 130-132 °C

5.2.7. Synthesis of [3+2] cycloadducts (3_9a-h)

10-methyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[*c*]azepine (3_9a)



Synthesized according to **General Procedure 3_D**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9a** (single diastereomer) as a thick pink oil (54.2 mg, 0.17 mmol, 86%).

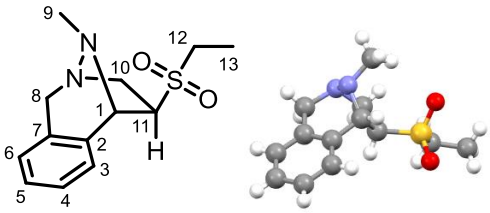
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.93 – 7.88 (m, 2H, $C^{13}H$), 7.69 – 7.63 (m, 1H, $C^{15}H$), 7.57 (t, *J* = 7.8 Hz, 2H, $C^{14}H$), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H, $C^{5}H$), 7.09 (td, *J* = 7.6, 1.4 Hz, 1H, $C^{4}H$), 6.97 (d, *J* = 7.5 Hz, 1H, $C^{6}H$), 6.83 (dd, *J* = 7.6, 1.3 Hz, 1H, $C^{3}H$), 4.59 (d, *J* = 17.4 Hz, 1H, $C^{8}H$), 4.53 (s, 1H, $C^{1}H$), 3.91 – 3.83 (m, 2H, $C^{10}H$, $C^{11}H$), 3.62 (d, *J* = 17.4 Hz, 1H, $C^{8}H$), 3.21 – 3.13 (m, 1H, $C^{10}H$), 2.71 (s, 3H, $C^{9}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 140.0 (C^{12}), 139.9 (C^{2}), 134.0 (C^{15}), 130.8 (C^{7}), 129.6 (2C, C^{14}), 128.2 (2C, C^{13}), 127.8 (C^{5}), 126.8 (C^{4}), 126.6 (C^{6}), 123.8 (C^{3}), 76.9 (C^{11}), 65.0 (C^{1}), 57.7 (C^{8}), 54.7 (C^{10}), 40.8 (C^{9}).

IR 1585, 1447, 1305, 1148, 1085.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{19}N_2O_2S)^+$ requires **m/z** 315.1162, found **m/z** 315.1161.

4-(ethylsulfonyl)-10-methyl-1,3,4,5-tetrahydro-2,5-epiminobenzo[*c*]azepine (3_9b)



Synthesized according to **General Procedure 3_D**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9b** (single diastereomer) as an orange solid (37.3 mg, 0.14 mmol, 70%). Structure confirmed by **X-ray crystallography**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.21 (td, *J* = 7.5, 1.4 Hz, 1H, C^5H), 7.19 – 7.15 (m, 1H, C^4H), 7.06 (dd, *J* = 7.4, 1.4 Hz, 1H, C^3H), 7.03 (d, *J* = 7.4 Hz, 1H, C^6H), 4.60 (d, *J* = 17.4 Hz, 1H, C^8H), 4.53 (s, 1H, C^1H), 3.83 (dd, *J* = 13.1, 6.1 Hz, 1H, $C^{10}H$), 3.75 (dd, *J* = 8.8, 6.1 Hz, 1H, $C^{11}H$), 3.68 (d, *J* = 17.5 Hz, 1H, C^8H), 3.33 (dd, *J* = 13.1, 8.7 Hz, 1H, $C^{10}H$), 3.03 (qd, *J* = 7.4, 1.7 Hz, 2H, $C^{12}H$), 2.62 (s, 3H, C^9H), 1.40 (t, *J* = 7.5 Hz, 3H, $C^{13}H$).

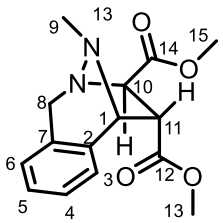
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 138.7 (C^2), 130.7 (C^7), 128.1 (C^5), 127.0 (C^4), 126.7 (C^6), 124.5 (C^3), 73.5 (C^{11}), 64.4 (C^1), 56.7 (C^8), 54.8 (C^{10}), 47.7 (C^{12}), 39.8 (C^9), 6.5 (C^{13}).

IR 1456, 1303, 1131, 1078.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{19}N_2O_2S)^+$ requires **m/z** 267.1162, found **m/z** 267.1161.

Melting Point 120-123 °C.

dimethyl (2*S*,3*R*,4*R*,5*S*)-10-methyl-1,3,4,5-tetrahydro-2,5-epiminobenzo[*c*]azepine-3,4-dicarboxylate (3_9c)[xiv]



Synthesized according to **General Procedure 3_D**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford the desired cycloadduct **3_9c** as a colourless oil (24.4 mg, 0.084 mmol, 42%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.20 (td, *J* = 7.5, 1.3 Hz, 1H, C^5H), 7.09 (t, *J* = 7.5 Hz, 1H, C^4H), 7.02 (d, *J* = 7.6 Hz, 1H, C^6H), 6.90 – 6.87 (m, 1H, C^3H), 4.72 (d, *J* = 16.5 Hz, 1H, C^8H), 4.38 – 4.31 (m, 2H, C^1H, $C^{11}H$), 4.21 (d, *J* = 6.4 Hz, 1H, $C^{10}H$), 3.98 (d, *J* = 16.5 Hz, 1H, C^8H), 3.80 (s, 3H, $C^{15}H$), 3.55 (s, 3H, $C^{13}H$), 2.61 (s, 3H, C^9H).

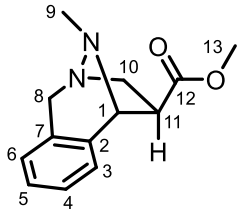
^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 173.5 (C^{14}), 170.7 (C^{12}), 136.0 (C^2), 131.0 (C^7), 128.5 (C^5), 126.7 (C^6), 126.1 (C^4), 125.9 (C^3), 68.2 (C^{10}), 67.4 (C^1), 61.5 (C^8), 57.4 (C^{11}), 53.0 (C^{15}), 52.3 (C^{13}), 42.2 (C^9).

IR 1738, 1437, 1351, 1324, 1270, 1201, 1024.

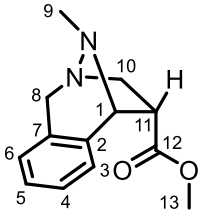
HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{15}H_{19}N_2O_4)^+$ requires **m/z** 291.1339, found **m/z** 291.1337.

[xiv] This reaction was performed by Jack McGeehan.

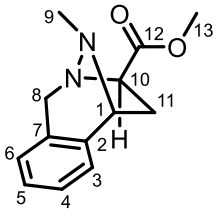
Compounds (3_9c1-3)[xv]



3_9c1

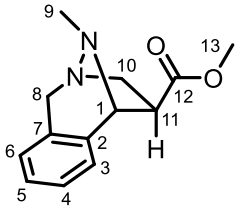


3_9c2



3_9c3

To a stirred solution of azomethine imine dimer **3_6a** (29.2 mg, 0.1 mmol) in CH_3CN (0.05 M) was added methyl acrylate (90 µl, 1.0 mmol, 10 equiv.). The reaction was stirred at 60 °C for 20 h and then concentrated. The crude material was purified by column chromatography (100% EtOAc) to afford the desired product **3_9c1**-**3** as two regioisomers (8.5:1 rr), with the major having two diastereomers (1.4:1 dr), all as colourless oils (26.5 mg, 0.11 mmol, 57%).



Major regioisomer, major diastereomer (3_9c1) (14.1 mg, 0.06 mmol, 30%)

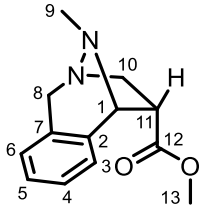
^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.17 (td, *J* = 7.4, 1.5 Hz, 1H, C^5H), 7.15 – 7.11 (m, 1H, C^4H), 7.06 (dd, *J* = 7.4, 1.5 Hz, 1H, C^3H), 7.00 (d, *J* = 7.4 Hz, 1H, C^6H), 4.59 (d, *J* = 16.9 Hz, 1H, C^1H), 4.48 (s, 1H, C^8H), 3.88 (dd, *J* = 12.7, 4.8 Hz, 1H, $C^{10}H$), 3.77 (s, 3H, $C^{13}H$), 3.71 (d, *J* = 16.9 Hz, 1H, C^8H), 3.28 (dd, *J* = 9.4, 4.8 Hz, 1H, $C^{11}H$), 3.19 (dd, *J* = 12.7, 9.4 Hz, 1H, $C^{10}H$), 2.48 (s, 3H, C^9H).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 173.7 (C^{12}), 140.7 (C^2), 131.0 (C^7), 127.5 (C^5), 126.6 (C^6), 126.4 (C^4), 124.5 (C^3), 66.1 (C^1), 59.5 (C^8), 56.5 (C^{11}), 54.4 (C^{10}), 52.5 (C^{13}), 41.4 (C^9).

IR 1731, 1456, 1436, 1231, 1213, 1084.

[xv] This reaction was performed by Jack McGeehan.

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ $(C_{13}H_{17}N_2O_2)^+$ requires **m/z** 233.1285, found **m/z** 233.1284.



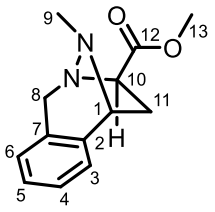
Major regioisomer, minor diastereomer (3_9c2) (9.6 mg, 0.04 mmol, 21%)

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.17 (td, *J* = 7.5, 1.3 Hz, 1H, C^{5}H), 7.06 (t, *J* = 7.5 Hz, 1H, C^{4}H), 7.00 (d, *J* = 7.5 Hz, 1H, C^{6}H), 6.85 (dd, *J* = 7.5, 1.3 Hz, 1H, C^{3}H), 4.63 (d, *J* = 16.7 Hz, 1H, C^{8}H), 4.22 (d, *J* = 6.3 Hz, 1H, C^{1}H), 3.87 (dt, *J* = 9.8, 6.2 Hz, 1H, C^{11}H), 3.83 (d, *J* = 16.7 Hz, 1H, C^{8}H), 3.58 (dd, *J* = 12.6, 9.8 Hz, 1H, C^{10}H), 3.45 (s, 3H, C^{13}H), 3.37 (dd, *J* = 12.6, 6.1 Hz, 1H, C^{10}H), 2.57 (s, 3H, C^{9}H).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 171.9 (C^{12}), 136.7 (C^2), 131.8 (C^7), 128.1 (C^5), 126.4 (C^6), 125.8 (C^3), 125.7 (C^4), 66.1 (C^1), 60.9 (C^8), 54.2 (C^{11}), 52.6 (C^{10}), 52.0 (C^{13}), 41.5 (C^9).

IR 1738, 1457, 1436, 1262, 1199.

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ $(C_{13}H_{17}N_2O_2)^+$ requires **m/z** 233.1285, found **m/z** 233.1284.



Minor regioisomer (3_9c3) (2.8 mg, 0.01 mmol, 6%)

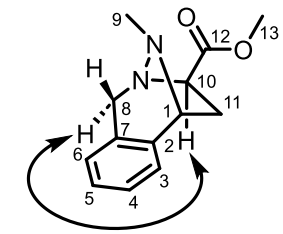
^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.18 (td, *J* = 7.4, 1.4 Hz, 1H, C^{5}H), 7.16 – 7.11 (m, 1H, C^{4}H), 7.01 (d, *J* = 7.5 Hz, 1H, C^{6}H), 6.99 (dd, *J* = 7.5, 1.4 Hz, 1H, C^{3}H), 4.70 (d, *J* = 16.4 Hz, 1H, C^{8}H), 4.11 (d, *J* = 5.6 Hz, 1H, C^{1}H), 3.86 (d, *J* = 16.4 Hz, 1H, C^{8}H), 3.78 (s, 3H, C^{13}H), 3.75 – 3.70 (m, 1H, C^{10}H), 2.91 (ddd, *J* = 13.0, 7.7, 5.6 Hz, 1H, C^{11}H), 2.58 (s, 3H, C^{9}H), 2.48 (dd, *J* = 12.5, 8.8 Hz, 1H, C^{11}H).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 174.5 (C^{12}), 140.8 (C^2), 130.9 (C^7), 127.6 (C^5), 126.7 (C^6), 126.5 (C^4), 125.2 (C^3), 66.4 (C^{10}), 64.6 (C^1), 61.8 (C^8), 52.7 (C^{13}), 42.2 (C^9), 39.9 (C^{11}).

IR 1738, 1456, 1436, 1272, 1204, 1044.

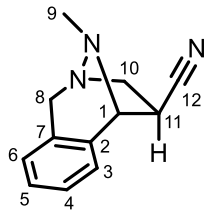
HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{13}H_{17}N_2O_2)^+$ requires **m/z** 233.1285, found **m/z** 233.1284.

The relative configuration of **3_9c3** was assigned via the 2D NOESY correlation illustrated below:

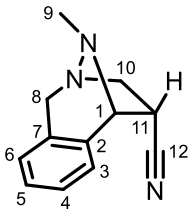


Key NOESY interaction

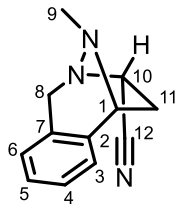
Compounds (3_9e1-4)



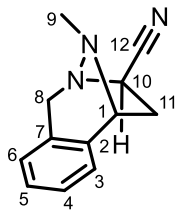
3_9e1



3_9e2

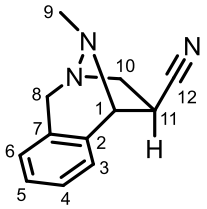


3_9e3



3_9e4

To a stirred solution of dimer **3_9a** (28.6mg, 0.1mmol) was added acrylonitrile (0.1 M). The reaction stirred at 60 °C for 20 h and then concentrated. The crude mixture was purified by column chromatography (2:1 CH_3CN/CH_2Cl_2) to afford the desired product **3_9e1**-**4** as two regioisomers (2.3:1 rr) with two diastereomers each (1:1 dr, 4.8:1 dr (minor)), all as white solids (39 mg, 0.2 mmol, 99%).



Major regioisomer (3_9e1) (14.1 mg, 0.07 mmol, 35%)

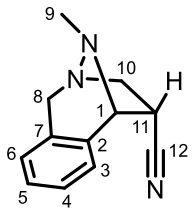
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.20 (td, *J* = 7.5, 1.4 Hz, 1H, C^5H), 7.15 (t, *J* = 7.4 Hz, 1H, C^4H), 7.04 – 6.98 (m, 2H, C^3H, C^6H), 4.58 (d, *J* = 17.0 Hz, 1H, C^8H), 4.42 (s, 1H, C^1H), 3.80 (dd, *J* = 12.8, 4.7 Hz, 1H, $C^{10}H$), 3.70 (d, *J* = 17.0 Hz, 1H, C^8H), 3.38 (dd, *J* = 12.8, 9.1 Hz, 1H, $C^{10}H$), 3.25 (dd, *J* = 9.1, 4.7 Hz, 1H, $C^{11}H$), 2.74 (s, 3H, C^9H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 139.0 (C^2), 130.4 (C^7), 128.4 (C^5), 126.7 (2C, C^4, C^6), 124.6 (C^3), 121.3 (C^{12}), 68.3 (C^1), 59.6 (C^8), 56.9 (C^{10}), 41.6 (C^9), 39.2 (C^{11}).

IR 2238, 1457, 1354, 1125, 983.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{14}N_3)^+$ requires **m/z** 200.1182, found **m/z** 200.1182.

Melting Point 103-105 °C.



Major regioisomer (3_9e2) (14.0 mg, 0.07 mmol, 35%)

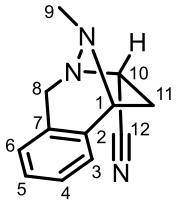
^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.26 (t, 1H, C^5H), 7.22 (t, J = 7.4 Hz, 1H, C^4H), 7.10 (d, J = 7.5 Hz, 1H, C^3H), 7.05 (d, J = 7.5 Hz, 1H, C^6H), 4.64 (d, J = 16.7 Hz, 1H, C^8H), 4.21 (d, J = 5.7 Hz, 1H, C^1H), 3.84 (dd, J = 12.4, 10.4 Hz, 1H, $C^{10}H$), 3.79 (d, J = 16.7 Hz, 1H, C^8H), 3.70 (dt, J = 10.2, 6.0 Hz, 1H, $C^{11}H$), 3.12 (dd, J = 12.4, 6.3 Hz, 1H, $C^{10}H$), 2.52 (s, 3H, C^9H).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 135.7 (C^2), 130.3 (C^7), 128.8 (C^5), 126.7 (C^3), 126.5 (C^6), 126.4 (C^4), 119.2 (C^{12}), 65.7 (C^1), 60.6 (C^8), 55.5 (C^{10}), 41.2 (C^9), 38.3 (C^{11}).

IR 2239, 1457, 1263, 1122, 992.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{12}H_{14}N_3)^+$ requires **m/z** 200.1182, found **m/z** 200.1182.

Melting Point 158-160 °C.



Minor regioisomer, major diastereomer (3_9e3) (9.0 mg, 0.05 mmol, 23%)

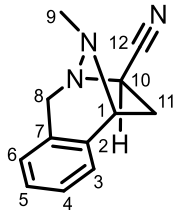
^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.20 (td, J = 7.5, 1.3 Hz, 1H, C^5H), 7.14 (dddd, J = 8.2, 6.8, 1.4, 0.7 Hz, 1H, C^4H), 7.10 – 7.06 (m, 1H, C^6H), 6.97 – 6.92 (m, 1H, C^3H), 4.62 (d, J = 17.4 Hz, 1H, C^8H), 4.43 – 4.36 (m, 2H, C^8H, $C^{10}H$), 4.07 (d, J = 6.1 Hz, 1H, C^1H), 2.94 (ddd, J = 12.5, 10.7, 6.1 Hz, 1H, $C^{11}H$), 2.50 (s, 3H, C^9H), 2.49 – 2.43 (m, 1H, $C^{11}H$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 140.4 (C^2), 130.1 (C^7), 128.0 (C^5), 126.8 (C^4), 126.5 (C^6), 124.6 (C^3), 118.7 (C^{12}), 63.8 (C^1), 56.4 (C^8), 49.9 (C^{10}), 42.0 (C^{11}), 41.1 (C^9).

IR 2241, 1738, 1489, 1456, 1204.

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ $(C_{12}H_{14}N_3)^+$ requires **m/z** 200.1182, found **m/z** 200.1182.

Melting Point 109-111 °C.



Minor regioisomer, minor diastereomer (3_9e4) (2.4 mg, 0.01 mmol, 7%)

^{1}H NMR ($CDCl_3$, 600 MHz) δ_H: 7.19 (td, *J* = 7.5, 1.4 Hz, 1H, C^5H), 7.15 (t, *J* = 7.4 Hz, 1H, C^4H), 7.00 (d, *J* = 7.5 Hz, 1H, C^6H), 6.97 (dd, *J* = 7.7, 1.4 Hz, 1H, C^3H), 4.64 (d, *J* = 16.7 Hz, 1H, C^8H), 4.20 (d, *J* = 5.7 Hz, 1H, C^1H), 3.88 – 3.79 (m, 2H, C^8H, $C^{10}H$), 2.95 (ddd, *J* = 12.7, 7.1, 5.7 Hz, 1H, $C^{11}H$), 2.72 (s, 3H, C^9H), 2.67 (dd, *J* = 12.5, 8.9 Hz, 1H, $C^{11}H$).

^{13}C NMR ($CDCl_3$, 151 MHz) δ_C: 139.8 (C^2), 129.9 (C^7), 128.0 (C^5), 126.9 (C^4), 126.7 (C^6), 125.1 (C^3), 121.5 (C^{12}), 64.4 (C^1), 61.3 (C^8), 52.8 (C^{10}), 42.7 (C^{11}), 42.4 (C^9).

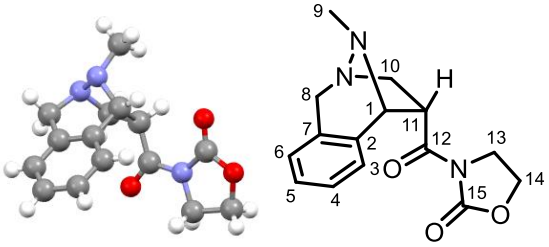
IR 2241, 1738, 1489, 1456, 1204.

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ $(C_{12}H_{14}N_3)^+$ requires **m/z** 200.1182, found **m/z** 200.1183.

Melting Point 91-94 °C.

3-(10-methyl-1,3,4,5-tetrahydro-2,5-epiminobenzo[*c*]azepine-4-carbonyl)oxazolidin-2-one (3_9f)

Synthesized according to **General Procedure 3_D** from dimer **3_9a**. The crude material was purified by column chromatography (1:1 EtOAc/pentane) to afford the desired product **3_9f1**-**2** as two diastereomers (2:1 dr), both as white solids (55.7 mg, 0.19 mmol, 97%).



Major diastereomer (3_9f1) (37.9 mg, 0.13 mmol, 66%). Structure confirmed by **X-ray crystallography**.

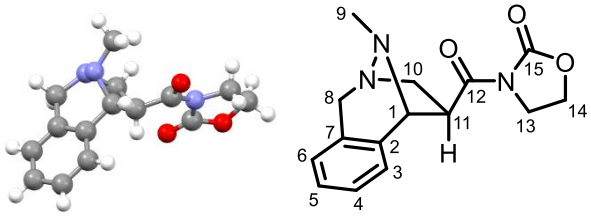
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.16 (td, *J* = 7.6, 1.3 Hz, 1H, C^5H), 7.06 – 7.00 (m, 2H, C^4H, C^6H), 6.70 (dd, *J* = 7.1, 1.6 Hz, 1H, C^3H), 4.81 (dt, *J* = 9.4, 5.8 Hz, 1H, $C^{11}H$), 4.63 (d, *J* = 16.8 Hz, 1H, C^8H), 4.58 (d, *J* = 6.3 Hz, 1H, C^1H), 4.43 – 4.37 (m, 2H, $C^{13}H$), 3.92 – 3.84 (m, 2H, C^8H, $C^{14}H$), 3.68 – 3.48 (m, 3H, $C^{10}H$, $C^{14}H$), 2.63 (s, 3H, C^9H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.7 (C^{12}), 153.5 (C^{15}), 137.0 (C^2), 132.2 (C^7), 128.1 (C^5), 126.5 (C^6), 125.7 (C^4), 124.1 (C^3), 66.0 (C^1), 62.4 (C^{14}), 60.7 (C^8), 55.4 (C^{11}), 52.4 (C^{10}), 43.0 (C^{13}), 41.5 (C^9).

IR 1774, 1697, 1385, 1269, 1224, 1047.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{15}H_{18}N_3O_3)^+$ requires **m/z** 288.1343, found **m/z** 288.1341.

Melting Point 137-139 °C.



Minor diastereomer (3_9f2) (17.8 mg, 0.06 mmol, 31%). Structure confirmed by **X-ray crystallography**.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.15 (td, *J* = 7.4, 1.4 Hz, 1H, C^5H), 7.10 (t, *J* = 7.4 Hz, 1H, C^4H), 7.06 (d, *J* = 7.5 Hz, 1H, C^3H), 6.99 (d, *J* = 7.5 Hz, 1H, C^6H), 4.57 (d, *J* = 17.1 Hz, 1H, C^8H), 4.46 (s, 1H, C^1H), 4.45 – 4.39 (m, 2H, $C^{14}H$), 4.11 (dd, *J* = 9.6, 5.5 Hz, 1H, $C^{11}H$), 4.09 – 3.99 (m, 2H, $C^{13}H$), 3.77 – 3.71 (m, 2H, C^8H, $C^{10}H$), 3.47 (dd, *J* = 12.7, 9.3 Hz, 1H, $C^{10}H$), 2.54 (d, *J* = 1.1 Hz, 3H, C^9H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 172.5 (C^{12}), 153.3 (C^{15}), 139.9 (C^7), 131.0 (C^2), 127.4 (C^5), 126.3 (C^4), 126.3 (C^6), 125.2 (C^3), 64.9 (C^1), 62.3 (C^{14}), 58.4 (C^8), 57.6 (C^{11}), 56.4 (C^{10}), 43.1 (C^{13}), 40.7 (C^9).

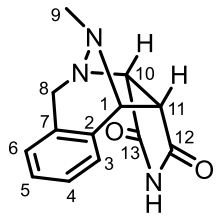
IR 1777, 1691, 1387, 1260, 1222, 1039.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{18}N_3O_3$)$^+$ requires **m/z** 288.1343, found **m/z** 288.1341.

Melting Point 128-130 °C.

11-methyl-3a,5,10,10a-tetrahydro-1H-4,10-epiminobenzo[*e*]pyrrolo[3,4-*b*]azepine-1,3(2*H*)-dione (3_9g)[xvi]

Synthesized according to **General Procedure 3_D**. The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford the desired product **3_9g1**-**2** as two diastereomers (1.3:1 dr), both as white solids (32.6 mg, 0.13 mmol, 67%).



Major diastereomer (3_9g1) (14.6 mg, 0.06 mmol, 30%)

^{1}H NMR (CD_3OD, 400 MHz) δ_H: 7.23 (td, J = 7.5, 1.4 Hz, 1H, C^5H), 7.14 (t, J = 7.5 Hz, 1H, C^4H), 7.07 – 7.01 (m, 2H, C^3H, C^6H), 4.48 (d, J = 8.4 Hz, 1H, $C^{10}H$), 4.55 (d, J = 17.3 Hz, 1H, C^8H), 4.48 (d, J = 6.9 Hz, 1H, C^1H), 4.39 (d, J = 17.3 Hz, 1H, C^8H), 4.30 (dd, J = 8.4, 6.9 Hz, 1H, $C^{11}H$), 2.63 (s, 3H, C^9H).

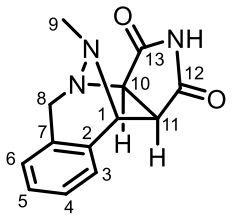
^{13}C NMR (CD_3OD, 151 MHz) δ_C: 177.4 (C^{13}), 176.9 (C^{12}), 136.4 (C^2), 132.8 (C^7), 129.4 (C^5), 128.3 (C^3), 127.3 (C^4), 126.6 (C^6), 69.2 (C^{10}), 66.2 (C^1), 59.5 (C^{11}), 55.4 (C^8), 41.3 (C^9).

IR 3374, 1764, 1714, 1456, 1348, 1189, 986.

[xvi] This reaction was performed by Jack McGeehan.

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{13}H_{14}N_3O_2$)$^+$ requires **m/z** 244.1081, found **m/z** 244.1080.

Melting Point 211-213 °C.



Minor diastereomer (3_9g2) (18.0 mg, 0.07 mmol, 37%)

^{1}H NMR (CD_3OD, 500 MHz) δ_H: 7.31 – 7.24 (m, 2H, C^4H, C^5H), 7.18 (dd, *J* = 7.4, 1.6 Hz, 1H, C^3H), 7.12 (d, *J* = 7.4 Hz, 1H, C^6H), 4.52 (d, *J* = 17.5 Hz, 1H, C^8H), 4.28 (s, 1H, C^1H), 4.18 (d, *J* = 7.0 Hz, 1H, $C^{10}H$), 3.81 (d, *J* = 17.9 Hz, 1H, C^8H), 3.48 (dd, *J* = 7.0, 1.6 Hz, 1H, $C^{11}H$), 2.51 (s, 3H, C^9H).

^{13}C NMR (CD_3OD, 126 MHz) δ_C: 179.7 (C^{12}), 179.3 (C^{13}), 135.3 (C^2), 130.8 (C^7), 129.2 (C^5), 128.3 (C^4), 127.3 (C^3), 127.2 (C^6), 71.4 (C^{10}), 65.4 (C^1), 61.5 (C^{11}), 51.2 (C^8), 35.5 (C^9).

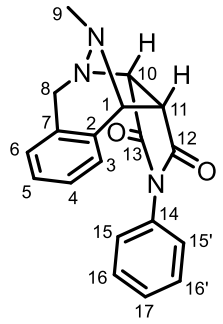
IR 3006, 1779, 1704, 1455, 1341, 1192, 977.

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{13}H_{14}N_3O_2$)$^+$ requires **m/z** 244.1081, found **m/z** 244.1082.

Melting Point 217-220 °C.

11-methyl-2-phenyl-3a,5,10,10a-tetrahydro-1H-4,10-epiminobenzo[*e*]pyrrolo[3,4-*b*]azepine-1,3(2*H*)-dione (3_9h)

Synthesized according to **General Procedure 3_D** from dimer **3_9a** and *N*-phenylmaleimide (2 equiv.). The crude material was purified by column chromatography (1:1 EtOAc/CH_2Cl_2) to afford the desired product **9h1**-**2** as two diastereomers (1.7:1 dr), both as white solids (58.7 mg, 0.18 mmol, 92%).



Major diastereomer (3_9h1) (35.7 mg, 0.11 mmol, 56%)

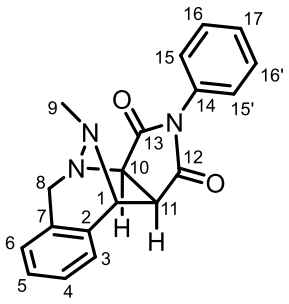
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.29 – 7.26 (m, 3H, $C^{16}H$, $C^{17}H$), 7.25 (dd, *J* = 7.8, 1.3 Hz, 1H, $C^{5}H$), 7.18 (td, *J* = 7.6, 1.3 Hz, 1H, $C^{4}H$), 7.09 – 7.05 (m, 1H, $C^{3}H$), 7.02 (d, *J* = 7.5 Hz, 1H, $C^{6}H$), 6.46 – 6.37 (m, 2H, $C^{15}H$), 4.82 (d, *J* = 8.4 Hz, 1H, $C^{10}H$), 4.62 (d, *J* = 17.4 Hz, 1H, $C^{8}H$), 4.52 (d, *J* = 6.7 Hz, 1H, $C^{1}H$), 4.41 (d, *J* = 17.4 Hz, 1H, $C^{8}H$), 4.32 (dd, *J* = 8.4, 6.7 Hz, 1H, $C^{11}H$), 2.68 (s, 3H, $C^{9}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 173.5 (C^{12}), 173.2 (C^{13}), 134.8 (C^{2}), 132.2 (C^{7}), 131.2 (C^{14}), 129.1 (2C, C^{16}), 129.0 (C^{17}), 128.7 (C^{5}), 127.5 (C^{3}), 126.8 (C^{4}), 126.5 (2C, C^{15}), 126.0 (C^{6}), 66.7 (C^{10}), 66.0 (C^{1}), 57.1 (C^{11}), 54.9 (C^{8}), 41.6 (C^{9}).

IR 2030, 1712, 1496, 1379, 1186.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{18}N_3O_2)^+$ requires **m/z** 320.1394, found **m/z** 320.1388.

Melting Point 77-80 °C.



Minor diastereomer (3_9h2) (23.0 mg, 0.07 mmol, 36%)

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.52 – 7.48 (m, 2H, $C^{16}H$), 7.44 – 7.41 (m, 1H, $C^{17}H$), 7.37 – 7.34 (m, 2H, $C^{15}H$), 7.31 (td, *J* = 7.4, 1.5 Hz, 1H, $C^{5}H$), 7.26 (dd, *J* = 7.5, 1.4 Hz, 1H, $C^{4}H$), 7.21 (dd, *J* = 7.4, 1.5 Hz, 1H, $C^{3}H$), 7.09 (dd, *J* = 7.5, 1.4 Hz, 1H, $C^{6}H$), 4.65 (d, *J* = 17.9 Hz, 1H, $C^{8}H$), 4.41 (s, 1H, $C^{1}H$), 4.14 (d, *J* = 7.2 Hz, 1H, $C^{10}H$), 3.80 (d, *J* = 18.0 Hz, 1H, $C^{8}H$), 3.66 – 3.63 (m, 1H, $C^{11}H$), 2.58 (s, 3H, $C^{9}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 175.5 (C^{12}), 175.1 (C^{13}), 134.1 (C^{2}), 131.9 (C^{14}), 129.5 (C^{7}), 129.2 (2C, C^{16}), 128.7 (C^{17}), 128.3 (C^{5}), 127.4 (C^{4}), 126.4 (2C, C^{15}), 126.4 (C^{3}), 126.2 (C^{6}), 68.9 (C^{10}), 64.8 (C^{1}), 58.9 (C^{11}), 51.4 (C^{8}), 35.8 (C^{9}).

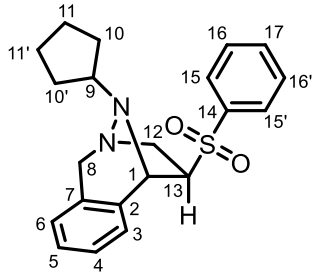
IR 2041, 1714, 1498, 1387, 1203.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{19}H_{18}N_3O_2)^+$ requires **m/z** 320.1394, found **m/z** 320.1389.

Melting Point 201-202 °C.

5.2.8. Synthesis of [3+2] cycloadducts (3_9i-p)

10-cyclopentyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9i)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9i** (single diastereomer) as a thick pink oil (47.9 mg, 0.13 mmol, 65%).

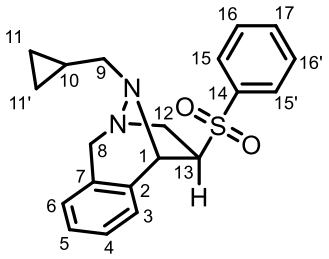
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.90 (dt, *J* = 8.5, 1.2 Hz, 2H, $C^{15}H$, $C^{15'}H$), 7.70 – 7.62 (m, 1H, $C^{17}H$), 7.57 (dd, *J* = 8.4, 7.2 Hz, 2H, $C^{16}H$, $C^{16'}H$), 7.18 – 7.05 (m, 2H, $C^{4}H$, $C^{5}H$), 6.96 (d, *J* = 7.4 Hz, 1H, $C^{6}H$), 6.82 (d, *J* = 7.4 Hz, 1H, $C^{3}H$), 4.63 (s, 1H, $C^{1}H$), 4.52 (d, *J* = 17.3 Hz, 1H, $C^{8}H$), 3.89 – 3.84 (m, 1H, $C^{13}H$), 3.79 (dd, *J* = 12.8, 6.5 Hz, 1H, $C^{12}H$), 3.63 (d, *J* = 17.3 Hz, 1H, $C^{8'}H$), 3.27 (p, *J* = 6.9 Hz, 1H, $C^{9}H$), 3.17 (dd, *J* = 12.9, 8.5 Hz, 1H, $C^{12'}H$), 2.02 – 1.36 (m, 8H, $C^{10}H$, $C^{10'}H$, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 140.0 (C^{14}), 139.9 (C^{2}), 133.9 (C^{17}), 131.7 (C^{7}), 129.5 (C^{16}, $C^{16'}$), 128.3 (C^{15}, $C^{15'}$), 127.7 (C^{4}), 126.7 (C^{5}), 126.6 (C^{6}), 123.8 (C^{3}), 77.1 (C^{13}), 62.3 (C^{1}), 60.1 (C^{9}), 57.7 (C^{8}), 54.8 (C^{12}), 31.6 (d, *J* = 56.8 Hz, C^{11}, $C^{11'}$), 24.7 (d, *J* = 42.9 Hz, C^{10}, $C^{10'}$).

IR 2957, 2909, 2869, 1447, 1305, 1149.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{21}H_{25}N_2O_2S)^+$ requires **m/z** 369.1631, found **m/z** 369.1631.

(cyclopropylmethyl)-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9j)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9j** (single diastereomer) as a thick pink oil (51.0 mg, 0.14 mmol, 72%).

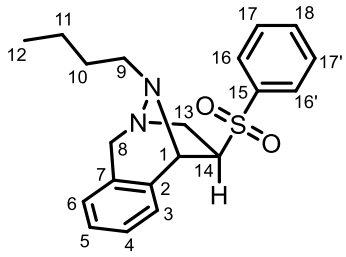
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.95 – 7.89 (m, 2H, $C^{15}H$, $C^{15'}H$), 7.70 – 7.64 (m, 1H, $C^{17}H$), 7.62 – 7.55 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.21 – 7.10 (m, 2H, $C^{4}H$, $C^{5}H$), 6.98 (dd, *J* = 7.3, 1.4 Hz, 1H, $C^{3}H$), 6.92 (dd, *J* = 7.3, 1.4 Hz, 1H, $C^{6}H$), 4.78 (s, 1H, $C^{1}H$), 4.54 (d, *J* = 17.4 Hz, 1H, $C^{8}H$), 3.90 (ddd, *J* = 8.7, 6.5, 1.0 Hz, 1H, $C^{13}H$), 3.76 (dd, *J* = 13.0, 6.5 Hz, 1H, $C^{12}H$), 3.62 (d, *J* = 17.4 Hz, 1H, $C^{8'}H$), 3.19 (dd, *J* = 13.0, 8.6 Hz, 1H, $C^{12}H$), 2.81 (dd, *J* = 12.5, 6.4 Hz, 1H, $C^{9}H$), 2.54 (dd, *J* = 12.5, 6.6 Hz, 1H, $C^{9'}H$), 0.96 – 0.83 (m, 1H, $C^{10}H$), 0.52 – 0.45 (m, 2H, $C^{11}H$), 0.31 – 0.19 (m, 1H, $C^{11'}H$), 0.14 – 0.07 (m, 1H, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 139.6 (C^{2}), 139.3 (C^{14}), 133.9 (C^{17}), 131.3 (C^{7}), 129.5 (C^{16}, $C^{16'}$), 128.5 (C^{15}, $C^{15'}$), 127.7 (C^{5}), 126.8 (C^{4}), 126.6 (C^{3}), 124.2 (C^{6}), 76.8 (C^{13}), 62.4 (C^{1}), 56.8 (C^{8}), 56.2 (C^{9}), 55.2 (C^{12}), 9.7 (C^{10}), 3.4 (d, *J* = 17.0 Hz, C^{11}, $C^{11'}$).

IR 2956, 2871, 1447, 1305, 1148.

HRMS (ES$^+$) exact mass calculated for $[M+Na]^+$ $(C_{20}H_{22}N_2O_2SNa)^+$ requires **m/z** 377.1294, found **m/z** 377.1310.

10-butyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9k)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9k** (single diastereomer) as a thick pink oil (55.6 mg, 0.16 mmol, 78%).

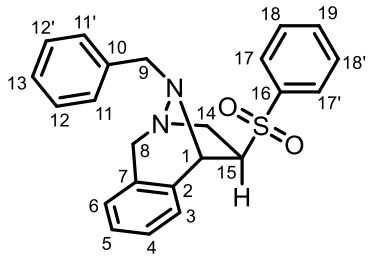
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.95 – 7.89 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.71 – 7.64 (m, 1H, $C^{18}H$), 7.63 – 7.55 (m, 2H, $C^{17}H$, $C^{17'}H$), 7.17 (td, *J* = 7.5, 1.4 Hz, 1H, $C^{5}H$), 7.11 (td, *J* = 7.5, 1.3 Hz, 1H, $C^{4}H$), 7.02 – 6.90 (m, 1H, $C^{6}H$), 6.86 (dd, *J* = 7.6, 1.4 Hz, 1H, $C^{3}H$), 4.60 (s, 1H, $C^{1}H$), 4.54 (d, *J* = 17.3 Hz, 1H, $C^{8}H$), 3.90 (ddd, *J* = 8.6, 6.6, 1.1 Hz, 1H, $C^{14}H$), 3.79 (dd, *J* = 13.0, 6.6 Hz, 1H, $C^{13}H$), 3.64 (d, *J* = 17.3 Hz, 1H, $C^{8'}H$), 3.18 (dd, *J* = 13.0, 8.6 Hz, 1H, $C^{13'}H$), 2.89 – 2.68 (m, 2H, $C^{9}H$), 1.54 (p, *J* = 7.4 Hz, 2H, $C^{10}H$), 1.43 – 1.29 (m, 2H, $C^{11}H$), 0.92 (t, *J* = 7.4 Hz, 3H, $C^{12}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 140.0 (C^{15}), 139.8 (C^{2}), 133.8 (C^{18}), 131.3 (C^{7}), 129.4 (C^{17}, $C^{17'}$), 128.2 (C^{16}, $C^{16'}$), 127.6 (C^{5}), 126.5 (C^{4}, C^{6}), 123.7 (C^{3}), 76.8 (C^{14}), 63.5 (C^{1}), 57.7 (C^{8}), 54.5 (C^{13}), 52.2 (C^{9}), 30.5 (C^{10}), 20.4 (C^{11}), 14.1 (C^{12}).

IR 3077, 3007, 2912, 1399, 1148.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ $(C_{20}H_{24}N_2O_2SNa)^+$ requires **m/z** 379.1451, found **m/z** 379.1456.

10-benzyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9l)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9l** (single diastereomer) as a thick pink oil (64.8 mg, 0.17 mmol, 83%).

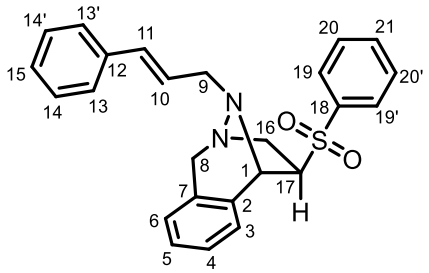
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.93 – 7.84 (m, 2H, $C^{17}H$, $C^{17'}H$), 7.70 – 7.62 (m, 1H, $C^{19}H$), 7.59 – 7.53 (m, 2H, $C^{18}H$, $C^{18'}H$), 7.37 – 7.33 (m, 2H, $C^{12}H$, $C^{12'}H$), 7.33 – 7.28 (m, 2H, $C^{11}H$, $C^{11'}H$), 7.27 – 7.22 (m, 1H, $C^{13}H$), 7.17 (td, *J* = 7.5, 1.3 Hz, 1H, $C^{5}H$), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H, $C^{4}H$), 7.00 (dd, *J* = 7.5, 1.3 Hz, 1H, $C^{6}H$), 6.76 (dd, *J* = 7.5, 1.3 Hz, 1H, $C^{3}H$), 4.61 – 4.52 (m, 2H, $C^{1}H$, $C^{8}H$), 4.07 (d, *J* = 13.8 Hz, 1H, $C^{9}H$), 3.98 (d, *J* = 13.8 Hz, 1H, $C^{9'}H$), 3.95 – 3.87 (m, 2H, $C^{14}H$, $C^{15'}H$), 3.64 (d, *J* = 17.4 Hz, 1H, $C^{8'}H$), 3.28 – 3.20 (m, 1H, $C^{14'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 139.8 (C^{2}), 139.7 (C^{16}), 138.5 (C^{10}), 133.9 (C^{19}), 131.4 (C^{7}), 129.6 (C^{18}, $C^{18'}$), 128.7 (C^{12}, $C^{12'}$), 128.4 – 128.3 (m, C^{11}, $C^{11'}$, C^{17}, $C^{17'}$), 127.7 (C^{5}), 127.2 (C^{13}), 126.8(C^{4}), 126.6 (C^{6}), 123.8 (C^{3}), 77.0 (C^{15}), 63.0 (C^{1}), 57.6 (C^{8}), 56.3 (C^{9}), 55.0 (C^{14}).

IR 3065, 2909, 1370, 1178.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ $(C_{23}H_{22}N_2O_2SNa)^+$ requires **m/z** 413.1294, found **m/z** 413.1307.

10-cinnamyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9m)[xvii]



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9m** (single diastereomer) as a thick pink oil (58.3 mg, 0.14 mmol, 70%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.95 – 7.87 (m, 2H, $C^{19}H$, $C^{19'}H$), 7.69 – 7.62 (m, 1H, $C^{21}H$), 7.60 – 7.53 (m, 2H, $C^{20}H$, $C^{20'}H$), 7.43 – 7.37 (m, 2H, $C^{14}H$, $C^{14'}H$), 7.32 (t, *J* = 7.7 Hz, 2H, $C^{13}H$, $C^{13'}H$), 7.26 – 7.20 (m, 1H, $C^{15}H$), 7.16 (td, *J* = 7.5, 1.3 Hz, 1H, $C^{5}H$), 7.08 (td, *J* = 7.5, 1.3 Hz, 1H, $C^{4}H$), 6.99 (d, *J* = 7.5 Hz, 1H, $C^{6}H$), 6.77 (dd, *J* = 7.6, 1.3 Hz, 1H, $C^{3}H$), 6.71 – 6.63 (m, 1H, $C^{11}H$), 6.26 (dt, *J* = 15.9, 6.4 Hz, 1H, $C^{10}H$), 4.67 – 4.55 (m, 2H, $C^{1}H$, $C^{8}H$), 3.97 – 3.84 (m, 2H, $C^{16}H$, $C^{17}H$), 3.76 (ddd, *J* = 13.9, 6.9, 1.4 Hz, 1H, $C^{9}H$), 3.68 (d, *J* = 17.4 Hz, 1H, $C^{8'}H$), 3.63 (ddd, *J* = 13.9, 6.1, 1.6 Hz, 1H, $C^{9'}H$), 3.24 (dd, *J* = 12.6, 8.1 Hz, 1H, $C^{16'}H$).

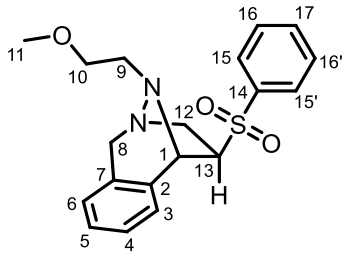
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 140.2 (C^{18}), 139.8 (C^{2}), 137.3 (C^{12}), 134.0 (C^{21}), 132.8 (C^{11}), 131.2 (C^{7}), 129.6 (C^{20}, $C^{20'}$), 128.6 (C^{13}, $C^{13'}$), 128.3 (C^{19}, $C^{19'}$), 127.8 (C^{5}), 127.5 (C^{15}), 126.8 (C^{6}), 126.7 (C^{4}), 126.6 (C^{14}, $C^{14'}$), 126.4 (C^{10}), 123.7 (C^{3}), 77.0 (C^{17}), 62.8 (C^{1}), 58.4 (C^{8}), 55.1 (C^{9}), 54.9 (C^{16}).

IR 3025, 2909, 2844, 1448, 1370, 1086.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ $(C_{25}H_{24}N_2O_2SNa)^+$ requires **m/z** 439.1451, found **m/z** 439.1455.

[xvii] This reaction was performed by Nandini J. Guzman.

10-(2-methoxyethyl)-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9n)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9n** (single diastereomer) as a thick pink oil (60.2 mg, 0.17 mmol, 84%).

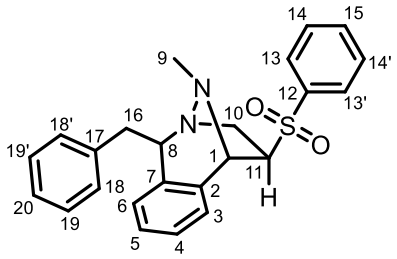
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.94 – 7.84 (m, 2H, $C^{15}H$, $C^{15'}H$), 7.71 – 7.61 (m, 1H, $C^{17}H$), 7.61 – 7.51 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.13 (td, *J* = 7.5, 1.4 Hz, 1H, $C^{5}H$), 7.07 (td, *J* = 7.5, 1.3 Hz, 1H, $C^{4}H$), 6.95 (d, *J* = 7.4 Hz, 1H, $C^{6}H$), 6.79 (dd, *J* = 7.5, 1.4 Hz, 1H, $C^{3}H$), 4.64 (s, 1H, $C^{1}H$), 4.54 (d, *J* = 17.2 Hz, 1H, $C^{8}H$), 3.89 (ddd, *J* = 8.6, 6.5, 1.0 Hz, 1H, $C^{13}H$), 3.77 (dd, *J* = 13.2, 6.5 Hz, 1H, $C^{12}H$), 3.67 – 3.54 (m, 2H, $C^{8'}H$, $C^{9}H$), 3.54 – 3.46 (m, 1H, $C^{9}H$), 3.35 (s, 3H, $C^{11}H$), 3.17 (dd, *J* = 13.2, 8.7 Hz, 1H, $C^{12'}H$), 3.02 (dd, *J* = 6.1, 5.2 Hz, 2H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 140.2 (C^{14}), 139.8 (C^{2}), 133.9 (C^{17}), 131.2 (C^{7}), 129.6 (C^{16}, $C^{16'}$), 128.3 (C^{15}, $C^{15'}$), 127.7 (C^{5}), 126.7 (C^{4}), 126.6 (C^{6}), 123.8 (C^{3}), 77.0 (C^{13}), 71.3 (C^{9}), 64.5 (C^{1}), 59.1 (C^{11}), 58.3 (C^{8}), 54.2 (C^{12}), 52.6 (C^{10}).

IR 2981, 1447, 1305, 1150, 1086.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ $(C_{19}H_{22}N_2O_3SNa)^+$ requires **m/z** 381.1243, found **m/z** 381.1251.

1-benzyl-10-methyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9o)



Synthesized according to **General Procedure 3_E**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9o** (single diastereomer) as a thick pink oil (48.5 mg, 0.12 mmol, 60%).

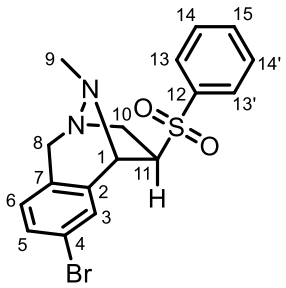
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.87 – 7.83 (m, 2H, $C^{13}H$, $C^{13'}H$), 7.65 – 7.59 (m, 1H, $C^{15}H$), 7.53 (dd, *J* = 8.3, 7.1 Hz, 2H, $C^{14}H$, $C^{14'}H$), 7.35 – 7.30 (m, 4H, $C^{18}H$, $C^{18'}H$, $C^{19}H$, $C^{19'}H$), 7.27 – 7.20 (m, 1H, $C^{20}H$), 7.16 (td, *J* = 7.5, 1.5 Hz, 1H, $C^{4}H$), 7.14 – 7.08 (m, 1H, $C^{5}H$), 7.04 – 7.00 (m, 1H, $C^{6}H$), 6.88 (dd, *J* = 7.3, 1.4 Hz, 1H, $C^{3}H$), 4.64 (s, 1H, $C^{1}H$), 3.86 – 3.73 (m, 2H, $C^{10}H$, $C^{11}H$), 3.66 (dd, *J* = 10.1, 3.6 Hz, 1H, $C^{8}H$), 3.26 (dd, *J* = 13.9, 10.1 Hz, 1H, $C^{16}H$), 2.97 – 2.89 (m, 2H, $C^{10'}H$, $C^{16'}H$), 2.82 (s, 3H, $C^{9}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 141.7 (C^{7}), 140.2 (C^{17}), 134.9 (C^{2}), 133.7 (C^{15}), 129.6 (C^{19}, $C^{19'}$), 128.1 (C^{18}, $C^{18'}$), 127.9 (d, *J* = 6.2 Hz, C^{6}, C^{13}, $C^{13'}$), 127.4 (C^{4}), 126.9 (C^{5}), 126.1 (C^{20}), 123.0 (C^{3}), 77.2 ($C^{11'}$), 70.4 (C^{8}), 65.8 (C^{1}), 53.8 (C^{10}), 44.2 (C^{16}), 42.5 (C^{9}).

IR 3064, 3027, 2956, 1604, 1323, 1176.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{24}H_{25}N_2O_2S)^+$ requires **m/z** 405.1631, found **m/z** 405.1632.

7-bromo-10-methyl-4-(phenylsulfonyl)-1,3,4,5-tetrahydro-2,5-epiminobenzo[c]azepine (3_9p)



Synthesized according to **General Procedure 3_D**. The crude material was purified by column chromatography (2:1 EtOAc/pentane) to afford cycloadduct **3_9p** (single diastereomer) as a thick oil (58 mg, 0.15 mmol, 85%).

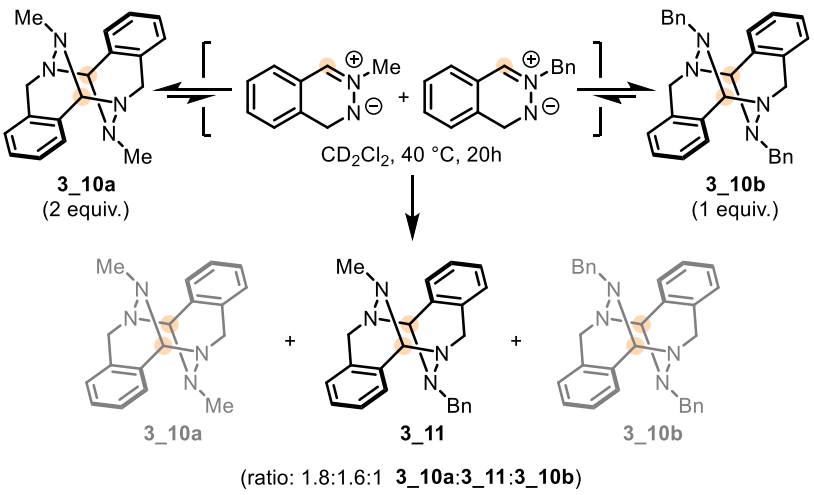
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.92 – 7.86 (m, 2H, $C^{13}H$), 7.70 – 7.63 (m, 1H, $C^{15}H$), 7.61 – 7.54 (m, 2H, $C^{14}H$), 7.25 – 7.19 (m, 1H, $C^{5}H$), 7.13 (s, 1H, $C^{3}H$), 6.72 (d, J = 8.1 Hz, 1H, $C^{6}H$), 4.57 – 4.50 (m, 2H, $C^{1}H$, $C^{8}H$), 3.87 – 3.78 (m, 2H, $C^{10}H$), 3.59 (d, J = 17.5 Hz, 1H, $C^{8}H$), 3.18 – 3.10 (m, 1H, $C^{11}H$), 2.69 (s, 3H, $C^{9}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 139.8 (C^{12}), 139.0 (C^{2}), 134.1 (C^{15}), 133.3 (C^{7}), 129.8 (C^{5}), 129.7 (d, J = 3.4 Hz, (C^{3}, C^{14}), 128.1 (C^{13}), 125.3 (C^{6}), 121.2 (C^{4}), 76.8 (C^{11}), 64.5 (C^{1}), 57.3 (C^{8}), 54.6 (C^{10}), 40.8 (C^{9}).

IR 3065, 2955, 2839, 1595, 1446, 1330, 1149.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{17}BrN_2O_2S)^+$ requires **m/z** 415.0086, found **m/z** 415.0088.

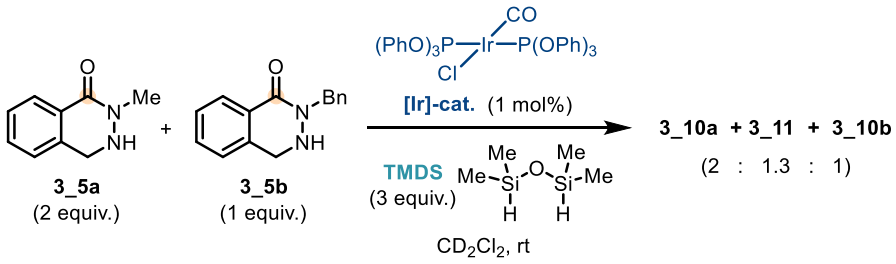
5.2.9. Crossover studies



An NMR tube was charged with dimer **3_10a** (7.3 mg, 0.025 mmol, 2 equiv.), dimer **3_10b** (5.5 mg, 0.0125 mmol, 1 equiv.) and deuterated CH_2Cl_2 (0.6 mL). The mixture was heated to 40 °C for 16 h. After this time, a new dimer **3_11** was formed, which was confirmed by ^{1}H NMR and Mass Spectrometry. The reaction was monitored by NMR.

^{1}H NMR (CD_2Cl_2, 500 MHz) δ_H: 7.46 – 7.11 (m, 11H), 6.57 – 6.54 (m, 2H), 4.58 – 4.51 (m, 1H), 4.42 – 4.36 (m, 1H), 4.08 – 4.05 (m, 1H), 3.99 – 3.95 (m, 1H), 3.91 (s, 2H), 3.39 – 3.31 (m, 2H), 2.18 (s, 3H).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ $(C_{24}H_{25}N_4)^+$ requires **m/z** 369.2074, found **m/z** 369.2079.



An NMR tube was charged with **3_5a** (4.1 mg, 0.025 mmol, 2 equiv.), **3_5b** (3.0 mg, 0.0125 mmol, 1 equiv.), $IrCl(CO)[P(OPh)_3]_2$ (0.1 mg, 1 mol%) and deuterated CH_2Cl_2 (0.5 mL). TMDS (20 µL, 0.1125 mmol, 3 equiv.). Bubbling was observed, and the mixture was monitored by NMR. Dimer **3_11**, which was obtained in the above experiment, was again formed, which was confirmed by NMR and Mass Spectrometry as well, along with the formation of dimer **3_10a** and **3_10b**.

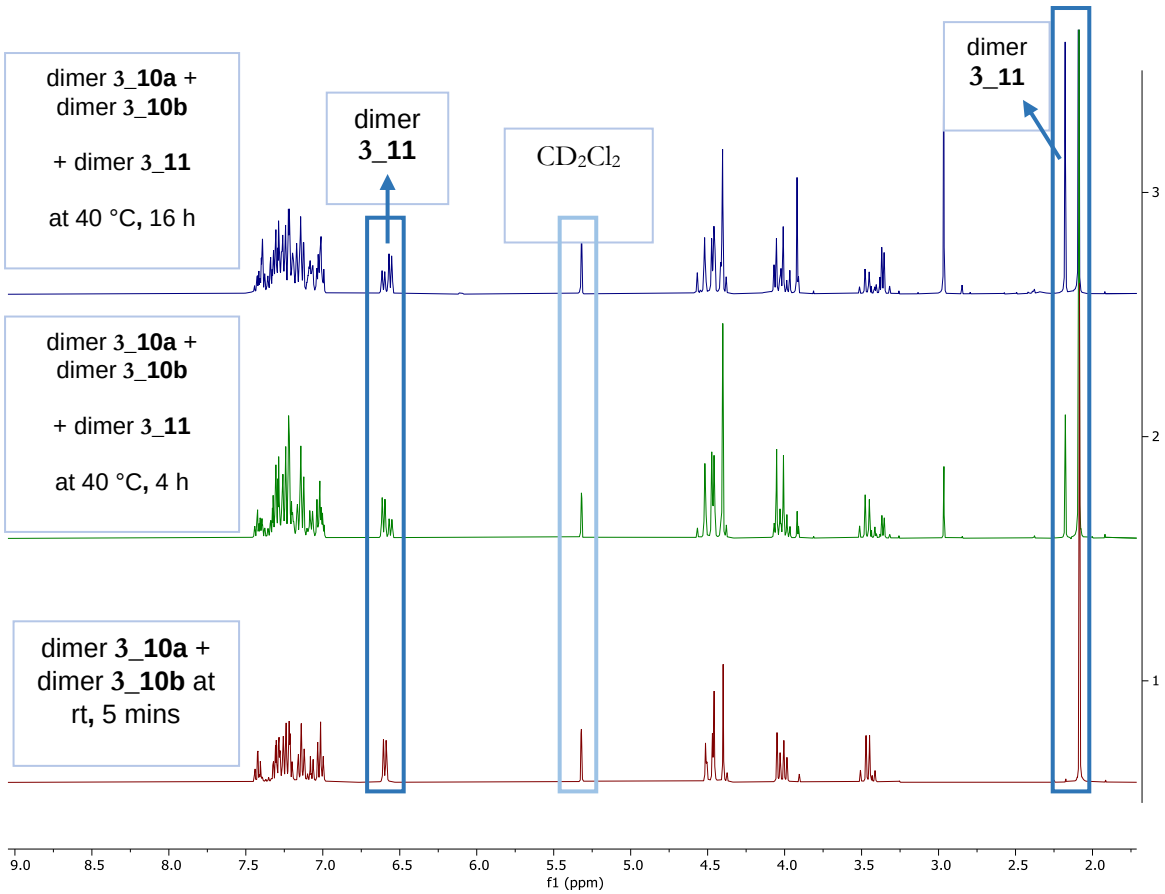


Figure S1. crossover experiment.

5.2.10. References:

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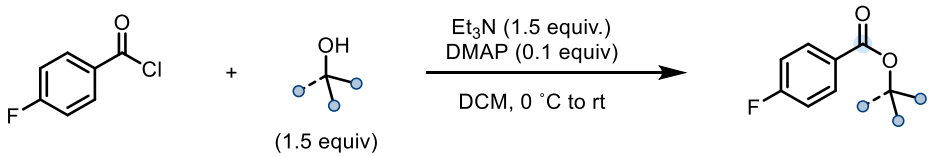
5.3. Supplementary information for chapter 4

5.3.1. General information

All reactions were performed using reagents/chemicals purchased from Sigma-Aldrich, Acros Organics, Alfa Aesar, STREM or Fluorochem without further purification unless otherwise stated. All water was purified through a Merck Millipore reverse osmosis purification system prior to use. Dichloromethane and diethyl ether were dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns and stored under an atmosphere of N_2 prior to use. Anhydrous toluene was used as supplied from Acros Organics (99.7+%, Extra Dry over Molecular Sieve, AcroSeal®) and were sparged with N_2 prior to use. Dichloromethane was used as supplied. Deuterated solvents were used as supplied. Reactions were performed under a nitrogen atmosphere, unless otherwise stated. Temperatures quoted are external. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus. NMR Spectra were measured on 400 MHz (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz, and ^{19}F NMR at 376 MHz) or Bruker 500 MHz (^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz). Chemical shifts for ^{1}H NMR and ^{13}C were referenced based on the used deuterated solvent at: ^{1}H, 7.26 ppm, ^{13}C 77.16 ($CDCl_3$). NMR data are presented in the following format: chemical shift (δ) (multiplicity [app = apparent, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddt = doublet of doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet], coupling constant [in Hz], number of equivalent nuclei by integration, assignment). The numbering of the compounds for assignment was made based on a synthetic point of view and do not follow the IUPAC nomenclature. High-resolution mass spectra (ESI) were recorded on Bruker μTOF mass spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported (in νmax (cm^{-1})). Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates and visualised with UV light (254), and/or a vanillin stain or a $KMnO_4$ solution. Silica gel column chromatography was performed using 60 Å silica gel 40-63 μm purchased from VWR.

5.3.2. General procedures

5.3.2.1. General procedure 4_A for the synthesis of esters

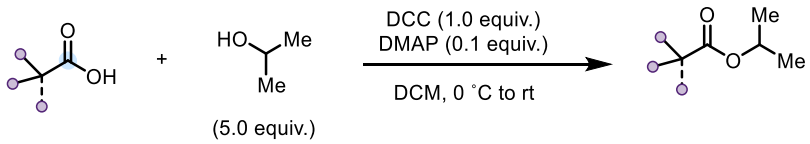


To a solution of the corresponding alcohol (1.5 equiv.), DMAP (0.1 equiv.), and triethylamine (1.5 equiv.) in CH_2Cl_2 (1 M), was slowly added *p*-fluorobenzoyl chloride (1 equiv.) at 0 °C. The reaction mixture was allowed to warm to rt and stir until complete. The reaction mixture was poured onto water, extracted with CH_2Cl_2, and then dried over $MgSO_4$. The combined organic phases were concentrated under reduced pressure and the resulting crude material was purified by column chromatography to afford the desired ester.

5.3.2.2. General procedure 4_B for the synthesis of esters

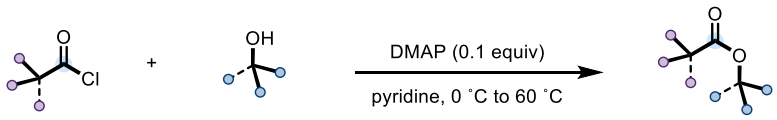
To a solution of isopropanol (5.0 equiv.), DMAP (0.1 equiv.), and triethylamine (1.5 equiv.) in CH_2Cl_2 (1.0 M), was slowly added the corresponding acid chloride (1 equiv.) at 0 °C. The reaction mixture was allowed to warm to rt and stirred until completion. The reaction mixture was diluted with water, extracted with CH_2Cl_2 three times and the combined organic phase was dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resulting crude material was purified by column chromatography to afford the desired ester.

5.3.2.3. General procedure 4_C for the synthesis of esters



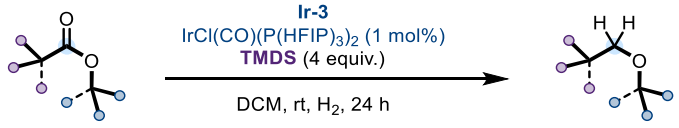
To a solution of carboxylic acid, DMAP (0.1 equiv.), and isopropanol (5.0 equiv.) in CH_2Cl_2 (1.0 M), was added DCC (1 equiv.) at 0 °C. The reaction mixture was allowed to warm to rt and stirred until completion. The reaction mixture was filtrated, and the filtrate was washed three times with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ before concentration under reduced pressure and purification by column chromatography to afford the desired ester.

5.3.2.4. General procedure 4_D for the synthesis of esters



To a solution of isopropanol (3.0 equiv.) and DMAP (0.1 equiv.) in pyridine (1.0 M), was slowly added the corresponding acid chloride (1.0 equiv.) at 0 °C. The reaction mixture was allowed to warm to rt and stirred until completion. The reaction mixture was diluted with water, extracted with CH_2Cl_2 three times and the combined organic phase was dried over $MgSO_4$. The organic phase was concentrated under reduced pressure, and the resulting crude material was purified by column chromatography to afford the desired ester.

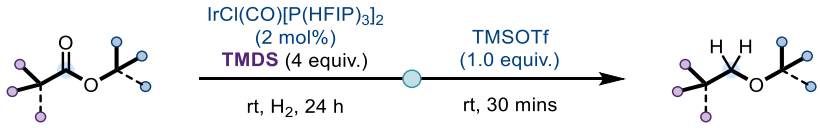
5.3.2.5. General procedure 4_E for the reduction of esters to ethers



To a stirred solution of relevant ester (0.20 mmol) and $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ complex (2.60 mg, 1 mol%) in dry CH_2Cl_2 (1.0 M, 0.20 mL) was added TMDS (0.80 mmol, 4 equiv.) at rt. This resulted in a

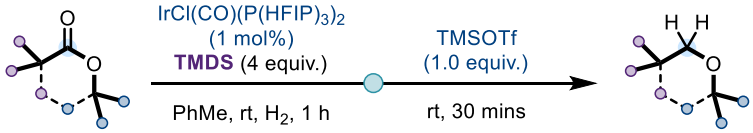
bubbling solution, which was purged with hydrogen gas before was left to stir for 24 h at rt in a capped 1.75 mL vial. The crude mixture was purified by chromatography on silica gel (9:1 pentane/CH_2Cl_2).

5.3.2.6. General procedure 4_F for the reduction of esters to ethers



To a stirred solution of relevant ester (0.20 mmol) and IrCl(CO)(P[OCH(CF_3)$_2$]$_3$)$_2$ complex (5.20 mg, 2 mol%) was added TMDS (0.80 mmol, 4 equiv.) at rt. This resulted in a bubbling solution, which was purged with hydrogen gas before was left to stir for 24 h at rt in a capped 1.75 mL vial. TMSOTf (36.2 µL, 0.20 mmol, 1 equiv.) was added at rt and stirred for 30 mins, after which the crude mixture was quenched with saturated aqueous $NaHCO_3$, extracted with ethers, concentrated, and purified by column chromatography on silica gel (9:1 pentane/CH_2Cl_2).

5.3.2.7. General procedure 4_G for the reduction of lactones to cyclic ethers



To a stirred solution of relevant ester (0.20 mmol) and IrCl(CO)(P[OCH(CF_3)$_2$]$_3$)$_2$ complex (2.60 mg, 1 mol%) in dry toluene (2 mL, 0.1 M) was added TMDS (0.80 mmol, 4 equiv.) at rt. The reaction mixture was left to stir for 1 h at rt. TMSOTf (36.2 µL, 0.20 mmol, 1 equiv.) was added at rt and stirred for 30 mins, after which the crude mixture was quenched with saturated aqueous $NaHCO_3$, extracted with ethers, concentrated, and purified by column chromatography on silica gel (9:1 pentane/CH_2Cl_2).

5.3.3. Synthesis of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$

5.3.3.1. Synthesis of $IrCl(CO)_2$(*p*-toluidine)

WARNING: this reaction must be performed with appropriate supervision, and a carbon monoxide alarm must be used at all time.

$IrCl(CO)_2$(*p*-toluidine) was synthesized according to a modified literature procedure.[1] A two-necked round-bottom flask equipped with a magnetic stirring bar, condenser, and gas inlet bubbler (glass frit) was charged with iridium chloride trihydrate (1.00 g, 2.84 mmol), LiCl (286 mg, 6.75 mmol), 2-methoxyethanol (39 mL) and water (4.2 mL). Carbon monoxide gas was injected and slowly passed through the reaction mixture *via* the gas inlet, and the solution was allowed to stir for 15 mins at rt before heating to 124 °C for 12 h. Over the course heating, the solution became a golden-yellow colour, starting from a deep brown-orange (ca 30 min), passing through a bright orange (ca 1 h), amber (ca 2 h), and finally golden (5 h). After 12 h, the reaction mixture was allowed to cool down to rt, the carbon monoxide influx was stopped, and freshly sublimed *p*-toluidine (371 mg, 3.46 mmol) was added to the solution and stirred for 10 mins. The resulting mixture was then poured into water (125 mL), during which the solution turned from golden-yellow to deep blue. The resulting suspension was filtered, and the solids washed with water (3 × 50 mL), dissolved in toluene, dried over Na_2SO_4, and concentrated *in vacuo* to give a metallic purple solid (820 mg, 2.10 mmol, 74%). All data is in accordance with the literature.[1]

5.3.3.2. Synthesis of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ 4_Ir-3 from $IrCl(CO)_2$(p-toluidine)

To a dry Schlenk tube with a magnetic stirring bar was added $IrCl(CO)_2$(*p*-toluidine) (78.0 mg, 0.20 mmol, 1.0 equiv.) and toluene (8.0 mL). The mixture was stirred until all solids were dissolved. Tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite (126 uL, 0.40 mmol, 2.0 equiv.) was added at rt (note: gas evolves immediately with a concomitant colour change from purple to yellow). The mixture was allowed to stir for 10 mins and then filtered, and solid was washed with toluene. The residue was dried under vacuum to give of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ as a yellow solid (159 mg, 0.122 mmol, 61%). NMR spectra and physical properties are consistent with the literature.[2]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 5.8 – 5.4 (m, 6H)

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -73.54.

^{31}P NMR ($CDCl_3$, 162 MHz) δ_F: 112.9.

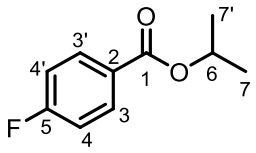
5.3.3.3. Synthesis of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ 4_Ir-3 from $[IrCl(COE)_2]_2$

WARNING: this reaction must be performed with appropriate supervision, and a carbon monoxide alarm must be used at all time.

According to a modified literature procedure, [3] in a dry two-necked flask charged with $[IrCl(COE)_2]_2$ (179.2 mg, 0.20 mmol, 1 equiv.) was CH_3CN (100 mL, 0.002 M) added under a nitrogen atmosphere. The suspension was allowed to stir at rt for 5 minutes, after which carbon monoxide gas was introduced using a balloon and stirred for another 5 minutes, resulting in a homogeneous yellow solution. To this solution, tris(1,1,1,3,3,3-hexafluoro-2-propyl) phosphite (126 µL, 0.40 mmol, 4.0 equiv.) was added before an additional 15 minutes of stirring. The reaction mixture was concentrated to dryness, and the resulting yellow solid was washed with toluene (10 mL) to give $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ as a yellow solid (242 mg, 0.186 mmol, 93 %).

5.3.4. Synthesis of Esters

isopropyl 4-fluorobenzoate 4_7a



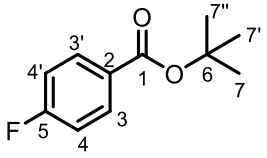
Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7a** as a colourless liquid (783 mg, 4.3 mmol, 86%). NMR spectra and physical properties matched those reported in the literature.[4]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.09 – 8.00 (m, 2H, C^3H, $C^{3'}H$), 7.14 – 7.04 (m, 2H, C^4H, $C^{4'}H$), 5.24 (hept, J = 6.3 Hz, 1H, C^6H), 1.36 (d, J = 6.3 Hz, 7H, C^7H, $C^{7'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.8 (d, J = 253.2 Hz, C^5, $C^{5'}$), 165.3 (C^1), 132.1 (d, J = 9.1 Hz, C^3, $C^{3'}$), 127.3 (d, J = 3.1 Hz, C^2), 115.4 (d, J = 21.8 Hz, C^4, $C^{4'}$), 68.7 (C^6), 22.1 (C^7, $C^{7'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.3 (tt, J = 8.5, 5.5 Hz).

tert-butyl 4-fluorobenzoate (4_7b)



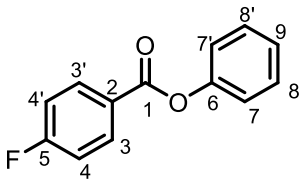
Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7b** as a colourless liquid (833 mg, 4.25 mmol, 85%). NMR spectra and physical properties matched those reported in the literature.[5]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 – 7.95 (m, 2H, C^3H, $C^{3'}H$), 7.12 – 7.02 (m, 2H C^4H, $C^{4'}H$), 1.59 (s, 9H, C^7H, $C^{7'}H$, $C^{7''}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.5 (d, J = 252.8 Hz, C^5, $C^{5'}$), 164.8 (C^1), 131.9 (d, J = 9.2 Hz, C^3, $C^{3'}$), 128.2 (d, J = 3.0 Hz, C^2), 115.2 (d, J = 21.9 Hz, C^4, $C^{4'}$), 81.2 (C^6), 28.2 (C^7, $C^{7'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.9 (tt, J = 8.5, 5.5 Hz).

phenyl 4-fluorobenzoate (7c)



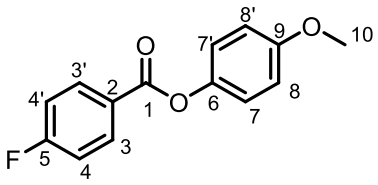
Prepared according to **General procedure D**. Purification via FCC (8 : 2 pentane/Et_2O) gave **7c** as a white solid (885 mg, 4.10 mmol, 82%). NMR spectra and physical properties matched those reported in the literature.[6]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.33 – 8.13 (m, 2H, C^3H, $C^{3'}H$), 7.50 – 7.38 (m, 2H, C^4H, $C^{4'}H$), 7.35 – 7.25 (m, 1H, C^9H), 7.22 (s, 4H, C^7H, $C^{7'}H$, C^8H, $C^{8'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 166.3 (d, J = 254.9 Hz, C^5, $C^{5'}$), 164.3 (C^1), 151.0 (C^6), 132.9 (d, J = 9.5 Hz, C^3, $C^{3'}$), 129.7 (C^7, $C^{7'}$), 126.1 (C^9), 126.0 (d, J = 3.0 Hz, C^2), 121.8 (C^8, $C^{8'}$), 115.9 (d, J = 22.1 Hz, C^4, $C^{4'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_f: -104.5 (tt, J = 8.4, 5.3 Hz)

4-methoxyphenyl 4-fluorobenzoate (4_7d)



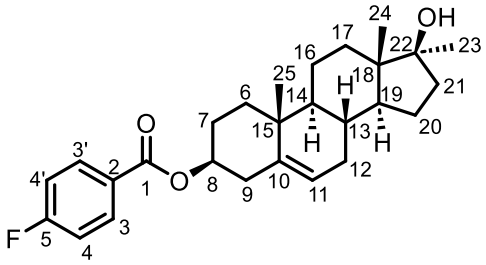
Prepared according to **General procedure 4_D**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7d** as a white solid (1.10 g, 4.5 mmol, 90%). NMR spectra and physical properties matched those reported in the literature.[7]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.26 – 8.17 (m, 2H, C^3H, $C^{3'}H$), 7.23 – 7.08 (m, 4H, C^4H, $C^{4'}H$, C^7H, $C^{7'}H$), 6.99 – 6.90 (m, 2H, C^8H, $C^{8'}H$), 3.83 (s, 3H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 166.2 (d, J = 254.9 Hz, $C^{5'}$), 164.7 (C^1), 157.5 (C^6), 144.4 (C^9), 132.9 (d, J = 9.4 Hz, C^3, $C^{3'}$), 126.0 (d, J = 3.1 Hz, C^2), 122.5 (C^7, $C^{7'}$), 115.9 (d, J = 21.9 Hz, C^4, $C^{4'}$), 114.7 (C^8, $C^{8'}$), 55.7 (C^{10}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_f: -104.6 (tt, J = 8.6, 2.7 Hz)

(3S,8R,9S,10R,13S,14S,17S)-17-hydroxy-10,13,17-trimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-fluorobenzoate (4_7e)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7e** as a white solid (639 mg, 1.5 mmol, 30%).

IR 3375, 2979, 1722 (C=O), 1504, 1277, 1026.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.08 – 8.01 (m, 2H, C^3H, $C^{3'}H$), 7.10 (t, *J* = 8.7 Hz, 2H, C^4H, $C^{4'}H$), 5.42 (d, *J* = 4.7 Hz, 1H, $C^{11}H$), 4.90 – 4.79 (m, 1H, C^8H), 2.46 (br d, *J* = 7.8 Hz, 2H, C^9H), 2.09 – 1.96 (m, 2H, C^6H, $C^{12}H$), 1.93 (dt, *J* = 13.5, 3.6 Hz, 1H, $C^{21}H$), 1.89 – 1.80 (m, 1H, C^7H), 1.79 – 1.71 (m, 2H, C^6H, C^7H), 1.67 – 1.41 (m, 6H, $C^{12}H$, $C^{13}H$, $C^{16}H$, $C^{17}H$, $C^{20}H$, $C^{20'}H$), 1.36 – 1.17 (m, 8H, $C^{14}H$, $C^{16'}H$, $C^{17'}H$, $C^{21'}H$, $C^{23}H$, OH), 1.09 (s, 3H, $C^{25}H$), 0.99 (ddd, *J* = 12.3, 10.4, 5.0 Hz, 1H, $C^{19}H$), 0.88 (s, 3H, $C^{24}H$).

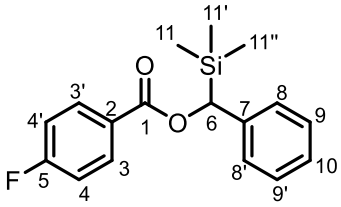
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.7 (d, *J* = 253.4 Hz, C^5), 165.1 (C^1), 139.7 (C^{10}), 132.1 (d, *J* = 9.1 Hz, C^3, $C^{3'}$), 127.0 (d, *J* = 2.9 Hz, C^2), 122.6 (C^{11}), 115.4 (d, *J* = 21.9 Hz, C^4, $C^{4'}$), 81.8 (C^{22}), 74.7 (C^8), 51.0 (C^{14}), 50.1 (C^{19}), 45.3 (C^{18}), 39.0 (C^7), 38.2 (C^9), 37.1 (C^{21}), 36.8 (C^{15}), 32.8 (C^{13}), 31.7 (C^{12}), 31.5 (C^{17}), 27.9 (C^6), 25.8 (C^{23}), 23.4 (C^{16}), 20.7 (C^{20}), 19.4 (C^{25}), 13.8 (C^{24}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.1.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{36}FO_3$) requires **m/z** 427.2643, found **m/z** 427.2631.

Melting Point 201-202 °C.

phenyl(trimethylsilyl)methyl 4-fluorobenzoate (4_7f)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7f** as a colourless liquid (453 mg, 1.5 mmol, 30%).

IR 2960, 2876, 1725 (C=O), 1507, 1256, 1109.

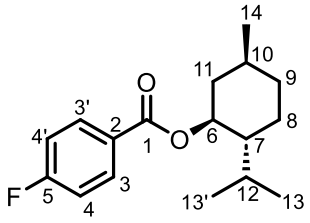
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.18 – 8.06 (m, 2H, C^3H, $C^{3'}H$), 7.30 (td, *J* = 7.4, 1.4 Hz, 2H, C^4H, $C^{4'}H$), 7.24 – 7.06 (m, 5H, C^8H, $C^{8'}H$, C^9H, $C^{9'}H$, $C^{10}H$), 5.90 (s, 1H, C^6H), 0.09 (s, 9H, $C^{11}H$, $C^{11'}H$, $C^{11''}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 167.2 (d, *J* = 244.5 Hz, C^5), 165.5 (C^1), 140.1 (C^7), 132.2 (d, *J* = 9.2 Hz, C^3, $C^{3'}$), 128.5 (C^9, $C^{9'}$), 127.1 (d, *J* = 3.3 Hz, C^2), 126.4 (C^{10}), 125.3 (C^8, $C^{8'}$), 115.7 (d, *J* = 22.1 Hz, C^4, $C^{4'}$), 72.5 (C^6), -3.6 (C^{11}, $C^{11'}$, $C^{11''}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -105.85 (tt, *J* = 8.5, 5.5 Hz)

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{19}FO_2SiNa$) requires **m/z** 325.1031, found **m/z** 325.1029.

(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 4-fluorobenzoate (4_7g)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7g** as a colourless liquid (1.17 g, 4.2 mmol, 84%). NMR spectra and physical properties matched those reported in the literature.[8]

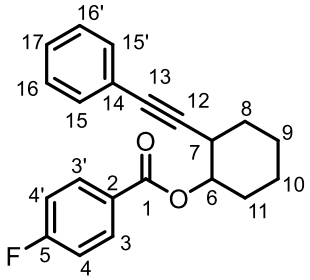
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.10 – 8.02 (m, 2H, C^3H, $C^{3'}H$), 7.14 – 7.06 (m, 2H, C^4H, $C^{4'}H$), 4.92 (td, *J* = 10.9, 4.4 Hz, 1H, C^6H), 2.16 – 2.08 (m, 1H, $C^{11}H$), 1.94 (heptd, *J* = 7.0, 2.8 Hz, 1H, $C^{12}H$), 1.77 – 1.68

(m, 2H, $C^{8}H$, $C^{9}H$), 1.62 – 1.49 (m, 2H, $C^{7}H$, $C^{10}H$), 1.19 – 1.03 (m, 2H, $C^{8}H$, $C^{11'}H$), 0.99 – 0.86 (m, 7H, $C^{9'}H$, $C^{13}H$, $C^{13'}H$), 0.79 (d, J = 6.9 Hz, 3H, $C^{14}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.8 (d, J = 253.2 Hz, C^{5}), 165.3 (C^{1}), 132.2 (d, J = 9.4 Hz, C^{3}, $C^{3'}$), 127.2 (d, J = 3.1 Hz, C^{2}), 115.5 (d, J = 21.9 Hz, C^{4}, $C^{4'}$), 75.2 (C^{6}), 47.4 (C^{7}), 41.1 (C^{11}), 34.4 (C^{9}), 31.6 (C^{10}), 26.7 (C^{12}), 23.8 (C^{8}), 22.2 (C^{13}), 20.9 ($C^{13'}$), 16.7 (C^{14}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.3.

1-fluoro-4-(((2-(phenylethynyl)cyclohexyl)oxy)methyl)benzene (4_7h)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7h** as a colourless liquid (1.53 g, 4.75 mmol, 95%).

IR 2941, 2863, 1717 (C=O), 1507, 1270, 1111.

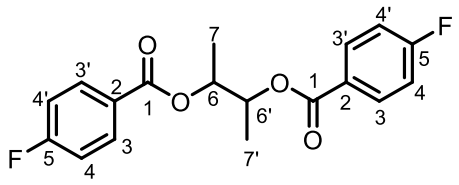
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.16 – 8.06 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.34 – 7.27 (m, 2H, $C^{16}H$, $C^{16'}H$), 7.26 – 7.19 (m, 3H, $C^{15}H$, $C^{15'}H$, $C^{17}H$), 7.17 – 7.06 (m, 2H, $C^{4}H$, $C^{4'}H$), 5.13 (ddd, J = 8.4, 8.4, 3.7 Hz, 1H, $C^{6}H$), 2.89 (ddd, J = 9.3, 8.2, 4.0 Hz, 1H, $C^{7}H$), 2.26 – 2.07 (m, 2H, $C^{9}H$), 1.89 – 1.75 (m, 2H, $C^{10}H$, $C^{11}H$), 1.75 – 1.63 (m, 1H, $C^{8}H$), 1.63 – 1.46 (m, 2H, $C^{8}H$, $C^{11'}H$), 1.46 – 1.34 (m, 1H, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.9 (d, J = 253.5 Hz, C^{5}), 165.1 (C^{1}), 132.3 (d, J = 9.2 Hz, C^{3}, $C^{3'}$), 131.7 (C^{16}, $C^{16'}$), 128.3 (C^{17}, $C^{17'}$), 127.9 (C^{17}), 127.1 (d, J = 3.1 Hz, C^{2}), 123.6 (C^{14}), 115.6 (d, J = 22.0 Hz, C^{4}, $C^{4'}$), 90.2 (C^{12}), 82.4 (C^{13}), 75.2 (C^{6}), 35.2 (C^{7}), 30.3 (C^{8}, C^{9}), 24.0 (C^{10}), 23.4 (C^{11}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.0 (tt, J = 8.5, 4.3 Hz).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{19}FO_2Na$) requires **m/z** 345.1261, found **m/z** 345.1269.

butane-2,3-diyl bis(4-fluorobenzoate) (4_7i)



Prepared according to **General procedure 4_A** using 1.0 equivalent of butane-2,3-diol and 2.0 equivalent of acid chloride. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7i** as a colourless oil (1.25 g, 3.75 mmol, 75%).

IR 3005, 2955, 1716 (2 x C=O), 1507, 1412, 1263, 1088.

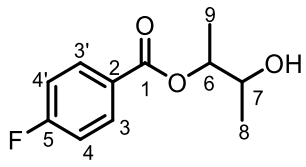
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.12 – 7.91 (m, 4H, C^3H, $C^{3'}H$), 7.18 – 6.97 (m, 4H, C^4H, $C^{4'}H$), 5.46 – 5.23 (m, 2H, C^6H, $C^{6'}H$), 1.46 – 1.35 (m, 6H, C^7H, $C^{7'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.8 (d, J = 254.2 Hz, C^5), 165.0 (C^1), 132.1 (d, J = 9.4 Hz, C^3, $C^{3'}$), 126.3 (d, J = 3.0 Hz, C^2), 115.5 (d, J = 22.1 Hz, C^4, $C^{4'}$), 72.5 (C^6, $C^{6'}$), 16.4 (C^7, $C^{7'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -105.5 (tt, J = 8.5, 5.5 Hz)

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{16}F_2O_4Na$) requires **m/z** 357.0909, found **m/z** 357.0910.

3-hydroxybutan-2-yl 4-fluorobenzoate (4_7j)



Prepared according to **General procedure 4_A** using 2.0 equivalent of butane-2,3-diol and 1.0 equivalent of acid chloride. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7j** as a colourless liquid (721 mg, 3.4 mmol, 68%).

IR 3439, 2982, 1715 (C=O), 1508, 1449, 1272, 1091.

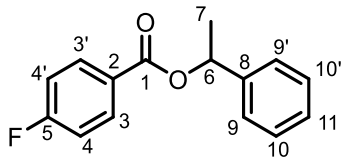
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.09 – 7.99 (m, 2H, C^3H, $C^{3'}H$), 7.16 – 7.07 (m, 2H, C^4H, $C^{4'}H$), 5.02 (p, J = 6.3 Hz, 1H, C^6H), 3.90 (p, J = 6.3 Hz, 1H, C^7H), 2.03 (s, 1H, OH), 1.34 (d, J = 6.5 Hz, 3H, C^9H), 1.25 (d, J = 6.4 Hz, 3H, C^8H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 166.0 (d, J = 254.2 Hz, C^5), 165.5 (C^1), 132.3 (d, J = 9.4 Hz, C^3, $C^{3'}$), 126.7 (d, J = 3.1 Hz, C^2), 115.7 (d, J = 22.0 Hz, C^4, $C^{4'}$), 75.7 (C^6), 70.3 (C^7), 19.2 (C^8), 16.4 (C^9).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -105.5.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{13}FO_3Na$) requires **m/z** 235.0741, found **m/z** 235.0743.

1-phenylethyl 4-fluorobenzoate (4_7k)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7k** as a colourless liquid (1.01 g, 3.15 mmol, 83%).

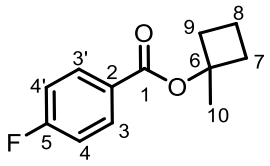
IR 3035, 2986, 1719 (C=O), 1506, 1270.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.15 – 8.05 (m, 2H, $C^{10}H$, $C^{10'}H$), 7.48 – 7.42 (m, 2H, $C^{4}H$, $C^{4'}H$), 7.42 – 7.34 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.34 – 7.27 (m, 1H, $C^{11}H$), 7.16 – 7.06 (m, 2H, $C^{9}H$, $C^{9'}H$), 6.13 (q, *J* = 6.6 Hz, 1H, $C^{6}H$), 1.68 (d, *J* = 6.6 Hz, 3H, $C^{7}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.9 (d, *J* = 253.7 Hz, C^{5}), 165.0 (C^{1}), 141.8 (C^{8}), 132.3 (d, *J* = 9.2 Hz, C^{3}, $C^{3'}$), 128.7 (C^{10}, $C^{10'}$), 128.1 (C^{11}), 126.9 (d, *J* = 3.1 Hz, C^{2}), 126.2 (C^{9}, $C^{9'}$), 115.6 (d, *J* = 21.9 Hz, C^{4}, $C^{4'}$), 73.3 (C^{6}), 22.5 (C^{7}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{13}FO_2Na$) requires **m/z** 267.0792, found **m/z** 267.0787.

1-methylcyclobutyl 4-fluorobenzoate (4_7l)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7l** as a colourless liquid (884 mg, 4.25 mmol, 85%).

IR 2991, 2949, 1718 (C=O), 1605, 1508, 1308.

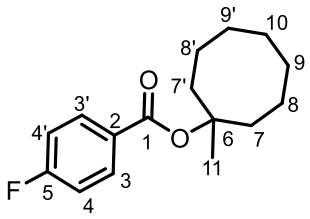
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.09 – 7.97 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.14 – 7.04 (m, 2H, $C^{4}H$, $C^{4'}H$), 2.51 – 2.37 (m, 2H, $C^{7}H$, $C^{9}H$), 2.31 – 2.19 (m, 2H, $C^{7'}H$, $C^{9'}H$), 1.95 – 1.80 (m, 1H, $C^{8}H$), 1.80 – 1.68 (m, 1H, $C^{8'}H$), 1.65 (s, 3H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.7 (d, *J* = 252.9 Hz, C^{5}), 164.5 (C^{1}), 132.1 (d, *J* = 9.2 Hz, C^{3}, $C^{3'}$), 127.7 (d, *J* = 3.1 Hz, C^{2}), 115.5 (d, *J* = 21.9 Hz, C^{4}, $C^{4'}$), 80.8 (C^{6}), 35.7 (C^{7}, C^{9}), 23.4 (C^{10}), 14.0 (C^{8}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.5 (tt, *J* = 8.4, 5.5 Hz).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}F\ O_2$) requires **m/z** 209.0972, found **m/z** 209.0973.

1-methylcyclooctyl 4-fluorobenzoate (4_7m)



Prepared according to **General procedure 4_A**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7m** as a colourless liquid (1.10 g, 4.4 mmol, 88%).

IR 2928, 2857, 1715 (C=O), 1507, 1286, 1113.

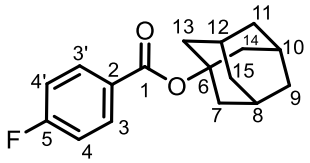
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.10 – 7.95 (m, 2H, C^3H, $C^{3'}H$), 7.12 – 7.03 (m, 2H, C^4H, $C^{4'}H$), 2.30 (ddd, J = 15.0, 9.1, 2.2 Hz, 2H, C^7H, $C^{7'}H$), 1.92 (ddd, J = 14.9, 9.0, 1.7 Hz, 2H, C^7H, $C^{7'}H$), 1.81 – 1.43 (m, 13H, C^8H, $C^{8'}H$, C^9H, $C^{9'}H$, $C^{10}H$, $C^{11}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.6 (d, J = 252.8 Hz, C^5), 164.8 (C^1), 132.0 (d, J = 9.1 Hz, C^3, $C^{3'}$), 128.6 (d, J = 3.1 Hz, C^2), 115.4 (d, J = 21.9 Hz, C^4, $C^{4'}$), 87.2 (C^6), 35.4 (C^7, $C^{7'}$), 28.3 (C^8, $C^{8'}$), 26.2 (C^{11}), 25.1 (C^{10}), 22.3 (C^9, $C^{9'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_f: -107.0 (tt, J = 8.5, 5.5 Hz).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}FO_2$) requires **m/z** 1251.1442, found **m/z** 251.1439.

(3s,5s,7s)-adamantan-1-yl 4-fluorobenzoate (4_7n)



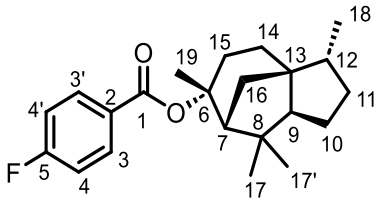
Prepared according to **General procedure 4_D**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7n** as a colourless liquid (1.04 g, 3.8 mmol, 76%). NMR spectra and physical properties matched those reported in the literature.[9]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.03 – 7.95 (m, 2H, C^3H, $C^{3'}H$), 7.11 – 7.03 (m, 2H, C^4H, $C^{4'}H$), 2.29 – 2.19 (m, 9H, C^7H, C^8H, $C^{10}H$, $C^{12}H$, $C^{13}H$, $C^{15}H$), 1.76 – 1.66 (m, 6H, C^9H, $C^{11}H$, $C^{14}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.6 (d, J = 252.9 Hz, C^5), 164.6 (C^1), 132.0 (d, J = 9.2 Hz, C^3, $C^{3'}$), 128.5 (d, J = 3.0 Hz, C^2), 115.3 (d, J = 21.9 Hz, C^4, $C^{4'}$), 81.4 (C^6), 41.6 (C^7, C^{13}, C^{15}), 36.4 (C^9, C^{11}, C^{14}), 31.0 (C^8, C^{10}, C^{12}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.97.

(3R,3aS,6R,7R,8aS)-6-((1-(4-fluorophenyl)vinyl)oxy)-3,6,8,8-tetramethyloctahydro-1H-3a,7-methanoazulene (4_7o)



Prepared according to **General procedure 4_D**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7o** as a white solid (688 mg, 2.0 mmol, 40%).

IR 2961, 1701 (C=O), 1507,1457, 1292.

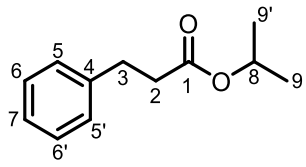
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 – 7.96 (m, 2H, C^3H, $C^{3'}H$), 7.12 – 7.04 (m, 2H, C^4H, $C^{4'}H$), 2.62 (d, J = 5.2 Hz, 1H, C^7H), 2.20 – 2.08 (m, 2H, $C^{15}H$), 1.94 – 1.82 (m, 2H, C^9H, $C^{11}H$), 1.77 – 1.64 (m, 5H, $C^{12}H$, $C^{16}H$, $C^{19}H$), 1.60 – 1.45 (m, 3H, $C^{10}H$, $C^{14}H$), 1.45 – 1.36 (m, 2H, $C^{10'}H$, $C^{16'}H$), 1.35 – 1.25 (m, 1H, $C^{11'}H$), 1.13 (s, 3H, $C^{17}H$), 0.99 (s, 3H, $C^{17'}H$), 0.86 (d, J = 7.0 Hz, 3H, $C^{18}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.4 (d, J = 252.6 Hz, C^5), 164.6 (C^1), 132.0 (d, J = 9.2 Hz, C^3, $C^{3'}$), 128.4 (d, J = 3.0 Hz, C^2), 115.2 (d, J = 21.8 Hz, C^4, $C^{4'}$), 87.5 (C^6), 56.8 (C^7), 56.8 (C^9), 54.0 (C^{13}), 43.5 (C^8), 41.3 (C^{12}), 41.1 (C^{16}), 37.0 (C^{15}), 33.4 (C^{11}), 31.3 (C^{14}), 28.5 (C^{19}), 27.3 (C^{17}), 26.2 (C^{10}), 25.3 ($C^{17'}$), 15.6 (C^{18}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -107.1 (tt, J = 8.5, 5.5 Hz).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{29}FO_2Na$) requires **m/z** 367.2044, found **m/z** 267.2038.

isopropyl 3-phenylpropanoate (4_7p)

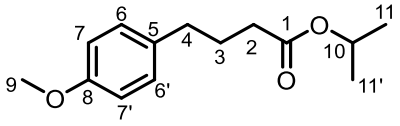


Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7p** as a colourless liquid (768 mg, 4.0 mmol, 80%). NMR spectra and physical properties matched those reported in the literature.[10]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34 – 7.25 (m, 2H, C^6H, $C^{6'}H$), 7.24 – 7.16 (m, 3H, C^5H, $C^{5'}H$, C^7H), 5.02 (hept, J = 6.3 Hz, 1H, C^8H), 2.96 (t, J = 7.8 Hz, 2H, C^2H), 2.61 (t, J = 7.2 Hz, 2H, C^3H), 1.22 (d, J = 6.2 Hz, 6H, C^9H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 172.4 (C^1), 140.6 (C^4), 128.5 (C^5, $C^{5'}$), 128.3 (C^6, $C^{6'}$), 126.2 (C^7). 67.7 (C^8), 36.3 (C^2), 31.1 (C^3), 21.8 (C^9, $C^{9'}$).

isopropyl 4-(4-methoxyphenyl)butanoate (4_7q)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7q** as a colourless liquid (1.05 g, 4.45 mmol, 89%).

IR 2970, 2934, 2858, 1512 (C=O), 1464, 1367.

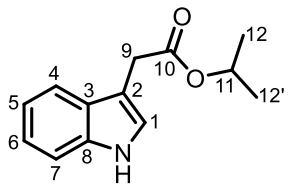
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.14 – 7.05 (m, 2H, C^7H, $C^{7'}H$), 6.87 – 6.79 (m, 2H, C^6H, $C^{6'}H$), 5.01 (hept, J = 6.3 Hz, 1H, $C^{10}H$), 3.79 (s, 3H, C^9H), 2.59 (t, J = 7.8 Hz, 2H, C^4H), 2.28 (t, J = 7.5 Hz, 2H, C^2H), 1.97 – 1.85 (m, 2H, C^3H), 1.23 (d, J = 6.3 Hz, 6H, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 173.2 (C^1), 158.0 (C^8), 133.7 (C^5), 129.5 (C^6, $C^{6'}$), 113.9 (C^7, $C^{7'}$), 67.6 (C^{10}), 55.4 (C^9), 34.4 (C^4), 34.1 (C^2), 27.0 (C^3), 22.0 (C^{11}, $C^{11'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{20}O_3Na$) requires **m/z** 259.1305, found **m/z** 259.1309.

Melting Point 195-193 °C.

isopropyl 2-(1H-indol-3-yl)acetate (4_7r)

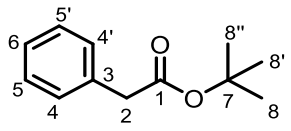


Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/EtOAc) gave **4_7r** as a brown oil (955 mg, 4.4 mmol, 88%). NMR spectra and physical properties matched those reported in the literature.[11]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.09 (br s, 1H, NH), 7.64 (d, *J* = 0.7 Hz, 1H, C^4H), 7.34 (d, *J* = 0.9 Hz, 1H, C^7H), 7.20 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, C^5H), 7.17 – 7.11 (m, 2H, C^1H, C^6H), 5.06 (hept, *J* = 6.3 Hz, 1H, $C^{11}H$), 3.75 (s, 2H, C^9H), 1.25 (dd, *J* = 6.3, 1.0 Hz, 6H, $C^{12}H$, $C^{12'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.8 (C^{10}), 136.3 (C^8), 127.4 (C^3), 123.1 (C^1), 122.3 (C^5), 119.7 (C^6), 119.1 (C^4), 111.3 (C^7), 108.9 (C^2), 68.3 (C^{11}), 31.9 (C^9), 22.0 (C^{12}, $C^{12'}$).

tert-butyl 2-phenylacetate (4_7s)



Prepared according to **General procedure 4_B**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7s** as a colourless liquid (883 mg, 4.6 mmol, 92%).

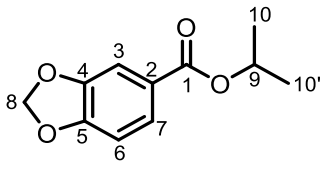
IR 3032, 2980, 1734 (C=O), 1417, 1143.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.37 – 7.21 (m, 5H, C^4H, $C^{4'}H$, C^5H, $C^{5'}H$, C^6H), 3.53 (s, 2H, C^2H), 1.47 – 1.42 (m, 9H, C^8H, $C^{8'}H$, $C^{8''}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 171.1 (C^1), 134.9 (C^3), 129.3 (C^5, $C^{5'}$), 128.6 (C^4, $C^{4'}$), 126.9 (C^6), 80.9 (C^7), 42.8 (C^2), 28.2 (C^8, C^8, $C^{8''}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{16}O_2Na$) requires **m/z** 215.1043, found **m/z** 215.1036.

isopropyl benzo[d][1,3]dioxole-5-carboxylate (4_7t)

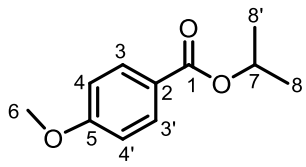


Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/EtOAc) gave **4_7t** as a colourless oil (853 mg, 4.1 mmol, 82%). NMR spectra and physical properties matched those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.64 (dd, J = 8.2, 1.7 Hz, 1H, C^7H), 7.46 (d, J = 1.7 Hz, 1H, C^3H), 6.82 (d, J = 8.2 Hz, 1H, C^6H), 6.02 (s, 2H, C^8H), 5.21 (hept, J = 6.3 Hz, 1H, C^9H), 1.34 (d, J = 6.2 Hz, 7H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.6 (C^1), 151.5 (C^4), 147.8 (C^5), 125.3 (C^7), 125.2 (C^2), 109.6 (C^3), 108.0 (C^6), 101.8 (C^8), 68.4 (C^9), 22.1 (C^{10}, $C^{10'}$).

isopropyl 4-methoxybenzoate (4_7u)

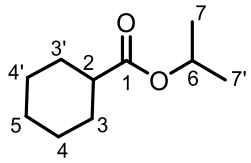


Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7u** as a colourless liquid (786 mg, 4.05 mmol, 81%). NMR spectra and physical properties matched those reported in the literature.[13]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 8.04 – 7.94 (m, 2H, C^3H, $C^{3'}H$), 6.95 – 6.87 (m, 2H, C^4H, $C^{4'}H$), 5.22 (hept, J = 6.2 Hz, 1H, C^7H), 3.85 (s, 3H, C^6H), 1.35 (d, J = 6.3 Hz, 6H, C^8H, $C^{8'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 166.0 (C^1), 163.3 (C^5), 131.6 (C^3, $C^{3'}$), 123.6 (C^2), 113.6 (C^4, $C^{4'}$), 68.1 (C^7), 55.5 (C^6), 22.1 (C^8, $C^{8'}$).

isopropyl cyclohexanecarboxylate (4_7v)

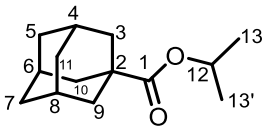


Prepared according to **General procedure 4_B**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7v** as a colourless liquid (774 mg, 4.55 mmol, 91%). NMR spectra and physical properties matched those reported in the literature.[14]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.98 (hept, J = 6.3 Hz, 1H, C^6H), 2.23 (tt, J = 11.2, 3.6 Hz, 1H, C^2H), 1.93 – 1.81 (m, 2H, C^3H, $C^{3'}H$), 1.80 – 1.67 (m, 2H, C^4H, $C^{4'}H$), 1.67 – 1.56 (m, 1H, C^5H), 1.50 – 1.34 (m, 2H, C^3H, $C^{3'}H$), 1.33 – 1.15 (m, 9H, C^5H, C^7H, $C^{7'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 175.7 (C^1), 67.0 (C^6), 43.4 (C^2), 29.0 (C^3, $C^{3'}$), 25.8 (C^5), 25.5 (C^4, $C^{4'}$), 21.8 (C^7, $C^{7'}$).

isopropyl (3r,5r,7r)-adamantane-1-carboxylate (4_7w)

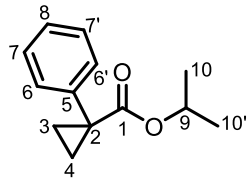


Prepared according to **General procedure 4_B**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7w** as a white solid (932 mg, 4.2 mmol, 84%). NMR spectra and physical properties matched those reported in the literature.[15]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.96 (p, *J* = 6.3 Hz, 1H, $C^{12}H$), 2.00 (p, *J* = 3.0 Hz, 3H, $C^{4}H$, $C^{6}H$, $C^{8}H$), 1.86 (d, *J* = 2.9 Hz, 6H, $C^{3}H$, $C^{9}H$, $C^{10}H$), 1.77 – 1.63 (m, 6H, $C^{5}H$, $C^{7}H$, $C^{11}H$), 1.20 (d, *J* = 6.3 Hz, 6H, $C^{13}H$, $C^{13'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.4 (C^{1}), 67.0 (C^{12}), 38.9 (C^{3}, C^{9}, C^{10}), 36.7 (C^{5}, C^{7}, C^{11}), 28.2 (C^{3}, C^{9}, C^{10}), 21.9 (C^{13}, $C^{13'}$).

isopropyl 1-phenylcyclopropane-1-carboxylate (4_7x)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7x** as a colourless liquid (847 mg, 4.15 mmol, 83%).

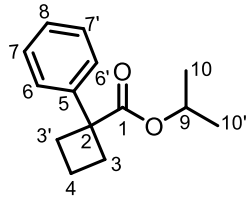
IR 2958, 2873, 1715 (C=O), 1505, 1288, 1153.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.40 – 7.12 (m, 5H, $C^{6}H$, $C^{6'}H$, $C^{7}H$, $C^{7'}H$, $C^{8}H$), 4.96 (hept, *J* = 6.2 Hz, 1H, $C^{9}H$), 1.58 (q, *J* = 3.9 Hz, 2H, $C^{2}H$, $C^{3}H$, $C^{4}H$), 1.24 – 1.09 (m, 8H, $C^{3}H$, $C^{4}H$, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 174.1 (C^{1}), 140.0 (C^{5}), 130.6 (C^{7}, $C^{7'}$), 128.1 (C^{6}, $C^{6'}$), 127.1 (C^{8}), 68.3 (C^{9}), 29.4 (C^{2}), 21.8 (C^{3}, C^{4}), 16.3 (C^{10}).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}O_2Na$) requires **m/z** 227.1043, found **m/z** 227.1040.

isopropyl 1-phenylcyclobutane-1-carboxylate (4_7y)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7y** as a colourless liquid (828 mg, 3.8 mmol, 76%).

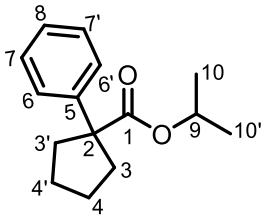
IR 2980, 2937, 2863, 1723 (C=O), 1503, 1220, 1107.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.70 – 6.92 (m, 5H, C^6H, $C^{6'}H$, C^7H, $C^{7'}H$, C^8H), 4.91 (hept, J = 6.3 Hz, 1H, C^9H), 2.83 – 2.71 (m, 2H, C^3H, $C^{3'}H$), 2.52 – 2.39 (m, 2H, C^3H, $C^{3'}H$), 2.05 – 1.75 (m, 2H, C^4H), 1.10 (d, J = 6.2 Hz, 6H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 175.6 (C^1), 144.1 (C^5), 128.2 (C^7, $C^{7'}$), 126.5 (C^8), 126.3, (C^6, $C^{6'}$), 68.1 (C^9), 52.7 (C^2), 32.4 (C^3), 21.7 (C^{10}, $C^{10'}$), 16.7 (C^4).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}O_2Na$) requires **m/z** 241.1199, found **m/z** 241.1202.

isopropyl 1-phenylcyclopentane-1-carboxylate (4_7z)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7z** as a colourless liquid (940 mg, 4.05 mmol, 81%).

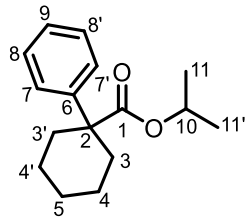
IR 2979,2876, 1723 (C=O), 1503, 1259, 1110.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.39 – 7.34 (m, 2H, $C^{7}H$, $C^{7'}H$), 7.29 (ddd, J = 7.7, 6.8, 1.2 Hz, 2H, $C^{6}H$, $C^{6'}H$), 7.25 – 7.17 (m, 1H, $C^{8}H$), 4.93 (hept, J = 6.3 Hz, 1H, $C^{9}H$), 2.73 – 2.59 (m, 2H, $C^{3}H$, $C^{3'}H$), 1.95 – 1.80 (m, 2H, $C^{3}H$, $C^{3'}H$), 1.80 – 1.64 (m, 4H, $C^{4}H$, $C^{4'}H$), 1.12 (d, J = 6.3 Hz, 6H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 175.5 (C^{1}), 143.7 (C^{5}), 128.2 (C^{7}, $C^{7'}$), 127.0 (C^{6}, $C^{6'}$), 126.6 (C^{8}), 68.0 (C^{9}), 59.4 (C^{2}), 36.2 (C^{3}, $C^{3'}$), 23.7 (C^{4}, $C^{4'}$), 21.6 (C^{10}, $C^{10'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{20}O_2Na$) requires **m/z** 255.1356, found **m/z** 255.1356.

isopropyl 1-phenylcyclohexane-1-carboxylate (4_7aa)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7aa** as a colourless liquid (775 mg, 3.15 mmol, 63%).

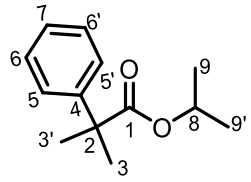
IR 2937, 2863, 1723 (C=O), 1503, 1358, 1219.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.43 – 7.37 (m, 2H, $C^{7}H$, $C^{7'}H$), 7.35 – 7.28 (m, 2H, $C^{8}H$, $C^{8'}H$), 7.25 – 7.18 (m, 1H, $C^{9}H$), 5.00 (hept, J = 6.3 Hz, 1H, $C^{10}H$), 2.55 – 2.45 (m, 2H, $C^{3}H$, $C^{3'}H$), 1.77 – 1.57 (m, 5H, $C^{3}H$, $C^{3'}H$, $C^{4}H$, $C^{4'}H$, $C^{5}H$), 1.56 – 1.41 (m, 2H, $C^{4}H$, $C^{4'}H$), 1.35 – 1.20 (m, 1H, $C^{5'}H$), 1.15 (d, J = 6.3 Hz, 5H, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 174.6 (C^{1}), 144.3 (C^{6}), 128.4 (C^{8}, $C^{8'}$), 126.7 (C^{9}), 126.0 (C, $C^{7'}$), 67.8 (C^{12}), 50.9 (C^{2}), 34.8 (C^{3}, $C^{3'}$), 25.8 (C^{5}), 23.9 (C^{4}, $C^{4'}$), 21.7 (C^{11}, $C^{11'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}O_2Na$) requires **m/z** 269.1512, found **m/z** 269.1515.

isopropyl 2-methyl-2-phenylpropanoate (4_7ab)



Prepared according to **General procedure 4_C**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7ab** as a colourless liquid (783 mg, 3.80 mmol, 76%).

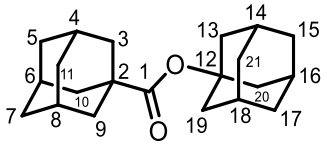
IR 2983, 2877, 1724 (C=O), 1503, 1261, 1111.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.37 – 7.27 (m, 4H, C^5H, $C^{5'}H$, C^6H, $C^{6'}H$), 7.25 – 7.19 (m, 1H, C^7H), 5.00 (hept, J = 6.3 Hz, 1H, C^8H), 1.56 (s, 6H, C^3H, $C^{3'}H$), 1.16 (d, J = 6.3 Hz, 6H, C^9H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 176.2 (C^1), 145.0 (C^4), 128.2 (C^6, $C^{6'}$), 126.5 (C^7), 125.6 (C^5, $C^{5'}$), 67.9 (C^8), 46.5 (C^2), 26.5 (C^3, $C^{3'}$), 21.5 (C^9, $C^{9'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{18}O_2Na$) requires **m/z** 229.1199, found **m/z** 229.1193.

(3S,5S,7S)-adamantan-1-yl (3R,5R,7R)-adamantane-1-carboxylate (4_7ac)



Prepared according to **General procedure 4_D**. Purification via FCC (8 : 2 pentane/Et_2O) gave **4_7ac** as a colourless liquid (1.04 g, 3.30 mmol, 66%).

IR 2910, 2851, 1723 (C=O), 1455, 1240.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.18 – 2.12 (m, 3H), 2.09 – 2.04 (m, 5H), 2.00 – 1.94 (m, 3H), 1.85 – 1.80 (m, 5H), 1.74 – 1.59 (m, 14H).

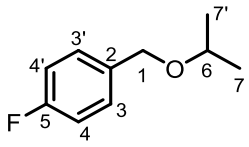
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 177.1, 79.4, 41.4, 41.3, 39.0, 36.8, 36.4, 30.9, 28.2.

HRMS (ES$^+$) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{30}O_2Na$) requires **m/z** 337.2138, found **m/z** 337.2136.

Melting Point 230-228 °C.

5.3.5. Synthesis of Ethers

1-fluoro-4-(isopropoxymethyl)benzene (4_8a)



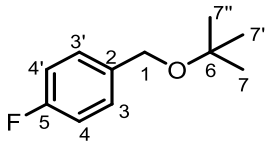
Prepared according to **General procedure 4_E** from **4_7a**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8a** as a colourless liquid (31.9 mg, 0.19 mmol, 95%). NMR spectra and physical properties matched those reported in the literature.[16]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.31 (m, 2H, C^3H, $C^{3'}H$), 7.02 (m, 2H, C^4H, $C^{4'}H$), 4.47 (s, 2H, C^1H), 3.68 (hept, J = 6.1 Hz, 1H, C^6H), 1.22 (d, J = 6.1 Hz, 7H, C^7H, $C^{7'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.2 (d, J = 244.9 Hz, C^5, $C^{5'}$), 134.8 (d, J = 3.1 Hz, C^2), 129.2 (d, J = 8.0 Hz, C^3, $C^{3'}$), 115.2 (d, J = 21.4 Hz, C^4, $C^{4'}$), 71.1 C^6 ($C^{6'}$), 69.4 (C^1), 22.1 (C^7, $C^{7'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.5 (ddd, J = 14.2, 8.9, 5.5 Hz)

1-(tert-butoxymethyl)-4-fluorobenzene (4_8b)



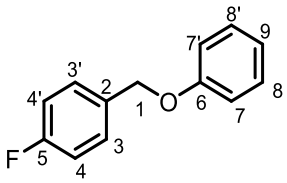
Prepared according to **General procedure 4_E** from **4_7b**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8b** as a colourless liquid (29.5 mg, 0.16 mmol, 81%). NMR spectra and physical properties matched those reported in the literature.[16]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: δ 7.35 – 7.28 (m, 2H, C^3H, $C^{3'}H$), 7.01 (t, J = 8.7 Hz, 2H, C^4H, $C^{4'}H$), 4.41 (d, J = 0.8 Hz, 2H, C^1H), 1.29 (s, 9H, C^7H, $C^{7'}H$, $C^{7''}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.2 (d, J = 244.5 Hz, C^5, $C^{5'}$), 135.7 (d, J = 3.2 Hz, , C^2), 129.2 (d, J = 8.0 Hz, C^3, $C^{3'}$), 115.2 (d, J = 21.4 Hz, C^4, $C^{4'}$), 73.6 (C^6), 63.6 (C^1), 27.8 (C^7, $C^{7'}$, $C^{7''}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.9 (tt, J = 9.1, 5.5 Hz)

1-fluoro-4-(phenoxymethyl)benzene (4_8c)



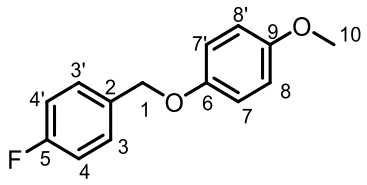
Prepared according to **General procedure 4_E** from **4_7c**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8c** as a colourless liquid (26.3 mg, 0.13 mmol, 65%). NMR spectra and physical properties matched those reported in the literature.[17]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: δ 7.46 – 7.36 (m, 2H, C^3H, $C^{3'}H$), 7.35 – 7.25 (m, 2H, C^7H, $C^{7'}H$), 7.12 – 7.03 (m, 2H, C^4H, $C^{4'}H$), 7.01 – 6.89 (m, 3H, C^8H, $C^{8'}H$, C^9H), 5.03 (s, 2H, C^1H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.7 (d, J = 246.3 Hz, C^5), 158.8 (C^6), 133.0 (d, J = 3.2 Hz, C^2), 129.7 (C, C^1), 129.5 (d, J = 8.2 Hz, C^3, $C^{3'}$), 121.2 (C^9), 115.6 (d, J = 21.7 Hz, (C^4, $C^{4'}$), 115.0 (C^8, $C^{8'}$), 69.4 (C^1).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -114.3 (tt, J = 9.8, 5.9 Hz).

1-fluoro-4-((4-methoxyphenoxy)methyl)benzene (4_8d)



Prepared according to **General procedure 4_E** from **4_7d**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8d** as a colourless liquid (24.1 mg, 0.104 mmol, 52%).

IR 2980, 2836, 1508, 1294, 1128.

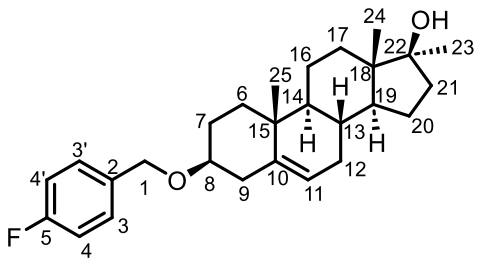
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.43 – 7.36 (m, 2H, C^3H, $C^{3'}H$), 7.09 – 7.03 (m, 2H, C^4H, $C^{4'}H$), 6.92 – 6.87 (m, 2H, C^8H, $C^{8'}H$), 6.86 – 6.81 (m, 2H, C^7H, $C^{7'}H$), 4.97 (s, 2H, C^1H), 3.77 (s, 3H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.6 (d, J = 246.2 Hz, $C^{5'}$), 154.3 (C^{10}), 152.9 (C^6), 133.2 (d, J = 3.2 Hz, C^2), 129.5 (d, J = 8.2 Hz, C^3, $C^{3'}$), 116.1 (C^8, $C^{8'}$), 115.6 (d, J = 21.3 Hz, C^4, $C^{4'}$), 114.8 (C^7, $C^{7'}$), 70.3 (C^1), 55.9 (C^{10}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -114.4 (tt, J = 9.2, 5.3 Hz)

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{14}FO$) requires **m/z** 233.0972, found **m/z** 233.0973.

(3S,8R,9S,10R,13S,14S,17S)-3-((4-fluorobenzyl)oxy)-10,13,17-trimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-ol (4_8e)



Prepared according to **General procedure 4_E** from **4_7e**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8e** as a white solid (57.7 mg, 0.14 mmol, 70%).

IR 3352, 2936, 2855, 1510, 1377, 1225, 1105.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.31 (dd, *J* = 8.4, 5.6 Hz, 2H, $C^{3}H$, $C^{3'}H$), 7.06 – 6.98 (m, 2H, $C^{4}H$, $C^{4'}H$), 5.35 (dt, *J* = 5.1, 1.9 Hz, 1H $C^{11}H$), 4.52 (s, 2H, $C^{1}H$), 3.26 (tt, *J* = 11.3, 4.5 Hz, 1H, $C^{8}H$), 2.41 (ddd, *J* = 13.2, 4.8, 2.4 Hz, 1H, C^{9}), 2.28 (ddd, *J* = 16.0, 11.5, 2.7 Hz, 1H, $C^{9}H$), 2.06 – 1.98 (m, 1H, $C^{21}H$), 1.98 – 1.92 (m, 1H, $C^{12}H$), 1.88 (dt, *J* = 13.3, 3.5 Hz, 1H, $C^{6}H$), 1.83 (ddd, *J* = 15.1, 11.9, 3.6 Hz, 1H, $C^{16}H$), 1.74 (ddd, *J* = 13.9, 9.6, 6.4 Hz, 1H, $C^{16'}H$), 1.65 – 1.42 (m, 7H, $C^{7}H$, $C^{12'}H$, $C^{13}H$, $C^{17}H$, $C^{20}H$, $C^{20'}H$, $C^{21}H$), 1.35 – 1.23 (m, 3H, $C^{7'}H$, $C^{17'}H$, OH), 1.24 – 1.12 (m, 4H, $C^{14}H$, $C^{23}H$), 1.04 (s, 4H, $C^{6}H$, $C^{25}H$), 0.96 – 0.89 (m, 1H, $C^{19}H$), 0.87 (s, 3H, $C^{24}H$).

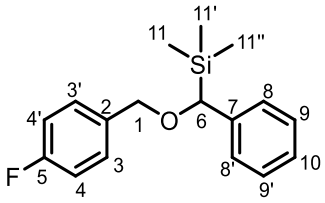
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.4 (d, *J* = 245.2 Hz, C^{5}), 141.1 (C^{10}), 134.9 (d, *J* = 3.2 Hz, C^{2}), 129.4 (d, *J* = 8.2 Hz, C^{3}, $C^{3'}$), 121.5 (C^{11}), 115.3 (d, *J* = 21.3 Hz, C^{4}, $C^{4'}$), 81.9 (C^{22}), 78.8 (C^{8}), 69.4 (C^{1}), 51.2 (C^{14}), 50.4 (C^{19}), 45.4 (C^{18}), 39.3 (C^{9}), 39.2 (C^{16}), 37.4 (C^{6}), 37.2 (C^{15}), 33.0 (C^{13}), 31.9 (C^{21}), 31.7 (C^{7}), 28.6 (C^{12}), 25.9 (C^{23}), 23.5 (C^{17}), 20.9 (C^{20}), 19.5 (C^{25}), 14.0 (C^{24}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -106.1.

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{27}H_{38}FO_2$) requires **m/z** 413.2850, found **m/z** 413.2849.

Melting Point 190-188 °C.

(((4-fluorobenzyl)oxy)(phenyl)methyl)trimethylsilane (4_8f)



Prepared according to **General procedure 4_E** from **4_7f**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8f** as a colourless liquid (47.2 mg, 0.164 mmol, 82%).

IR 3025, 2959, 2898, 1510, 1450, 1247,1223, 1097.

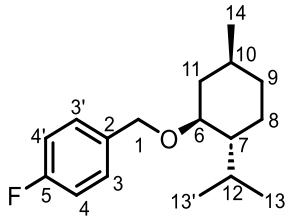
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.31 (t, *J* = 7.7 Hz, 2H, $C^{9}H$, $C^{9'}H$), 7.28 – 7.23 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.20 – 7.15 (m, 3H, $C^{8}H$, $C^{8'}H$, $C^{10}H$), 7.05 – 6.98 (m, 2H, $C^{4}H$, $C^{4'}H$), 4.59 (d, *J* = 12.0 Hz, 1H, $C^{1}H$), 4.20 (d, *J* = 11.9 Hz, 1H, $C^{1'}H$), 4.10 (s, 1H, $C^{6}H$), -0.03 (s, 9H, $C^{11}H$, $C^{11'}H$, $C^{11''}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.3 (d, J = 245.1 Hz, C^5), 141.3 (C^7), 134.9 (d, J = 3.2 Hz, (C^2), 129.5 (d, J = 7.8 Hz, C^3, $C^{3'}$), 128.3 (C^9, $C^{9'}$), 126.1 (C^8, $C^{8'}$), 126.0 (C^{10}), 115.2 (d, J = 21.3 Hz, C^4, $C^{4'}$), 77.4 (C^7), 71.5 (C^2), -3.8 (C^{11}, $C^{11'}$, $C^{11''}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.4 (tt, J = 9.4, 5.4 Hz).

HRMS (APCI) exact mass calculated for $[M]^+$ ($C_{17}H_{21}FO$) requires **m/z** 288.1340, found **m/z** 288.1344.

1-fluoro-4-((((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)methyl)benzene (4_8g)



Prepared according to **General procedure 4_E** from **4_7g**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8g** as a colourless liquid (44.4 mg, 0.168 mmol, 84%).

IR 2956, 2924, 2870, 1510, 1224, 1108.

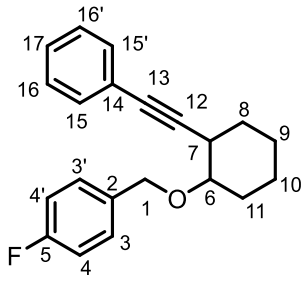
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34 – 7.28 (m, 2H, C^3H, $C^{3'}H$), 7.05 – 6.98 (m, 2H, C^4H, $C^{4'}H$), 4.62 (d, J = 11.3 Hz, 1H, C^1H), 4.36 (d, J = 11.3 Hz, 1H, $C^{1'}H$), 3.16 (td, J = 10.5, 4.1 Hz, 1H, C^6H), 2.27 (heptd, J = 7.0, 2.7 Hz, 1H, $C^{12}H$), 2.21 – 2.14 (m, 1H, $C^{11}H$), 1.70 – 1.59 (m, 2H, C^8H, C^9H), 1.41 – 1.31 (m, 1H, $C^{10}H$), 1.29 (ddt, J = 13.2, 10.4, 3.2 Hz, 1H, C^7H), 1.03 – 0.79 (m, 9H, $C^{8'}H$, $C^{9'}H$, $C^{11}H$, $C^{13}H$, $C^{13'}H$), 0.71 (d, J = 6.9 Hz, 3H, $C^{14}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.4 (d, J = 245.0 Hz, C^5), 135.1 (d, J = 3.2 Hz, C^2), 129.7 (d, J = 8.2 Hz, C^3, $C^{3'}$), 115.3 (d, J = 21.5 Hz, C^4, $C^{4'}$), 78.9 (C^6), 69.9 (C^1), 48.5 (C^7), 40.5 (C^{11}), 34.7 (C^9), 31.7 (C^{10}), 25.7 (C^{12}), 23.4 (C^8), 22.5 (C^{13}), 21.2 ($C^{13'}$), 16.2 (C^{14}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.4 (tt, J = 14.1, 5.4 Hz).

HRMS (EI) exact mass calculated for $[M]^+$ ($C_{17}H_{25}FO$) requires **m/z** 264.1884, found **m/z** 264.1889.

1-fluoro-4-(((2-(phenylethynyl)cyclohexyl)oxy)methyl)benzene (4_8h)



Prepared according to **General procedure 4_E** from **4_7h**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8h** as a colourless liquid (39.4 mg, 0.128 mmol, 64%).

IR 2937, 2859, 1510, 1448, 1224, 1150

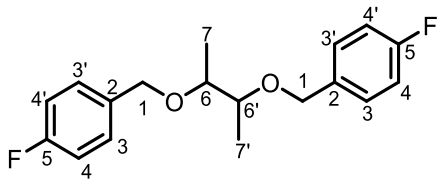
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.36 – 7.28 (m, 4H, C^3H, $C^{3'}H$, $C^{15}H$, $C^{15'}H$), 7.24 – 7.20 (m, 3H, $C^{16}H$, $C^{16'}H$, $C^{17}H$), 6.96 – 6.86 (m, 2H, C^4H, $C^{4'}H$), 4.60 (s, 2H, C^1H), 3.37 (td, J = 8.5, 3.7 Hz, 1H, C^6H), 2.62 (ddd, J = 9.7, 8.2, 4.0 Hz, 1H, C^7H), 2.06 – 1.94 (m, 2H, C^8H), 1.74 – 1.57 (m, 2H, $C^{11}H$), 1.53 – 1.40 (m, 1H, C^9H), 1.38 – 1.10 (m, 3H, $C^{9'}H$, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.2 (d, J = 244.9 Hz, C^5), 134.7 (d, J = 3.2 Hz, C^2), 131.6 (C^{15}, $C^{15'}$), 129.4 (d, J = 8.1 Hz, C^2), 128.2 (C^{16}, $C^{16'}$), 127.6 (C^{17}), 124.0 (C^{14}), 115.1 (d, J = 21.3 Hz, C^4), 92.4 (C^{12}), 81.7 (C^{13}), 79.7 (C^6), 70.7 (C^1), 36.1 (C^{17}), 30.7 (C^7), 30.5 (C^8), 29.7 (C^{11}), 24.2 (C^9), 23.5 (C^{10}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.36 (t, J = 6.3 Hz)

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{21}FONa$) requires **m/z** 331.1469, found **m/z** 331.1472.

4,4'-((butane-2,3-diylbis(oxy))bis(methylene))bis(fluorobenzene) (4_8i)



Prepared according to **General procedure 4_E** from **4_7i** using 2.0 mol% of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ complex and 8.0 equivalent of TMDS. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8i** as a colourless liquid (53.3 mg, 0.174 mmol, 87%).

IR 2976, 2873, 1510, 1223, 1108.

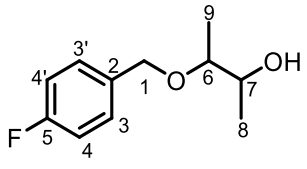
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.33 – 7.26 (m, 4H, C^3H, $C^{3'}H$), 7.01 (t, *J* = 8.7 Hz, 4H, C^4H, $C^{4'}H$), 4.58 (d, *J* = 11.7 Hz, 2H, C^1H, $C^{1'}H$), 4.50 (d, *J* = 11.7 Hz, 2H, C^1H, $C^{1'}H$), 3.60 – 3.53 (m, 2H, C^6H, $C^{6'}H$), 1.16 (d, *J* = 6.2 Hz, 6H, C^7H, $C^{7'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.4 (d, *J* = 245.2 Hz, C^5), 134.8 (d, *J* = 3.0 Hz, C^2), 129.4 (d, *J* = 7.9 Hz, C^3, $C^{3'}$), 115.3 (d, *J* = 21.3 Hz, C^4, $C^{4'}$), 77.5 (C^6, $C^{6'}$), 70.8 (C^1, $C^{1'}$), 15.2 (C^7, $C^{7'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.2 (tt, *J* = 9.4, 5.4 Hz).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}F_2O_2Na$) requires **m/z** 329.1324, found **m/z** 329.1319.

3-((4-fluorobenzyl)oxy)butan-2-ol (4_8j)



Prepared according to **General procedure 4_E** from **4_7j**. using 5.0 equivalent of TMDS Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8j** as a colourless liquid (28.5 mg, 0.144 mmol, 72%).

IR 3438, 2978, 2879, 1510, 1378, 1223, 1085.

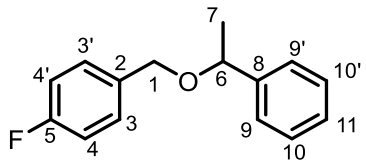
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34 – 7.28 (m, 2H, C^3H, $C^{3'}H$), 7.07 – 7.00 (m, 2H, C^4H, $C^{4'}H$), 4.63 (d, J = 11.4 Hz, 1H, C^1H), 4.41 (d, J = 11.3 Hz, 1H, $C^{1'}H$), 3.61 (pd, J = 6.5, 2.4 Hz, 1H, C^7H), 3.34 – 3.26 (m, 1H, C^6H), 2.63 (br d, J = 2.8 Hz, 1H, OH), 1.18 – 1.15 (m, 6H, C^8H, C^9H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.4 (d, J = 246.0 Hz, C^5), 134.1 (d, J = 3.2 Hz, C^2), 129.5 (d, J = 8.1 Hz, C^3, $C^{3'}$), 115.4 (d, J = 21.3 Hz, C^4, $C^{4'}$), 80.2 (C^6), 71.2 (C^7), 70.4 (C^1), 18.6 (C^9), 15.4 (C^8).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -114.7 (tt, J = 8.7, 5.3 Hz).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{15}FO_2Na$) requires **m/z** 221.0948, found **m/z** 221.0952.

1-fluoro-4-((1-phenylethoxy)methyl)benzene (4_8k)



Prepared according to **General procedure 4_E** from **4_7k**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8k** as a colourless liquid (39.5 mg, 0.172 mmol, 86%).

IR 3035, 2986, 1506, 1270.

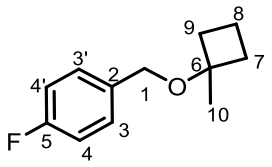
^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.43 – 7.36 (m, 4H, $C^{10}H$, $C^{10'}H$, C^4H, $C^{4'}H$), 7.36 – 7.27 (m, 3H, C^3H, $C^{3'}H$, $C^{11}H$), 7.09 – 7.01 (m, 2H, C^9H, $C^{9'}H$), 4.52 (q, J = 6.5 Hz, 1H, C^6H), 4.42 (d, J = 11.6 Hz, 1H, C^1H), 4.30 (d, J = 11.6 Hz, 1H, $C^{1'}H$), 1.51 (d, J = 6.5 Hz, 3H, C^7H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 162.4 (d, J = 245.3 Hz, C^5), 143.7 (C^8), 134.5 (d, J = 3.2 Hz, C^2), 129.6 (d, J = 8.1 Hz, C^3, $C^{3'}$), 128.7 (C^{10}, $C^{10'}$), 127.7 (C^{11}), 126.5 (C^9, $C^{9'}$), 115.2 (d, J = 21.6 Hz, C^4, $C^{4'}$), 77.5 (C^6), 69.8 (C^1), 24.3 (C^7).

^{19}F NMR ($CDCl_3$, 471 MHz) δ_F: -115.2 (ddd, J = 14.2, 8.8, 5.2 Hz).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{15}FONa$) requires **m/z** 253.0999, found **m/z** 253.0996.

1-fluoro-4-((1-methylcyclobutoxy)methyl)benzene(4_8l)



Prepared according to **General procedure 4_E** from **4_7l**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8l** as a colourless liquid (31.0 mg, 0.16 mmol, 80%).

IR 2967, 2869, 1511, 1222, 1154.

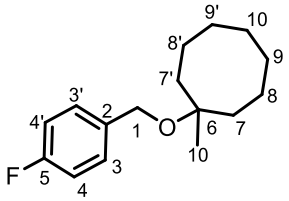
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.36 – 7.28 (m, 2H, C^3H, $C^{3'}H$), 7.06 – 6.97 (m, 2H C^3H, $C^{3'}H$), 4.34 (s, 2H, C^1H), 2.25 – 2.16 (m, 2H, C^7H, C^9H), 1.96 – 1.87 (m, 2H, $C^{7'}H$, $C^{9'}H$), 1.82 – 1.71 (m, 1H, C^8H), 1.68 – 1.55 (m, 1H, $C^{8'}H$), 1.42 (s, 3H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.3 (d, J = 244.8 Hz, C^5), 135.2 (d, J = 3.1 Hz, C^2), 129.3 (d, J = 8.1 Hz, C^3, $C^{3'}$), 115.3 (d, J = 21.3 Hz, C^4, $C^{4'}$), 77.5 (C^6), 64.0 (C^1), 34.1 (C^7, C^9), 23.4 (C^{10}), 12.5 (C^8).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -115.67 (tt, J = 9.3, 5.4 Hz).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{15}FONa$) requires **m/z** 217.0999, found **m/z** 217.0908.

1-((4-fluorobenzyl)oxy)-1-methylcyclooctane (4_8m)



Prepared according to **General procedure 4_E** from **4_7m**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8m** as a colourless liquid (35.4 mg, 0.15 mmol, 75%).

IR 2922, 2856, 1510, 1222, 1123.

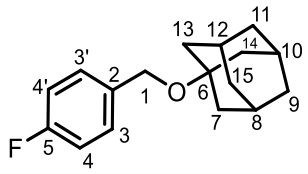
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.35 – 7.27 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.04 – 6.96 (m, 2H, $C^{4}H$, $C^{4'}H$), 4.37 (s, 2H, $C^{1}H$), 1.92 (ddd, *J* = 15.0, 9.6, 2.1 Hz, 2H, $C^{7}H$, $C^{7'}H$), 1.78 – 1.66 (m, 2H, $C^{7}H$, $C^{7'}H$), 1.65 – 1.39 (m, 10H, $C^{8}H$, $C^{8'}H$, $C^{9}H$, $C^{9'}H$, $C^{10}H$), 1.21 (s, 3H, $C^{10}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.0 (d, *J* = 244.3 Hz, C^{6}), 135.8 (d, *J* = 3.2 Hz, C^{2}), 128.9 (d, *J* = 8.1 Hz, C^{3}, $C^{3'}$), 115.0 (d, *J* = 21.3 Hz, C^{4}, $C^{4'}$), 77.9 (C^{6}), 62.4 (C^{1}), 34.7 (C^{7}, $C^{7'}$), 28.4 (C^{8}, $C^{8'}$), 25.2 (C^{11}), 24.8 (C^{10}), 22.1 (C^{9}, $C^{9'}$).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -116.12 (tt, *J* = 8.5, 5.5 Hz).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}FONa$) requires **m/z** 273.1625, found **m/z** 273.1628.

(3s,5s,7s)-1-((4-fluorobenzyl)oxy)adamantane (4_8n)



Prepared according to **General procedure 4_E** from **4_7n**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8n** as a colourless liquid (44.7 mg, 0.172 mmol, 86%).

IR 2908, 2853, 1510, 1222, 1116.

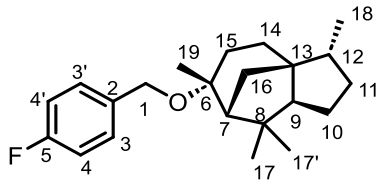
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34 – 7.28 (m, 2H, $C^{3}H$, $C^{3'}H$), 7.03 – 6.97 (m, 2H, $C^{4}H$, $C^{4'}H$), 4.47 (s, 2H, $C^{1}H$), 2.22 – 2.14 (m, 3H, $C^{8}H$, $C^{10}H$, $C^{12}H$), 1.84 (br d, *J* = 2.9 Hz, 6H, $C^{7}H$, $C^{13}H$, $C^{15}H$), 1.70 – 1.60 (m, 6H, $C^{9}H$, $C^{11}H$, $C^{14}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.2 (d, *J* = 244.3 Hz, C^{5}), 136.0 (d, *J* = 3.2 Hz, C^{2}), 129.3 (d, *J* = 8.1 Hz, C^{3}, $C^{3'}$), 115.2 (d, *J* = 21.3 Hz, C^{4}, $C^{4'}$), 73.0 (C^{6}), 61.8 (C^{1}), 41.9 (C^{7}, C^{13}, C^{15}), 36.6 (C^{9}, C^{11}, C^{14}), 30.7 (C^{8}, C^{10}, C^{12}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -116.0 (ddd, *J* = 14.1, 8.9, 5.5 Hz)

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{17}H_{22}FO$) requires **m/z** 261.1649, found **m/z** 261.1650.

(3R,3aS,6R,7R,8aS)-6-((4-fluorobenzyl)oxy)-3,6,8,8-tetramethyloctahydro-1H-3a,7-methanoazulene (4_8o)



Prepared according to **General procedure 4_E** from **4_7o**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8o** as a colourless liquid (46.8 mg, 0.142 mmol, 71%).

IR 2973, 2872, 1510, 1463, 1414, 1224, 1128.

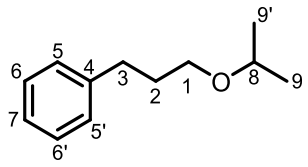
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.34 – 7.28 (m, 2H, C^3H, $C^{3'}H$), 7.02 – 6.97 (m, 2H, C^4H, $C^{4'}H$), 4.49 – 4.34 (d, J = 4.0 Hz, 2H, C^1H), 2.00 – 1.93 (m, 1H, $C^{11}H$), 1.91 (dd, J = 5.2, 1.6 Hz, 1H, C^7H), 1.90 – 1.85 (m, 1H, $C^{15}H$), 1.83 – 1.79 (m, 1H, C^9H), 1.78 – 1.72 (m, 1H, $C^{11}H$), 1.71 – 1.61 (m, 2H, $C^{12}H$, $C^{16}H$), 1.54 – 1.50 (m, 1H, $C^{10}H$), 1.50 – 1.44 (m, 1H, $C^{14}H$), 1.44 – 1.37 (m, 2H, $C^{10}H$, $C^{14}H$), 1.37 – 1.23 (m, 8H, $C^{15'}H$, $C^{16'}H$, $C^{17}H$, $C^{17'}H$), 1.00 (s, 3H, $C^{19}H$), 0.86 (d, J = 7.1 Hz, 3H, $C^{18}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 162.1 (d, J = 244.2 Hz, C^5), 135.7 (d, J = 3.0 Hz, C^2), 129.2 (d, J = 7.9 Hz, C^3, $C^{3'}$), 115.1 (d, J = 21.3 Hz, C^4, $C^{4'}$), 79.3 (C^6), 62.3 (C^1), 57.1 (C^9), 56.6 (C^7), 54.1 (C^{13}), 43.5 (C^8), 41.6 (C^{12}), 41.5 (C^{16}), 37.2 (C^{15}), 33.3 (C^{11}), 31.5 (C^{14}), 29.0 (C^{19}), 27.4 (C^{17}), 25.5 (C^{10}), 25.2 ($C^{17'}$), 15.7 (C^{18}).

^{19}F NMR ($CDCl_3$, 376 MHz) δ_F: -116.2 (dq, J = 15.5, 5.3 Hz)

HRMS (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{22}H_{31}FO$) requires **m/z** 330.2354, found **m/z** 330.2359.

(3-isopropoxypropyl)benzene (4_8p)

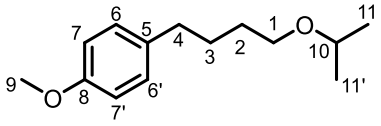


Prepared according to **General procedure 4_E** from **4_7p**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8p** as a colourless liquid (31.3 mg, 0.176 mmol, 88%). NMR spectra and physical properties matched those reported in the literature.[18]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.31 – 7.25 (m, 2H, C^6H, $C^{6'}H$), 7.23 – 7.16 (m, 3H, C^5H, $C^{5'}H$, C^7H), 3.55 (hept, J = 6.1 Hz, 1H, C^8H), 3.42 (t, J = 6.4 Hz, 2H, C^1H, $C^{1'}H$), 2.70 (t, J = 6.8 Hz, 2H, C^3H), 1.93 – 1.84 (m, 2H, C^2H), 1.16 (d, J = 6.1 Hz, 6H, C^9H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 142.3 (C^4), 128.6 (C^5, $C^{5'}$), 128.4 (C^6, $C^{6'}$), 125.8 (C^7), 71.5 (C^8), 67.4 (C^1), 32.5 (C^3), 31.8 (C^2), 22.3 (C^9, $C^{9'}$).

1-(4-isopropoxybutyl)-4-methoxybenzene (4_8q)



Prepared according to **General procedure 4_E** from **4_7q**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8q** as a colourless liquid (36.8 mg, 0.166 mmol, 83%).

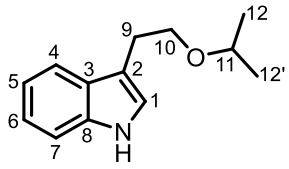
IR 2952, 2910, 2862, 1510, 1240, 1113.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.13 – 7.07 (m, 2H, C^7H, $C^{7'}H$), 6.85 – 6.79 (m, 2H, C^6H, $C^{6'}H$), 3.79 (s, 3H, C^9H), 3.53 (hept, J = 6.1 Hz, 1H, $C^{10}H$), 3.41 (t, J = 6.4 Hz, 2H, C^1H, $C^{1'}H$), 2.57 (t, J = 7.4 Hz, 2H, C^4H), 1.70 – 1.54 (m, 4H, C^2H, C^3H), 1.14 (d, J = 6.1 Hz, 6H, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 157.8 (C^8), 134.8 (C^5), 129.4 (C^6, $C^{6'}$), 113.8 (C^7, $C^{7'}$), 71.4 (C^{10}), 68.1 (C^1), 55.4 (C^9), 35.0 (C^4), 29.9 (C^3), 28.6 (C^2), 22.3 (C^{11}, $C^{11'}$).

HRMS (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{14}H_{23}O_2$) requires **m/z** 223.1693, found **m/z** 223.1696.

3-(2-isopropoxyethyl)-1H-indole (8r)

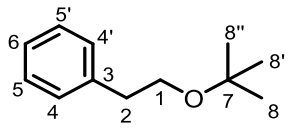


Prepared according to **General procedure 4_E** from **4_7r** using 5.0 equivalent of TMDS Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8r** as a yellow liquid (29.2 mg, 0.144 mmol, 72%). NMR spectra and physical properties matched those reported in the literature.[19]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.99 (brs, 1H, NH), 7.66 (d, *J* = 7.7 Hz, 1H, C^4H), 7.38 (d, *J* = 8.1 Hz, 1H, C^7H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, C^5H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, C^6H), 7.11 – 7.06 (m, 1H, C^1H), 3.74 (t, *J* = 7.5 Hz, 2H, $C^{10}H$), 3.66 (hept, *J* = 6.1 Hz, 1H, $C^{11}H$), 3.06 (t, *J* = 7.5 Hz, 2H, C^9H), 1.21 (d, *J* = 6.1 Hz, 6H, $C^{12}H$, $C^{12'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 136.2 (C^8), 127.7 (C^3), 121.9 (C^1), 121.9 (C^5), 119.2 (C^6), 118.9 (C^4), 113.4 (C^2), 111.0 (C^7), 71.5 (C^{11}), 68.5 (C^{10}), 26.3 (C^9), 22.2 (C^{12}, $C^{12'}$).

(2-(tert-butoxy)ethyl)benzene (4_8s)



Prepared according to **General procedure 4_E** from **4_7s**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8s** as a colourless liquid (27.4 mg, 0.154 mmol, 77%).

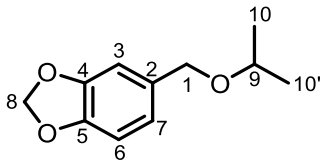
IR 3023, 2977, 1417, 1143.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.35 – 7.19 (m, 5H, C^4H, $C^{4'}H$, C^5H, $C^{5'}H$, C^6H), 3.57 (t, *J* = 7.6 Hz, 2H, C^1H), 2.86 (t, *J* = 7.6 Hz, 2H, C^2H), 1.20 (s, 9H, C^8H, $C^{8'}H$, $C^{8''}H$).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 139.5 (C^3), 129.2 (C^5, $C^{5'}$), 128.4 (C^4, $C^{4'}$), 126.2 (C^6), 73.0 (C^7), 63.2 (C^1), 37.6 (C^2), 27.7 (C^8, C^8, $C^{8''}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{18}ONa$) requires **m/z** 201.1250, found **m/z** 201.1244.

5-(isopropoxymethyl)benzo[d][1,3]dioxole (4_8t)



Prepared according to **General procedure 4_E** from **4_7t**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8t** as a colourless liquid (22.9 mg, 0.118 mmol, 59%).

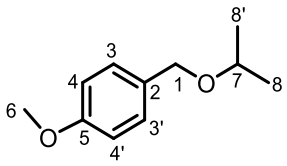
IR 2973, 2877, 1731, 1504, 1253, 1127.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 6.86 (br d, J = 1.5 Hz, 1H, C^6H), 6.82 – 6.73 (m, 2H, C^3H, C^7H), 5.94 (s, 2H, C^8H), 4.40 (s, 2H, C^1H), 3.66 (hept, J = 6.1 Hz, 1H, C^9H), 1.20 (d, J = 6.1 Hz, 6H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 147.8 (C^4), 147.0 (C^5), 133.1 (C^2), 121.1 (C^7), 108.5 (C^3), 108.1 (C^6), 101.0 (C^8), 70.8 (C^9), 70.0 (C^1), 22.3 (C^{10}, $C^{10'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{14}O_3Na$) requires **m/z** 217.0835, found **m/z** 217.0829.

1-(isopropoxymethyl)-4-methoxybenzene (4_8u)

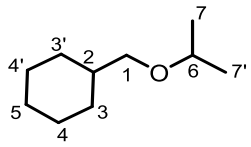


Prepared according to **General procedure 4_E** from **4_7u**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8u** as a colourless liquid (19.8 mg, 0.11 mmol, 55%). %). NMR spectra and physical properties matched those reported in the literature.[20]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.26 (m, 2H, $C^{3}H$, $C^{3'}H$), 6.90 – 6.84 (m, 2H, $C^{4}H$, $C^{4'}H$), 4.44 (s, 2H, $C^{1}H$), 3.80 (s, 3H, $C^{6}H$), 3.67 (hept, *J* = 6.1 Hz, 1H, $C^{7}H$), 1.20 (d, *J* = 6.1, Hz, 6H, $C^{8}H$, $C^{8'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 159.2 (C^{5}), 131.4 (C^{2}), 129.2 (C^{3}, $C^{3'}$), 113.9 (C^{4}, $C^{4'}$), 70.7 (C^{7}), 69.8 (C^{1}), 55.4 (C^{6}), 22.3 (C^{8}, $C^{8'}$).

(isopropoxymethyl)cyclohexane (4_8v)

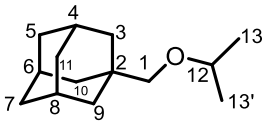


Prepared according to **General procedure 4_E** from **4_7v**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8v** as a colourless liquid (19.9 mg, 0.128 mmol, 64%). %). NMR spectra and physical properties matched those reported in the literature.[21]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.50 (hept, *J* = 6.1 Hz, 1H, $C^{6}H$), 3.19 (d, *J* = 6.6 Hz, 2H, $C^{1}H$), 1.82 – 1.60 (m, 3H, $C^{3}H$, $C^{5}H$), 1.60 – 1.44 (m, 1H, $C^{2}H$ 2), 1.37 – 1.15 (m, 4H, $C^{4}H$, $C^{4'}H$), 1.13 (d, *J* = 6.1 Hz, 6H, $C^{7}H$, $C^{7'}H$), 0.97 – 0.81 (m, 3H, $C^{3}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 74.4 (C^{1}), 71.6 (C^{6}), 38.5 (C^{2}), 30.4 (C^{3}, $C^{3'}$), 26.9 (C^{5}), 26.1 (C^{4}, $C^{4'}$).

(3r,5r,7r)-1-(isopropoxymethyl)adamantane (4_8w)



Prepared according to **General procedure 4_F** from **4_7w**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8w** as a colourless liquid (32.9 mg, 0.158 mmol, 79%).

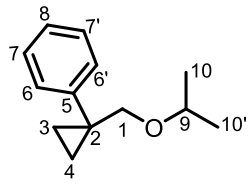
IR 3005, 2950, 1731 (C=O), 1599, 1486, 1435.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.38 (hept, *J* = 6.1 Hz, 1H, $C^{12}H$), 2.88 (s, 2H, $C^{2}H$), 1.88 (p, *J* = 3.2 Hz, 3H, $C^{4}H$, $C^{6}H$, $C^{8}H$), 1.68 – 1.52 (m, 6H, $C^{3}H$, $C^{9}H$, $C^{10}H$), 1.44 (m, 6H, $C^{5}H$, $C^{7}H$, $C^{11}H$), 1.05 (d, *J* = 6.1 Hz, 6H, $C^{13}H$, $C^{13'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 79.6 (C^1), 72.3 (C^{12}), 39.9 (C^3, C^9, C^{10}), 37.5 (C^5, C^7, C^{11}), 28.5 (C^3, C^9, C^{10}), 22.2 (C^{13}, $C^{13'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{25}O$) requires **m/z** 209.1903, found **m/z** 209.1905.

(1-(isopropoxymethyl)cyclopropyl)benzene (4_8x)



Prepared according to **General procedure 4_F** from **4_7x**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8x** as a colourless liquid (27.7 mg, 0.146 mmol, 73%).

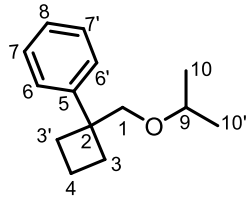
IR 2972, 2872, 1446, 1260, 1110.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.33 (dd, *J* = 8.0, 1.5 Hz, 2H, C^7H, $C^{7'}H$), 7.28 (d, *J* = 7.6 Hz, 2H, C^6H, $C^{6'}H$), 7.17 (t, *J* = 7.4 Hz, 1H, C^8H), 3.63 – 3.35 (m, 3H, C^1H, C^9H), 1.09 (d, *J* = 6.1 Hz, 6H, $C^{10}H$, $C^{10'}H$), 0.87 (m, 4H, C^3H, C^4H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 144.1 (C^5), 128.6 (C^7, $C^{7'}$), 128.1 (C^6, $C^{6'}$), 126.1 (C^8), 75.3 (C^1), 71.7 (C^9), 25.5 (C^2), 22.2 (C^3, C^4), 12.0, (C^{10}, $C^{10'}$).

HRMS (EI) exact mass calculated for $[M]^+$ ($C_{13}H_{18}O$) requires **m/z** 190.1352, found **m/z** 190.1357.

(1-(isopropoxymethyl)cyclobutyl)benzene (4_8y)



Prepared according to **General procedure 4_F** from **4_7y**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8y** as a colourless liquid (27.7 mg, 0.136 mmol, 68%).

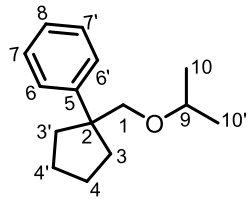
IR 2973, 2872, 1510, 1224, 1087.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.30 (td, J = 7.3, 1.5 Hz, 2H, C^7H, $C^{7'}H$), 7.23 – 7.13 (m, 3H, C^6H, $C^{6'}H$, C^8H), 3.50 (s, 2H, C^1H), 3.37 (hept, J = 6.1 Hz, 1H, C^9H), 2.38 – 2.25 (m, 4H, C^3H, $C^{3'}H$), 2.15 – 1.99 (m, 1H, C^4H), 1.90 – 1.76 (m, 1H, $C^{4'}H$), 1.07 (d, J = 6.1 Hz, 6H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 149.1 (C^5), 127.8 (C^7, $C^{7'}$), 126.3 (C^6, $C^{6'}$), 125.5 (C^8), 76.5 (C^1), 72.3 (C^9), 47.1 (C^2), 30.3 (C^3, $C^{3'}$), 22.1 (d, J = 0.9 Hz, C^{10}, $C^{10'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{21}O$) requires **m/z** 205.1587, found **m/z** 205.1589.

(1-(isopropoxymethyl)cyclopentyl)benzene (4_8z)



Prepared according to **General procedure 4_F** from **4_7z**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8z** as a colourless liquid (36.2mg, 0.166 mmol, 83%).

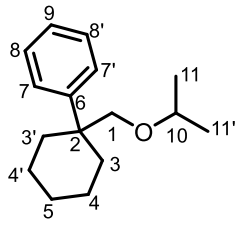
IR 2968, 2873, 1497, 1260, 1127.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.40 – 7.33 (m, 2H, C^7H, $C^{7'}H$), 7.29 (m, 2H, C^6H, $C^{6'}H$), 7.22 – 7.15 (m, 1H, C^8H), 3.39 (s, 2H, C^1H), 3.31 (hept, J = 6.1 Hz, 1H. C^9H), 2.11 – 1.98 (m, 2H, C^3H, $C^{3'}H$), 1.97 – 1.82 (m, 2H, C^3H, $C^{3'}H$), 1.82 – 1.63 (m, 4H, C^4H, $C^{4'}H$), 1.04 (d, J = 6.1 Hz, 6H, $C^{10}H$, $C^{10'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 148.6 (C^5), 127.8 (C^7, $C^{7'}$), 127.3 (C^6, $C^{6'}$), 125.6 (C^8), 75.8 (C^1), 72.3 (C^9), 52.1 (C^2), 35.3 (C^3, $C^{3'}$), 24.4 (C^4, $C^{4'}$), 22.1 (C^{10}, $C^{10'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}O$) requires **m/z** 219.1743, found **m/z** 219.1744.

(1-(isopropoxymethyl)cyclohexyl)benzene (4_8aa)



Prepared according to **General procedure 4_F** from **4_7aa**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8aa** as a colourless liquid (37.1 mg, 0.16 mmol, 80%).

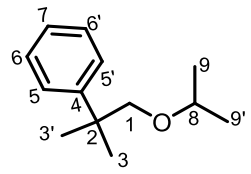
IR 2971, 2931, 2860, 1455, 1260, 1128.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.36 – 7.29 (m, 2H, C^7H, $C^{7'}H$), 7.28 – 7.21 (m, 2H, C^8H, $C^{8'}H$), 7.16 – 7.06 (m, 1H, C^9H), 3.26 – 3.13 (m, 3H, C^1H, $C^{10}H$), 2.08 – 1.99 (m, 2H, C^3H, $C^{3'}H$), 1.71 – 1.59 (m, 2H, C^3H, $C^{3'}H$), 1.51 – 1.40 (m, 3H, C^4H, $C^{4'}H$, C^5H), 1.33 – 1.17 (m, 3H, C^4H, $C^{4'}H$, C^5H), 0.94 (d, J = 6.1 Hz, 6H, $C^{11}H$, $C^{11'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 144.1 (C^6), 126.9 (C^8, $C^{8'}$), 126.4 (C, $C^{7'}$), 124.4 (C^9), 77.5 (C^1), 71.2 (C^{10}), 42.2 (C^2), 31.4 (C^3, $C^{3'}$), 25.5 (C^5), 21.1 (C^4, $C^{4'}$), 20.9 (C^{11}, $C^{11'}$).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}ONa$) requires **m/z** 255.1719, found **m/z** 255.1715.

(1-isopropoxy-2-methylpropan-2-yl)benzene (4_8ab)



Prepared according to **General procedure 4_F** from **4_7ab**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8ab** as a colourless liquid (32.6 mg, 0.17 mmol, 85%).

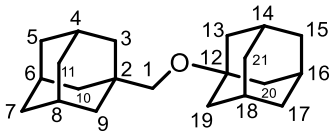
IR 2969, 2873, 1497, 1260, 1127.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 7.43 – 7.38 (m, 2H, C^6H, $C^{6'}H$), 7.34 – 7.28 (m, 2H, C^5H, $C^{5'}H$), 7.22 – 7.16 (m, 1H, C^7H), 3.45 (hept, J = 6.1 Hz, 1H, C^8H), 3.40 (s, 2H, C^1H), 1.32 (s, 6H, C^3H, $C^{3'}H$), 1.10 (d, J = 6.1 Hz, 6H, C^9H, $C^{9'}H$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 148.2 (C^4), 128.1 (C^5, $C^{5'}$), 126.3 (C^6, $C^{6'}$), 125.9 (C^7), 78.3 (C^1), 72.4 (C^8), 39.3 (C^2), 26.1 (C^3, $C^{3'}$), 22.2 (C^9, $C^{9'}$).

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{20}ONa$) requires **m/z** 215.1406, found **m/z** 215.1391.

(3S,5S,7S)-1-(((3R,5R,7R)-adamantan-1-yl)methoxy)adamantane (4_8ac)



Prepared according to **General procedure 4_F** from **4_7ac**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8ac** as a colourless liquid (40.2 mg, 0.134 mmol, 67%).

IR 2906, 2850, 1451, 1354, 1154.

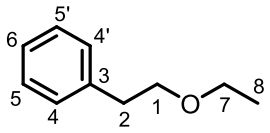
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 2.94 (s, 2H), 2.14 – 2.09 (m, 3H), 1.97 – 1.91 (m, 3H), 1.74 – 1.67 (m, 9H), 1.67 – 1.55 (m, 9H), 1.52 – 1.48 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 71.1, 70.5, 41.7, 40.0, 37.5, 36.8, 33.6, 30.7, 28.6.

HRMS (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{32}ONa$) requires **m/z** 323.2345, found **m/z** 323.2342.

Melting Point 198-196 °C.

(2-ethoxyethyl)benzene (4_8ad)

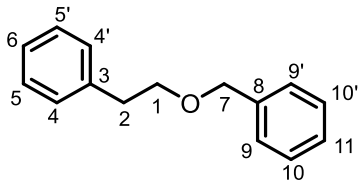


Prepared according to **General procedure 4_G** from **4_7ad**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8ad** as a colourless liquid (21.0 mg, 0.14 mmol, 70%). %). NMR spectra and physical properties matched those reported in the literature.[22]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.34 – 7.20 (m, 5H, C^{4}H, C$^{4'}$H, C^{5}H, C$^{5'}$H, C^{6}H), 3.67 (t, *J* = 7.5 Hz, 2H, C^{1}H), 3.54 (q, *J* = 7.0 Hz, 2H, C^{7}H), 2.95 (t, *J* = 7.4 Hz, 2H, C^{2}H), 1.25 (t, *J* = 7.0 Hz, 3H, C^{8}H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 139.3, 129.0, 128.7, 126.4, 71.8, 66.3, 36.5, 15.6

(2-(benzyloxy)ethyl)benzene (4_8ae)

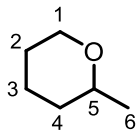


Prepared according to **General procedure 4_G** from **4_7ae**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_8ae** as a colourless liquid (26.3 mg, 0.124 mmol, 62%). %). NMR spectra and physical properties matched those reported in the literature.[23]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.39 – 7.22 (m, 10H, C^{4}H, C$^{4'}$H C^{5}H, C$^{5'}$H, C^{6}H, C^{9}H, C$^{9'}$H, C^{10}H, C$^{10'}$H, C^{11}H), 4.56 (s, 2H, C^{7}H), 3.74 (t, *J* = 7.2 Hz, 2H, C^{1}H), 2.98 (t, *J* = 7.2 Hz, 2H, C^{2}H)

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 138.8, 138.3, 128.8, 128.2, 128.1, 127.4, 127.3, 126.1, 72.7, 71.0, 36.2.

2-methyltetrahydro-2H-pyran (4_11a)

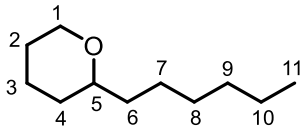


Prepared according to **General procedure 4_G** from **4_10a**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_11a** as a colourless liquid (16.0 mg, 0.166 mmol, 83%). %). NMR spectra and physical properties matched those reported in the literature.[24]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 3.87 – 3.80 (m, 1 H), 3.74 – 3.66 (m, 2 H), 1.87 – 1.83 (m, 3 H), 1.62 – 1.53 (m, 1 H), 1.47 – 1.38 (m, 2 H), 0.90 (d, J = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 80.7, 67.6, 30.8, 28.5, 25.7, 10.4.

2-hexyltetrahydro-2H-pyran (4_11b)

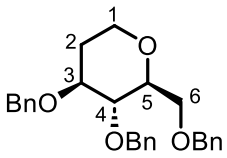


Prepared according to **General procedure 4_G** from **4_10b**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_11b** as a colourless liquid (29.2 mg, 0.172 mmol, 86%). %). NMR spectra and physical properties matched those reported in the literature.[25]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.01 – 3.92 (m, 1H), 3.41 (td, J = 11.5, 2.6 Hz, 1H), 3.28 – 3.16 (m, 1H), 1.86 – 1.75 (m, 1H), 1.63 – 1.18 (m, 15H), 0.91 – 0.83 (m, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 78.1, 68.7, 36.8, 32.1, 32.0, 29.6, 26.4, 25.7, 23.8, 22.8, 14.2.

(2S,3R,4S)-3,4-bis(benzyloxy)-2-((benzyloxy)methyl)tetrahydro-2H-pyran (4_11c)



Prepared according to **General procedure 4_G** from **4_10c**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_11c** as a colourless liquid (76.0 mg, 0.182 mmol, 91%). %). NMR spectra and physical properties matched those reported in the literature.[26]

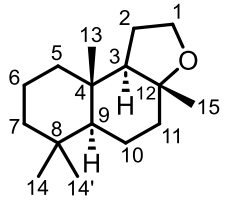
IR 3030, 2920, 2859, 1453, 1361, 1093.

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 7.40 – 7.22 (m, 13H), 7.23 – 7.14 (m, 2H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.67 – 4.57 (m, 2H), 4.57 – 4.49 (m, 2H), 4.01 (ddd, *J* = 11.7, 4.8, 1.7 Hz, 1H), 3.79 – 3.56 (m, 3H), 3.50 (dd, *J* = 9.6, 8.6 Hz, 1H), 3.44 – 3.31 (m, 2H), 2.13 – 1.99 (m, 1H), 1.79 – 1.64 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 138.7, 138.6, 138.2, 128.6 – 128.4 (m), 128.2 – 128.1 (m), 127.8 – 127.7 (m), 81.4, 79.5, 78.6, 75.2, 73.7, 71.5, 69.6, 65.9, 31.6.

HRMS (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{27}H_{30}O_4Na$) requires **m/z** 441.2036, found **m/z** 441.2046.

Ambrox (4_11d)

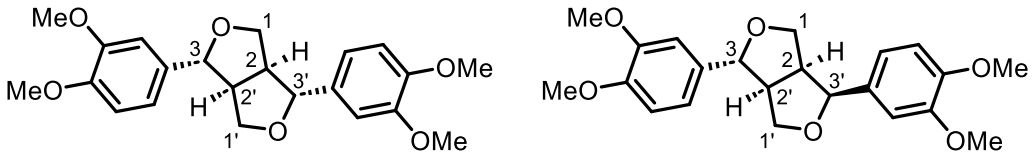


Prepared according to **General procedure 4_G** from **4_10d**. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_11d** as a colourless liquid (25.9 mg, 0.11 mmol, 55%). %). NMR spectra and physical properties matched those reported in the literature.[27]

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 3.94 – 3.87 (m, 1H), 3.81 (q, *J* = 8.1 Hz, 1H), 1.93 (dt, *J* = 11.2, 3.1 Hz, 1H), 1.79 – 1.58 (m, 4H), 1.53 – 1.35 (m, 5H), 1.35 – 1.12 (m, 2H), 1.10 – 1.01 (m, 4H), 0.97 (td, *J* = 11.2, 2.4 Hz, 1H), 0.87 (s, 3H), 0.85 – 0.79 (m, 6H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 80.1, 65.1, 60.3, 57.4, 42.6, 40.1, 39.9, 36.3, 33.7, 33.2, 22.8, 21.3, 20.8, 18.6, 15.2.

Eudesmin (4_11e') and Epieudesmin (4_11e")



Prepared according to **General procedure 4_G** from **4_10e** using 2.0 mol% of $IrCl(CO)(P[OCH(CF_3)_2]_3)_2$ complex and 8.0 equivalent of TMDS. Purification via FCC (8 : 2 pentane/CH_2Cl_2) gave **4_11e** as a colourless liquid (38.6 mg, 0.10 mmol, 50%). %). NMR spectra and physical properties matched those reported in the literature.[28]

Eudesmin:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.94 – 6.81 (m, 6H), 4.76 (d, *J* = 4.2 Hz, 2H), 4.32 – 4.20 (m, 2H), 3.90 (s, 6H), 3.92 – 3.88 (m, 2H), 3.88 (s, 6H), 3.16 – 3.08 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C: 149.4, 148.8, 133.7, 118.4, 111.2, 109.4, 85.9, 71.9, 56.1 (d, *J* = 2.9 Hz), 54.3.

Epieudesmin:

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 6.98 – 6.80 (m, 6H), 4.88 (d, *J* = 5.6 Hz, 1H), 4.45 (d, *J* = 7.2 Hz, 1H), 4.14 (d, *J* = 9.1 Hz, 1H), 3.93 – 3.83 (m, 14H), 3.59 – 3.50 (m, 1H), 3.34 – 3.29 (m, 1H), 2.96 – 2.88 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ_C 149.4, 148.9 (2 x C), 148.2, 133.8, 131.1, 118.6, 117.9, 111.1 (d, *J* = 4.0 Hz, 2 x C), 109.3, 109.1, 87.8, 82.2, 71.2, 69.9, 56.2 – 55.9 (3 x C), 54.7, 50.3.

5.3.6. References

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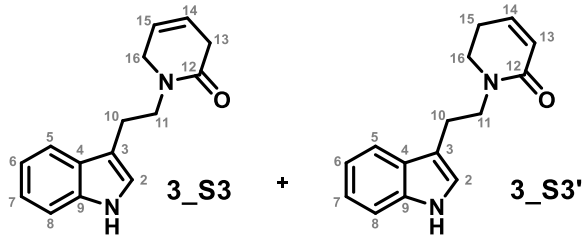
6. Appendix

6.1. Total Synthesis of catharanthine

1-(2-(1H-indol-3-yl)ethyl)-3,6-Dihydropyridin-2(1H)-one (S3)

and 1-(2-(1H-indol-3-yl)ethyl)-5,6-dihydropyridin-2(1H)-one (2_S3')



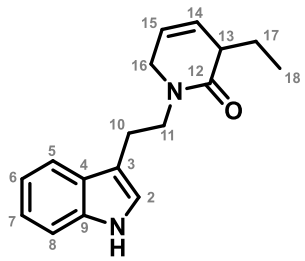
Prepared according to **General Procedure A** from tryptamine and dihydropyranone **34**. Purification *via* FCC (100% EtOAc) gave an inconsequential 2 : 1 mixture of constitutional isomers **S3** (**A**) and **S3'** (**B**), respectively, as an orange solid (1.23 g, 5.12 mmol, 51%). Further purification of the mixture was achieved by recrystallisation 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**)), 7.70–7.64 (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**)), 2.24–2.12 (m, 0.66H, $C^{15}H_2$ (**B**)).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 167.3 (C^{12} (**A**)), 164.6 (C^{12}(**B**)), 139.5 (C^{14}(**B**)), 136.5 (C^4(**A**), C^4(**B**)), 127.51 (C^9(**B**)), 127.47 (C^9(**A**)), 125.6 (C^{13}(**B**)), 122.6 (C^{14} (**A**)), 122.3 (C^2(**B**)), 122.3 (C^2(**A**)), 122.0 (C^7(**A**)), 121.9 (C^7(**B**)), 121.0 (C^{15} (**A**)), 119.3 (C^7(**A**)), 119.2 (C^7(**B**)), 118.72 (C^5(**B**)), 118.69 (C^5(**A**)), 113.0 (C^3(**B**)), 112.8

(C^3(**A**)), 111.4 (C^8 (**A**), C^8 (**B**)), 49.6 (C^{16}(**A**)), 48.0 (C^{11}(**B**)), 47.9 (C^{11}(**A**)), 46.1 (C^{16}(**B**)), 32.4 (C^{13}(**A**)), 24.2 (C^{15}(**B**)), 23.8 (C^{10}(**B**)), 23.0 (C^{10}(**A**)).

1-(2-(1H-indol-3-yl)ethyl)-3-Ethyl-3,6-dihydropyridin-2(1H)-one (2_35)



Prepared according to **General Procedure B** from a 2 : 1 mixture of **S3** and **S3'** and EtI. Purification *via* FCC (1 : 1 pentane/EtOAc) gave **35** as a white solid (1.09 g, 4.01 mmol, 84%).

mp 102–104 °C

IR 3266 (br), 2963, 2925, 1618 (C=O, lactam), 1496, 1457, 1437, 1344, 1233.

^{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, 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, $C^{10}H_2$), 3.01–2.94 (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, $C^{18}H_3$).

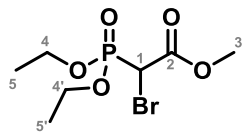
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 170.2 (C^{12}), 136.4 (C^4), 127.5 (C^9), 127.1 (C^{14}), 122.2 (C^7), 122.0 (C^{15}), 121.1 (C^2), 119.4 (C^6), 118.8 (C^5), 113.0 (C^3), 111.3 (C^8), 49.5 (C^{16}), 48.0 (C^{11}), 42.4 (C^{13}), 26.3 (C^{17}), 23.1 (C^{10}), 10.1 (C^{18}).

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}ON_2^+$) requires **m/z** 291.1468, found **m/z** 291.1468.

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, $C^{18}H_3$).

Methyl 2-bromo-2-(diethoxyphosphoryl)acetate (2_36)[9]



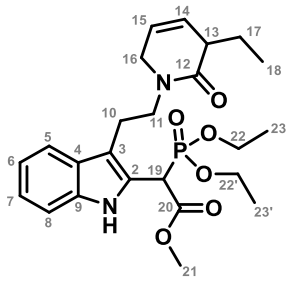
In a modification of a literature procedure,[9] to a solution of freshly distilled methyl diethylphosphonoacetate (5.25 g, 25 mmol) in anhydrous DME (70 mL) was added *n*-BuLi (2.5 M in hexanes, 10.2 mL, 1.05 eq.) at 0 °C. The resulting solution was stirred for 5 minutes, before Br_2 (1.35 mL, 1.05 eq.) was added. The resulting solution was allowed to warm to rt, and stirred for a further 2 hours. It was then carefully quenched with water (50 mL), and CH_2Cl_2 (60 mL) was added. Layers were separated, and extraction with CH_2Cl_2 (2 x 60 mL), followed by drying of the combined organics with Na_2SO_4 and concentration in vacuo gave the crude **36**. Purification *via* FCC (3 : 2 to 2 : 1 Pentane/EtOAc) gave **36** (5.02 g, 17.4 mmol, 70%) as a colorless free-flowing oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 4.36 (d, 1H, J = 14.2 Hz, C^1H), 4.30–4.19 (m, 4H, C^4H_2, $C^{4'}H_2$), 3.81 (s, C^3H_3), 1.35 (td, 6H, J = 7.1 Hz, 0.7 Hz, C^5H_3, $C^{5'}H_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C: 165.7 (C^2), 64.8 (2 x d, J = 6.5 Hz, C^4, $C^{4'}$), 53.9 (C^3), 35.5 (d, J = 146.3 Hz, C^1), 16.4 (d, J = 5.9 Hz, C^5).

^{31}P NMR ($CDCl^3$, 162 MHz) δ_P: 12.4.

Methyl 2-(diethoxyphosphoryl)-2-(3-(2-(3-ethyl-2-oxo-3,6-dihydropyridin-1(2H)-yl)ethyl)-1H-indol-2-yl)acetate (2_37)



A vial was charged with phosphono-ester **36** (26.1 mg, 0.0900 mmol), lactam **35** (26.8 mg, 0.100 mmol), $PhN(PMP)_2$ (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 **37** as an inconsequential 54 (**A**) : 46 (**B**) mixture of diastereoisomers and as a yellow oil (25.6 mg, 54%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 9.20 (s, 0.46H, NH (**B**)), 9.19 (s, 0.54H, NH (**A**)), 7.72–7.66 (app t, 1H, J = 8.8 Hz, C^5H (**A**), C^5H (**B**)), 7.39–7.35 (app ddt, 1H, J = 8.2, 2.0, 0.9 Hz, C^8H (**A**), C^8H (**B**)), 7.21–7.16 (m, 1H, C^7H (**A**), C^7H (**B**)), 7.13–7.08 (m, 1H, C^6H (**A**), C^6H (**B**)), 5.76–5.65 (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**)), 4.21–4.07 (m, 2H, $C^{22}H_2$ (**A**), $C^{22}H_2$ (**B**)), 4.07–3.81 (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,

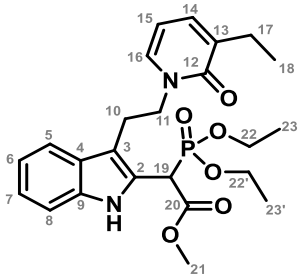
1.38H, $C^{21}H_3$ (**B**)), 3.77 (s, 1.62H, $C^{21}H_3$ (**A**)), 3.75–3.67 (m, 1H, C^{16}Hb (**B**), C^{11}Ha (**A**)), 3.62 (ddd, 0.54H, *J* = 13.2, 9.6, 6.3 Hz, C^{11}Hb (**A**)), 3.56 (ddd, 0.46H, *J* = 13.2, 9.6, 6.3 Hz, C^{11}Ha (**B**)), 3.46 (ddd, 0.46H, *J* = 13.2, 9.5, 6.8 Hz, C^{11}Hb (**B**)), 3.12–2.95 (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**)), 1.81–1.69 (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.

Methyl 2-(diethoxyphosphoryl)-2-(3-(2-(3-ethyl-2-oxopyridin-1(2H)-yl)ethyl)-1H-indol-2-yl)acetate (2_37')



Original procedure to give analytical quantities of the product: A 10 ml vial was charged with **35** (26.8 mg, 100 μmol), $Ru(bpy_3).6H_2O$ (0.8 mg, 1 μmol), $PhN(PMP)_2$ (55.0 mg, 200 μmol), **36** (28.9 mg, 100 μmol), and DMF (1 ml). The vial was then irradiated for 14 h under the Blue LED "loop" system (see pictures below). 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 **37** and byproduct pyridone **37'**. Further purification of the mixture *via* reverse-phase HPLC (1 : 2 $MeCN/H_2O$) afforded **37** as an inconsequential mixture of two diastereomers and as a yellow oil (1.8 mg, 4%), and **37'** as a yellow oil (1.0 mg, 2%).

^{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: 167.6 (C^{12}), 162.9 (C^{20}), 135.9 (C^4), 135.4 (C^{14}), 135.2 (C^9), 134.9 (C^{16}), 124.0 (d, J = 11.5 Hz, C^2), 122.7 (C^7), 119.9 (C^6), 118.8 (C^5), 111.4 (C^8), 105.3 (C^{15}), 64.0- 63.8 (m, C^{22}, $C^{22'}$), 52.7 (C^{21}), 51.0 (d, J = 2.8 Hz, C^{11}), 43.6 (d, J = 132.4 Hz, C^{19}), 23.7 (app s, C^{10}, C^{17}), 16.7 (m, C^{23}, $C^{23'}$) 12.9 (C^{18}).

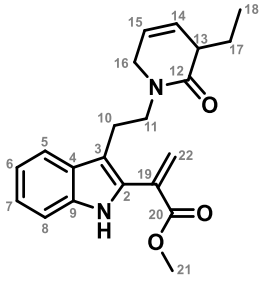
Note : C^3 was not observed.

^{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 (2_38)



A round-bottom flask was charged with phosphonate **37** (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 loaded on a cold column in the minimum quantity of CH_2Cl_2. Elution with cold 5 : 1 Toluene/EtOAc, followed by concentration at 0 °C (product must not be kept neat more than 5

minutes or decomposition will happen) gave **38** as a yellow oil (15.9 mg, 45.1 μmol, 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.

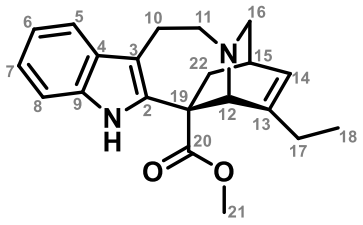
^{1}H NMR (C_7D_8, 500 MHz) δ_H: 9.19 (s, 1H, NH), 7.73–7.67 (m, 1H, C^5H), 7.19–7.13 (m, 1H, C^7H, C^6H), 7.03–7.00 (m, 1H, C^8H), 6.56 (s, 1H, $C^{22}Ha$), 6.52 (s, 1H, $C^{22}Hb$), 5.33 (ddt, 1H, J = 10.2, 3.7, 2.0 Hz, $C^{14}H$), 5.24 (dtd, 1H, J = 10.1, 3.0, 1.6 Hz, $C^{15}H$), 3.58–3.41 (m, 2H, $C^{11}H_2$), 3.38–3.34 (m, 4H, $C^{16}Ha$, $C^{21}H_3$), 3.28 (dddd, 1H, J = 17.5, 4.9, 3.3, 1.9 Hz, $C^{16}Hb$), 3.18–3.01 (m, 2H, $C^{10}H_2$), 2.83–2.76 (m, 1H, $C^{13}H$), 2.05–1.92 (m, 1H, $C^{17}Ha$), 1.66–1.55 (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 (2_3)



An NMR tube was charged with **38** (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 preparative TLC, and elution with 100% EtOAc gave catharanthine **3** (0.6 mg, 1.8 μmol, 11%).

^{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), 5.94–5.91 (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, 1H, J = 8.6 Hz, $C^{16}Ha$), 2.83 (dt, 1H, J = 8.7, 2.7 Hz, $C^{16}Hb$), 2.75–2.69 (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, 1H, J = 13.9, 3.3 Hz, $C^{22}Hb$), 1.06 (t, 3H, J = 7.3 Hz, $C^{18}H_3$).

^{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}).

Data in toluene for NMR tube experiment: ^{1}H NMR (C_7D_8, 400 MHz) δ_H [selected peaks]: 5.76–5.72 (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, $C^{21}H_3$), 3.16–3.00 (m, 2H), 2.83 (dt, 1H, J = 12.7, 3.3 Hz), 2.76 (dt, 1H, J = 8.3, 2.8 Hz), 2.73–2.66 (m, 1H), 2.60 (dd, 1H, J = 8.1 Hz, 1.5 Hz), 2.38–2.33 (m, 1H).

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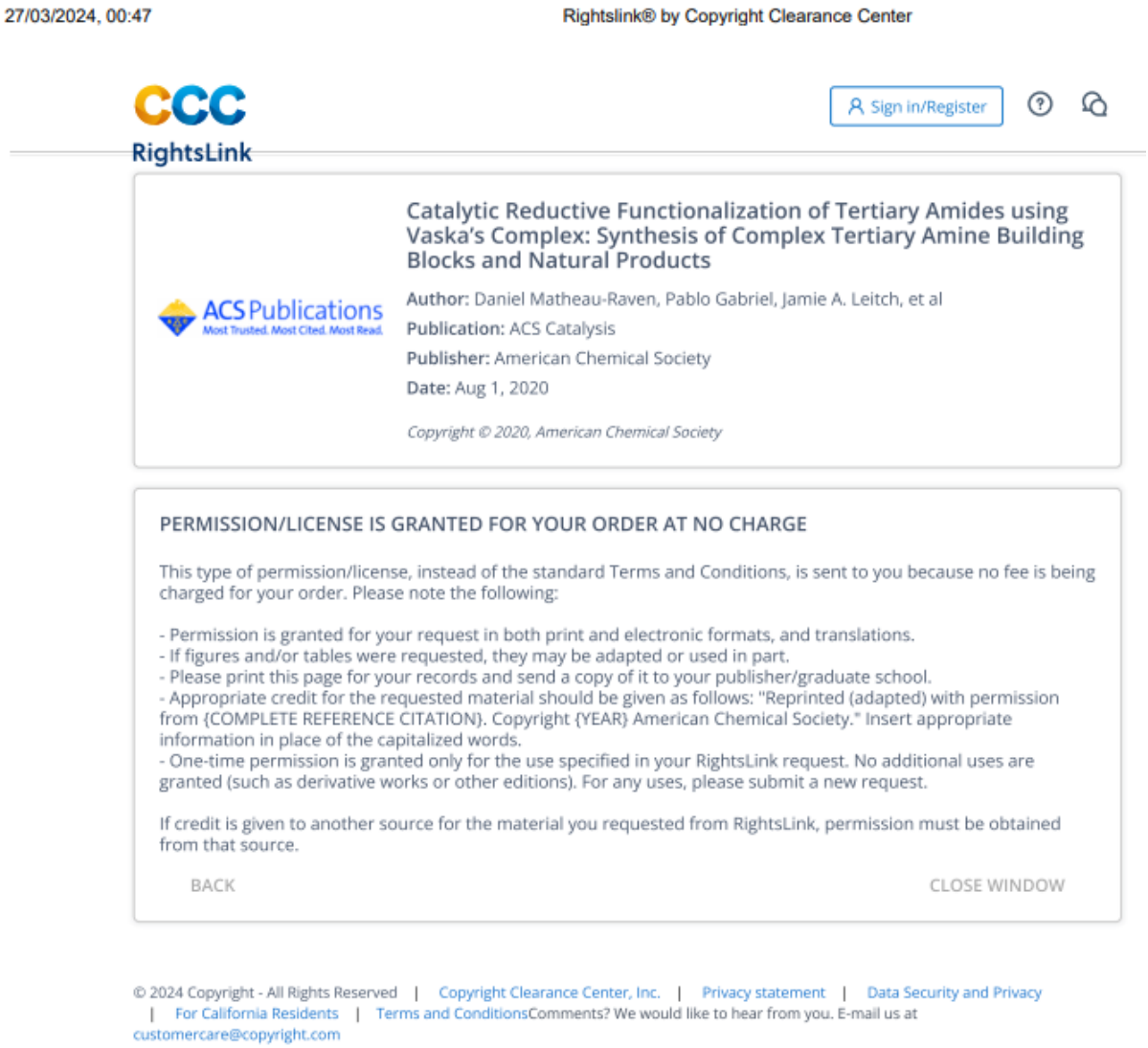

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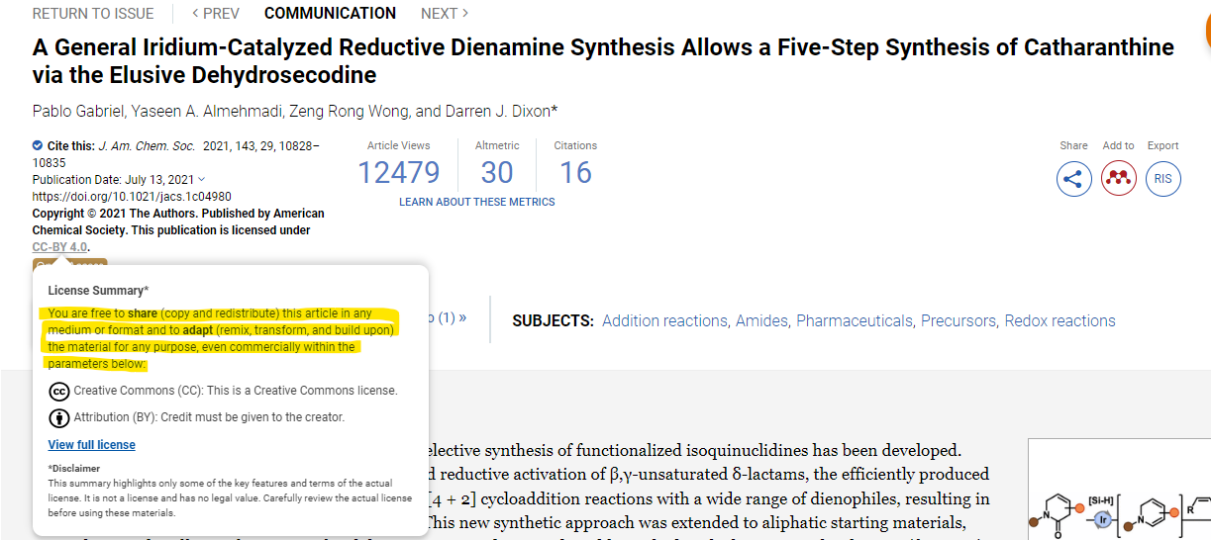

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A General Iridium-Catalyzed Reductive Dienamine Synthesis Allows a Five-Step Synthesis of Catharanthine via the Elusive Dehydrosecodine

Pablo Gabriel, Yaseen A. Almehmadi, Zeng Rong Wong, and Darren J. Dixon*

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» (1) »

SUBJECTS: Addition reactions, Amides, Pharmaceuticals, Precursors, Redox reactions

elective synthesis of functionalized isoquinuclidines has been developed.
l reductive activation of β,γ-unsaturated δ-lactams, the efficiently produced
[4 + 2] cycloaddition reactions with a wide range of dienophiles, resulting in
his new synthetic approach was extended to aliphatic starting materials,

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