



Development of a Deoxygenative Ring Contraction Reaction for Nitrogen Heterocycle Synthesis

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Abstract

Small nitrogen-containing saturated heterocycles are ubiquitous motifs found in a vast number of organic molecules that include natural products, active pharmaceuticals and agrochemicals. Hence, inexpensive, accessible and practical strategies for making these heterocycles is of great interest to the chemical industry. Fortunately, deoxygenative ring contractions provide a novel way of synthesising substituted amines of this type that would otherwise be very hard to obtain by classical synthesis methods. 3,6-Dihydro-2*H*-1,2-oxazines can be valuable synthesis precursors to highly functionalised heterocycles. Hence, they constitute attractive starting points for the synthesis of unsymmetrical substituted 3-pyrrolines and pyrrolidines that would represent challenging targets using more conventional strategies.

An iridium-catalysed deoxygenative ring contraction of N–O containing heterocycles using phenylsilane as a terminal reductant has been demonstrated. The N–O containing heterocycles were largely obtained from the nitroso Diels-Alder reaction between a nitroso compound and a diene. This deoxygenative ring contraction reaction has been applied to a range of different 1,2-oxazine and 1,2-oxazinane substrates to give the ring contracted heterocycles in 19-76% yield without the rigorous exclusion of air and moisture. Hence, this represents a unique convergent strategy in which these saturated nitrogen heterocycles can be built up rapidly from a sequential cycloaddition/deoxygenative ring contraction process. Investigations towards the total synthesis of the natural product (±)-DMDP have been outlined, in which the deoxygenative ring contraction is used as the key step.

A plausible mechanism has been proposed based on experimental and spectroscopic observations that accounts for the formation of observed intermediates. During these studies a novel alkylation of amines with non-racemic alcohols has been discovered. Preliminary optimisation of this reaction has enabled a chiral tertiary amine product to be obtained in 43% yield and 89% e.e with an inversion of configuration.

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Abbreviations

3c-2e	3 Centre-2 electron
3c-4e	3 Centre-4 electron
9-BBN	9-Borabicyclo[3.3.1]nonane
acac	Acetylacetonate
APCI	Atmospheric pressure chemical ionisation
ATR	Attenuated total reflection
BDE	Bond dissociation energy
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BMEA	Bis(methoxyethyl)amine
calcd.	Calculated
CAN	Ceric ammonium nitrate
COE	Cyclooctene
COD	1,5-Cyclooctadiene
COSY	Correlation spectroscopy
D4	Octamethylcyclotetrasiloxane
DBB	Di- <i>tert</i> -butylbiphenyl
DBCOT	Dibenzo[<i>a,e</i>]cyclooctatetraene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
dme	Dimethoxyethane
DMF	Dimethylformamide
Dmp	Dimesitylphenyl
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
d.r.	Diastereomeric ratio
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl
DTBM-SEGHOS	5,5'-Bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole

Abbreviations

EDTA	Ethylenediaminetetraacetic acid
e.e.	Enantiomeric excess
equiv.	Equivalents
ESI	Electrospray ionisation
EWG	Electron withdrawing group
FFA	Furan fatty acid
HAT	Hydrogen atom transfer
HMBC	Heteronuclear multiple bond correlation spectroscopy
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
IPA	Isopropyl alcohol
IR	Infra-red spectroscopy
<i>J</i>	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
LC-MS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
M	Molecular ion
MAO	Monoamine oxidase
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
MIDA	<i>N</i> -Methyliminodiacetic acid
MO	Molecular orbital
MOM	Methoxymethyl
m.p.	Melting point
MSM	Methylsulfonylmethane
MTBE	Methyl <i>tert</i> -butyl ether
mu	Mass units
NBS	<i>N</i> -Bromosuccinimide
NIS	<i>N</i> -Iodosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
PMHS	Polymethylhydrosiloxane
PMP	<i>p</i> -Methoxyphenyl
ppm	Parts per million
ppy	2-Phenylpyridine

Abbreviations

PYPHOS	2-[2-(Diphenylphosphanyl)ethyl]pyridine
r.t.	Room temperature
RCM	Ring closing metathesis
SEM	Trimethylsilylethoxymethyl
SFC-MS	Supercritical fluid chromatography-mass spectrometry
TBAF	Tetrabutylammonium fluoride
TBS	<i>tert</i> -Butyldimethylsilyl
TCCA	Trichloroisocyanuric acid
TCE	1,1,2,2-Tetrachloroethane
temp.	Temperature
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFDO	Methyl(trifluoromethyl)dioxirane
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMDS	1,1,3,3-Tetramethyldisiloxane
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TPP	5,10,15,20-Tetraphenyl-21 <i>H</i> ,23 <i>H</i> -porphine
TPQ	Topaquinone
TTMSS	Tris(trimethylsilyl)silane
UPLC-MS	Ultra-high performance liquid chromatography-mass spectrometry
UV	Ultraviolet
WHO	World Health Organisation
μw	Microwaves

1. Introduction

1.1. The Importance and Characteristics of Silicon and its Compounds

Owing to the high abundance of silicon on Earth (approximately 28% of the Earth's crust by mass and second only to oxygen), chemists have been continually probing the properties and reactivity of silicon-containing compounds and materials. Indeed, in its abundance silicon exceeds the combined total of all other crustal elements. As such, the use of silicon and silicon-containing compounds has become an integral part of modern society with its uses spanning from cosmetics to computers.^{1,2}

Of particular interest to organic synthesis chemists are organosilicon compounds (chemical compounds containing carbon-silicon bonds), first discovered by Friedel and Crafts in 1863 through the reaction of diethylzinc with silicon tetrachloride. The area of organosilicon chemistry has greatly evolved since this first inception, with significant initial developments being made by Kipping in the early 20th century after the reporting of the reaction between silicon tetrachloride and Grignard reagents.^{3,4} Following these early reports and the successful development of silicone polymers, organosilicon chemistry became a widely studied field.^{5,6}

Currently in organic synthesis, organosilicon compounds find uses in: protecting group chemistry for alcohols,⁷⁻⁹ as enolate equivalents in the form of silyl enol ethers;^{10,11} as hydride donors in reduction reactions when at least one Si-H bond is present,^{12,13} or hydrogen atom donors in radical chemistry;^{14,15} in allylation chemistry;¹⁶ as well as being manipulated to install other functional groups in its place such as in the Hiyama-Denmark coupling,^{17,18} Peterson olefination,^{19,20} and Fleming-Tamao oxidation.^{21,22}

Group 14		Element	Pauling electronegativity	Atomic radius/ Å	$\delta^+ \quad \delta^-$ R_3Si-H $\delta^- \quad \delta^+$ R_3C-H reversed polarity of Si-H bond relative to C-H bond
Period 2	⁶ C	H	2.20	0.31	
Period 3	¹⁴ Si	C	2.55	0.76	
		Si	1.90	1.11	
Period 4	³² Ge	O	3.44	0.66	
		F	3.98	0.57	
		Sn	1.96	1.39	

Figure 1. General properties of silicon.

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Comparisons are often made between the chemistry of organosilicon compounds and their analogous carbon counterparts, owing to the fact that silicon lies directly below carbon in group 14 (Figure 1). The differences in reactivity of these compounds can be attributed to the greater size of the silicon atom²³ as well as silicon being less electronegative than both carbon and hydrogen (Pauling electronegativities of Si, C and H respectively are 1.90, 2.55 and 2.20). Furthermore, silicon can also form very strong bonds with electronegative elements such as oxygen and fluorine, often providing a useful driving force for transformations involving organosilicon reagents.²⁴

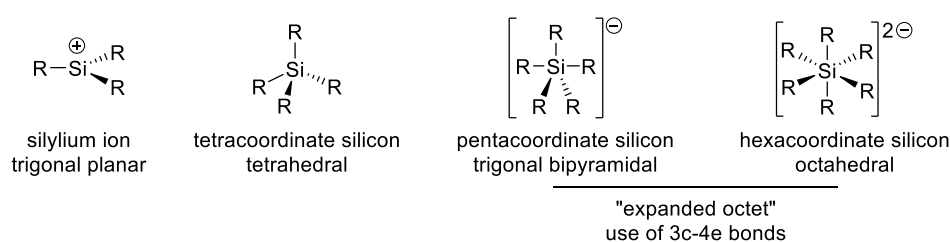


Figure 2. Commonly encountered valencies of silicon compounds including hypercoordinate silicon compounds facilitated by 3c-4e bonds. Left to right: three-coordinate, four-coordinate, five-coordinate, six-coordinate.

However, these comparisons are only appropriately made when considering tetravalent organosilicon reagents. In contrast to carbon, silicon is able to expand its octet and form five- or six-coordinate species – negatively charged ‘ate’ complexes (Figure 2). Complexes of this nature are often referred to as ‘hypervalent’²⁵ compounds; however, hypercoordinate²⁶ is starting to become a favoured term. The true nature of the bonding of these compounds is still somewhat disputed.²⁷ Initially, these species were considered to employ d-orbitals,^{28,29} however, despite the requirement for the inclusion of d-orbital functions in calculations for accurate results, recent computational data suggest negligible involvement of these orbitals in the bonding of these compounds.³⁰ Instead, more modern descriptions consider the employment of 3-centre 4-electron (3c-4e) bonds,^{31,32} a concept independently proposed by Hach,³³ Rundle^{34–36} and Pimentel.³⁷

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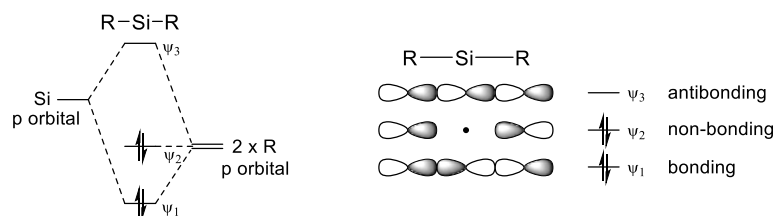


Figure 3. Orbital description of 3c-4e bonding.

Formation of these 3c-4e bonds requires a collinear arrangement of (typically electronegative) ligands about a central atom (Figure 3). A single p-orbital of the central atom overlaps with one p-orbital from each of the two peripheral atoms in the collinear linkage. These three atomic orbitals combine to form a bonding, a non-bonding and an antibonding molecular orbital (MO).³⁸ Two electrons occupy the bonding MO ψ_1 and participate in the bonding interactions between the central atom and the two adjacent atoms. The remaining two electrons from each of the peripheral atoms are effectively retained by their respective atoms as they occupy the non-bonding MO ψ_2 , which has no presence on the central atom. This additional electron density is, therefore, spread exclusively over the ligand atoms, hence why highly electronegative atoms such as halogens or oxygen stabilise 3c-4e bonding in hypervalent molecules. Due to the additional negative charge associated with the extra ligands, the central silicon atom experiences an increased effective positive charge. Consequently, hypercoordinate silicate species can be strongly Lewis acidic and this phenomenon has been exploited in the development of novel reaction methodologies featuring organosilicon compounds.³⁹

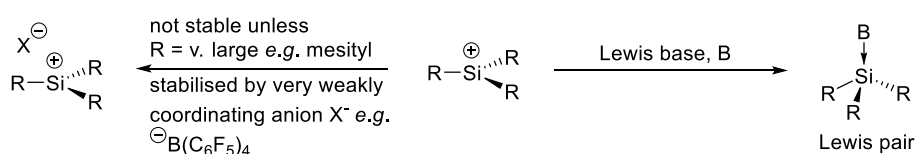


Figure 4. Requirements for the formation of stable silylium ions.

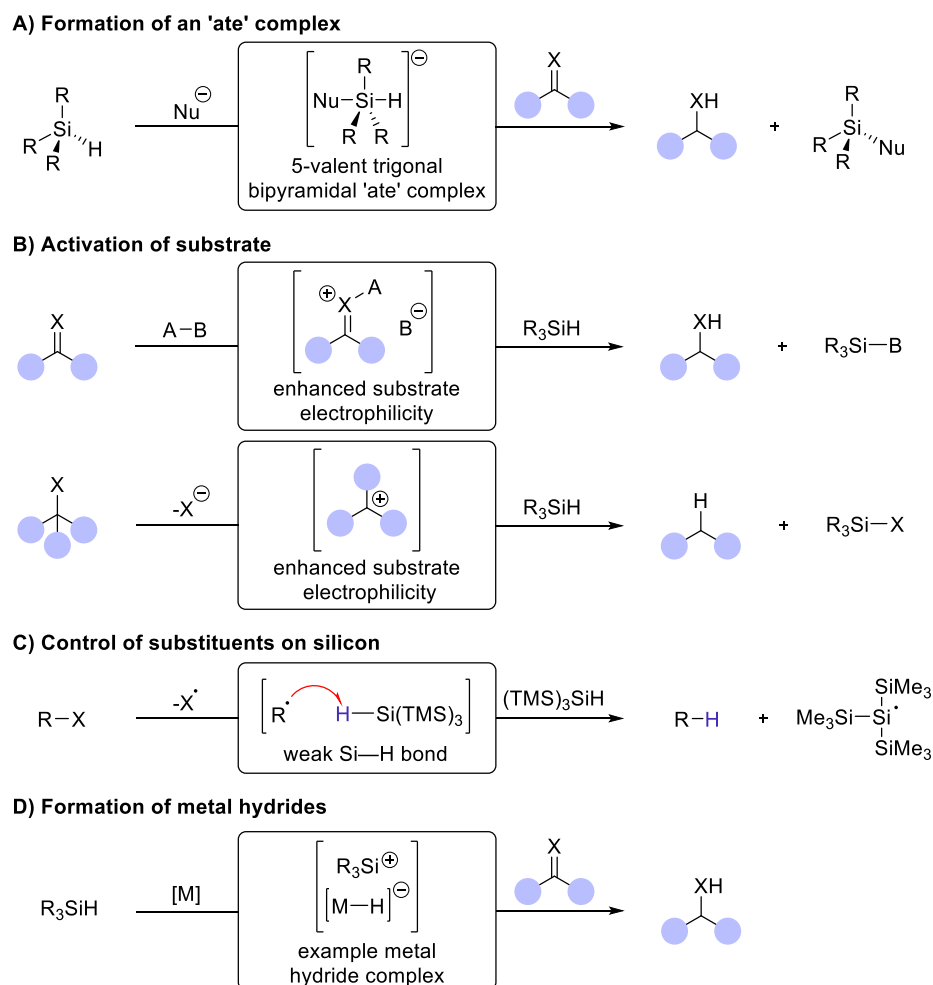
Silicon also distinguishes itself from carbon when considering trivalent species of these two elements. Where the existence of carbocations of the structure R_3C^+ has been described for over a century,^{40,41} identification of the analogous silylium ions, R_3Si^+ , in condensed phases (solution or solid phase) has remained elusive until recently.^{42,43} It was expected that, due to silicon being the more electropositive element, R_3Si^+ should be more stable than R_3C^+ because the silicon should better stabilise the positive charge. However, silylium ions are extremely Lewis acidic,

dictating that the correct choice of solvent and weakly coordinating counteranion (*i.e.* both required to be poorly Lewis basic) be made to avoid the formation of undesired Lewis pairs (Figure 4). Consequently, unless sterically shielded around silicon, the vast majority of silylium ions are inter- or intramolecularly stabilised by a Lewis-basic moiety.⁴⁴ Despite these setbacks and limitations, the use of silylium ions in the design and development of new organic methodologies is gaining traction.^{45,46}

1.2. Activation of Silane Si-H Bonds for Use in Reduction Chemistry

Silanes have found extensive use as reductants and hydride sources in many transformations.^{13,47} They represent attractive reducing agents since they are not typically pyrophoric, overtly toxic or impractically water sensitive. Furthermore, in the majority of cases (for commonly used, commercially available silanes) they are miscible with organic solvents unlike ionic reducing agents such as NaBH_4 , NaCNBH_3 or LiAlH_4 that are typically used to effect similar transformations.^{48,49} However, many reactions using silanes as reductants may not occur without a catalyst or stoichiometric additive that activates the Si-H bond towards the desired reaction as tetravalent organosilicon hydrides are poor nucleophiles.

As described above, organosilicon reagents are able to form five-coordinate negatively charged 'ate' complexes. A consequence of this, other than the aforementioned increase in Lewis acidity, is the increase in the hydridic nature of the Si-H bond of hydrosilane reagents (Scheme 1A).³⁹ The use of additives such as CsF ,⁵⁰ TBAF^{51,52} and even lithium amides⁵³ to activate these silanes has provided a number of practical methods for the reduction of carbonyl compounds and their derivatives.



Scheme 1. Modes of activation for silane-based reductions. A) Addition of a nucleophile to increase hydride donor ability. B) Substrate activation with Brønsted or Lewis acids enables direct reduction with unmodified silanes. C) Radical reductions using silanes bearing weak Si-H bonds. D) Activation with a metal to increase hydride donor ability or forming a metal hydride (see below). Metal activation can occur through several distinct modes (Figure 5).

In addition to the activation of Si-H bonds for the reduction of functional groups, activation of the substrate to enhance the electrophilicity of the functional group of interest (Scheme 1B) can allow even unmodified tetravalent hydrosilanes to carry out reduction processes (e.g. on carbocations or carbonyl compounds and their derivatives). Examples vary greatly, including the reduction of *N*-sulfonyl aldimines to sulfonamides using I₂ and Et₃SiH,⁵⁴ the reduction of alcohols to alkanes with Et₃SiH under strong Brønsted⁵⁵ or Lewis⁵⁶ acidic conditions or the Brønsted acid-mediated reduction of phosphine oxides to phosphines with tetramethyldisiloxane (TMDS).⁵⁷

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In 1988, Chatgililoglu observed that tris(trimethylsilyl)silane (TTMSS) possesses a significantly weaker Si-H bond (BDE 79 kcal/mol)⁵⁸ relative to other silanes such as Me₃Si-H (BDE 90.3 kcal/mol)²⁴, making it potentially useful for applications in radical chemistry (Scheme 1C).⁵⁹ The similar bond strength of this Si-H bond to the Sn-H bond found in Bu₃SnH (BDE 73 kcal/mol) enables its use as an effective HAT reagent in place of the more commonly used toxic tin compounds.^{15,60,61} As such, TTMSS has been used to facilitate the reduction of a range of functional groups such as alcohols,⁶² azides,¹⁴ halides¹⁴ and alkynes⁶³ under radical conditions.

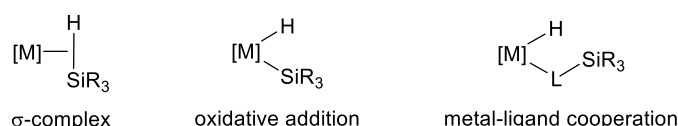


Figure 5. Modes of silane activation using metal catalysts.

Transition metal catalysts can be highly versatile for the activation of Si-H bonds for reductive purposes (Scheme 1D).⁶⁴ This activation can occur by a few different modes of action: formation of σ -complexes, oxidative addition or by metal-ligand cooperation (Figure 5). A detailed overview of the nature of the structure and bonding in these complexes has been published by Lin.⁶⁵ σ -Bond complexes form when a filled σ -bonding orbital (in this case a Si-H bond) acts as a two-electron donor to coordinate to a metal – forming a 3c-2e bond.^{65–67} This leads to the elongation and weakening of the Si-H bond depending upon the degree of back bonding from the metal into the Si-H σ^* antibonding orbital. Silane-metal σ -complexes have been used in the hydrosilylation of ketones⁶⁸ and are known to be powerful silylating agents.^{69,70}

Oxidative addition is perhaps the most prevalent mode of transition metal-mediated Si-H bond activation, resulting in a complex where the silicon and hydrogen are bonded directly to the metal.⁷¹ Although oxidative addition complexes have been reported for many transition metals, electron-rich late transition metal centres (those belonging to groups 9 and 10) are most widely observed.^{72,73} Although complexes with early electron-deficient transition metal centres (such as group 3 and 4 metals), have been documented, they lack the necessary d-electrons to form through an oxidative addition pathway and are instead formed *via* σ -bond metathesis. These types of complex are commonly used in hydrosilylation and reduction chemistry with a recent focus being on rendering these reactions enantioselective.^{73–77}

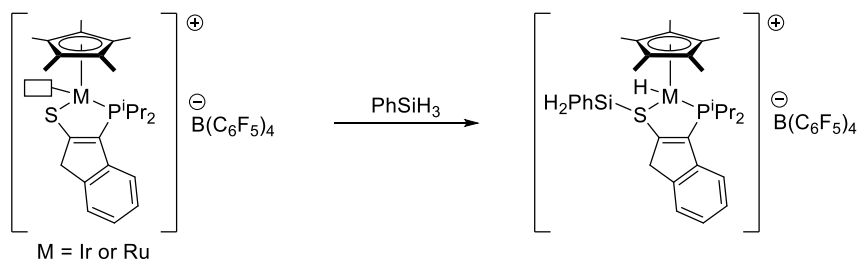
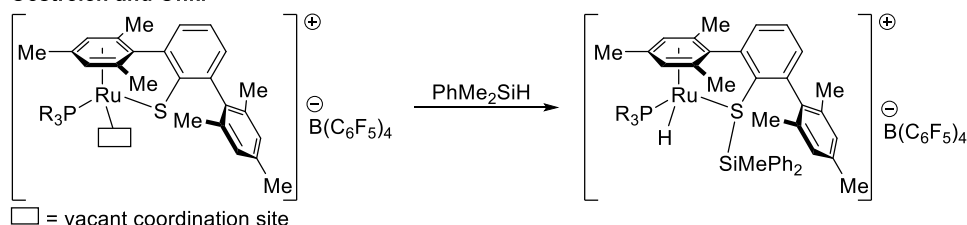
Stradiotto and co-workers**Oestreich and Ohki**

Figure 6. Top: Stradiotto's catalysts for the activation of PhSiH_3 by metal-ligand cooperation. Bottom: Oestreich and Ohki's catalyst for silane activation by metal-ligand cooperation.

Additionally, ligand assisted activation of Si-H bonds has gathered considerable interest in recent years. Metal-ligand cooperation utilises both the metal centre and a ligand in the cleavage of the Si-H bond and in the formation of the new R-Si/R-H bonds.^{78–80} The groups of Stradiotto, Oestreich and Ohki have contributed significant advancements to this field by developing an assortment of metal thiolate complexes based on ruthenium and iridium (Figure 6).^{78,81,82} In these systems, the Si-H σ -bond adds across the polar metal-sulfur bond of a coordinatively unsaturated complex. This generates a metal hydride, capable of fulfilling reductive roles, with a connected thiosilane ligand, which acts as a silylium cation surrogate. The catalytic applications of these complexes have been demonstrated in the context of a number of successful transformations including hydrodefluorination,⁸³ 1,4-hydrosilylation of pyridines,⁸⁴ hydrogenation⁷⁸ and C-H silylation.^{82,85,86}

1.3. Occurrence and Application of Pyrrolidines and 3-Pyrrolines

The topic of this thesis concerns using silicon chemistry for the construction of saturated nitrogen heterocycles. Of particular interest in this work are pyrrolidine and 3-pyrroline heterocycles — as well as their derivatives, which are not only valuable synthesis targets but also represent convenient synthetic reagents and intermediates for the construction of such molecules.

1.3.1. Pyrrolidines

Small heterocyclic rings are amongst the most prevalent motifs found in organic molecules that include natural products, active pharmaceuticals and agrochemicals.^{87,88} For this reason, inexpensive, accessible and practical strategies for making these heterocycles are of great interest to the chemical industry.

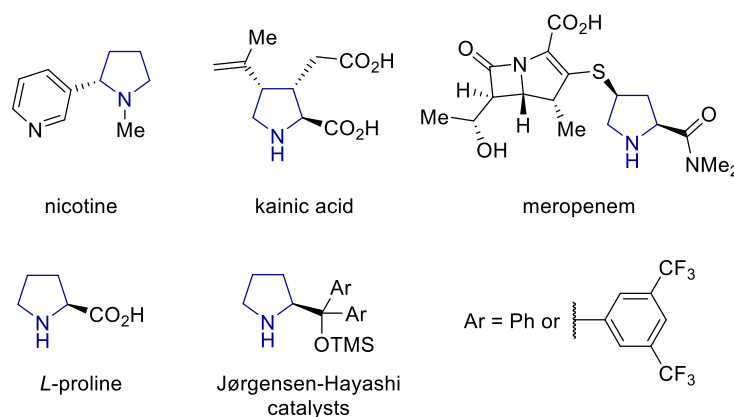


Figure 7. Examples of pyrrolidine-containing compounds, including natural products, pharmaceuticals and organocatalysts.

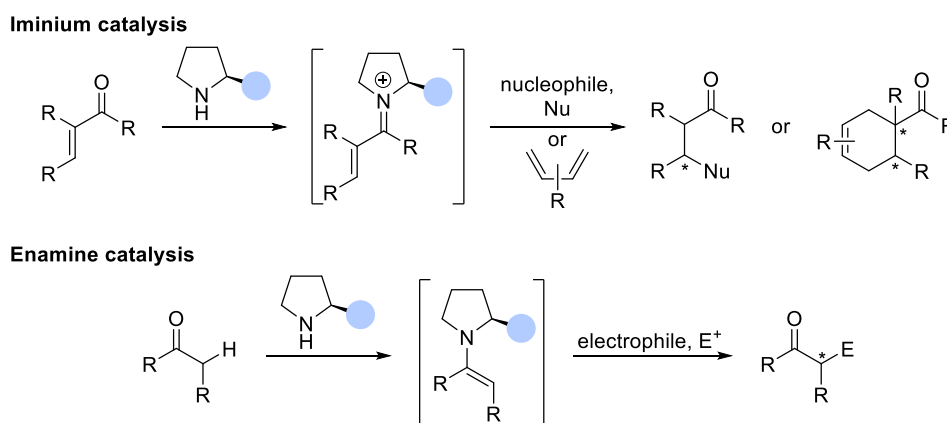
Pyrrolidines form an integral part of many chemical structures (Figure 7) from alkaloids such as kainic acid and nicotine, to successfully established active pharmaceuticals such as meropenem (Merrem), an antibiotic on the WHO's list of essential medications used to treat a variety of bacterial infections.⁸⁹

Inflexible molecules are highly desirable in medicinal chemistry as they minimise the entropic penalties associated with the ligand adopting a suitable conformation for binding. This can lead to enhanced potency towards a biological target.⁹⁰ Additionally, amines are one of the most widespread functionalities found in pharmaceuticals, due to their ability to form hydrogen bonds, impart great structural variation into molecules and ionise to enhance aqueous solubility.⁹¹ For these reasons, pyrrolidines (and 3-pyrrolines) find themselves in a range of approved medicines and targets of considerable pharmaceutical interest.

As well as making up the core framework of many biologically active molecules, one of the most significant applications of pyrrolidine-containing compounds is their use as reagents and catalysts in organic synthesis. Over the last 20 years in particular, the field of organocatalysis

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using chiral pyrrolidine-based molecules has seen considerable development.^{92–94} A pyrrolidine ring makes up one of the 20 naturally occurring amino acids; *L*-proline is the only proteinogenic amino acid that contains a secondary amine. The accessibility of this naturally occurring chiral secondary amine has made it an attractive target in the development of many asymmetric organocatalytic transformations. Originally, these enantioselective reactions relied on the use of unmodified naturally occurring *L*-proline.⁹⁵ However, since these initial reports, more versatile analogues have been developed and are commercially available, for instance, the Jørgensen-Hayashi organocatalysts^{96,97} which now see significant use in industry and have been used on scales greater than 100 kg.⁹⁸



Scheme 2. Most common modes of action for secondary amine catalysis.

Two activation modes are typically considered for secondary amine catalysts using these proline derivatives – iminium catalysis and enamine catalysis (Scheme 2). Iminium catalysis relies upon the LUMO-lowering effect of forming an iminium ion from a parent carbonyl compound. The resulting chiral iminium is then able to direct the formation of new bonds preferentially to one face of the molecule over the other. Numerous reports of this strategy have been disclosed with the most common transformations being enantioselective Diels-Alder cycloadditions⁹⁹ and the asymmetric conjugate addition of C-^{100,101}, N-^{102,103}, O-^{104,105} and S-^{106,107} nucleophiles to α,β -unsaturated carbonyls.¹⁰⁸ The latter methodologies represent an indispensable tool in the synthetic chemist's arsenal for the efficient enantioselective construction of β -functionalised enals and enones from readily available starting materials.

On the other hand, enamine catalysis requires the condensing carbonyl to have α -protons, enabling the formation of an enamine *in situ*.¹⁰⁹ The enamine is then able to act as a convenient

enolate equivalent and can be intercepted by a range of different electrophiles.¹¹⁰ Typically, enamine catalysis is used for the α -functionalisation of aldehydes and ketones in which electrophilic partners such as aldehydes,¹¹¹ ketones,¹¹² imines¹¹³ and electron-deficient olefins^{114,115} are most commonly deployed. Furthermore, these approaches of iminium and enamine organocatalysis using pyrrolidine-containing compounds have been synergistically paired with transition metal-catalysed,^{116,117} photoredox^{118,119} or enzymatic^{120,121} manifolds to broaden the scope of these transformations.

1.3.2. 3-Pyrrolines

Like pyrrolidines, the 3-pyrroline motif can be found in a number of natural products, especially pyrrolizidine alkaloids such as jacobine or heliotrine (Figure 8). Many of these compounds, as well as a number of nature-inspired synthetic analogues, are of significant pharmaceutical interest due to the wide range of biological activity that they exhibit, spanning from promising antiarrhythmic agents,¹²² to potential radioprotectors for cancer radiotherapy.¹²³

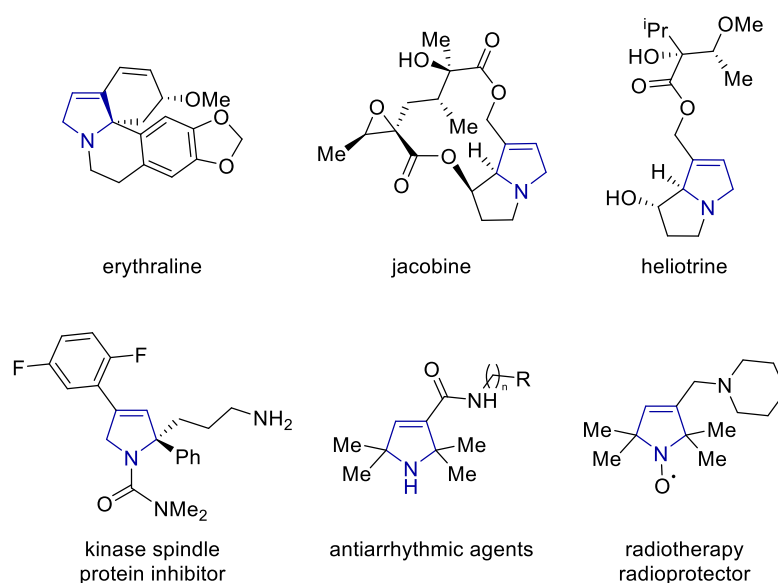
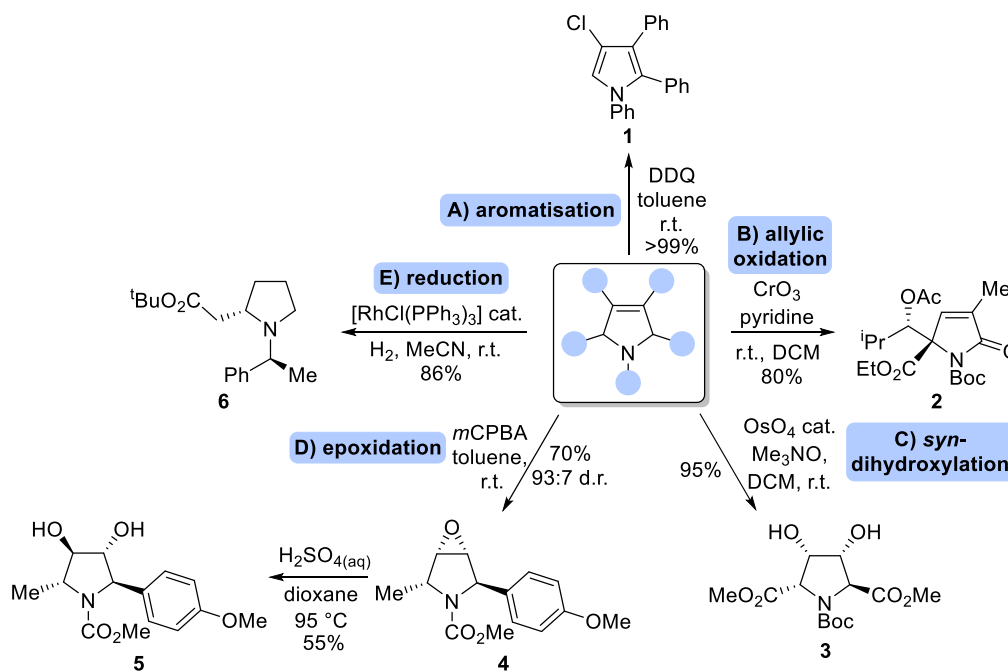


Figure 8. Examples of 3-pyrroline-containing compounds including natural products and promising potential pharmaceutical agents.

Furthermore, small 3-pyrroline containing molecules can also function as monoamine oxidase (MAO) inhibitors, used to treat depression, social anxiety disorder and Parkinson's disease. More specifically, Sayre and co-workers illustrated that 3-pyrrolines can act as cofactor-directed irreversible inactivators of topaquinone (TPQ)-dependent amine oxidases.^{124–126}

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In addition to the variety of uses that 3-pyrrolines have seen (discussed above), arguably their most common application is as valuable highly functionalisable intermediates in synthesis. Scheme 3 shows a brief overview of some of the most common transformations performed on 3-pyrrolines.



Scheme 3. Examples of the use of 3-pyrrolines as highly versatile synthetic intermediates. A) Aromatisation to pyrroles with DDQ. B) Chromium-mediated allylic oxidation to pyrrolinones. C) Osmium-catalysed syn-dihydroxylation to syn-diols. D) Olefin epoxidation followed by epoxide opening to give trans-diols. E) Hydrogenation to pyrrolidines.

There is an abundance of pyrrole-containing natural products and so the aromatisation of 3-pyrroline intermediates can be a valuable route to these targets.¹²⁷ In 2011, Sai and Matsubara demonstrated that this aromatisation can be conducted quickly and efficiently on 3-pyrrolines with DDQ to give the corresponding pyrrole **1** in nearly quantitative yield (Scheme 3A).¹²⁸

Recently, a number of pyrrolinone-containing molecules have captured the attention of medicinal chemists owing to their promising activities as anti-inflammatories, anti-cancer and anti-bacterial medications. Although the independent synthesis of these units may be more efficient,¹²⁹ the oxidation of 3-pyrrolines still represents a viable alternative route to these heterocycles. Generally, the 2-oxidation of 3-pyrrolines to the corresponding pyrrolinones is achieved using Cr(VI) compounds. Donohoe and co-workers explored the possibility of a

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chromium-mediated allylic oxidation of 3-pyrrolines in their syntheses of the 20S proteasome inhibitors, lactacystin and *clasto*-lactacystin- β -lactone (Scheme 3B).¹³⁰ Despite the chemoselective oxidation working smoothly (80%), the resulting pyrrolinone product **2** was not amenable to the subsequent reactions necessary to complete their synthesis route to the natural product.

The dihydroxylation of 3-pyrrolines has been demonstrated by a number of groups to be an efficient method for the synthesis of polyhydroxylated pyrrolidine and pyrrolizidine alkaloids. Naturally, the most common method for this derivatisation uses an osmium-catalysed *syn*-dihydroxylation of the C3-C4 olefin (Scheme 3C). Donohoe has used this concept to execute an efficient *syn*-dihydroxylation of a 3-pyrroline intermediate in the total synthesis of ($\pm$)-1-epiaustraline.¹³¹ Application of Poli's standard dihydroxylation conditions (catalytic OsO₄ and stoichiometric Me₃NO as the terminal oxidant) to the required 3-pyrroline gave a single diastereoisomer of the *syn*-diol product **3** in an excellent yield of 95%.¹³²

However, this method has not been the only dihydroxylation strategy employed. An intrinsic characteristic of the mechanism of these osmium-catalysed dihydroxylation reactions means that this is not a viable approach to construct *trans* 3,4-dihydroxylated pyrrolidine heterocycles. The suprafacial addition of OsO₄ to the 3-pyrroline *cis*-alkene is a concerted process in which both of the new C-O bonds form simultaneously on the same face of the ring to give the *syn*-diol products.¹³³ Fortunately however, the ring-opening of an epoxide formed across the 3,4-olefin of the 3-pyrroline ring with oxygen nucleophiles provides a route to *trans* 3,4-dihydroxylated pyrrolidines. Under aqueous conditions, a *cis*-epoxide will open with an inversion of stereochemistry to yield the *trans*-diol products. This is exemplified in the synthesis of (-)-codonopsinine reported by Severino and Correia (Scheme 3D).¹³⁴ Treatment of a 2,5-disubstituted-3-pyrroline with *m*CPBA successfully formed the epoxide **4**, which after heating in aqueous H₂SO₄, furnished the desired *trans*-diol product **5** in an acceptable yield (39% over 2 steps).

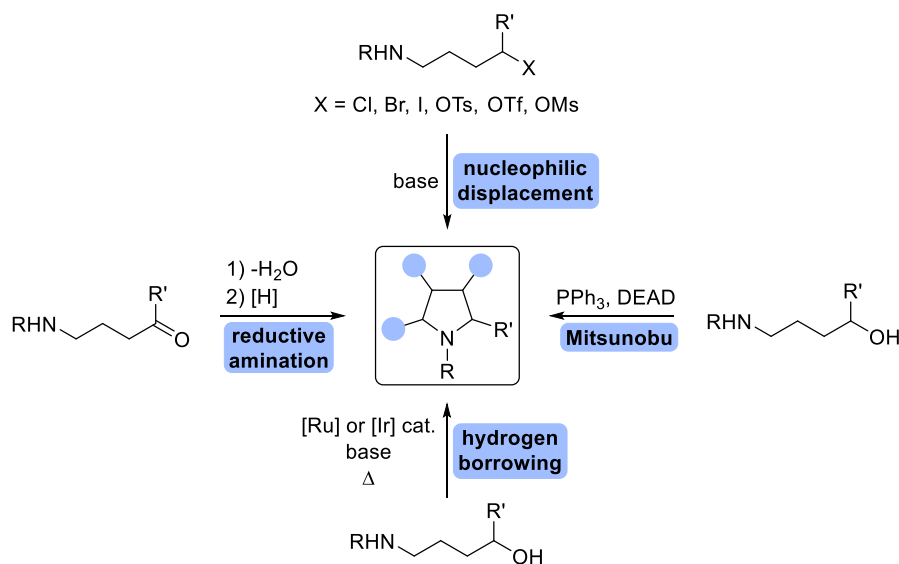
Conversely, reductive transformations of 3-pyrrolines have also proven to be highly effective. A convenient method for the synthesis of pyrrolidines involves a ring closing metathesis/reduction strategy. The catalytic hydrogenation of the C3-C4 olefin of 3-pyrrolines is easily

achievable in a selective manner. In Davies and co-workers' asymmetric synthesis of (*S*)-homoproline, their attempts at the catalytic hydrogenation of the olefin using a conventional Pd/C method predominantly furnished the corresponding pyrrole. However, as shown in Scheme 3E, use of Wilkinson's catalyst facilitated the desired reduction of the 3-pyrroline alkene.¹³⁵ Two subsequent transformations on the pyrrolidine product **6** yielded the target in 46% over 5 total steps.

1.4. Synthesis of Pyrrolidines and 3-Pyrrolines

1.4.1. Synthesis Methods to Pyrrolidines

Due to the prevalence of natural and non-natural pyrrolidines, there are many documented methods for their construction. In the following section, a few examples of the most common synthesis methods are outlined.



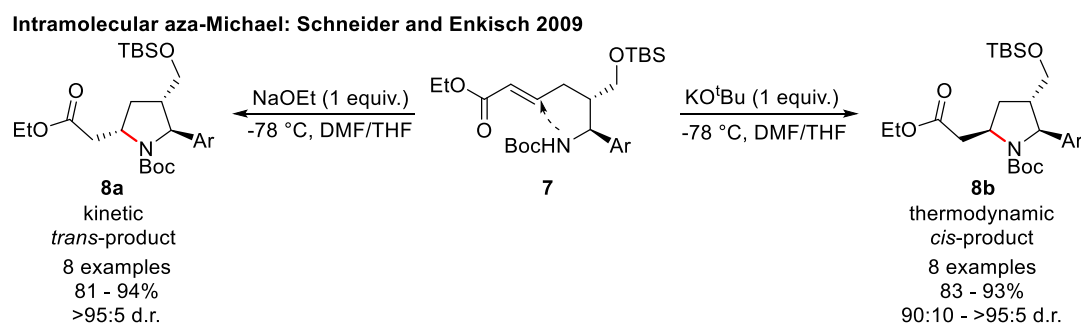
Scheme 4. Simplest general cyclisation methods of amines to make pyrrolidine rings.

As both 5-*exo-trig* and 5-*exo-tet* cyclisations are favourable according to Baldwin's rules, the simplest methods often involve the cyclisation of amines *via* reductive amination,^{136,137} *N*-alkylation through Mitsunobu chemistry¹³⁸ or the nucleophilic displacement of a halide¹³⁹/pseudo halide¹⁴⁰ (Scheme 4). In the case of reductive aminations, although more bespoke methods may have been developed,¹⁴¹ conventional methodologies in which an amine cyclises on to an aldehyde or ketone in the same molecule, followed by imine reduction, are more routinely called upon. Likewise, *N*-alkylation strategies usually rely upon more conventional

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established reaction conditions; however, methods such as hydrogen borrowing are becoming more popular due to the ease of access and handling of the amino alcohol precursors.^{142,143} Furthermore, hydrogen borrowing methods can offer good redox and atom economy thus minimising synthesis step counts and reagent waste. Typically, these methods are often limited to the cyclisation of simple alkyl chains, as more complex acyclic precursors can often require lengthy preparations.

Unsaturated carbonyl compounds also represent good electrophiles for the 1,4-addition of amines in the synthesis of pyrrolidines. Both intra- and intermolecular Michael additions of amine nucleophiles to unsaturated carbonyl compounds have been described.^{144–147} By incorporating an amine into a fragment containing a suitable Michael acceptor, a base-mediated cyclisation to the five-membered nitrogen heterocycle *via* an intramolecular aza-Michael reaction can be achieved.



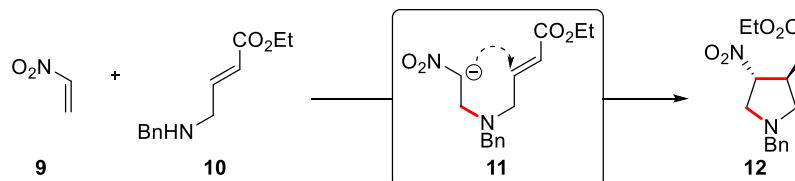
Scheme 5. Synthesis of trisubstituted pyrrolidines via an intramolecular aza-Michael reaction of an amine onto a tethered Michael acceptor as described by Schneider and Enkisch.¹⁴⁸

Schneider and Enkisch report a series of amines **7** – obtained from a Mannich reaction – undergo an intramolecular aza-Michael addition to give 2,3,5-trisubstituted pyrrolidines **8** (Scheme 5).¹⁴⁸ However, it was noted that exchanging bases permitted control of the relative configuration of the 2- and 5-substituents. In the presence of NaOEt the 2,5-*trans*-pyrrolidines **8a** were obtained as the major products in excellent diastereoselectivities whereas the use of KO^tBu encouraged the formation of the *cis*-products **8b**. This observation was attributed to KO^tBu being a stronger base than NaOEt (^tBuOH pK_a 32.0 (DMSO); EtOH pK_a 29.8 (DMSO))¹⁴⁹, thus enabling the deprotonation of the pyrrolidine products to generate the ester enolate. This facilitated a retro-

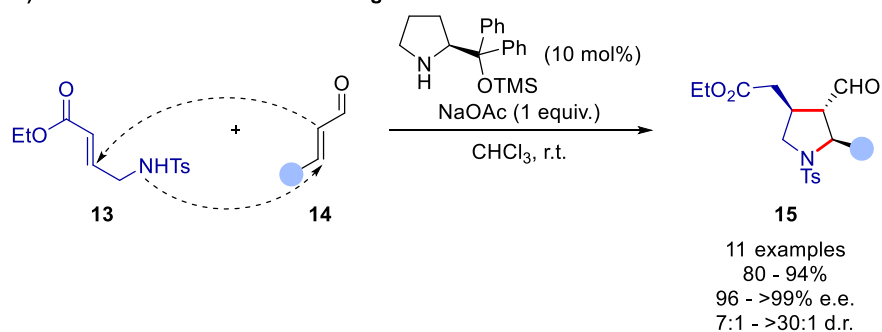
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aza-Michael reaction allowing the formation of the thermodynamic *cis*-products (as supported by DFT calculations).

A) Intermolecular aza-Michael: Spalluto and co-workers 1990



B) Intermolecular aza-Michael: Wang and co-workers 2008



Scheme 6. Pyrrolidine synthesis via intermolecular aza-Michael reactions between an amine and electron-deficient olefin followed by an intramolecular Michael addition.

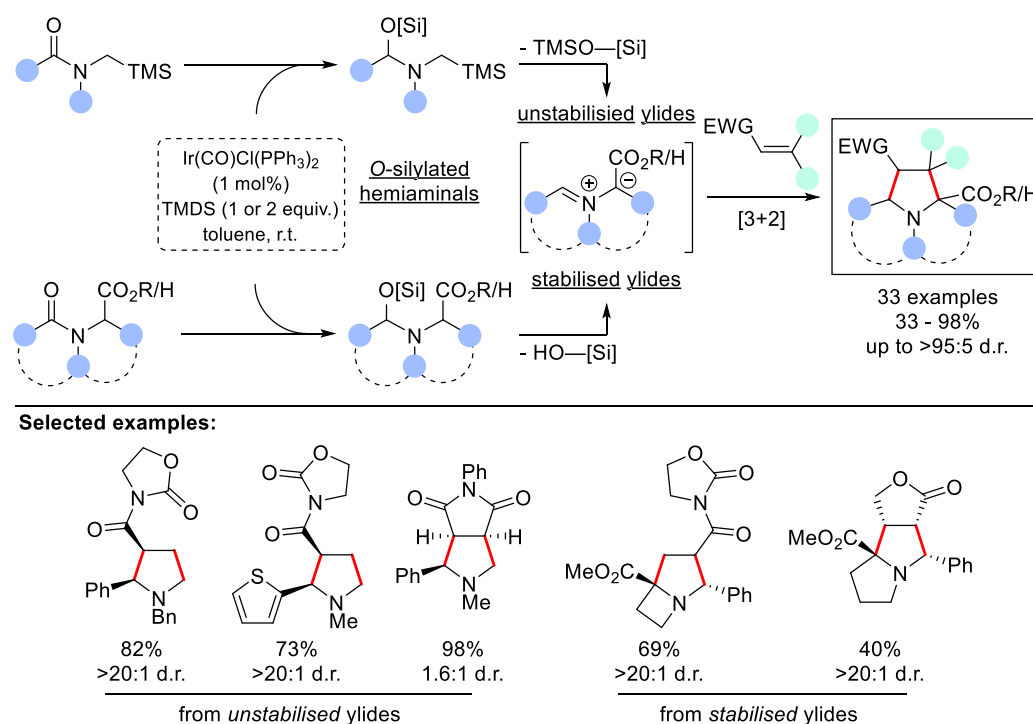
By contrast, research conducted by Spalluto and co-workers has demonstrated an intermolecular conjugate addition of an amine nucleophile **10** to nitroethylene **9** in which the intermediate nitronate **11** undergoes a subsequent cyclisation onto a second, built-in unsaturated acceptor leading to the *trans* pyrrolidine product **12** (Scheme 6A).¹⁵⁰ Many groups have built on this early concept, with asymmetric examples of aza-Michael/Michael cascade reactions to pyrrolidines having been recently disclosed.^{151–153} As displayed in Scheme 6B, using one of the Jørgensen-Hayashi-based chiral organocatalysts Wang and co-workers were able to synthesise functionalised trisubstituted chiral pyrrolidines **15** from simple achiral substrates **13** and **14** with high levels of enantio- and diastereoselectivity.¹⁵¹

The (3+2) cycloaddition between an azomethine ylide and an alkene has emerged as a powerful tool for the convergent synthesis of pyrrolidines.^{154–158} This method enables the direct construction of two of the five bonds that make up the saturated five-membered ring system with potential control over up to four newly formed stereogenic centres. The atom economical nature of the (3+2) cycloaddition makes it a popular choice in the chemical industry for the construction of complex pyrrolidine ring systems, and is used on multi-kg scales.^{159,160}

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The dominant orbital interaction for this reaction is considered to involve overlap between the HOMO of the azomethine ylide and the LUMO of the alkene π -system; azomethine ylides are typically considered to be electron-rich and react well with electron-deficient alkenes, thus maximising this orbital overlap. Despite this, (3+2) cycloadditions between azomethine ylides and unactivated¹⁶¹ or electron-rich¹⁶² alkenes are also known.

Azomethine ylides are most frequently generated from the deprotonation, decarboxylation or desilylation of imines or iminium salts or the thermal ring opening of aziridine rings. However, as shown in Scheme 7, Dixon and co-workers used an iridium-catalysed partial reduction of tertiary amides and lactams to form azomethine ylides *in situ* and demonstrated a general (3+2) cycloaddition methodology to access highly decorated pyrrolidines (and pyrrolizidines).¹⁶³



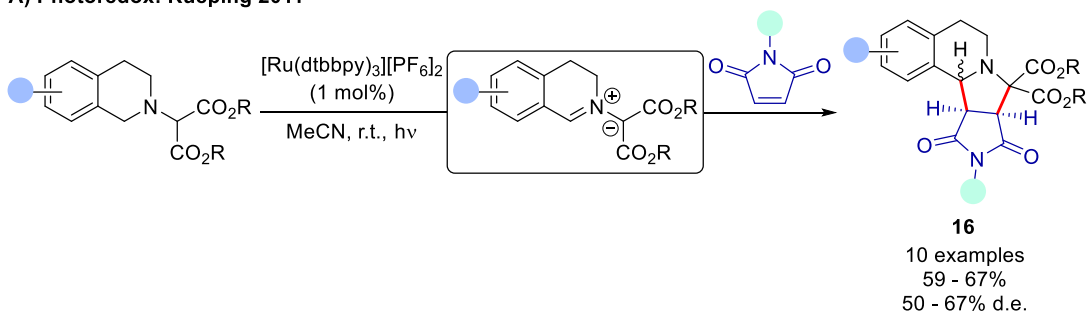
Scheme 7. Dixon and co-workers' pyrrolidine synthesis via an iridium-catalysed reductive azomethine ylide generation from tertiary amides and lactams followed by (3+2) cycloaddition with electron-deficient alkenes.

The amides under study were reduced in the presence of the dipolarophile using a combination of Vaska's complex and tetramethyldisiloxane (TMDS) to give the *O*-silylated hemiaminals. The 1,3-dipoles required for the cycloaddition reaction were then generated after elimination of the silanolate from these hemiaminals followed by deprotonation (for stabilised ylides) or desilylation (for unstabilised ylides) of the iminium by this anion. Both stabilised and

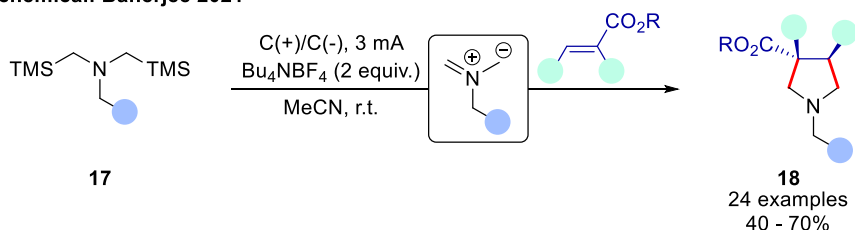
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unstabilised azomethine ylide species were generated using these conditions, affording a variety of highly and diversely substituted pyrrolidines and polycyclic amine products after cycloaddition in typically good yields and diastereoselectivities. Furthermore, Dixon and co-workers demonstrated that, with the introduction of a chiral auxiliary into the alkene fragment, it was possible for the reaction to give diastereo- and enantiomerically enriched pyrrolidines after removal of the auxiliary.

A) Photoredox: Rueping 2011



B) Electrochemical: Banerjee 2021

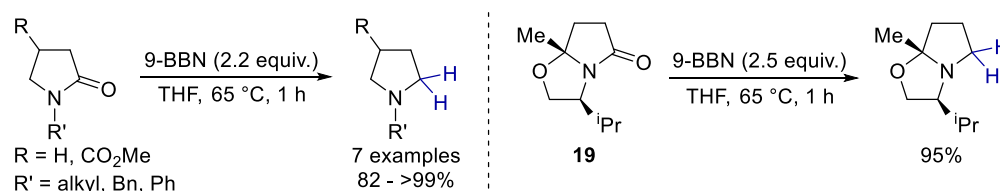


Scheme 8. Alternative methods for azomethine ylide formation. A) Rueping's photoredox-mediated generation of stabilised azomethine ylides.¹⁶⁴ B) Banerjee's electrochemical generation of unstabilised azomethine ylides.¹⁶⁵

Recently research has focussed on the sustainable execution of chemical reactions such as removing or limiting quantities of reaction solvents and stoichiometric reagents or reducing the production of chemical waste. To that end, in 2011, Rueping and co-workers disclosed a (3+2) cycloaddition of azomethine ylides in which the 1,3-dipoles were generated under photoredox conditions using a Ru catalyst and white visible light (Scheme 8A).¹⁶⁴ In the presence of *N*-substituted maleimides, the cycloaddition occurred to form a range of tetracyclic pyrrolidine products **16** in respectable yields. Similarly, Banerjee and co-workers have used electrochemical conditions to form azomethine ylides *in situ* (Scheme 8B).¹⁶⁵ In this study, a pair of graphite electrodes were used to promote a double desilylation process of symmetric C-silylated amines **17** and the resulting non-stabilised azomethine ylides were captured by acrylates and cinnamates to give the corresponding cycloadducts **18**.

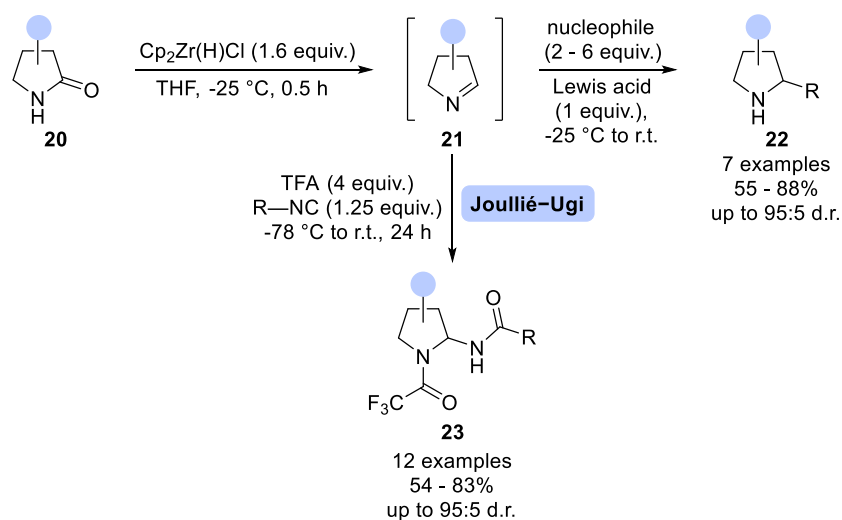
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Pyrrolidines can also be accessed from the manipulation of compounds that already have the core five-membered ring in place. The amide reduction of γ -lactams can often be a simple and efficient method to access pyrrolidines, as there are many known conditions for the reduction of amides and a number of simple γ -lactam substrates are commercial available.¹⁶⁶ In many cases though, more complex pyrrolidines are desired and so the necessary γ -lactams are typically synthesised from cyclisations of γ -amino acid derivatives or the *N*-alkylation of aliphatic amides to form the five-membered ring.



Scheme 9. Reduction of γ -lactams to pyrrolidines using 9-BBN.

Using this approach, Singaram and co-workers described a simple and mild reduction of γ -lactams to pyrrolidines using 9-borabicyclo[3.3.1]nonane (9-BBN).¹⁶⁷ The successful reductions of a number of simple commercially available lactams bearing alkyl, aryl and benzylic moieties in very high yields was reported, in addition to the reduction of the enantiopure bicycle **19** (Scheme 9). Furthermore, in this study they demonstrated the chemoselective reduction of the lactam in the presence of a methyl ester using the 9-BBN conditions without significant depreciation in the yield. Thus, the conditions the authors described present a good alternative reducing system for γ -lactam substrates that would not tolerate the harsher reducing conditions of reagents such as LiAlH₄ as demonstrated by Katritzky and co-workers.^{168,169} The use of terminal reductants such as silanes in combination with a metal catalyst¹⁷⁰ or additive,¹⁷¹ NaBH₄,¹⁷² or Pd/C with hydrogen gas¹⁷³ have also been shown to effectively reduce pyrrolidinones to pyrrolidines.



Scheme 10. Furman's one-pot sequential lactam reduction/functionalisation pyrrolidine syntheses via a cyclic imine.^{174,175}

Although a number of amide reductions using more conventional reducing systems have been reported for γ -lactams, more intricate methodologies have also been documented. For example, Furman and co-workers have described a synthesis of substituted polyhydroxylated pyrrolidines *via* a one-pot sequential lactam reduction followed by nucleophilic addition reaction (Scheme 10).¹⁷⁴ Using Schwartz's reagent, a polyhydroxylated γ -lactam **20** is reduced to a cyclic imine **21**. Using nucleophiles such as allyltributylstannane, Grignard reagents, cyanide and silyl enol ethers to intercept the imine intermediate, the authors were able to directly access functionalised aza-sugar derivatives **22**. Contrary to other reduction strategies, this methodology provides a means of functionalising the position α to nitrogen that previously bore the amide carbonyl. In a later publication, Furman and co-workers captured the imines with an isocyanide and carboxylic acid in a subsequent Joullié-Ugi three-component coupling reaction to furnish hydroxylated prolinamides, **23**, in generally good yields and diastereoselectivities.¹⁷⁵

1.4.2. Synthesis Methods to 3-Pyrrolines

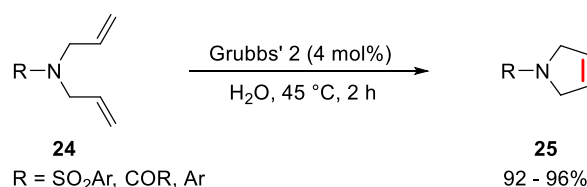
Over the past 100 years, various syntheses of 3-pyrrolines have been proposed that focus on the construction of different bonds around the ring. The earliest syntheses relied on simple nucleophilic displacement reactions to form the C-N bonds of the ring.¹⁷⁶⁻¹⁷⁸ However, traditionally these strategies had limited scope and only gave simple 3-pyrroline products. It is

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only over the past ten to twenty years that these methods have really developed to allow for the formation of more structurally and functionally diverse 3-pyrroline architectures.¹⁷⁹

One of the most efficient and widely used synthesis methods for the construction of cyclic products is ring-closing metathesis (RCM). Hence, RCM using one of the Grubbs' ruthenium precatalysts represents a popular method for the effective formation of the 3,4-olefin of simple 3-pyrrolines. In 2002, Davies *et al.* utilised this approach in their asymmetric syntheses of (*S*)-homopiperic acid, (*S*)-homoproline and (*S*)-coniine.¹³⁵ Their route to (*S*)-homoproline relied on the formation of a 3-pyrroline intermediate. As described previously (Scheme 3E, Section 1.3), a subsequent catalytic hydrogenation of the unsaturated nitrogen heterocycle gave the fully saturated pyrrolidine core of **6** found in the target product.

In 2008, Polshettiwar and Varma demonstrated a similar olefin ring closing metathesis strategy using Grubbs' second generation ruthenium precatalyst.¹⁸⁰ Scheme 11 shows their synthesis route to an assortment of *N*-substituted 3-pyrrolines **25** using various tertiary diallyl amines **24**.



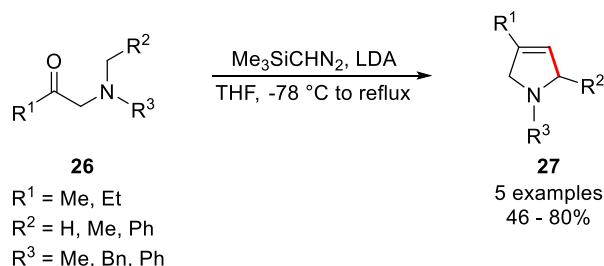
Scheme 11. Synthesis of N-substituted 3-pyrrolines using ruthenium-catalysed ring closing metathesis described by Polshettiwar and Varma.¹⁸⁰

Despite this method giving high yields with short reaction times and under mild conditions, the authors reported no examples of *C*-substituted 3-pyrrolines being synthesised by this approach. To acquire a 2- or 3-substituted 3-pyrroline, a substituted allyl group would have to be present in the starting amine. Consequently, this would create longer and more complex synthesis sequences. Furthermore, although the reaction proceeds under mild reaction conditions and can be conducted in aqueous media, it does require the use of an expensive ruthenium catalyst (£295/mmol, Sigma-Aldrich, 2022) of limited commercial availability, thus restricting the scalability of this synthesis approach.

Another route to 3-pyrrolines capitalises on a 1,5-CH insertion reaction of an alkylidene carbene. This methodology was first reported by Walsh and Bottini in 1970.¹⁸¹ In this work, the alkylidene

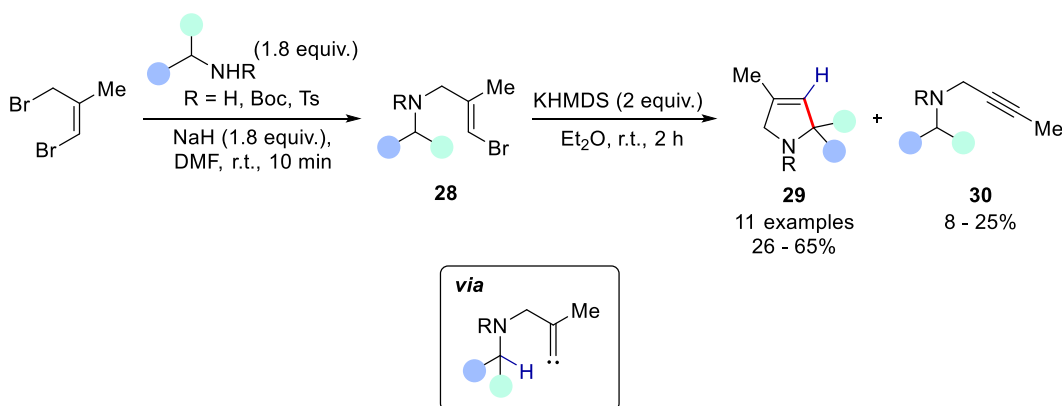
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carbene was generated from the reaction of the corresponding 1-halo-3-alkyl-aminopropenes with KO^tBu. This reaction was found to produce a complex mixture of amines, which included the 3-pyrrolines. Regrettably, this pioneering method suffered from a limited substrate scope and poor yields, the highest of which was 36%.



*Scheme 12. Shioiri and Aoyama's cyclisation of *N,N*-disubstituted α -amino ketones using (trimethylsilyl)diazomethane.¹⁸²*

This procedure was improved upon by Shioiri and Aoyama who formed the reactive carbene intermediate using lithio(trimethylsilyl)diazomethane on a range of 1-alkylamino-2-propanones **26** (Scheme 12).¹⁸² Despite seeing yields of 3-pyrrolines **27** of up to 80% – a significant improvement over Walsh's work – Shioiri and Aoyama only explored this transformation using five simple *N,N*-disubstituted α -amino ketones. However, they further developed this methodology to allow for the synthesis of 3-pyrrolinones from *N,N*-dialkylamides of α -keto acids and lithio(trimethylsilyl)diazomethane.^{183,184}



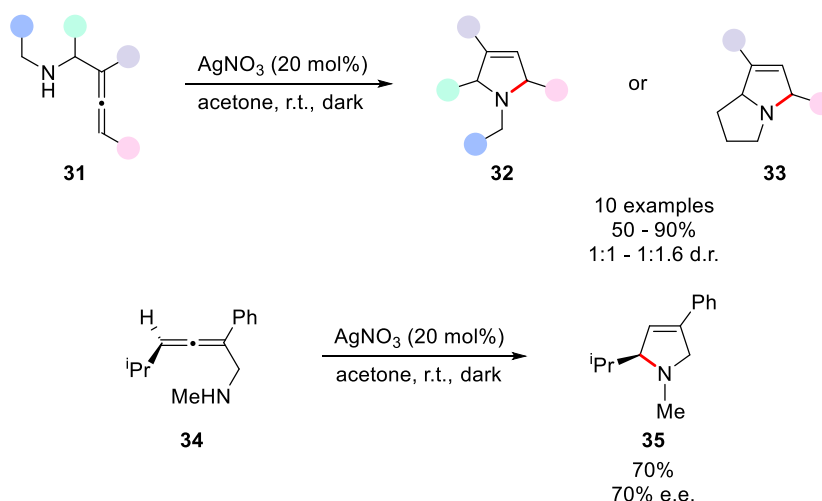
*Scheme 13. Synthesis of 2,2-disubstituted 3-pyrrolines **29** via 1,5-CH insertion of alkylidene carbenes described by Hayes and co-workers.¹⁸⁵*

More recently, Hayes and co-workers have developed a 1,5-CH insertion reaction as a way to generate more substituted 3-pyrrolines (Scheme 13).¹⁸⁵ Initially, a primary amine was

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monoalkylated with 1,3-dibromo-2-methylpropene to form amine **28** which, upon treatment with KHMDS at room temperature, generated an alkylidene carbene. This carbene subsequently underwent ring closure *via* a 1,5-CH insertion into the highlighted tertiary C-H bond to give a variety of 2,2-disubstituted 3-pyrrolines **29** in yields ranging from 43-65%. However, a significant disadvantage to this method is the potential for alternative insertions to occur. In particular, notable quantities of alkyne **30** were isolated as a result of insertion into the C-C bond of the terminal methyl group in **28**. This procedure was then shown to work with *N*-protected amines to give the corresponding *N*-substituted 3-pyrrolines but with typically lower yields. Hayes and co-workers demonstrated the utility of this approach by making a key 3-pyrroline intermediate in their enantioselective formal synthesis of (+)-lactacystin.¹⁸⁶

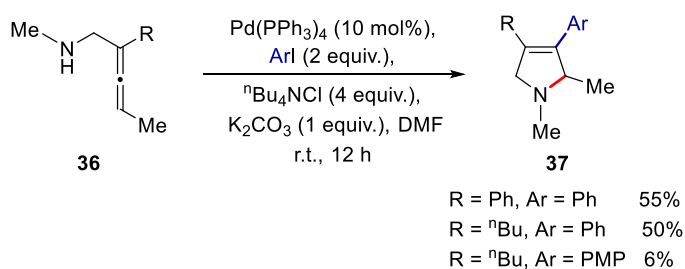
The cyclisations of allenes containing proximal nucleophilic amino groups have garnered substantial attention as promising and highly atom-economical routes to functionalised 3-pyrrolines. The 5-*exo-dig* or 5-*endo-trig* cyclisations are commonly promoted under the influence of bases¹⁸⁷ or by transition metal catalysts.¹⁷⁹ In the case of transition metal-mediated cyclisation, the mechanism is highly dependent on the nature of the catalyst. Soft Lewis acidic metals such as silver or gold show a preference for complexation to the terminal olefin of the unsaturated system, thus activating the allene towards nucleophilic attack of the amino functionality. Conversely, harder Lewis acidic metals like palladium exhibit stronger interactions with the more electron-rich olefin of the allene.¹⁸⁸



Scheme 14. Dieter and Yu's 5-*endo-trig* cyclisations of α -amino allenes catalysed by silver.¹⁸⁹

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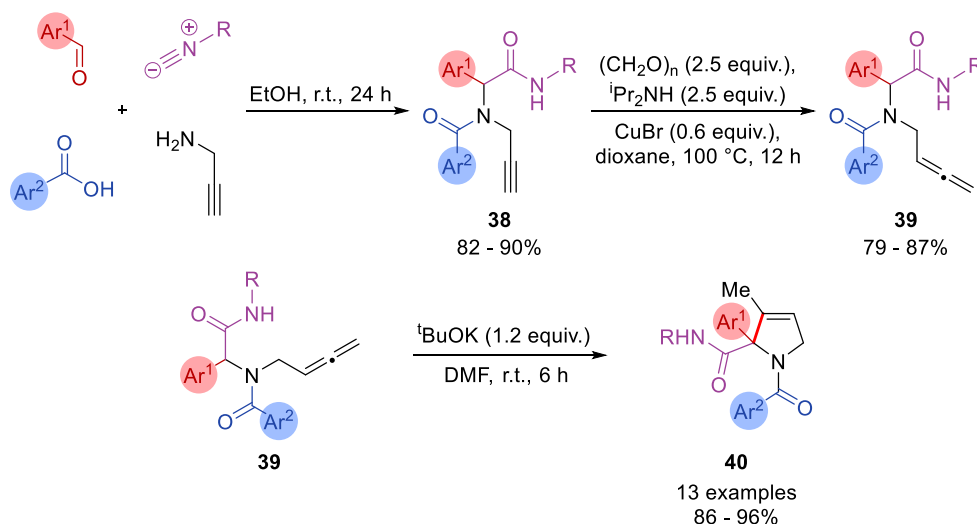
Silver is an especially prevalent metal catalyst for these cyclisations.^{128,179,190,191} Dieter and Yu subjected a range of racemic α -amino allenes **31** to 20 mol% of AgNO₃ in acetone at room temperature. When performed in the dark the resulting 3-pyrrolines **32** and tetrahydropyrrolizines **33** were obtained in good to excellent yields (Scheme 14). Following this, Dieter and Yu applied their 5-*endo-trig* cyclisation to enantioenriched allene **34** (83% e.e.) which furnished chiral 3-pyrroline **35** in good yield and with good enantiomeric excess (70% e.e.). This protocol however, prohibits the incorporation of substituents at the C-3 position of the 3-pyrroline. Hence, an additional palladium-mediated cyclisation was established, that facilitated a cross coupling reaction to install aryl substituents at this position (Scheme 15). Using this method allenes **36** were cyclised to substituted 3-pyrrolines **37**.



Scheme 15. Dieter and Yu's 5-*endo-trig* cyclisations of α -amino allenes catalysed by palladium.¹⁸⁹

An example of a base-mediated intramolecular allene cyclisation is depicted in Scheme 16. In this case, Al-Harrasi and co-workers cyclised allenic Ugi-adducts **39** with stoichiometric quantities of ^tBuOK at room temperature in excellent yields.¹⁹² The reaction of benzylic aldehydes and carboxylic acids with isocyanides and propargylamine furnished the Ugi products **38**, which upon Crabbé homologation with paraformaldehyde and sub-stoichiometric CuBr, gave allenes **39**.¹⁹² Base-promoted intramolecular cyclisation of these allenes gave the 3-pyrrolines **40**. The average yield over the three steps was 64% with the lowest being 61%.

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*Scheme 16. Al-Harrasi and co-workers' route to the allene starting materials **39** via an Ugi/ Crabbé homologation followed by base promoted cyclisation of allenes **39** to 3-pyrrolines **40**.¹⁹²*

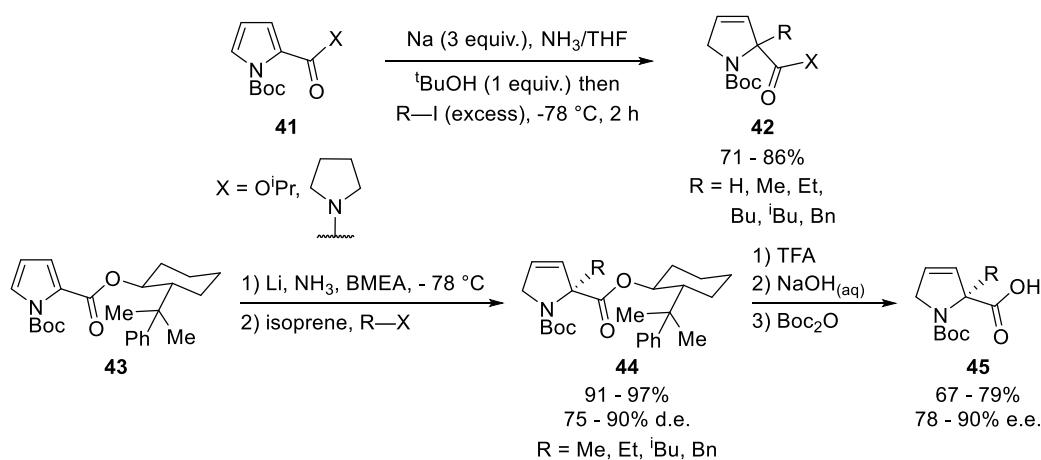
The mechanism of the transformation involves KO^tBu deprotonation α to the secondary amide carbonyl. The resulting enolate then attacks the central carbon of the allene *via* a 5-*exo-dig* cyclisation. Al-Harrasi and co-workers considered the possibility of deprotonation of the amide nitrogen. In order to get a better understanding of this possibility, a DFT analysis of the reaction was carried out at the B3LYP/6-31G(d) PCM (DMF) level in the gas phase. These calculations predicted that the enolate ion had a relative free energy and chemical hardness of 1.1 kcal/ mol and 0.72 eV, respectively, lower than the analogous amide ion.¹⁹³ Consequently, they concluded that the enolate ion is more likely to form and is more reactive than the amide anion. Additionally, calculation of the activation energy barriers to six different transition states showed that the 5-*exo-dig* cyclisation of the enolate ion onto the central allene carbon, which lead to the observed products, had the lowest barrier.

The scope of the reaction was investigated and found to produce a range of tetra-substituted 3-pyrrolines. From the aldehyde fragment, the cyclisation tolerated phenyl rings with both electron-withdrawing and electron-donating groups. Similarly, the carboxylic acid component could incorporate phenyl rings with both electron-donating and withdrawing groups in various substitution patterns. Finally, for the isocyanide component, only ^tBu and Cy groups were tested and gave two different secondary amides substituted in the 2-position of the 3-pyrrolines **40**.

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The partial reduction of pyrroles to pyrrolines has been known for over 100 years. However, the earliest strategies required harsh conditions only applicable to simple substrates.^{177,194} Due to the electron-rich character of the pyrrole ring system, conventional nucleophilic hydride species are not capable of reducing these heterocycles. However, protonation of the pyrrole under acidic conditions followed by reduction of the resultant iminium intermediates provides a succinct albeit harsh route to 3-pyrrolines. Despite the limitations of this method, progress has been made to broaden the range of suitable pyrroles to develop a viable route to functionalised 3-pyrrolines.^{195–197}

The dearomatisation of aromatic rings *via* dissolving metal reductions has been an especially concise method for the synthesis of functionalised heterocycles for many years.^{198–200} Unfortunately, due to the high electron density of pyrroles, the addition of an electron in the first step of a Birch reduction is impeded, making this method generally unsuitable for the partial reduction of these aromatic heterocycles.²⁰¹ Despite this, research conducted by the Donohoe group has enabled a range of 3-pyrroline heterocycles to be accessed from pyrrole precursors. By thoroughly exploring this transformation, their method enables the reaction to proceed under significantly milder reaction conditions than previously reported. They validated the synthetic utility of their methodologies in the context of the synthesis of numerous natural products.^{130,131,202–204}



Scheme 17. Birch reduction of electron-deficient pyrroles as described by Donohoe *et al.*^{205,206}

The first iteration of their method, using sodium and liquid ammonia, reductively alkylated electron-deficient substrates such as 2-amido and 2-carboxylate *N*-Boc pyrroles **41** to 3-

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pyrrolines **42** in good yields (Scheme 17 Top).^{205,207} The Boc group proved to be essential not only to stop the deprotonation of the acidic pyrrole N-H under the reducing conditions but also to further reduce the electron density of the pyrrole core. With the introduction of an asymmetric ester at the 2-position Donohoe *et al.* found that it was possible to direct the addition of the electrophile to a specific face of the molecule facilitating the synthesis of chiral 2,2-disubstituted 3-pyrrolines **44** from the corresponding pyrroles **43** in excellent yields and diastereoselectivities (Scheme 17 Bottom).²⁰⁶ Hydrolysis of the chiral auxiliary gave the corresponding *N*-protected amino acids **45** in good to excellent yields and enantioselectivities over three steps.

Further advances were made by Donohoe and co-workers for the induction of asymmetry into the 3-pyrroline products of these Birch reductions. These include enzymatic desymmetrisation of the resulting 3-pyrrolines²⁰⁸ and chiral protonation of the anionic intermediate using the acidic proton of enantiopure (-)-ephedrine.²⁰⁹

Naturally, the use of liquid ammonia as a solvent for these transformations is not desirable or practical. Furthermore, this nucleophilic solvent restricts the number of electrophiles that can quench the heterocyclic anion to alkyl halides and non-enolisable aldehydes. Consequently, in 2000, an ammonia-free variation of the reductive alkylation methodology was introduced, allowing a greater breadth of reactive electrophiles to be used.²¹⁰ A subsequent adjustment to this methodology, in 2002, used a mixture of BMEA (bis(methoxyethyl)amine), lithium metal and DBB (di-*tert*-butylbiphenyl) to effect reduction; the latter two reagents reacting to form the radical anion LiDBB (Figure 9).²¹¹

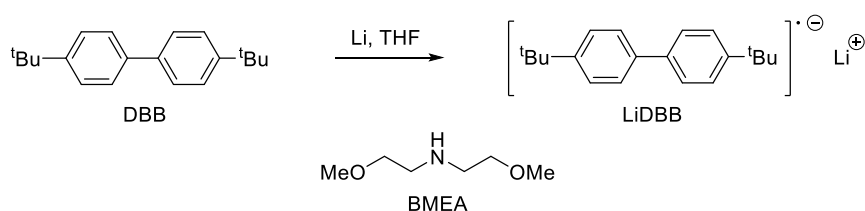
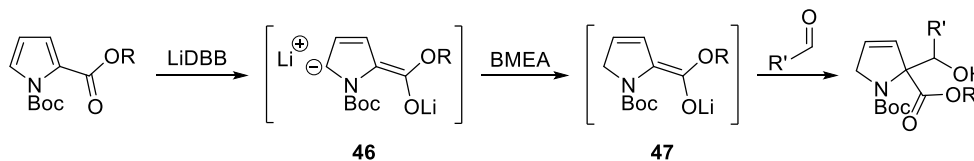


Figure 9. Ammonia substitutes used in Donohoe's ammonia-free Birch reduction of pyrroles.

Although the combination of LiDBB and BMEA acts as a milder substitute to the harsh dissolving metal conditions, compromises to the yield were observed. LiDBB was the new electron source whilst BMEA was acidic enough to protonate the unsubstituted anion of dianion **46** but not acidic

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enough to protonate the enolate monoanion **47** that formed thereafter (Scheme 18). This left the enolate available to be quenched by the electrophiles, which included disulfides, aldehydes and acid chlorides.¹³⁰



Scheme 18. Mechanism of the ammonia-free Birch reduction of pyrroles using LiDBB and BMEA. The ammonia-free conditions enable a wider variety of electrophiles to be used.

1.5. Reductive Ring Contractions

Access to smaller cyclic systems *via* the contraction of larger rings can pose a significant synthesis challenge and so has been of great interest to organic chemists for many years. Early examples of these types of transformations have been known since the late 19th century with some of the most notable being the Favorskii rearrangement^{212,213} and Wolff-rearrangement²¹⁴ of cyclic α -diazo ketones.²¹⁵ Since these early reports, the state of the art has witnessed substantial development. The methods discussed below show great variety in the range of compatible substrates, reaction conditions and modes of action and so will be categorised according to the class of product formed.

1.5.1. Deoxygenative Ring Contractions to Nitrogen Heterocycles

Saturated nitrogen heterocycles are significant structural elements found in medicinal chemistry. Fortunately, ring contraction provides a novel means of synthesising substituted amines of this type that would otherwise be difficult to obtain by classical synthesis methods. 3,6-Dihydro-2H-1,2-oxazines have proven to be valuable synthesis precursors to highly functionalised saturated nitrogen heterocycles. These precursors are easily accessible cycloadducts from [4+2] cycloaddition reactions. Hence, they constitute attractive starting points for the synthesis of unsymmetrical, substituted 3-pyrrolines and pyrrolidines that would represent challenging targets using more conventional strategies.

Sequential ring opening/ring closing methods that proceed *via* an intermediate 1,4-amino alcohol have proven to be a popular choice. These methods capitalise on the facile cleavage of

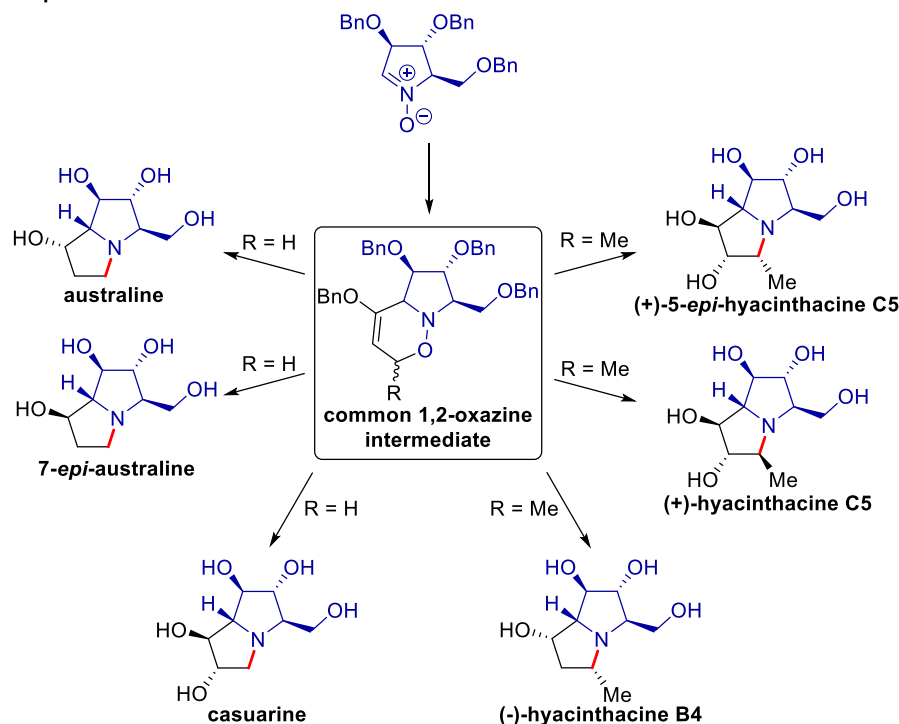
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the weak N-O bond found in 3,6-dihydro-2*H*-1,2-oxazines and 1,2-oxazinane substrates (BDE ~45-55 kcal/ mol).²¹⁶ A variety of different approaches and reagents have been used for N-O bond cleavage including zinc-acid reductions,²¹⁷ samarium iodide,²¹⁸ molybdenum hexacarbonyl²¹⁹ and hydrogenolysis facilitated by metal catalysts.²²⁰ The subsequent activation of the revealed alcohol (for example using mesyl chloride) promotes ring closure under basic conditions, to give the 3-pyrroline and pyrrolidine products.

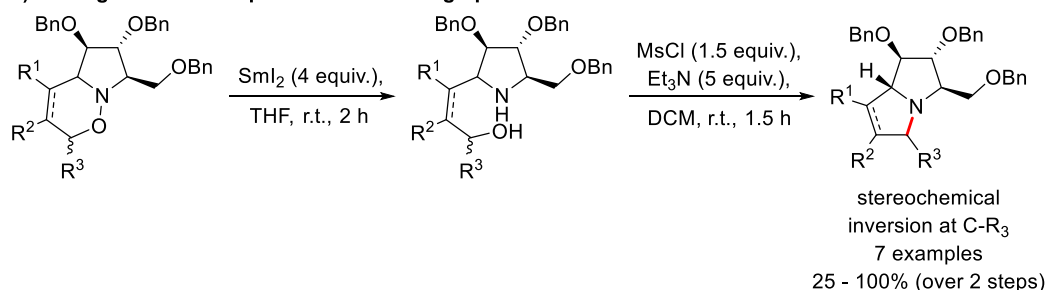
The Reissig group have employed this strategy on a number of occasions. In their initial reports, the ring contractions of 3,6-dihydro-2*H*-1,2-oxazines were effected using H₂ in combination with either palladium on carbon or Raney nickel catalysts to give fully saturated pyrrolidine products.²²⁰⁻²²⁴ Unfortunately, the high pressures of H₂ required limited the pragmatism of this strategy. Consequently, the scope of tolerated substrates can be quite narrow, with the presence of easily reducible functional groups being inappropriate.

However, the Reissig group's later reports of this transformation using 1,2-oxazine and 1,2-oxazinane substrates detailed the adoption of the mild single-electron reductant samarium iodide for the ring opening step to great effect.^{218,225,226} As such, this enabled the use of benzyl protecting groups on both alcohol and amine functionalities without fear of removal under the modified reaction conditions. As shown in Scheme 19A, the applicability of this method to the assembly of several polyhydroxylated pyrrolizidines has been demonstrated in their total syntheses of (-)-hyacinthacine B₄,²²⁷ (+)-hyacinthacine C₅,²²⁷ casuarine²²⁸ and australine²²⁸ from a common 1,2-oxazine intermediate. In these cases, the ring closure *via* nucleophilic displacement by the amine results in an inversion of configuration at the carbon bearing the R³ substituent (Scheme 19B).

A) Natural products from a common intermediate



B) All ring contractions proceeded via a ring opened amino alcohol

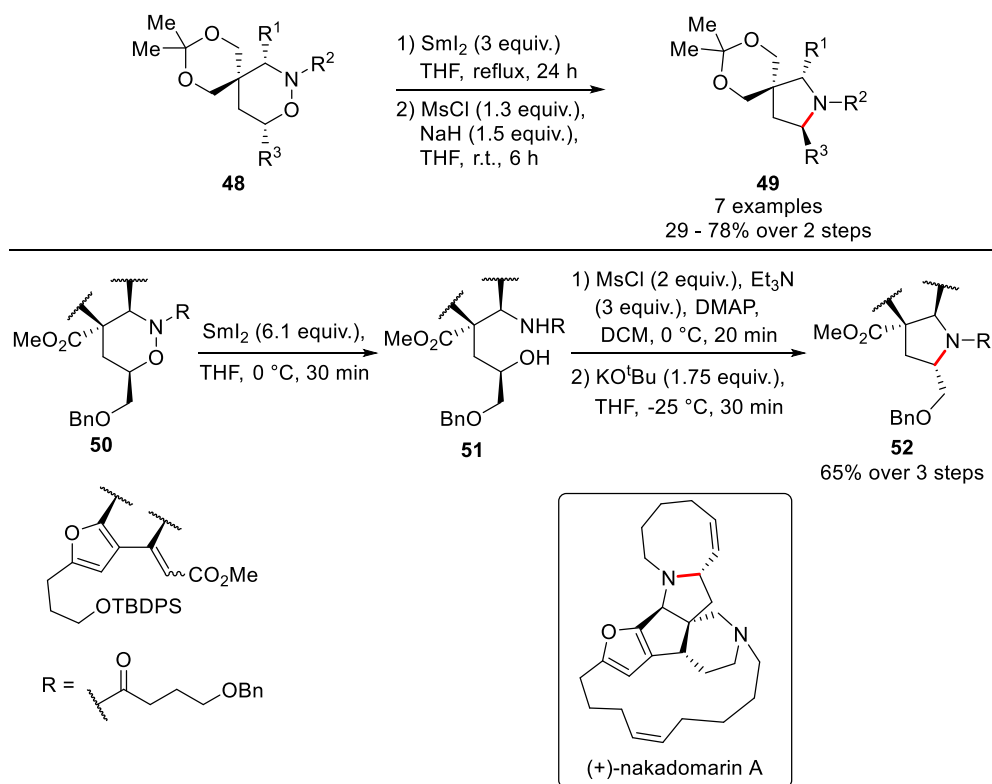


Scheme 19. A) Synthesis of six pyrrolizidine natural products from a common 1,2-oxazine intermediate using a ring opening/ring closing strategy. B) Ring contractions to the pyrrolidine and 3-pyrroline products proceeded via a ring opened amino alcohol.

Likewise, in 2005 Kerr and co-workers presented a similar deoxygenative ring contraction of 3,6-*cis*-substituted 1,2-oxazinane substrates **48** obtained from, what they call, a nitron-cyclopropane [3+3] cycloaddition.²²⁹ The subsequent samarium iodide-mediated N-O bond cleavage followed by cyclisation of the mesyl chloride-activated alcohol lead to an inversion of configuration at the 6-position (C-R³) to give the deoxygenated pyrrolidine products **49** (Scheme 20 Top). The breadth of this approach was illustrated on substrates bearing aliphatic, alkenyl, aromatic and heteroaromatic substituents to give a range of 2,5-*trans*-substituted pyrrolidines **49** in moderate to good yields.

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As an extension of this work, the construction of the tetracyclic core of the natural product nakadomarin A was later demonstrated (Scheme 20 Bottom).²³⁰ The core pyrrolidine unit **52** was synthesised from 1,2-oxazinane **50** *via* amino alcohol **51** using this ring opening/deoxygenative ring closure methodology.



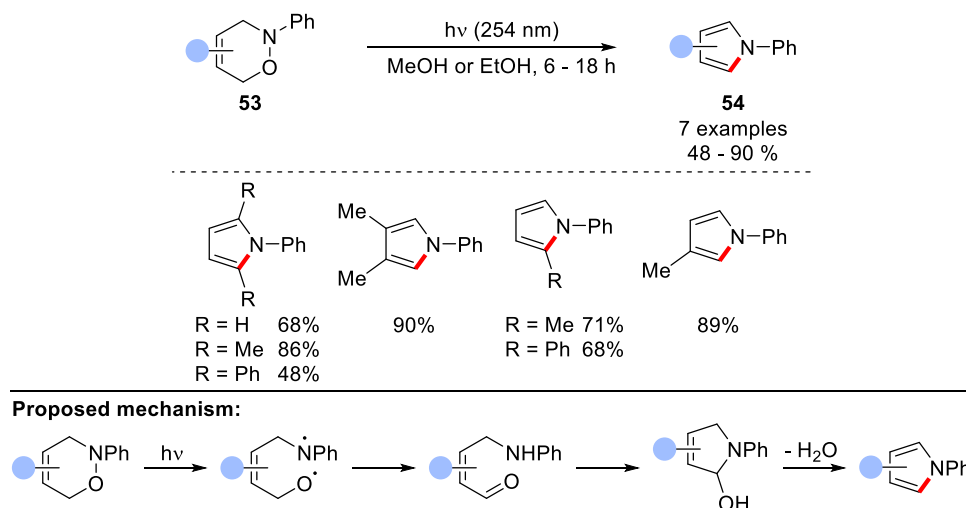
Scheme 20. Kerr's total synthesis of (+)-nakadomarin A using a deoxygenative ring contraction to install the pyrrolidine ring of the tetracyclic core **52**.^{229,230}

Substituted pyrroles are common heterocycles found in many biologically active molecules. Currently, the deoxygenation of 1,2-oxazines to pyrroles is the most documented deoxygenative ring contraction of the types discussed here and has been described as early as 1968.²³¹ Frequently, these ring contraction methods are coupled with nitroso Diels-Alder reactions as an expedient route to *N*-aryl pyrroles from common aryl nitroso precursors.

An early description of a photochemical deoxygenative ring contraction of 3,6-dihydro-2*H*-1,2-oxazines to pyrroles was presented by Scheiner and co-workers in 1969 (Scheme 21).²³² The photolysis of a handful of 1,2-oxazines **53** occurred under irradiation with 254 nm UV light in a variety of solvents, with degassed MeOH or EtOH facilitating the cleanest reactions. Using these

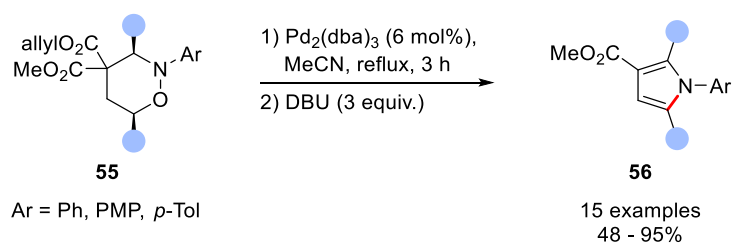
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conditions, moderate to excellent yields (48-90%) of pyrroles **54** could be obtained from the contraction of seven 1,2-oxazines **53** bearing aliphatic, aromatic or no substituents.



*Scheme 21. Scheiner's photolysis of 1,2-oxazines **53** to pyrroles **54** and the proposed mechanism for the transformation.²³²*

It was proposed that the mechanism of this contraction commenced with homolytic N-O bond cleavage to give a diradical. Intramolecular HAT of the diradical generated an unsaturated amino carbonyl, which formed the pyrrole after condensation and aromatisation. However, traces of the analogous ring-contracted furan and aniline suggested that a competitive pathway involving the denitrogenative cyclisation of a hydroxy imine was operative. This observation was subsequently noted by others.²³³ Since this early report, more elaborate deoxygenative ring contractions have been established.

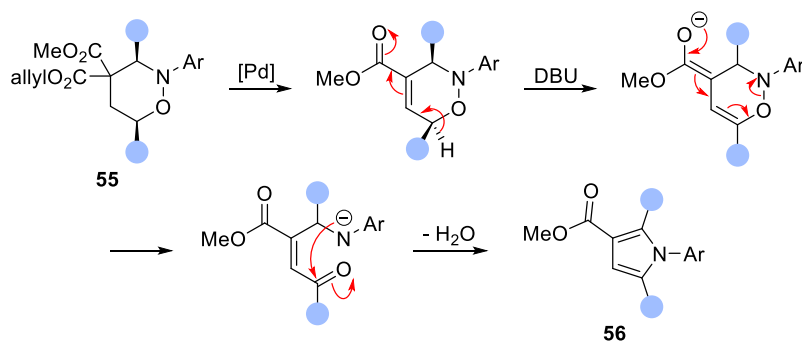


*Scheme 22. Kerr's Tsuji dehydrogenative decarbonylation and base-mediated ring contraction of 1,2-oxazinan-3-one **55** to pyrroles **56** offers access to substituted pyrroles.²³⁴*

Kerr and co-workers developed a mild palladium(0)/palladium(II)-catalysed dehydrocarbonylative dehydration of 1,2-oxazinan-3-one **55** to pyrroles **56**.²³⁴ The three-component coupling of an aldehyde, hydroxylamine and 1,1-cyclopropanediester gave 1,2-oxazinan-3-one **55**

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via the 'cycloaddition' of the *in situ* formed nitron and cyclopropanediester.²³⁵ A subsequent Tsuji dehydrogenative decarbonylation²³⁶ of 1,2-oxazinanes **55** introduced the 4,5-alkene moiety which, in the presence of base, rapidly generated the pyrroles **56** (Scheme 22). Kerr and co-workers reported that the transformations can be performed as a one-pot procedure with no appreciable change in yield, thus removing any requirement to isolate the 1,2-oxazine intermediates.

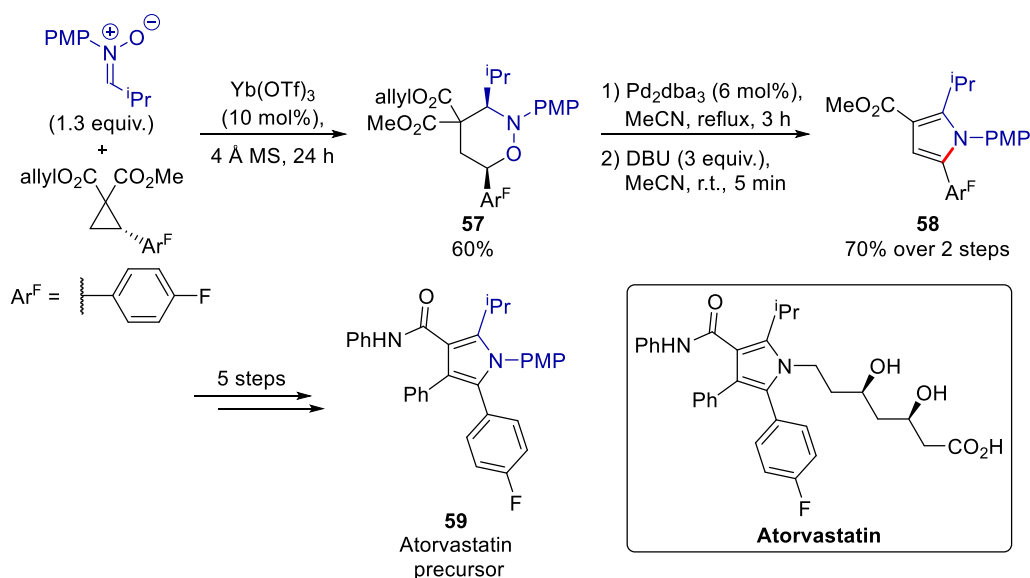


Scheme 23. Proposed mechanism of palladium(0)-catalysed dehydrocarbonylative dehydration of 1,2-oxazinanes **55**.

The ring contraction itself is promoted by the addition of a base, operating *via* the deprotonation of the γ -position of the α,β unsaturated ester (Scheme 23). A subsequent E1cB-type elimination of nitrogen gives a carbonyl and amide anion, which, after condensation and tautomerisation gives the pyrrole products **56**. Consequently, this contraction is highly substrate dependent, relying not only on the presence of an α,β unsaturated ester but also a suitably acidic proton in the 6-position of the 1,2-oxazines. Nevertheless, Kerr demonstrated a broad substrate scope with alkyl, alkenyl, aromatic and heteroaromatic substituents all being compatible functionalities on the 1,2-oxazine ring.

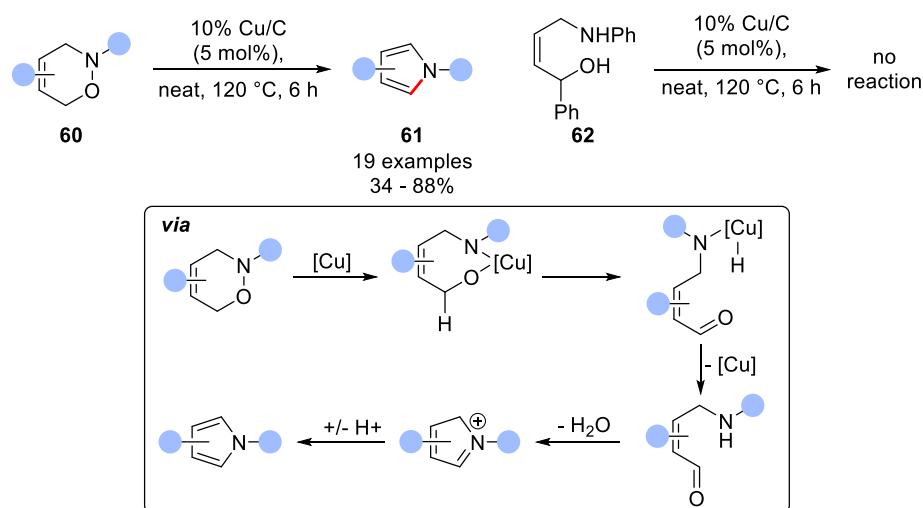
The practicality of this deoxygenative ring contraction approach was demonstrated in the synthesis of the pyrrole core of atorvastatin (Lipator®). As shown in Scheme 24, the one-pot two-step contraction methodology was applied to 1,2-oxazinane **57** to give the pyrrole core **58** in good yield. Further simple derivatisation of this core including amidation of the ester moiety with aniline, appendage of a phenyl group in the vacant 4-position of the pyrrole, deprotection and alkylation of the pyrrole nitrogen provides the target, atorvastatin.

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Scheme 24. Kerr's synthesis of an atorvastatin precursor **59** using their palladium-catalysed deoxygenative ring contraction methodology.²³⁴

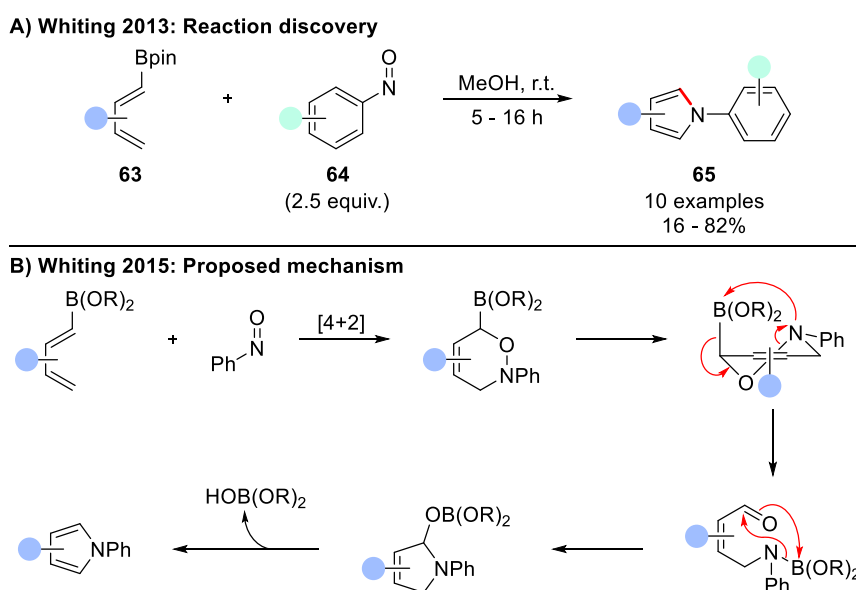
Another reported example sees 3,6-dihydro-2*H*-1,2-oxazines **60**, obtained from the nitroso Diels-Alder reaction, contracted to the corresponding pyrroles **61** under the influence of a Cu/C catalyst (Scheme 25).²³⁷ This method boasts high atom economy – having water as the sole by-product – solvent-free conditions and the capacity to run the nitroso Diels-Alder and ring contraction in one pot. Interestingly, the presence of a solvent (H_2O , MeCN, DMF or toluene) in the ring contraction led to significant quantities of starting material being recovered with minimal pyrrole formation observed.



Scheme 25. Synthesis of substituted pyrroles **61** via a copper-catalysed deoxygenative ring contraction of substituted 1,2-oxazines **60** as reported by Sawama and co-workers.²³⁷

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Sawama and co-workers report a broad scope of compatible 6-substituted 1,2-oxazine substrates **60** that cleanly converted to the pyrrole products **61**. These 6-substituents comprise benzyl groups, heteroaromatics and aromatic groups that bear electron-donating or electron-withdrawing functionalities in *ortho*-, *meta*- and *para*-positions around the ring. Alternative substitution patterns around the 1,2-oxazine starting material were also tolerated, however, the lack of an aromatic substituent adjacent to oxygen resulted in diminished yields. Unusually, when the corresponding amino alcohol **62** was subjected to the reaction conditions only the starting material was recovered. This was explained by the mechanism proceeding through an amino ketone intermediate, which forms a cyclic iminium that subsequently aromatises to the pyrrole product.



Scheme 26. A) Synthesis of *N*-aryl pyrroles **65** from a boronodiene **63** and aryl nitroso compound **64**.²³⁸ B) The transformation is proposed to go via a [4+2] cycloaddition followed by deoxygenative ring contraction.²³⁹

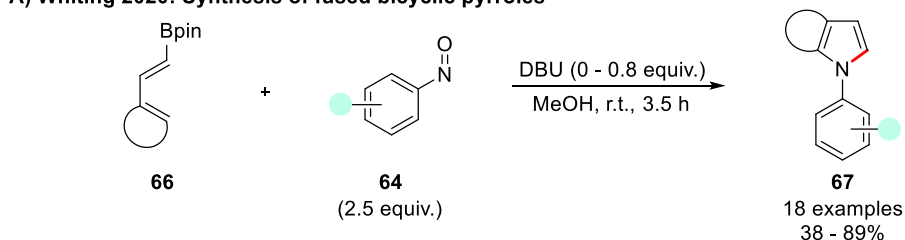
In 2013, Whiting and co-workers reported the unexpected formation of *N*-aryl pyrroles **65** from 1-boronodienes **63** and aryl nitroso dienophiles **64**, instead of the anticipated boronated 3,6-dihydro-1,2-oxazine cycloadducts (Scheme 26A).²³⁸ A range of substituted aryl nitroso compounds were shown to react smoothly with boronated diene **63** with no apparent inhibitory electronic effects being observed from the varied substituents. However, when **63** was exchanged for a more sterically hindered boronated diene or a diene with *cis* geometry with respect to the boron substituent, substantially reduced yields were observed. The equivalent

reaction using a trifluoroboronated analogue of **63** was reported to work with similar efficacy to diene **63**, however, the MIDA ester furnished only the corresponding cycloadducts. To account for this, they tentatively proposed that the reaction operates through a [4+2] cycloaddition/ring contraction cascade process in which the transient 1,2-oxazine intermediate spontaneously undergoes N-O bond fragmentation followed by cyclisation of the resulting amino acyl species (Scheme 26B).

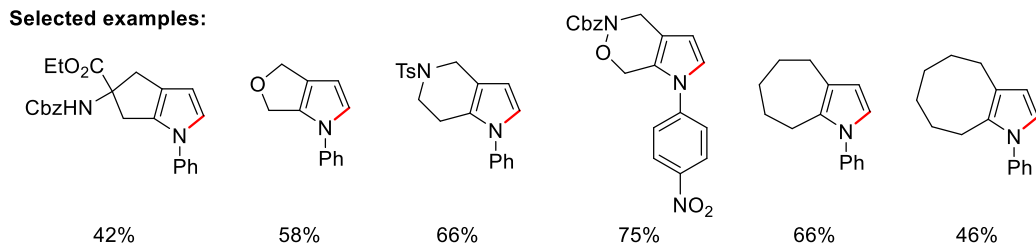
A later publication by Whiting supplied further evidence that corroborated their initial mechanistic proposal; namely that the use of diethanolamine boronate esters lead to the identification of the elusive [4+2] cycloadduct intermediate before the subsequent contraction to the pyrrole product occurred.²³⁹ In these cases it was posited that after the cycloaddition, the tetrahedral boronate underwent methanolysis to give a boronic ester that facilitates the proceeding ring contraction reaction. Furthermore, they demonstrated the superior reactivity of this tetracoordinated boronate ester in the cascade process on a sterically hindered diene that had previously given a poor yield of the pyrrole product. This was attributed to the boronate ester being less electron-withdrawing than the pinacol ester, thus showing greater reactivity towards the nitroso dieneophiles.

The scope of this transformation was later expanded such that fused bicyclic pyrroles **67** could be obtained from the corresponding sterically hindered dienes **66** and nitroso compounds **64** (Scheme 27A).²⁴⁰ However, it was established that the addition of a substoichiometric amount of the amidine base DBU was necessary in order to facilitate the reaction in acceptable yields. Consequently, cycloadducts annulated with substituted 5- to 8-membered carbocycles, piperidines, pyrrolidines, tetrahydrofurans, tetrahydropyrans and 1,2-oxazines became accessible.

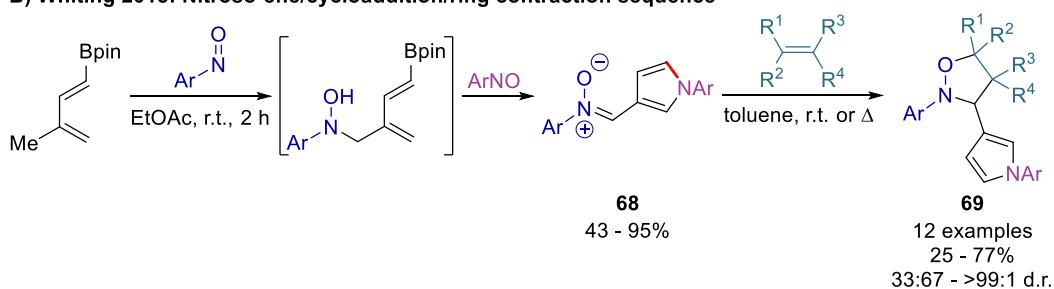
A) Whiting 2020: Synthesis of fused bicyclic pyrroles



Selected examples:



B) Whiting 2018: Nitroso-ene/cycloaddition/ring contraction sequence

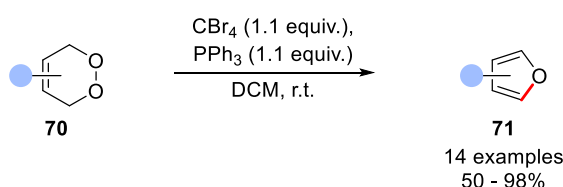


Scheme 27. A) Whiting and co-workers expanded the scope of the transformation to facilitate the synthesis of fused bicyclic pyrroles **67**.²⁴⁰ B) Synthesis of pyrrolyl isoxazolidines **69** via a nitroso-ene/[4+2] cycloaddition/ring contraction/(3+2) cycloaddition sequence from a boronodiene and an excess of nitroso compound.²⁴¹

In 2018 Whiting showed that using a significant excess of the aryl nitroso compound in ethyl acetate lead to the formation of pyrrolyl nitrones **68** via a nitroso-ene/cycloaddition/ring contraction sequence (Scheme 27B).²⁴¹ The reaction was demonstrated using six different substituted aryl nitroso compounds where electron-withdrawing groups gave a higher proportion of the pyrrolyl nitrone **68** relative to just the pyrrole (such as **65** formed from the [4+2]/ring contraction cascade shown in Scheme 26A) than electron-donating substituents. Additionally, the inclusion of a stoichiometric amount of TEMPO appeared to suppress the occurrence of possible radical side reactions, leading to enhanced yields of the pyrrolyl nitrones **68**. Further derivatisation using these nitrones was delineated in the (3+2) dipolar cycloaddition with a series of activated alkenes to give isoxazolidines **69** in good yields. The challenging purification of the nitrones lead Whiting and co-workers to conduct the nitrone formation and subsequent (3+2) cycloaddition as a one-pot procedure.

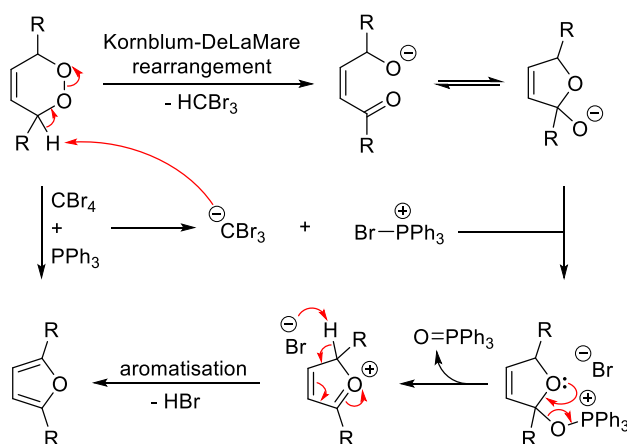
1.5.2. Deoxygenative Ring Contractions to Oxygen Heterocycles

Although the synthesis of highly substituted furans is possible using more traditional methods such as the Paal-Knorr or Feist-Benary syntheses, the requisite dicarbonyl compounds can often involve lengthy synthesis sequences. Recently, attention has shifted toward the development of new reactions that offer convenient, mild routes to these heterocycles from easily accessible starting materials. The deoxygenative ring contraction of endoperoxide cycloadducts resulting from the hetero Diels-Alder reaction between singlet oxygen and a 1,3-diene can be a valuable and efficient way to build complex furan scaffolds.



*Scheme 28. Deoxygenative ring contraction of endoperoxides **70** to furans **71** using conventional Appel reaction conditions.²⁴²*

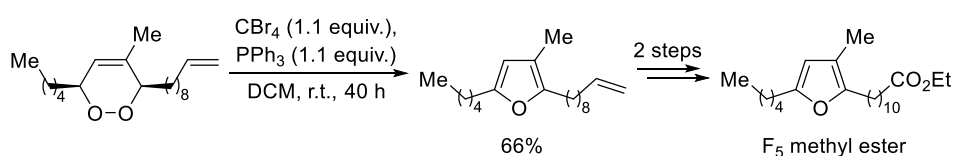
Recently, Kimber and co-workers found that endoperoxides **70** can be contracted giving highly substituted electron-rich furans **71** *via* a biosynthetically inspired metal- and acid-free deoxygenative ring contraction strategy using conventional Appel reaction conditions (Scheme 28).²⁴² Their interest lay in the synthesis of furan fatty acids (FFAs), a group of natural products shown to inhibit the development of human chronic inflammatory diseases. Treatment of the endoperoxide starting materials with slight excesses of both CBr_4 and PPh_3 at room temperature gave typically excellent yields of the furan products.



Scheme 29. Proposed mechanism for the CBr_4 and PPh_3 -mediated deoxygenative ring contraction of endoperoxides.

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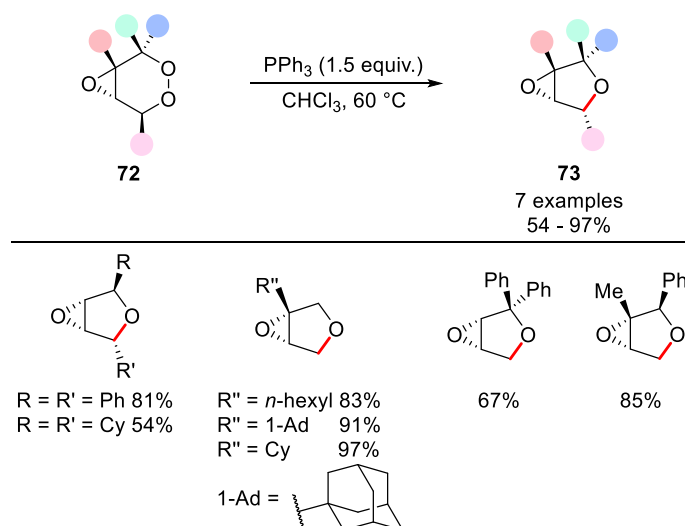
Initially, as with the Appel reaction, the reaction between CBr_4 and PPh_3 results in the formation of the phosphonium bromide/carbanion ion pair (Scheme 29). The carbanion deprotonates the peroxide, promoting the Kornblum-DeLaMare rearrangement to the 4-alkoxy enone which exists in equilibrium with the cyclic dihydrofuran. Activation of the hydroxyl group by the phosphonium bromide leads to the dehydration of the hydroxy dihydrofuran to give the phosphine oxide and furan, after aromatisation. The process was tolerant to a mixture of substitution patterns around the furan core in addition to alkyl, cyclopropyl, alkenyl, aromatic, ester, silyl ether and bromide functional groups. The suitability of the method to the construction of FFAs was highlighted in the use of this deoxygenative process in the total synthesis of the FFA F_5 methyl ester (Scheme 30).



Scheme 30. Kimber and co-workers synthesis of the FFA F_5 methyl ester via the deoxygenative ring contraction of an endoperoxide using Appel reaction conditions.²⁴²

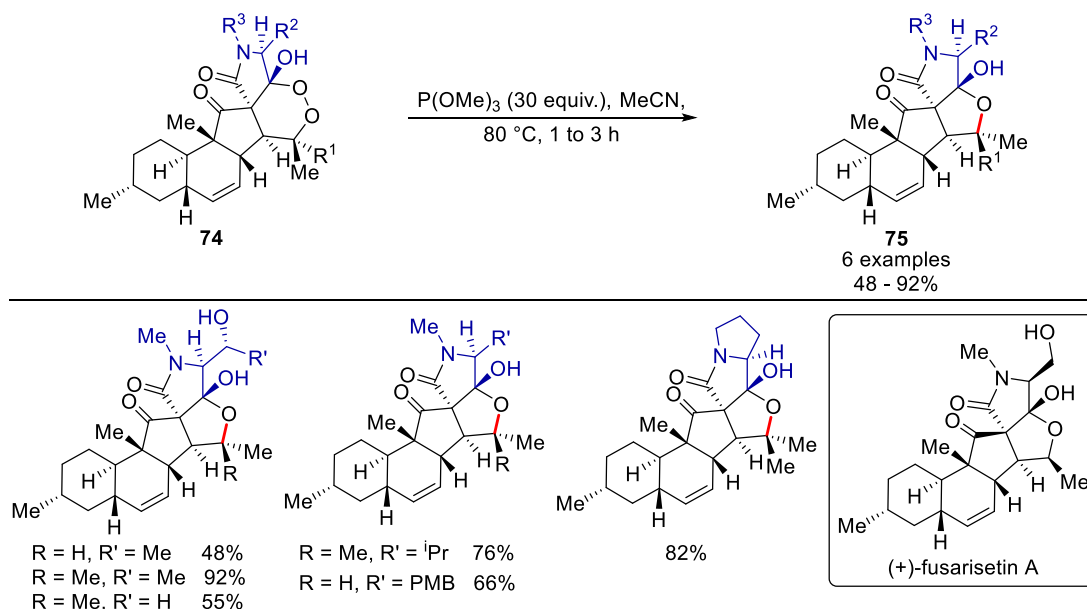
Substituted tetrahydrofurans can represent valuable targets for medicinal chemists and bioorganic chemists, especially when functionalised with multiple hydroxyl groups, due to the large range of sugar derivatives that can be accessed. In addition to the furan products obtainable (*vide supra*), endoperoxide cycloadducts are also appropriate precursors to substituted tetrahydrofurans.

One of the most widely used set of deoxygenation conditions for this transformation uses a phosphorus(III) species that both reductively cleaves the weak O-O bond (BDE ~35-45 kcal/mol)²⁴³ and facilitates ring closure.²⁴⁴⁻²⁴⁷ In 2004 Greatrex and Taylor treated a number of endoperoxide [4+2] cycloadducts **72** (where the olefin had been epoxidised) with triphenylphosphine at 60 °C (Scheme 31).²⁴⁵ They reported good to excellent yields of the ring-contracted dihydrofuran oxide products **73** (54-97%) across a small range of simple substrates. Moreover, Greatrex and Taylor subjected three 3,6-dihydro-2*H*-1,2-dioxines to these reaction conditions to yield the corresponding 2,5-dihydrofurans which were subsequently converted to the epoxy tetrahydrofurans in quantitative yields.



Scheme 31. Greatrex's PPh_3 -mediated reductive ring contraction of endoperoxides **72** to tetrahydrofurans **73**.²⁴⁵

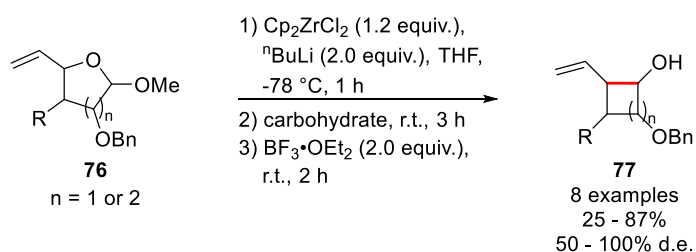
Gao and co-workers utilised a similar methodology in the total synthesis of derivatives of fusarisetin A **75** (Scheme 32).²⁴⁷ The efficiency of this strategy was demonstrated when treatment of endoperoxides **74** with P(OMe)_3 in acetonitrile at 80 °C afforded the fusarisetin A derivatives **75** in 48-92% yields. Having previously functionalised the peroxide precursors earlier in the sequence with a range of amino acids (highlighted blue in Scheme 32), the phosphorus(III)-mediated reductive ring contraction was then employed as the concluding step in the creation of this library of natural product derivatives. In the context of fusarisetin A, both Theodorakis²⁴⁸ and Gao^{249,250} have demonstrated similar reductive ring contractions of an endoperoxide intermediate using thiourea and Zn/AcOH reducing conditions respectively.



Scheme 32. Synthesis of fusarisetin A derivatives **75** via the $P(OMe)_3$ -mediated deoxygenative ring contraction of endoperoxides **74**.

1.5.3. Deoxygenative Ring Contractions to Carbocyclic Products

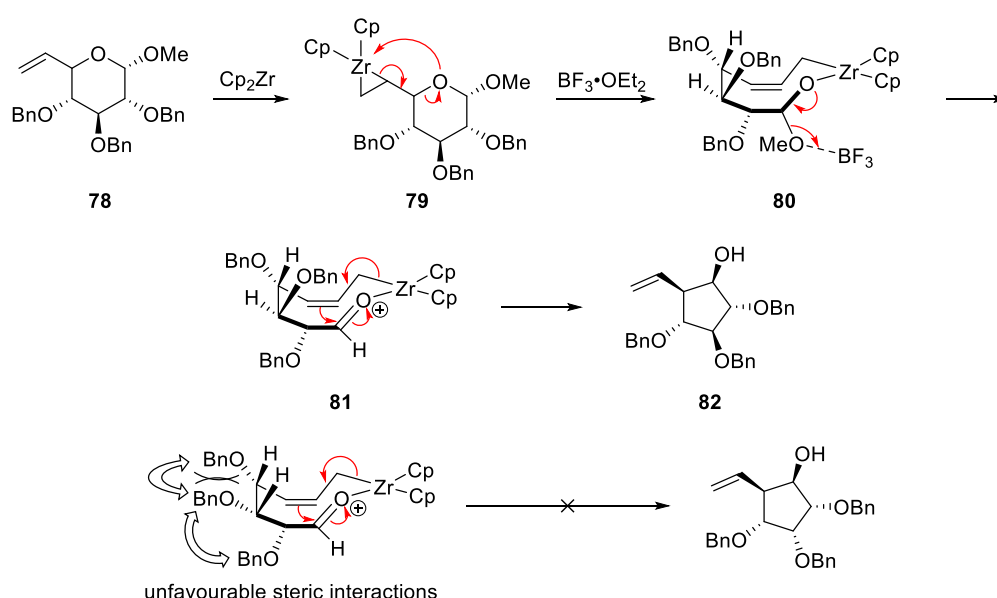
The ring contraction of cyclic ethers to carbocycles is not an unfamiliar transformation in organic synthesis and has been known for some time.^{251–253} However, the complete *deoxygenative* ring contraction of cyclic ethers is less well documented. Even with the examples currently known, although strictly deoxygenative in definition, they do not expunge the ring oxygen, but rather an adjacent anomeric oxygen to give a contracted hydroxylated carbocycle.



Scheme 33. First reported example of the deoxygenative ring contraction of cyclic ethers **76** using zirconocene by Taguchi and co-workers in 1993.²⁵⁴

Using reaction conditions previously developed for the preparation of allyl zirconium species, Taguchi and co-workers reported the deoxygenative ring contraction of cyclic ethers to carbocycles in 1993 using a combination of “ Cp_2Zr ” (generated from the reaction between zirconocene dichloride and n -BuLi) and $BF_3 \cdot OEt_2$ (Scheme 33).²⁵⁴ The process was demonstrated

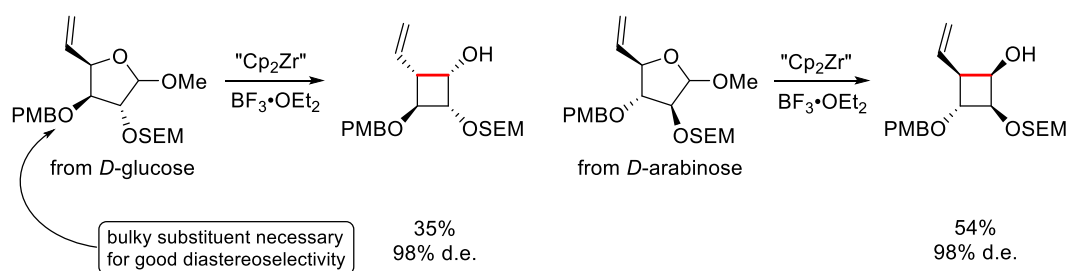
on eight different vinyl-substituted pyranoside and furanosides **76** to give the deoxygenated cyclopentane and cyclobutane products **77** in 25-87% yield and typically very high diastereoselectivities. The procedure relies on the high oxophilicity of zirconium as well as its capacity to effectively form a zirconacycle with allylic ethers. The diastereomeric ratio of the products was found to be highly dependent on the number and size of other substituents on the ring. In cases where there were only one or two small substituents, the product distribution was more even. However, with the introduction of a large group on the ring – one that could preferentially be removed later – exclusively one diastereoisomer was obtained in good yield.



Scheme 34. Proposed mechanism of the zirconocene-mediated deoxygenative ring contraction of cyclic ethers.

The mechanism, typified in Scheme 34, was proposed to commence with the coordination of the zirconocene to the vinyl alkene (**78** to **79**).²⁵⁵ Nucleophilic attack of the ring oxygen on the zirconium facilitates β -elimination to give the ring-expanded zirconacycle **80**. The Lewis acid-assisted elimination of the anomeric OMe gives oxonium **81** which cyclises *via* a chair-like transition state with loss of the zirconocene to give the carbocyclic product **82**. As a consequence of this transition state, a *cis* relative relationship between the vinyl substituent and the newly revealed adjacent hydroxyl group of the products is observed.

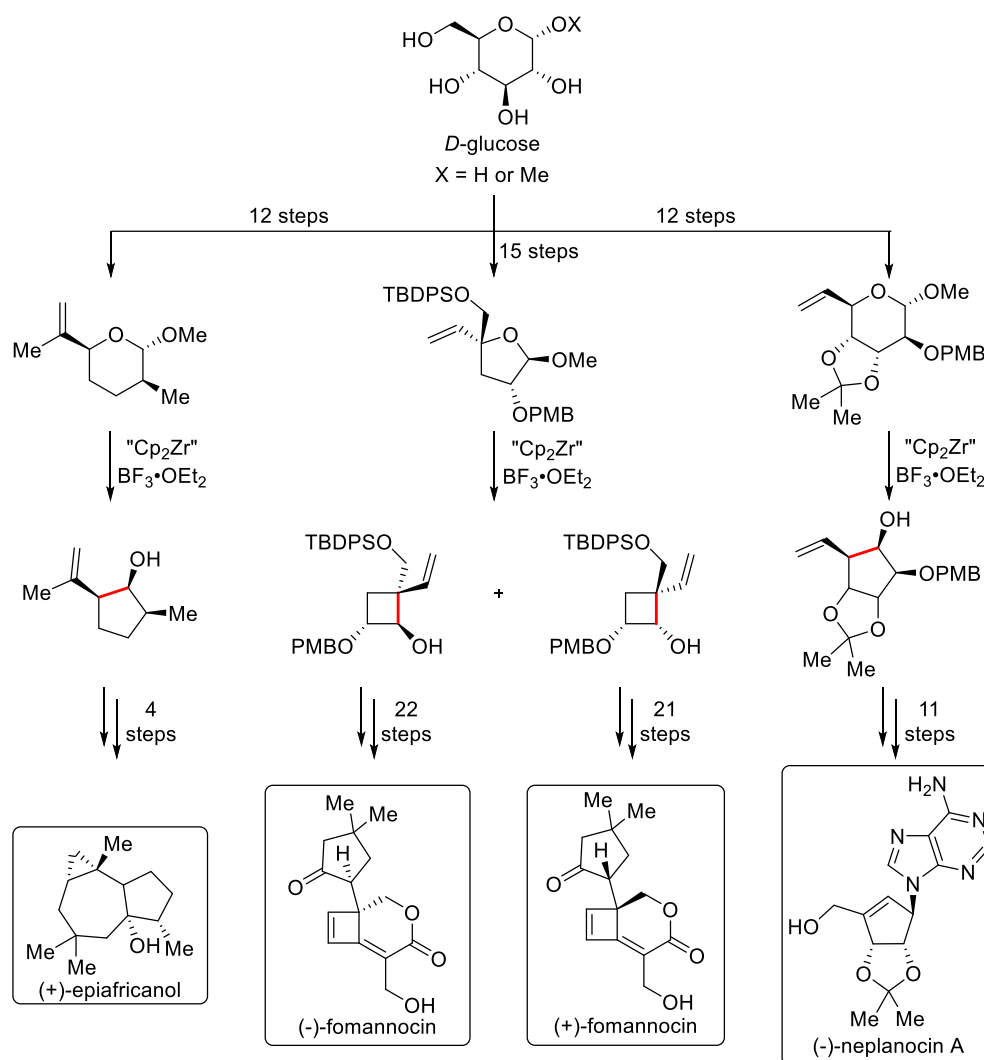
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Scheme 35. Paquette's deoxygenative ring contraction of vinyl-substituted furanosides to cyclobutanes.²⁵⁶

The Paquette group has explored the breadth of this reaction in significant detail using a variety of carbohydrate-based starting materials. In 2002, Paquette and Cunière began their endeavours studying the ring contraction of vinyl-substituted furanosides initially derived from the readily accessible carbohydrates *D*-glucose and *D*-arabinose (Scheme 35).²⁵⁶ Using the reaction conditions initially disclosed by Taguchi and co-workers, modest yields of the cyclobutane derivatives were achieved. Furthermore, they report that exchanging the solvent for toluene and removing the Lewis acid provided a noticeable improvement in reaction efficiency.

Following from this, Paquette and co-workers employed this reaction as a key step in the unique total synthesis of (+)-epiafricanol, a previously unknown stereoisomer of the natural product africanol (Scheme 36).²⁵⁷ Starting from a readily available carbohydrate, methyl α -*D*-glucopyranoside was transformed into a functionalised tetrahydropyran in 12 steps (Scheme 36 left). Zirconium-mediated deoxygenative ring contraction of this gave the ring contracted cyclopentane in 63% yield which after four concluding steps gave the natural product derivative. Furthermore, using this protocol, the Paquette group have successfully synthesised (-)-neplanocin A²⁵⁸ as well as both natural (+)-fomannocin²⁵⁹ and a non-natural (-)-fomannocin²⁶⁰ from *D*-glucose (Scheme 36). In the case of the fomannocin total syntheses, the ring contraction of a common furanoside intermediate provided a pair of diastereomeric cyclobutanes which served as a branching point for the synthesis of the two configurationally distinct products.

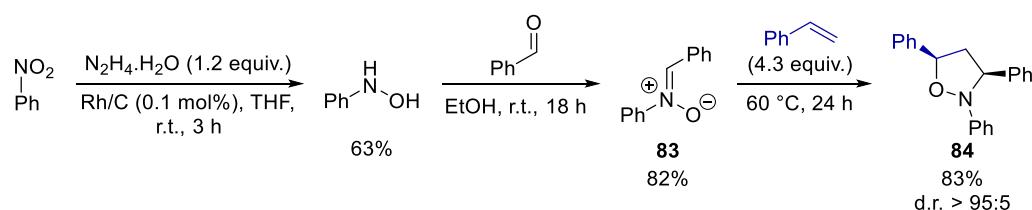


Scheme 36. Paquette and co-workers' synthesis of the natural products (+)-epiafricanol, (-)-fomannocin, (+)-fomannocin and (-)-neplanocin A from *D*-glucose.^{258–260}

1.6. Previous Work in the Denton Group

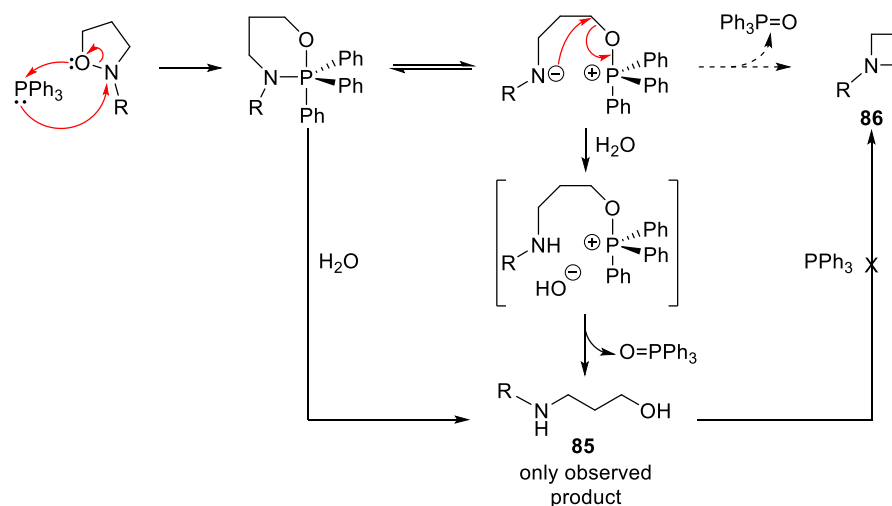
Previously in the Denton group, a deoxygenative ring contraction of isoxazolidines to azetidines has been discovered.²⁶¹ Although the ring contraction of isoxazolidines has been reported in the literature,^{262–264} at present to the best of our knowledge, there is no direct method currently known for the ring contraction of isoxazolidines into azetidines. The primary isoxazolidine of interest in the investigations was obtained *via* a three-step synthesis in which nitrobenzene underwent a partial reduction followed by condensation with benzaldehyde to form nitrone **83** (Scheme 37). The (3+2) dipolar cycloaddition between nitrone **83** and styrene gave the isoxazolidine **84** in very good yield and diastereoselectivity.²⁶⁵

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Scheme 37. Three-step synthesis of the test isoxazolidine substrate **84** from nitrobenzene.

Originally it was proposed that the ring contraction of **84** could be conducted using a phosphine. However, the first attempts at the ring contraction were unsuccessful, with only the starting material being returned. No change was observed until the isoxazolidine and PPh_3 were heated at 150 °C in TCE, when the corresponding ring-opened amino alcohol **85** was formed with no further reaction to azetidine **86** occurring (Scheme 38). Regrettably, an independently synthesised sample of amino alcohol **85** was resistant to cyclodehydration to azetidine **86**. Exchanging PPh_3 for a dioxyphosphorane compound, which are known to facilitate the cyclodehydration of amino alcohols, failed to give the desired azetidine products.²⁶⁶ Because of these problems, further investigation into the application of phosphorus for this transformation was ceased.

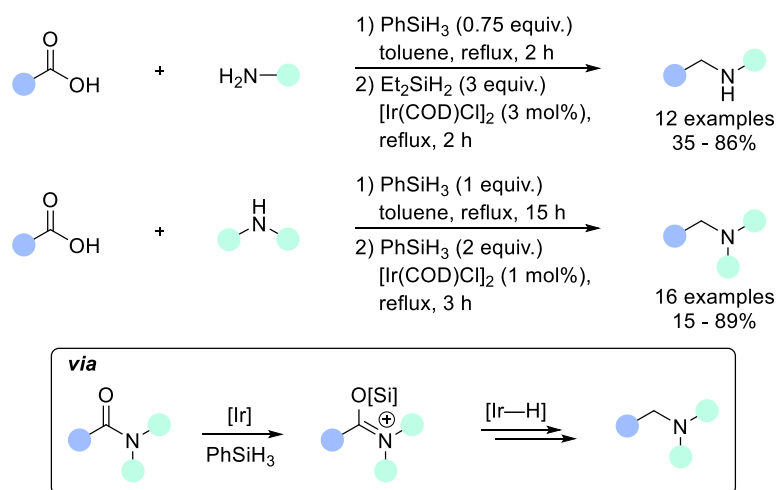


Scheme 38. Mechanistic reasoning for the phosphorus-mediated ring contraction of isoxazolidines to azetidines.

Further inspiration for the means to accomplish the deoxygenative ring contraction of isoxazolidines was derived from the conditions employed in a novel reductive amination procedure (developed in the Denton group) that uses phenylsilane and an $[\text{Ir}(\text{COD})\text{Cl}]_2$ catalyst (Scheme 39).²⁶⁷ Initially, a direct amidation reaction between a range of carboxylic acids and

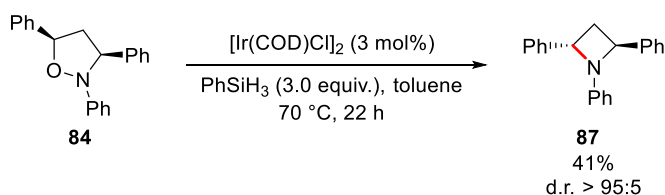
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primary as well as secondary amines using phenylsilane affords the secondary and tertiary amide products respectively. With the subsequent addition of more phenylsilane (or diethylsilane in the case of the secondary amides – as used in an amide reduction described by Brookhart and co-workers²⁶⁸) and the iridium catalyst, the amides were reduced to the amine products. The reaction was shown to be both structurally and functional group tolerant to a range of carboxylic acids and amines, allowing the *N*-alkylated amine products to be obtained in generally good to excellent yields.



Scheme 39. Denton's iridium-catalysed reductive *N*-alkylation of amines using carboxylic acids.²⁶⁷

Critically, it was proposed that the reduction phase of this reaction commenced with the activation of the Lewis-basic amide through *O*-silylation from a metal complex of the type $R_3Si-[Ir]-H$, derived from the oxidative addition of a Si-H bond of a silane species to the iridium catalyst. A reduction of the activated amide by an Ir-H species (as proposed by Brookhart and co-workers²⁶⁸) can then follow. This reaction has been further developed in the group allowing for a much cheaper $Zn(OAc)_2$ catalyst to be used in place of iridium.²⁶⁹



Scheme 40. Reductive ring contraction of isoxazolidine **84** to azetidine **87** previously established in the group.²⁶¹

Using the deoxygenative conditions of this iridium-catalysed amide reduction, the initial attempt at the ring contraction of isoxazolidine **84** yielded a promising result, showing that a contraction to the desired azetidine product **87** occurred in 12% yield. Spawning from this success, brief reaction optimisation studies were carried out that tested the effects of temperature, reaction time, concentration, and quantities of catalyst and silane. However, the best conditions (Scheme 40) only produced the desired azetidine **87** in 41% isolated yield. The reaction proceeded with an inversion of stereochemistry, with the *cis*-isoxazolidine giving the *trans*-azetidine product. Owing to the C₂ axis of symmetry in the *trans*-diastereoisomer, the two protons of the methylene bridge of the azetidine product are equivalent. Conversely, the lack of this symmetry in the *cis*-diastereomer makes the two methylene protons inequivalent. Fortunately, this distinction was easily observed by ¹H NMR spectroscopy allowing the major product to be assigned as the *trans*-diastereomer.²⁶¹ The mechanism of this transformation was tentatively proposed to involve a ring opening/ ring closure sequence going *via* the corresponding amino alcohol intermediate which undergoes the observed inversion of configuration.

Additionally, the (3+2) cycloaddition and subsequent ring contraction has successfully been streamlined into a one-pot procedure giving azetidine **87** in 17% over 2 steps. This shows its great potential utility as a general cycloaddition-deoxygenative ring contraction process. In an attempt to further develop this cycloaddition-deoxygenative ring contraction strategy, we wished to apply this methodology to other systems that could be constructed in this way.

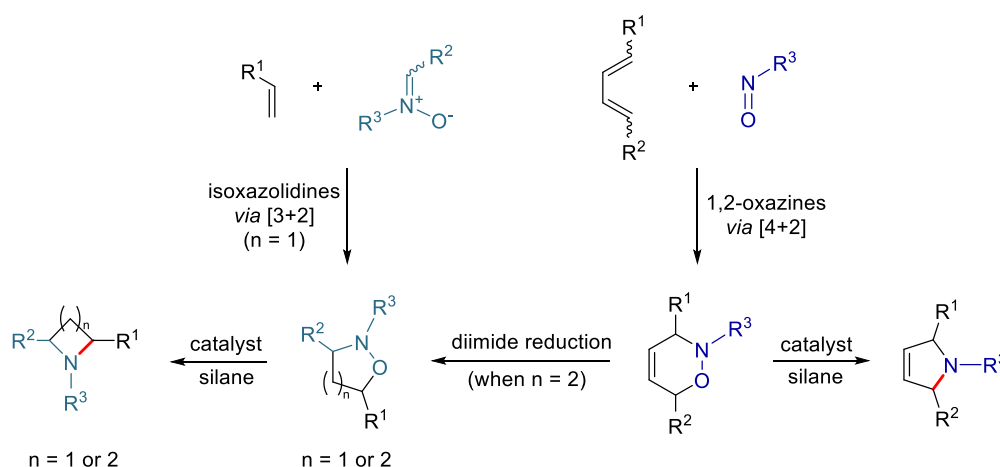
1.7. Project Aims

As part of our previous research efforts directed towards the silane-mediated reductive ring contraction of isoxazolidines to azetidines, we sought to apply this methodology to other N-O containing heterocycles. Based on the above (Section 1.5), 3,6-dihydro-2*H*-1,2-oxazines represent a promising precursor to both 3-pyrrolines and pyrrolidines if a way to extrude oxygen and facilitate ring closure is found. To the best of our knowledge, no direct transformation of 1,2-oxazines to 3-pyrrolines has been documented so far. Thus, we discuss our investigations of the reductive ring contraction of 1,2-oxazines, which can be easily accessed *via* the nitroso Diels-

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Alder reaction (Scheme 41). Consequently, this represents another instance of where a general cycloaddition-deoxygenative ring contraction process could be developed.

The ability to access the functionalised N-O containing heterocycles through only a few operational simple steps is a key advantage for our developed methodology. Pairing the deoxygenative ring contraction with the short synthesis sequences of the starting nitroso Diels-Alder cycloadducts provides a powerful tool for the convergent construction of functionalised 3-pyrroline and pyrrolidine cores in just a few steps. This principle is one of the key concepts in the design and development of this project.



Scheme 41. Catalytic reductive ring contraction of N-O containing heterocycles using silanes to form the contracted nitrogen heterocycles.

Improvements to the mediocre yields obtained in the ring contraction of isoxazolidines were highly desirable; hence, further reaction optimisation for the ring contraction process was investigated. Firstly, we wished to optimise the deoxygenative ring contraction for the synthesis of 3-pyrroline and pyrrolidine heterocycles by conducting a detailed screen of reaction conditions. The conditions investigated were based on known metal-catalysed methods for carbonyl reductions, hydrosilylation, Si-H bond activation, catalytic hydrogenation and many more, which employ silanes as terminal reductants. The expectation was that these systems may have effectively facilitated the reductive ring contraction of 1,2-oxazines to 3-pyrroline and pyrrolidine products.

Following on from this, we wished to examine the scope of this reaction, testing a variety of substituted 1,2-oxazines and 1,2-oxazinanes to give the corresponding ring contracted

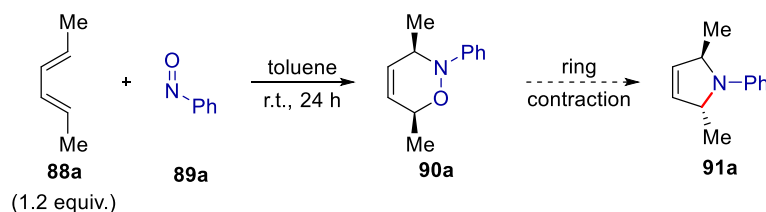
Introduction

heterocycles. With the understanding gained from the scope development, we hoped to demonstrate the utility and versatility of our reaction manifold in the synthesis of one or more targets, whether they be active pharmaceuticals or natural products. Finally, in order to make future developments to the reaction, we wished to deepen our understanding of a possible mechanism for the transformation.

2. Results and Discussion

2.1. Optimisation of the Deoxygenative Ring Contraction

Our investigation commenced with the optimisation of the deoxygenative ring contraction of 1,2-oxazines **90** to 3-pyrrolines **91**. Ideally, for the optimisation study, the model 1,2-oxazine substrate needed to be easy to synthesise on a moderate scale and structurally simple so as to limit the influence of any steric or electronic factors during the ring contraction reaction. Consequently, 1,2-oxazine **90a** was identified as a suitable target due to its simple structure and the practicality and ease of its synthesis and purification. **90a** could be made on a large scale from the commercially available starting materials *trans, trans*-2,4-hexadiene **88a** and nitrosobenzene **89a** (Scheme 42).²⁷⁰

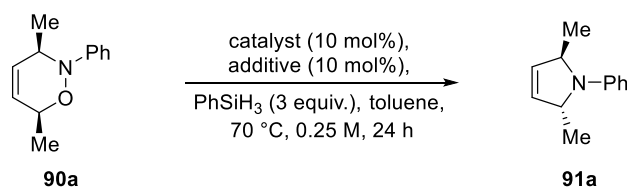


Scheme 42. Synthesis of model 1,2-oxazine substrate **90a** via the nitroso Diels-Alder reaction of 2,4-hexadiene **88a** and nitrosobenzene **89a**.

2.1.1. Catalyst Optimisation

All of the optimisation reactions discussed below were conducted on a 0.2 mmol scale with respect to 1,2-oxazine **90a** and the yields were determined by ¹H NMR spectroscopy using methylsulfonylmethane (MSM) as the internal standard. This compound was chosen because its single ¹H NMR signal appears in a predominantly vacant region of the ¹H NMR spectra (δ_{H} 3.00 ppm. in CDCl₃) of the reductive ring contraction crude reaction mixtures.

Initial screening focused on different catalysts, as this was anticipated to most notably influence the yield of the reaction. Given that the successful conditions employed for the deoxygenative ring contraction of isoxazolidine **84** were derived from those used to reduce amides,^{267,268} choosing other catalytic systems known to reduce amides in combination with a silane seemed to be a sensible starting point (Table 1).



Entry	Catalyst	Additive	90a Yield/ % ^a	91a Yield/ % ^a
1	[Ir(COD)Cl] ₂	-	0	36
2	NiCl ₂ •dme	-	91	0
3	Ni(OAc) ₂ •4H ₂ O	-	59	0
4	Cu(acac) ₂	BINAP	92	0
5	Cu(OTf) ₂	ⁱ Pr-PYBOX	15	0
6	B(C ₆ F ₅) ₃	-	0	0
7	Co(acac) ₂	DPEPhos	0	0
8	Fe ₃ (CO) ₁₂	-	0	4
9	[Ir(COE) ₂ Cl] ₂	-	0	45
10	InBr ₃	-	64	0
11	(PPh ₃) ₂ ReOCl ₂	-	50	0

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 1. Catalyst optimisation for the deoxygenative ring contraction of 90a. These catalysts are known in the literature to catalyse the reduction of amides and esters in conjunction with a silane.

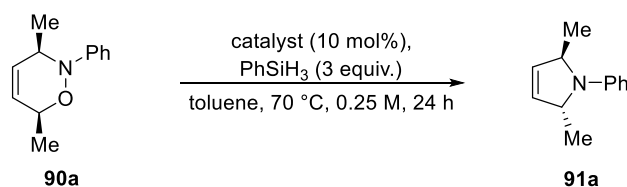
Frequently, the literature reports that catalysts used in similar transformations are only effective with a specific silane; others resulting in no reaction.²⁷¹ Consequently, the vast majority of catalysts were tested with five different silanes: PhSiH₃, Et₃SiH, Et₂SiH₂, (EtO)₃SiH and TMDS in order to find the optimal combination of catalyst and silane. Unfortunately, in every tested case all silanes, with the exception of PhSiH₃, lead to either no reaction or a complex mixture of products containing none of the desired 3-pyrroline **91a**. Consequently, the results in which silanes other than PhSiH₃ were used have been omitted from this table for brevity. A complete version of this data can be seen in the Experimental section (Section 3.4, Supplement 1).

Optimisation of the reductive ring contraction of 1,2-oxazine **90a** began with the [Ir(COD)Cl]₂ conditions previously established for isoxazolidine **84**. This preliminary result would serve as a benchmark for future improvements in the yield. Pleasingly, the combination of [Ir(COD)Cl]₂ and PhSiH₃ (Table 1, Entry 1) gave the desired 3-pyrroline **91a** in 36% yield after 24 hours.

Ideally, we had hoped that the reaction could be catalysed by simple commercially available transition metal salts, possibly with the addition of a ligand. $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ²⁷² and $\text{NiCl}_2 \cdot \text{dme}$ ²⁷³ are both recognised in the literature to catalyse the reduction of secondary and tertiary amides in concert with PMHS and PhSiH_3 , respectively. These precatalysts are reported to give the corresponding amine products in good yields under similar reaction conditions to those initially found to facilitate our reductive ring contraction. Sadly, in the case of $\text{NiCl}_2 \cdot \text{dme}$ no significant reaction occurred (Entry 2). Likewise, when using $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, there was incomplete consumption of **90a** with none of the 3-pyrroline product present (Entry 3). Similar observations were made with common Cu(II) amide reduction catalysts; $\text{Cu}(\text{acac})_2$ /BINAP²⁷⁴ failed to react whilst $\text{Cu}(\text{OTf})_2$ /ⁱPr-PYBOX²⁷⁵ gave a complex mixture of products containing 15% unreacted **90a** (Entries 4 and 5). The highly reactive Lewis acid $\text{B}(\text{C}_6\text{F}_5)_3$, known to catalyse a number of transformations including amide hydrosilylations under mild conditions,²⁷⁶ resulted in a complex mixture containing neither the starting 1,2-oxazine **90a** nor the 3-pyrroline product **91a** (Entry 6). $\text{Co}(\text{acac})_2$ /DPEPhos²⁷⁷ and $\text{Fe}_3(\text{CO})_{12}$,^{278,279} which are capable of performing the more challenging reduction of primary amides, both generated complex mixtures of products (Entries 7 and 8). The first notable improvement in yield was seen with $[\text{Ir}(\text{COE})_2\text{Cl}]_2$ (used by Brookhart and co-workers for the reduction of secondary amides, COE: cyclooctene),²⁶⁸ producing **91a** in 45% yield (Entry 9). The silane/ InBr_3 -mediated ester reduction²⁸⁰ and $(\text{PPh}_3)_2\text{ReOCl}_3$ -catalysed nitro reduction²⁸¹ conditions reported in the literature only induced a partial reaction of the 1,2-oxazine after 24 hours (Entries 10 and 11, respectively).

A number of the catalysts discussed above resulted in limited or no conversion of the starting material, therefore, alternative complexes were tried. Table 2 shows the results obtained using different hydrogenation catalysts in the ring contraction of 1,2-oxazine **90a**.

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Entry	Catalyst	90a Yield/ % ^a	91a Yield/ % ^a
1	[(COD)IrP(Cy) ₃ Py]PF ₆	41	26 ^b
2	(PPh ₃) ₃ RhCl	26	1
3	RuCl(<i>p</i> -cymene)[(<i>R,R</i>)-Ts-DPEN]	77	10
4	Cp ^{Ph} Ru(CO) ₂ Cl	69	0

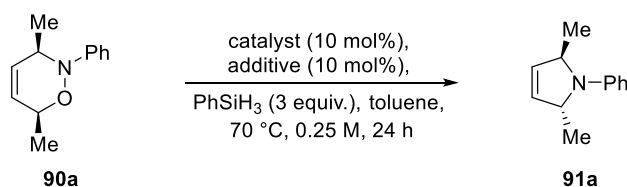
^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 2. Trialling common hydrogenation catalysts as part of the catalyst optimisation for the deoxygenative ring contraction.

Pleasingly, Crabtree's catalyst (Table 2, Entry 1) mediated the desired transformation, despite the incomplete consumption of starting material, and gave the product in 26% yield. Unfortunately, the ¹H NMR spectrum of the crude reaction mixture showed a complex array of products making detailed analysis difficult. In contrast, Wilkinson's hydrogenation catalyst (Entry 2) only gave traces of the desired product in addition to 5% of the reduced starting material. However, there was no clear evidence that the fully saturated pyrrolidine product had formed. Noyori's transfer hydrogenation catalyst (Entry 3) and Bäckvall's alcohol racemisation catalyst (Entry 4) were both somewhat inactive towards the deoxygenative ring contraction returning the starting material in 77% and 69% yields respectively.

The next class of catalysts tested were those reported to efficiently hydrosilylate ketones, aldehydes, imines and alkenes (Table 3). Given that Noyori's transfer hydrogenation catalyst (Table 2, Entry 3) and dimeric iridium complexes (Table 1, Entries 1 and 9) both appeared to form the desired 3-pyrroline product **91a**, the dimeric ruthenium catalyst [Ru(*p*-cymene)Cl₂]₂, which is known to facilitate the hydrosilylation of aldehydes, was a logical next step.²⁸²

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Entry	Catalyst	Additive	90a Yield/ % ^a	91a Yield/ % ^a
1	[Ru(<i>p</i> -cymene)Cl ₂] ₂	-	10	28
2	CuCl	DMTB-SEGPHOS	83	0
3	(AcO) ₂ Rh(PheBox)(OH ₂)	-	21	3
4 ^{b,c}	[(SDmp)RuP(<i>p</i> -FC ₆ H ₄) ₃]Cl	Na[B(C ₆ F ₅) ₄]	0	0
5 ^{b,c}	[(SDmp)RuP(<i>p</i> -FC ₆ H ₄) ₃]Cl	Na[B(C ₆ F ₅) ₄]/ NaOMe	93	0

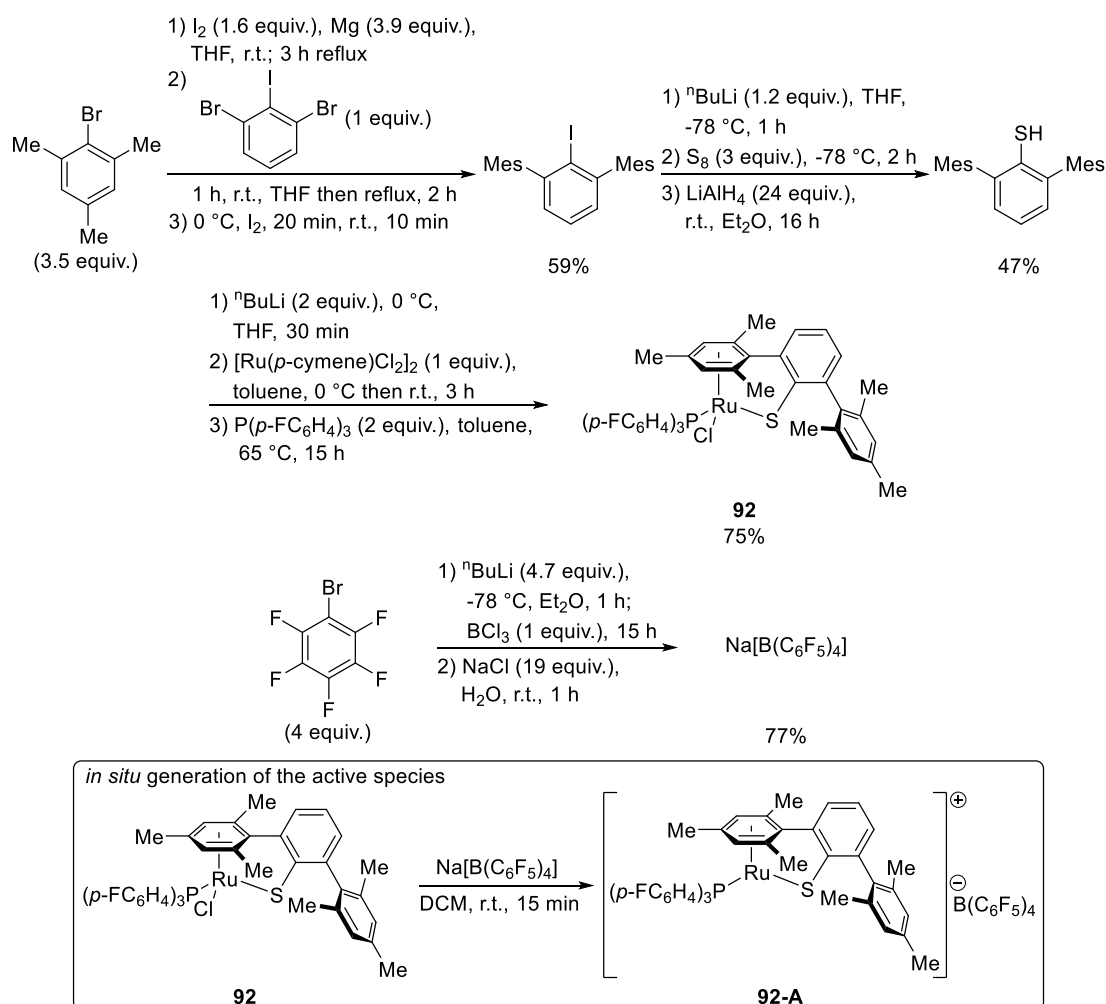
^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard. ^bReaction performed in DCM at 40 °C. ^c12 mol% of Na[B(C₆F₅)₄] used.

Table 3. Attempted use of catalysts known for the hydrosilylation of carbonyls, imines and alkenes in the deoxygenative ring contraction reaction.

Sadly, although the majority of 1,2-oxazine **90a** had reacted, the 3-pyrroline product **91a** was only formed in 28% yield (Table 3, Entry 1). CuCl/ DMTB-SEGPHOS (ketone hydrosilylation)²⁸³ and (AcO)₂Rh(PheBox)(OH₂) (alkene hydrosilylation)²⁸⁴ offered similarly disappointing results (Entries 2 and 3) giving essentially none of the 3-pyrroline **91a**.

Based on the methods of Si-H bond activation described previously (Section 1.2), the Oestreich-Ohki ruthenium-thiolate complex **92** seemed ideally suited for our transformation – being able to act as a source of a silylium ion and a metal hydride. This catalyst was synthesised according to literature procedures outlined in Scheme 43.^{83,86,285,286} The active species **92-A** was successfully formed *in situ* (indicated by a stark red to green colour change) by mixing the ruthenium precatalyst with Na[B(C₆F₅)₄] in degassed DCM.

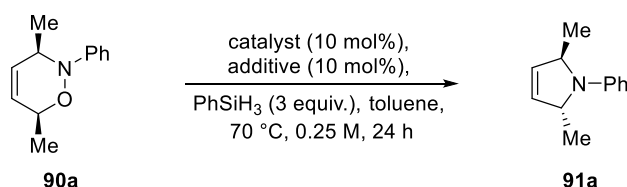
Results and Discussion



Scheme 43. Synthesis route and in-situ activation of the Oestreich-Ohki catalyst.

Disappointingly, this system generated an extremely complex mixture of products upon reaction with **90a** making it unclear as to whether remaining starting material or the 3-pyrroline product were present (Entry 4). Furthermore, the addition of NaOMe (Entry 5), which is reported to somewhat curb the reactivity of the active species, sadly resulted in no reaction occurring. However, in this case, catalyst deactivation could also have resulted from traces of water or atmospheric O_2 being present in the system.

At this point, with the exception of $[Ru(p\text{-cymene})Cl_2]_2$ (Table 3, Entry 1), only iridium-based catalysts seemed to reliably generate the desired 3-pyrroline product **91a**. However, due to the observed lower yield of the desired 3-pyrroline and 10% of **90a** remaining after 24 hours, further investigations into ruthenium-based catalysts were ceased in favour of the more successful iridium-based systems. To test the efficacy of this transition metal in the deoxygenative ring contraction a variety of iridium-based systems were explored (Table 4).



Entry	Catalyst	Additive	90a Yield/ % ^a	91a Yield/ % ^a
Table 1 Entry 1	[Ir(COD)Cl] ₂	-	0	36
Table 1 Entry 9	[Ir(COE) ₂ Cl] ₂	-	0	45
1	IrCl ₃	-	67	8
2	IrCl ₃	PPh ₃	87	0
3	IrCl ₃	BINAP	92	0
4	IrCl ₃	PYPHOS	91	0
5	IrCl ₃	PYBOX	97	<1
6	IrCl ₃	TMEDA	93	0
7	[Ir(COD)OMe] ₂	-	0	15
8	[(ppy) ₂ IrCl] ₂	-	0	32
9	[Cp*Ir] ₂	-	0	35
10	[Cp*IrCl ₂] ₂	-	0	48
11 ^b	[Cp*IrCl ₂] ₂	TMSOTf	0	0
12 ^b	[Ir(DBCOT)Cl] ₂	-	0	47

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard. ^bReaction performed in DCM at 40 °C with 5 equivalents of PhSiH₃.

Table 4. Iridium-based catalysts tested in the deoxygenative ring contraction reaction.

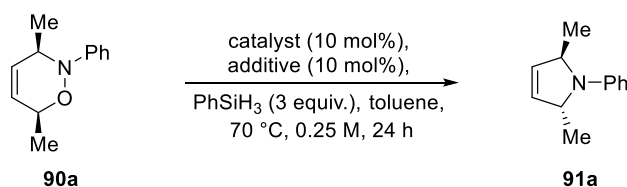
Our hypothesis about iridium being active with respect to our transformation was validated when IrCl₃, with no additional ligand, resulted in 33% consumption of **90a** giving 3-pyrroline **91a** in 8% yield (Table 4, Entry 1). Unusually, the addition of a ligand resulted in no reaction, clearly negating any catalytic activity exhibited by the IrCl₃ (Entries 2-6). Thankfully, returning to dimeric iridium catalysts proved to be more fruitful, leading to complete consumption of 1,2-oxazine **90a** in all tested cases. [Ir(COD)OMe]₂ may only have given the 3-pyrroline product in 15% yield (Entry 7), but [(ppy)₂IrCl]₂ (a precursor to many photocatalysts, ppy: 2-phenylpyridyl) and [Cp*Ir]₂ were as effective as [Ir(COD)Cl]₂ in the deoxygenative ring contraction of **90a** (Entries 8 and 9). The analogous dimers [Cp*IrCl₂]₂ and [Ir(DBCOT)Cl]₂ (DBCOT: dibenzo[*a,e*]cyclooctene) each gave a substantial increase in yield over [Ir(COD)Cl]₂, producing the 3-pyrroline product

91a in 48% and 47% yields, respectively (Entries 10 and 12). The use of TMSOTf as an additive was investigated, in the expectation that it might activate the 1,2-oxazine oxygen towards ring opening processes with $[\text{Cp}^*\text{IrCl}_2]_2$ and PhSiH_3 . Unfortunately, however, the addition of TMSOTf failed to promote the desired transformation, instead leading to a complex mixture of products (Entry 11).

Using these iridium-based catalysts, despite seeing complete consumption of the starting 1,2-oxazine, the 3-pyrroline product was generally only obtained in 45-50% yields. The ^1H NMR spectra of the reactions showed generally less complex mixtures with fewer apparent side products when using these catalysts. The possible identities of some of these side products are discussed later (Section 2.3). However, at this time the missing mass balance was suspected to be largely due to the formation of the reductively ring opened amino alcohol which, after activation of the alcohol under the reaction conditions (see Section 2.3 for details), has the potential to oligomerise. Polymeric species of this nature would then be hard to identify by ^1H NMR analysis of the crude reaction mixtures.

To determine whether other Group 9 metals would exhibit similar catalytic behaviour as the above iridium complexes, cobalt and rhodium-based catalytic systems were examined (Table 5). As with IrCl_3 , RhCl_3 catalysed the reaction without the addition of a ligand (Entry 1) but to a greater extent, and gave 3-pyrroline **91a** in 20% yield. However, as seen previously the introduction of a ligand suppressed this catalytic activity resulting in the negligible consumption of 1,2-oxazine **90a** (Entries 2 and 3). In contrast, the rhodium analogue of $[\text{Ir}(\text{COD})\text{Cl}]_2$, $[\text{Rh}(\text{COD})\text{Cl}]_2$, did not result in complete consumption of **90a**. Furthermore, using this metal complex produced diminished yields of 3-pyrroline **91a** (Entry 4) relative to $[\text{Ir}(\text{COD})\text{Cl}]_2$. The tetraphenyl porphyrin (TPP) complex of Co(II) ($\text{Co}[\text{TPP}]$) yielded an ambiguous result due to substantial line broadening of the ^1H NMR spectrum of the crude reaction mixture. However, despite the lack of quantitative analysis, it was clear that the desired product was not a significant component of the reaction mixture (Entry 5). A similar result was also observed with the dimeric complex $[\text{CpFe}(\text{CO})_2]_2$ (Entry 8).

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Entry	Catalyst	Additive	90a Yield/ % ^a	91a Yield/ % ^a
1	RhCl ₃	-	0	20
2	RhCl ₃	PYBOX	88	0
3	RhCl ₃	BiOx	93	0
4	[Rh(COD)Cl] ₂	-	23	21
5 ^b	Co[TPP]	-	- ^b	- ^b
6	Pd(PPh ₃) ₄	-	96	0
7	[Ru(bpy) ₃ Cl ₂]•6H ₂ O	-	96	0
8 ^b	[CpFe(CO) ₂] ₂	-	- ^b	- ^b
9 ^{c,d,e}	[Cp*IrCl ₂] ₂	TBAF	53	0

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard. ^bBroadening of the ¹H NMR spectra made quantitative NMR yield determination impossible. ^cReaction performed in DCM at 40 °C. ^dPhMe₂SiH was used in place of PhSiH₃. ^e1 equiv of TBAF used.

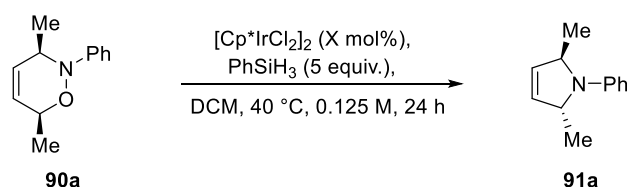
Table 5. Use of other transition metal catalysts in the deoxygenative ring contraction reaction.

No reaction of 1,2-oxazine **90a** was observed when either Pd(PPh₃)₄ or the common photoredox catalyst, [Ru(bpy)₃]Cl₂•6H₂O (without visible light irradiation), were employed as precatalysts (Entries 6 and 7). Finally, a stoichiometric quantity of TBAF was used in the presence of the most successful catalyst, [Cp*IrCl₂]₂ (Entry 9), in an attempt to activate the PhSiH₃ by forming a five-coordinate -ate complex adduct thus increasing the hydride donating ability of the hydrogens on silicon as described in Section 1.2. Unfortunately, this system was inferior to those seen previously (Table 4), offering none of the 3-pyrroline product.

After an exhaustive screen of different catalytic systems, that drew inspiration from a range of sources and transformations, [Cp*IrCl₂]₂ was chosen as the catalyst for the deoxygenative ring contraction of 1,2-oxazines due to the higher yields it offered and its commercial availability.

An investigation into the optimum amount of catalyst required for the deoxygenative ring contraction followed (Table 6). Despite observing formation of the desired product, less than 5 mol% of [Cp*IrCl₂]₂ did not lead to the full consumption of the starting material after 24 hours

(Entries 1-3). Table 6, Entry 4 shows that a minimum quantity of 5 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$ is required to promote the full consumption of 1,2-oxazine **90a** in the ring contraction in a reasonable time. Having 10 mol% of the catalyst (Entry 6) over 8 mol% (Entry 5) did not provide any enhancement to the yield but curiously, a further increase to 20 mol% (Entry 7) resulted in a small drop in the yield of **91a**.



Entry	Catalyst amount/ mol%	90a Yield/ % ^a	91a Yield/% ^a
1	0.5	71	15
2	1	57	14
3	2	36	28
4	5	0	49
5	8	0	55
6	10	0	55
7	20	0	46

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 6. Optimisation of the ideal quantity of the $[\text{Cp}^*\text{IrCl}_2]_2$ catalyst for the deoxygenative ring contraction.

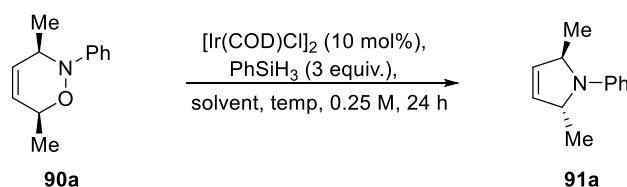
2.1.2. Solvent Optimisation

For the optimisation of the solvent $[\text{Ir}(\text{COD})\text{Cl}]_2$ was chosen as the catalyst for the transformation due to its substantially lower cost and greater availability relative to $[\text{Cp}^*\text{IrCl}_2]_2$ ($[\text{Ir}(\text{COD})\text{Cl}]_2$: £106/ mmol vs. $[\text{Cp}^*\text{IrCl}_2]_2$: £459/ mmol, Sigma Aldrich 2022). The results of the solvent screen were quite promising, showing that the reaction is compatible with a wide range of solvents including halogenated, non-halogenated, non-polar and aromatic solvents (Table 7). This makes the method applicable to a range of scenarios where the use of a specific solvent is necessary.

As seen previously the $[\text{Ir}(\text{COD})\text{Cl}]_2$ -catalysed deoxygenative ring contraction of 1,2-oxazine **90a** in toluene furnished the 3-pyrroline product **91a** in 36% yield (Table 7, Entry 1). Using the common fluorinated substitute to toluene, trifluorotoluene, resulted in the complete

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consumption of 1,2-oxazine **90a** providing a slight improvement to the yield of **91a** (Entry 2). This improvement was similarly observed in the screening of an assortment of other halogenated aromatic solvents (Entries 3-7). The less toxic fluorobenzene did not provide any further improvement (Entry 3) but switching to chlorobenzene gave 3-pyrroline **91a** in 49% yield (Entry 4). More substituted aromatic halogenated solvents (Entries 5 and 6) lowered the yields of the product with bromopentafluorobenzene (Entry 7) even returning traces of unreacted 1,2-oxazine **90a**.



Entry	Solvent	Temperature/ °C	90a Yield/ % ^a	91a Yield/ % ^a
1	toluene	70	0	36
2 ^b	trifluorotoluene	70	0	42
3	fluorobenzene	70	0	41
4	chlorobenzene	70	0	49
5 ^b	1,2-dichlorobenzene	70	1	47
6	1,3,5-trichlorobenzene	70	0	39
7 ^b	bromopentafluorobenzene	70	3	40
8	anisole	70	0	46
9 ^b	diphenyl ether	70	0	47
10	THF	70	18	37
11	cyclosiloxane-D4	70	35	24
12	MeCN	70	91	0
13 ^b	TFE	70	0	0
14	DCM	40	0	49
15	DCE	70	0	45
16	CHCl_3	62	0	47
17	-	70	0	23

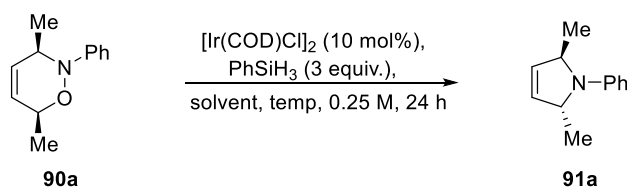
^aYields determined by ^1H NMR spectroscopy using MSM as the internal standard. ^bReaction stirred at room temperature for 16 h and then at 70 °C for 10 h.

Table 7. Optimisation of the solvent for the deoxygenative ring contraction.

Anisole is a popular alternative solvent to toluene, due to its high boiling point, similar polarity and reduced health and environmental impact. Pleasingly, anisole out-performed toluene in the deoxygenative ring contraction of **90a**, giving **91a** in 46% yield. Likewise, a similar success was seen with a comparable aromatic ether (Entry 9) however, the aliphatic ether THF (Entry 10) did not offer complete consumption of the starting material. Despite generating **91a** in 24% yield, the cyclic siloxane octamethylcyclotetrasiloxane (D4) was inefficient at promoting the deoxygenative ring contraction, returning 1,2-oxazine **90a** in 35% yield after 24 hours (Entry 11). The poor consumption of the starting material was attributed to the low solubility of $[\text{Ir}(\text{COD})\text{Cl}]_2$ in this solvent. The polar solvents MeCN and trifluoroethanol (TFE) were both inferior reaction media (Entries 12 and 13). When conducted in MeCN no significant reaction of 1,2-oxazine **90a** was observed, likely due to the poisoning or quenching of the active catalytic species by the solvent. However, in the case of TFE a complex mixture was obtained in which none of the starting 1,2-oxazine **90a** or ring contracted product **91a** were present.

The most consistent solvents for the deoxygenative ring contraction were aliphatic chlorinated solvents (Entries 14-16). Of these, DCM (Entry 14) gave the highest yield of 3-pyrroline **91a** but the higher boiling variants, DCE and CHCl_3 , worked with comparable efficiency that is within the error of the calculated ^1H NMR yields. Encouragingly, the reaction can be conducted in the absence of a solvent (Entry 17). Understandably, the yield was much lower, as the higher concentration of the reagents in the reaction mixture could be expected to promote unwanted side reactions such as the potential polymerisation reaction mentioned above (Section 2.1.1).

After identifying the most appropriate solvents for the ring contraction in this initial solvent screen, the most promising results were retested with $[\text{Cp}^*\text{IrCl}_2]_2$ to confirm the optimal solvent (Table 8). Similar trends to $[\text{Ir}(\text{COD})\text{Cl}]_2$ were observed, with the aromatic halogenated solvents performing marginally better than toluene. Ultimately, DCM was chosen for future deoxygenative ring contraction reactions, thus allowing the reaction to be conducted at a lower temperature without detriment to the conversion of the 1,2-oxazine starting material.

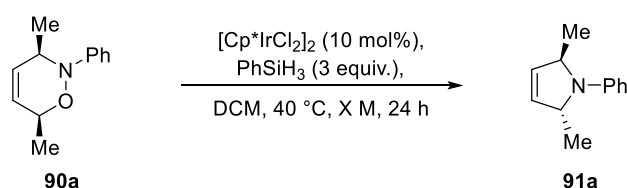


Entry	Solvent	Temperature/ °C	90a Yield/ % ^a	91a Yield/% ^a
1	toluene	70	0	48
2	fluorobenzene	70	0	54
3	chlorobenzene	70	4	51
4	DCM	40	0	56
5	CHCl ₃	60	0	43

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 8. Second solvent screen using [Cp*IrCl₂]₂ as the catalyst.

In addition to the solvent, the concentration of the 1,2-oxazine **90a** in the reaction mixture was expected to have a notable impact on the efficiency of the reaction. Higher concentrations were anticipated to facilitate unwanted polymerisation reactions (see Section 2.3 for details) whereas low concentrations would be detrimental to the rate of reaction. However, this trend is only observed at the extremes.



Entry	Concentration X/ M	90a Yield/ % ^a	91a Yield/ % ^a
1	0.250	0	55
2	0.125	0	56
3	0.0625	0	53
4	0.0250	30	33

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

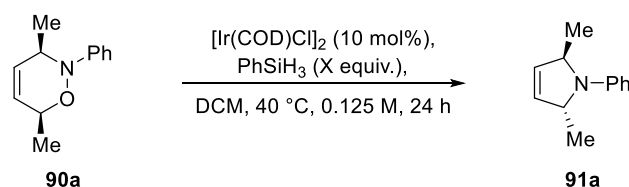
Table 9. Determination of the ideal concentration for the reductive ring contraction.

Very high concentrations (*i.e.* neat; Table 7, Entry 17 *vide supra*) did lead to significant losses of the product whilst very dilute conditions gave incomplete consumption of 1,2-oxazine **90a** (Table 9, Entry 4). In contrast, the intermediate concentrations investigated had an

unappreciable influence on the yield of **91a**. A concentration of 0.125 M with respect to **90a** was selected for future experiments, which represented a good compromise between an acceptable rate of reaction and the possible suppression of polymerisation side reactions. Furthermore, during these investigations into the optimal reaction solvent it was revealed that an inert atmosphere and anhydrous conditions were not required. This was found to be the case when a reaction performed in non-dried Winchester grade solvent under an atmosphere of air gave the same yield as one using Schlenk conditions in which an argon atmosphere and anhydrous conditions were used.

2.1.3. Optimisation of the Silane Reductant

It is often observed in the literature that silane-mediated transformations will only work effectively with a few different silane compounds.^{171,268,287,288} As mentioned above (Section 2.2.1), many of the catalysts screened for the deoxygenative ring contraction were tested in concert with five different silanes (Section 3.4, Supplement 1). From this initial investigation, it was concluded that PhSiH₃ was likely the optimal silane for the transformation. Consequently, improvements to the yield were first sought by varying the number of equivalents of PhSiH₃ used in the reaction (Table 10).



Entry	PhSiH ₃ Equivalents	90a Yield/ % ^a	91a Yield/ % ^a
1	1	41	13
2	2	6	42
3	3	0	47
4	5	0	50
5 ^b	5	0	60
6 ^b	10	0	61

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard. ^b[Cp*IrCl₂]₂ (8 mol%) used.

Table 10. Optimisation of the number of equivalents of the silane reductant.

Each molecule of PhSiH_3 has three silicon-hydrogen bonds and so can provide up to three hydride equivalents in a given reduction process. When the deoxygenative ring contraction was conducted with one molar equivalent of PhSiH_3 (Table 10, Entry 1), a substantial quantity of 1,2-oxazine **90a** remained unreacted (41%) after 24 hours. Increasing the number of equivalents of PhSiH_3 had a profound impact on the yield, with two equivalents consuming the majority of the starting 1,2-oxazine **90a** (Entry 2). Whilst both three and five equivalents of PhSiH_3 drove the reaction to completion, five equivalents provided a marginally higher yield of 3-pyrroline **91a** (Entries 3 and 4). Further increasing the number of equivalents of PhSiH_3 offered no additional benefit (Entry 5 vs. Entry 6), thus five equivalents were used going forward.

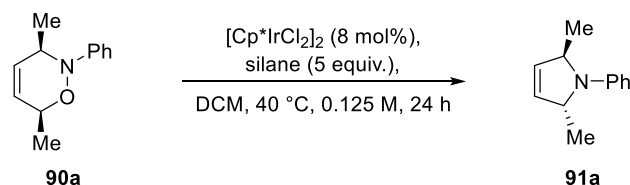
The requirement for a significant excess of silane may arise from a competitive dehydropolymerisation of PhSiH_3 . This would result in a reduced amount of silane available to facilitate the deoxygenative ring contraction, given that polymeric silanes do not promote the desired transformation (Table 11, *vide infra*). Although the $[\text{Cp}^*\text{IrCl}_2]_2$ - or $[\text{Ir}(\text{COD})\text{Cl}]_2$ -catalysed dehydropolymerisation of PhSiH_3 has not been reported in the literature, a number of main-group and transition metal catalysts exist for this transformation.^{289–291}

Having established the benefit of increased silane stoichiometry, the question of silane identity was addressed. A range of different monomeric and polymeric mono-, di- and trihydridic silanes were considered (Table 11). In these reactions, the same number of molar equivalents of silane were used, irrespective of the number of hydride equivalents the silane contained. As previously mentioned, the correct catalyst/ silane combination can be critical to a successful reaction and so the established optimal catalyst, $[\text{Cp}^*\text{IrCl}_2]_2$, was chosen for the screening of the silane.

Monomeric dihydridic silanes (Entry 4) and monomeric monohydridic silanes (Entries 6–10) all failed to promote any significant reaction of 1,2-oxazine **90a** after 24 hours, with the exception of Et_2SiH_2 (Entry 5), which produced a complex mixture of products. The polymeric PhSiH_3 (Entry 2) was synthesised in the group²⁹² according to a literature procedure²⁹³ and has been used successfully in an amidation reaction developed in the group.²⁶⁷ Despite this success however, the polymeric silanes were typically less effective at promoting the deoxygenative ring contraction than the monomeric silanes (Entries 2, 11 and 12), returning large quantities of the unreacted starting material **90a**. Although the exact nature of the catalytically active species is

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unknown, the lack of reactivity observed by these silanes (Entries 2, 4 and 6-12) could be a result of the greater steric demand around the silicon atom. This large steric bulk could inhibit the approach of the silane component to the iridium catalyst, thus preventing its activation. As a result, minimal consumption of the 1,2-oxazine starting material would be observed.



Entry	Silane	90a Yield/ % ^a	91a Yield/ % ^a
1	PhSiH ₃	0	60
2	polymeric PhSiH ₃	86	0
3	ⁿ OctSiH ₃	3	45
4	Ph ₂ SiH ₂	70	0
5 ^b	Et ₂ SiH ₂	0	0
6	Ph ₃ SiH	81	0
7	PhMe ₂ SiH	68	0
8	Et ₃ SiH	65	0
9	(EtO) ₃ SiH	76	2
10	(Me ₃ Si) ₃ SiH	66	0
11	PMHS	73	0
12	TMDS	79	0

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard. ^bReaction performed in toluene at 70 °C with an [Ir(COD)Cl]₂ catalyst

Table 11. Evaluation of different silanes in the deoxygenative ring contraction reaction.

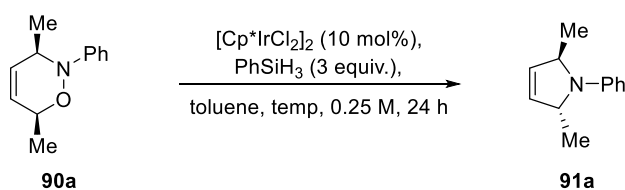
Pleasingly though, the silane component was not just limited to PhSiH₃. The commercially available trihydridic silane ⁿOctSiH₃ (Entry 3) gave 3-pyrroline **91a** as the major product albeit in a slightly lower yield of 45%. Thus, seemingly, the [Cp*IrCl₂]₂-catalysed deoxygenative ring contraction of 1,2-oxazine **90a** is only viable when trihydridic silanes are used. This could be the result of the Si-H bonds in these silanes being more accessible for activation by the metal catalyst as there is reduced steric hindrance around these bonds. Due to the higher yields

obtained, greater accessibility and lower cost of PhSiH₃ relative to ⁿOctSiH₃ (PhSiH₃: £0.31/mmol vs. ⁿOctSiH₃: £1.49/mmol, Fluorochem, 2022), this silane was selected as the optimal choice for the deoxygenative ring contraction.

2.1.4. Further Optimisation of the Reaction Conditions

In addition to the changes described above, other factors were considered. Firstly, slow addition of the reagents to the reaction mixture was investigated. The slow dropwise addition of a solution of 1,2-oxazine **90a** in DCM to a solution of PhSiH₃ and [Cp*IrCl₂]₂ in DCM over 3 hours proved to be detrimental to the yield. After 24 hours, the ring contracted product had only formed in 24% yield with 26% of 1,2-oxazine **90a** remaining unreacted. Regrettably, the reverse case of adding PhSiH₃ dropwise over 2 hours to a solution of 1,2-oxazine **90a** and the catalyst gave a very similar result (29% of 3-pyrroline **91a** and 28% of 1,2-oxazine **90a**) after 24 hours.

The effect of temperature on the deoxygenative ring contraction was next investigated and is depicted in Table 12. Although the deoxygenative ring contraction does occur at room temperature, the reaction is slow since 26% of the 1,2-oxazine starting material remained after 24 hours (Entry 1). Heating the reaction naturally increases the rate of reaction, however, when using temperatures around 110 °C the yield was reduced (Entry 3). This is possibly due to the thermal instability of the 1,2-oxazine and/or 3-pyrroline. Extended reaction times at temperatures of 70 °C and below did not have an appreciable effect on the yield of the product (Entry 2).



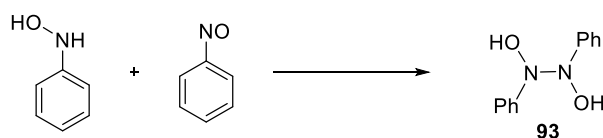
Entry	Temperature/ °C	90a Yield/ % ^a	91a Yield/ % ^a
1	20	26	30
2	70	0	36
3	110	0	30

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 12. Considering the effects of temperature on the reaction.

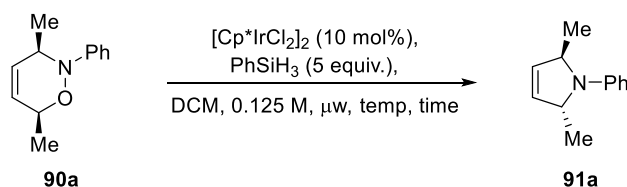
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At elevated temperatures, the efficient fragmentation of 1,2-oxazines *via* a retro nitroso Diels-Alder reaction is possible.²⁹⁴ The resulting nitrosobenzene, could then be reduced to the corresponding hydroxylamine or aniline under the reducing reaction conditions. The nitrosobenzene and *N*-phenylhydroxylamine could then react together to form the dimeric hydroxy-hydrazine **93** (Scheme 44).²⁹⁵ A similar observation was made previously in the group during the optimisation of the ring contraction of isoxazolidine **84** to azetidine **87**, in which a retro (3+2) reaction was observed followed by reduction of the nitrone **83** to *N*-benzylaniline.²⁶¹



Scheme 44. Possible reaction of N-phenylhydroxylamine and nitrosobenzene.

Finally, the deoxygenative ring contraction reaction has been demonstrated to operate under microwave irradiation. When **90a** was heated in the microwave at 70 °C under the optimised conditions for 4 minutes the 3-pyrroline product **91a** was obtained in 56% yield (Table 13, Entry 2). However, the reaction appeared to be more capricious using this methodology, resulting in large variations in yield. When the reaction was heated at 80 °C the lower yield of 3-pyrroline **91a** and 23% remaining 1,2-oxazine **90a** could be explained by the occurrence of a retro nitroso Diels-Alder reaction as discussed above. The retro nitroso Diels-Alder reaction of similar 1,2-oxazines to aromatic nitroso compounds and dienes has been reported when heated in a microwave at 100 °C.²⁹⁴



Entry	Temperature/ °C	Time/ min	90a Yield/ % ^a	91a Yield/ % ^a
1	65	2.5	9	50
2	70	4	0	56
3	80	4	23	36
4	50	6	25	35

^aYields determined by ¹H NMR spectroscopy using MSM as the internal standard.

Table 13. Deoxygenative ring contraction of 1,2-oxazines via microwave irradiation.

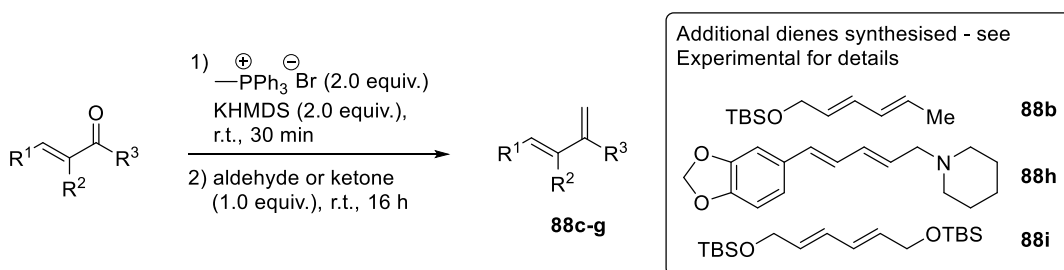
Having thoroughly explored all of the reaction parameters systematically, the reaction conditions for the deoxygenative ring contraction were revised and applied to the synthesis of a number of 3-pyrrolines and pyrrolidines.

2.2. Scope of the Deoxygenative Ring Contraction

2.2.1. Synthesis of 1,2-Oxazine and 1,2-Oxazinane Substrates

With the identification of the most effective reaction conditions to promote the deoxygenative ring contraction, the scope of 1,2-oxazine and 1,2-oxazinane substrates suitable for this methodology was evaluated. Due to its operational simplicity, the nitroso Diels-Alder reaction was selected as the primary synthesis method for the generation of the 1,2-oxazine substrates, requiring only a nitroso compound and a diene. In the nitroso Diels-Alder reaction between a 1,4-disubstituted diene and a nitroso compound the stereochemistry of the two carbon-carbon double bonds in the diene component is translated into the stereochemistry of the 1,2-oxazine products *i.e.* a *trans, trans* diene would give a 3,6-*cis* substituted 1,2-oxazine whereas a *cis, trans* diene would result in a 3,6-*trans* substituted 1,2-oxazine.

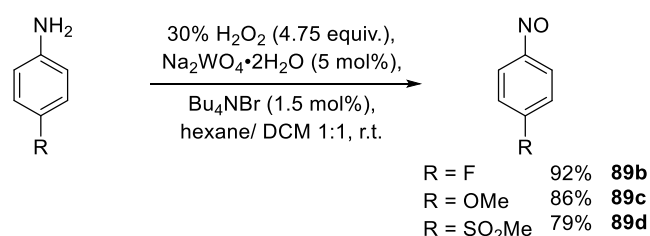
The majority of the diene components for these reactions were obtained from commercial sources and used as supplied. However, the commercially available dienes containing alcohol functionalities were protected with a bulky silicon protecting group to avoid unwanted deoxygenation reactions during the ring contraction step. Additional more complex dienes were synthesised from the corresponding unsaturated aldehydes or ketones through standard Wittig reaction conditions (Scheme 45).



Scheme 45. Left: Synthesis of diene components **88** via a Wittig reaction of unsaturated aldehydes ($R^3 = \text{H}$) or ketones. Right: Dienes synthesised by alternative methods (see Experimental for details).

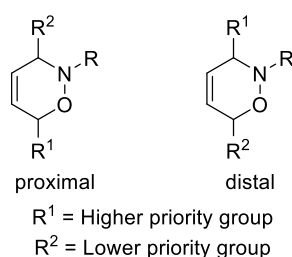
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On the other hand, only a handful of nitroso compounds are commercially available, with these being limited to simple aryl nitroso compounds such as nitrosobenzene **89a**. Consequently, in order to introduce more diversity into the products, additional aryl nitroso compounds **89** were smoothly synthesised *via* a known Na_2WO_4 -catalysed H_2O_2 oxidation of the requisite aniline (Scheme 46).²⁹⁶



Scheme 46. Synthesis of nitroso compounds via oxidation of the corresponding aniline.

The nitroso Diels-Alder reaction between dienes **88** and aryl nitroso compounds **89** was used to generate a range of 1,2-oxazine substrates **90** possessing differing substitution patterns and functionality around the 1,2-oxazine ring. In cases where unsymmetrical dienes were used, a mixture of regioisomeric (proximal and distal) 1,2-oxazine products could be obtained; the identity of the major regioisomer being determined from analysis of 2D NOESY ^1H NMR spectra. The proximal isomer has the highest priority substituent (by Cahn-Ingold-Prelog priority) nearest to the oxygen atom of the 1,2-oxazine product whereas the distal isomer has the highest priority substituent closest to the nitrogen atom in the cycloadduct (Scheme 47).

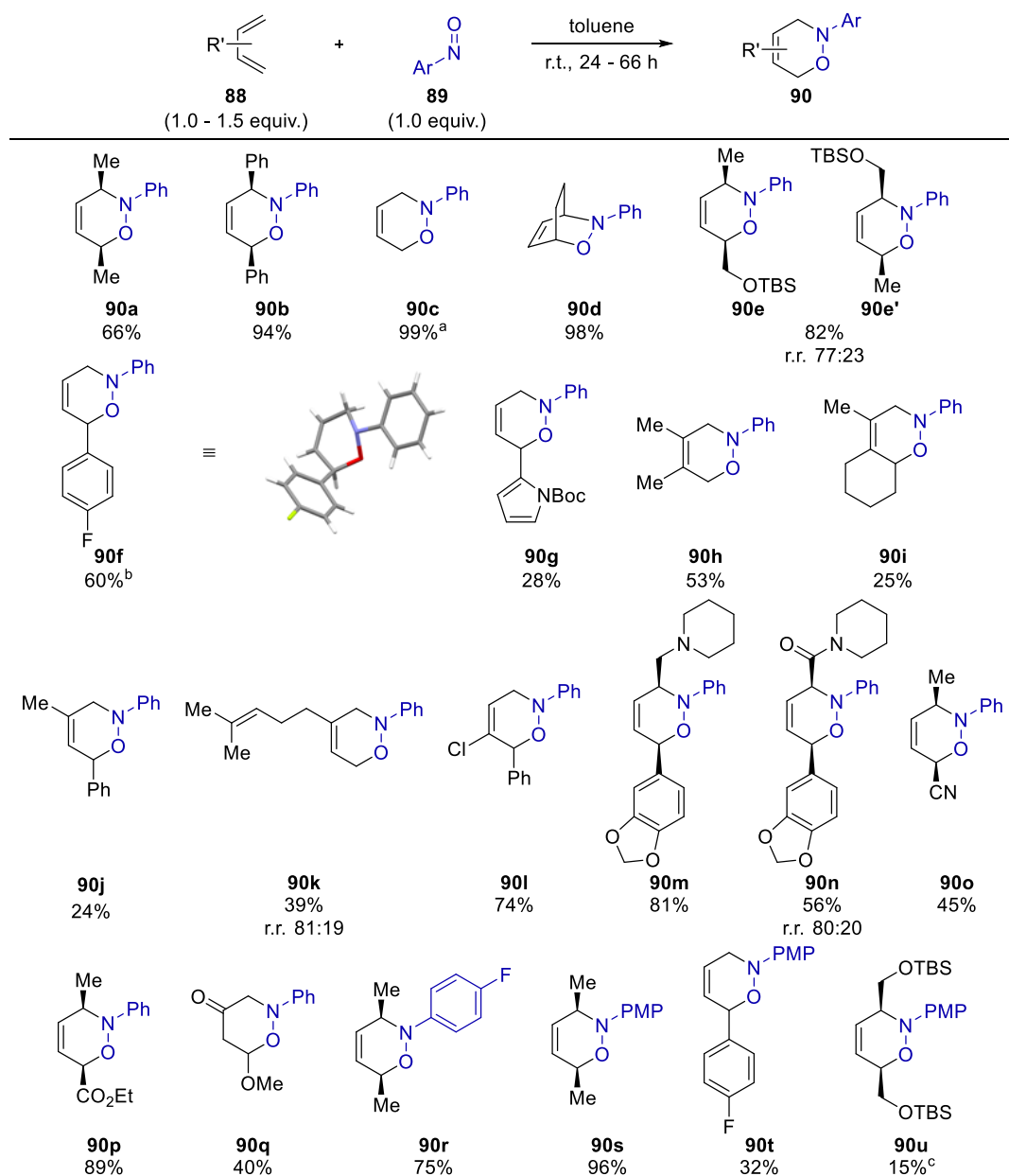


Scheme 47. Proximal and distal isomers of 1,2-oxazines.

Following the original method as described by Wichterle in his original disclosure of the nitroso Diels-Alder reaction, a range of 1,2-oxazines **90** were synthesised (Scheme 48). We began with the synthesis of the model substrate **90a** used for the optimisation of the ring contraction reaction above, which was obtained in a respectable yield. Pleasingly, the closely related 3,6-*cis*

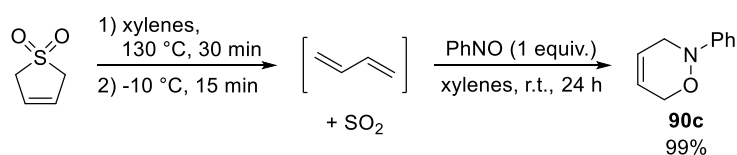
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substrate **90b**, derived from *trans, trans*-1,4-diphenylbutadiene and nitrosobenzene was obtained in excellent yield. The synthesis of unsubstituted substrate **90c** required the use of 1,3-butadiene in the nitroso Diels-Alder procedure. However, the low boiling point of 1,3-butadiene (-4 °C) and the high toxicity of this diene makes its use in conventional glassware challenging. Fortunately however, 1,3-butadiene can be rapidly generated *in situ* in a sealed vessel by heating sulfolene at temperatures above 120 °C.²⁹⁷



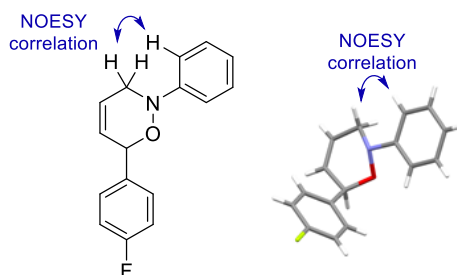
Scheme 48. Synthesis of 1,2-oxazine substrates **90** via the nitroso Diels-Alder reaction of a diene **88** and nitroso compound **89**. ^aReaction conducted according to Scheme 49. ^b1.0 equiv. of diene **88c** and 1.05 equiv. of nitrosobenzene used. ^cReaction stirred at room temperature for 31 h then heated at 60 °C for 18 h.

In the first attempt at this reaction sulfolene was heated at 130 °C in a sealed vessel in the presence of nitrosobenzene. However, after heating for 1 hour followed by stirring at room temperature for 16 hours, only a complex mixture of products was obtained. Consequently, the two stages of this reaction were separated; first enabling the initial formation of the 1,3-butadiene at 130 °C, followed by the room temperature nitroso Diels-Alder reaction after addition of the nitrosobenzene. Heating sulfolene in a sealed vessel at 130 °C for 30 minutes and then cooling the reaction down to -10°C allowed 1,3-butadiene to condense. Subsequent addition of nitrosobenzene to the sealed mixture and stirring at room temperature for 24 hours yielded the unsubstituted 1,2-oxazine **90c** in quantitative yield (Scheme 49).



*Scheme 49. Synthesis of unsubstituted 1,2-oxazine **90c** via the nitroso Diels-Alder of nitrosobenzene and in situ generated 1,3-butadiene from sulfolene.*

Following the standard nitroso Diels-Alder procedure, bicyclic 3,6-*cis* substrate **90d** derived from 1,3-cyclohexadiene and nitrosobenzene was also obtained in excellent yield (Scheme 48). However, when the TBS-protected *trans, trans* sorbic alcohol **88b** was used as the diene a separable mixture of regioisomers **90e** and **90e'** was obtained with the proximal isomer being confirmed as the major regioisomer from the 2D NOESY ¹H NMR spectrum. Singly substituted dienes were used to synthesise 6-aryl substituted 1,2-oxazines **90f** and **90g** with the NOESY assignment of **90f** as the proximal isomer being confirmed by X-ray crystallography (Scheme 48 and Scheme 50).

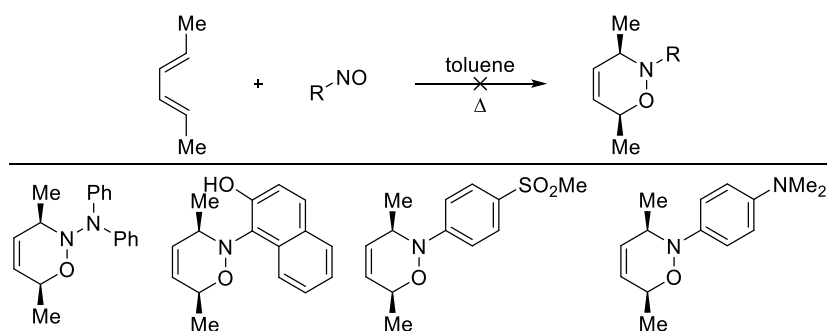


*Scheme 50. Proximal isomer of **90f** determined by observed NOESY correlations and validated by X-ray crystallography.*

Substrates bearing more substituted alkenes were also desired. However, these diene starting materials typically reacted poorly with nitrosobenzene, which when paired with the more challenging isolation of these cycloadducts, gave 1,2-oxazines **90h** to **90l** in generally poor to average yields. These substrates were isolated as single regioisomers with the exception of **90k**, which was obtained as an 81:19 inseparable mixture of distal to proximal isomers.

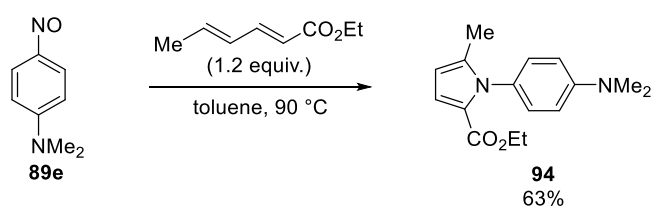
Owing to the reductive nature of the optimised deoxygenative ring contraction reaction conditions, a number of 1,2-oxazines were synthesised that would allow the functional group tolerance of the reaction to be sufficiently explored. The amine analogue of the naturally occurring *trans, trans* diene piperine (**88h**) efficiently gave 1,2-oxazine **90m** exclusively as the distal isomer. Furthermore, using this nitroso Diels-Alder protocol, cycloadducts containing reducible amide (**90n**), nitrile (**90o**), ester (**90p**) and ketone (**90q**) functional groups were cleanly obtained. However, the 1,2-oxazine **90n** derived from piperine was formed as an inseparable mixture of regioisomers, whereas for substrates **90o** to **90q** only a single regioisomer was isolated.

Finally, the introduction of alternative groups on the nitrogen of the 1,2-oxazine was explored using other aromatic nitroso compounds in the cycloaddition reaction. Pleasingly, both *para*-fluorophenyl and *para*-methoxyphenyl groups could be introduced onto the nitrogen of the 1,2-oxazine ring with good efficiency to give substrates **90r** to **90u**. Sadly, in the case of substrate **90u** – although TLC analysis suggested complete and relatively clean conversion of nitroso **89c** into 1,2-oxazine **90u** – only a small amount of the product could be isolated due to its extremely rapid decomposition during column chromatography using normal phase silica gel or alumina stationary phases.



Scheme 51. Unsuccessful nitroso Diels-Alder reactions.

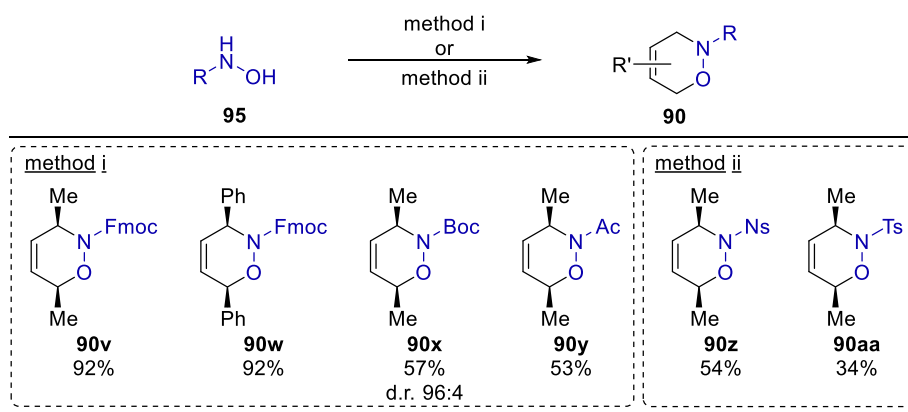
Additional aryl nitroso compounds were also subjected to the nitroso Diels-Alder reaction conditions, as shown in Scheme 51. However, in these cases no reaction was observed between these nitroso compounds and 2,4-hexadiene even after heating for prolonged periods (>48 hours). Interestingly however, in an attempt to promote more favourable orbital interactions between the nitroso compound and the diene, heating nitroso **89e** in toluene in the presence of ethyl sorbate gave the unexpected ring contracted pyrrole **94** in a respectable yield as the major product (Scheme 52). Sadly, this result could not be replicated upon exchanging nitroso **89e** for the similarly electron-rich nitroso **89c** and investigation into this reaction was not pursued further.



Scheme 52. [4+2] cycloaddition/ ring contraction of nitroso compound **89e** to pyrrole **94**.

In order to enhance the practicality and generality of the ring contraction method, a more conventional protecting group on nitrogen such as Boc or Fmoc was desired. These types of protecting group would therefore require the use of the corresponding acyl nitroso compounds. However, acyl nitroso compounds are significantly more reactive than aromatic nitroso compounds and so they are typically made and trapped *in situ*.^{298,299} Due to the practical simplicity of the method and availability of the starting materials, the oxidation of the hydroxamic acids or hydroxylamines was chosen (Scheme 53).

Two different methods were selected for this oxidation/ nitroso Diels-Alder sequence. The first was a copper-catalysed aerobic oxidation of hydroxamic acids published by Read de Alaniz.³⁰⁰ This method provided substrates possessing Fmoc (**90v** and **90w**), Boc (**90x**) and Ac (**90y**) protecting groups on nitrogen in good to excellent yields (Scheme 53). The diastereomeric ratio observed in the isolation of **90x** likely arose from the 2,4-hexadiene which was bought and used as a mixture of stereoisomers containing *ca.* 75% of the *trans, trans* isomer (determined by ¹H NMR spectroscopy).

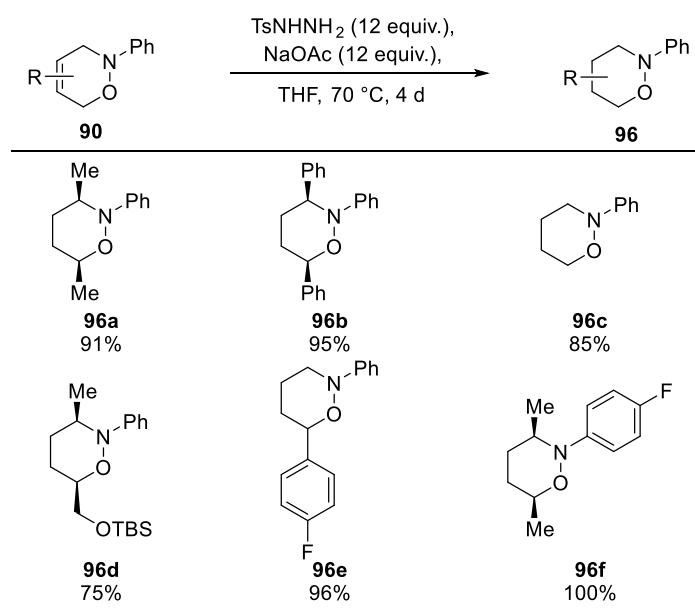


Scheme 53. Sequential oxidation/ nitroso Diels-Alder procedure for the synthesis of N-acyl and N-sulfonyl 1,2-oxazines **90**. Method i) CuCl (20 mol%), pyridine (5 mol%), diene (1.2 equiv.), THF, r.t. or 60 °C; Method ii) NaIO₄ (1.5 equiv.), diene (2.5-5 equiv.), 0 °C, MeOH/H₂O (3:1).

The second oxidation method involved the *in situ* oxidation of N-hydroxysulfonamides **95a** and **95b** with NaIO₄ in the presence of the diene to form the 3,6-*cis* N-sulfonyl protected [4+2] cycloadducts **90z** and **90aa** respectively in acceptable yields. Despite the successful synthesis of the prerequisite TrNHOH **95c**, no 1,2-oxazines containing the trityl protecting group could be synthesised using these methods. In all tested cases no reaction would occur, presumably due to the bulky nature of the triyl group, which blocks the approach of the oxidant and dienes.

The introduction of other nitrogen protecting groups derived from nitroso compounds containing protons α to the nitroso group such as benzyl, *para*-methoxybenzyl, SEM and MOM cannot be synthesised *via* these oxidation/ [4+2] cycloaddition routes. In these cases, the nitroso compounds are not stable due to the extremely rapid tautomerisation to the more stable oxime tautomer. This tautomerisation occurs too rapidly for the nitroso compound to react with the diene partner preventing the formation of the corresponding 1,2-oxazine cycloadducts.

The final class of substrates of interest was 1,2-oxazinanes **96** (Scheme 54) – [4+2] nitroso Diels-Alder cycloadducts whose olefin has been reduced to give the fully saturated heterocycle. Traditional palladium-based hydrogenation conditions have been shown to readily cleave the reductively labile N-O bond.^{220,221,223} Fortunately, a reduction of 1,2-oxazines using diimide enables the facile hydrogenation of the unpolarised olefin in the presence of the weak N-O bond.



Scheme 54. Synthesis of 1,2-oxazinan-3-ones **96** from 1,2-oxazines **90** by the diimide reduction.

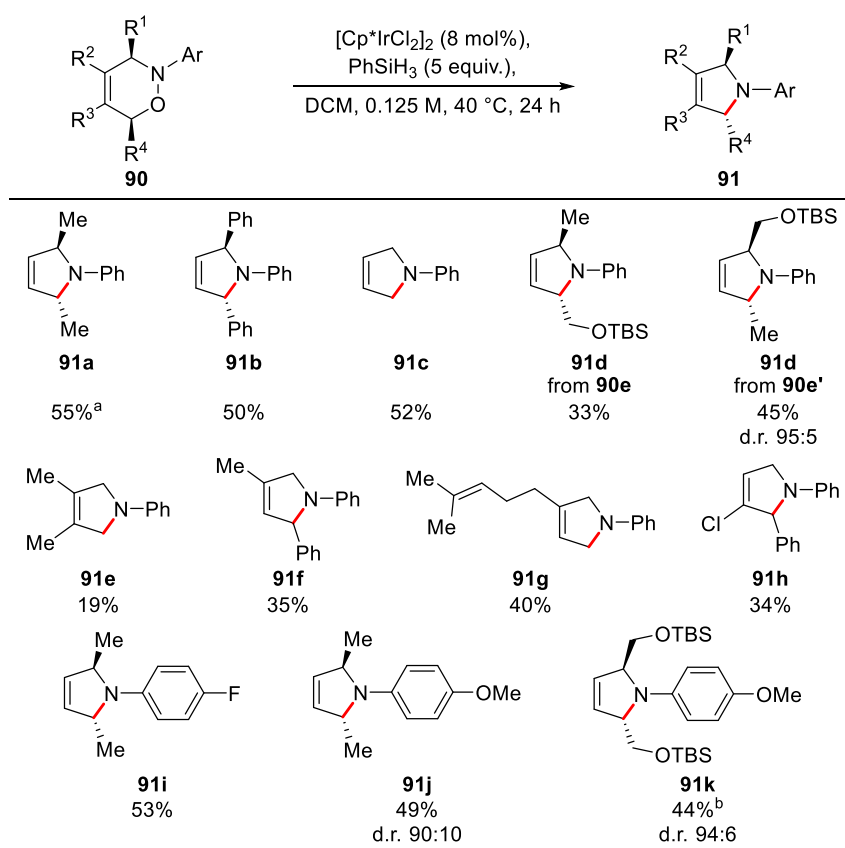
Pleasingly, despite the long reaction times, the selectively reduced fully saturated 1,2-oxazinane substrates **96** were obtained in excellent yields as shown in Scheme 54. Regrettably, despite the observation of the complete consumption of the corresponding 1,2-oxazines, no *N*-PMP protected substrates could be isolated *via* this method due to rapid decomposition of the products during purification by column chromatography using normal phase silica gel.

The ability to access the functionalised N-O containing heterocycles **90** and **96** through only a few operational simple steps is a key advantage for our developed methodology. Pairing the deoxygenative ring contraction with the short synthesis sequences of the starting 1,2-oxazines and 1,2-oxazinan-3-ones provides a powerful tool for the convergent construction of functionalised 3-pyrroline and pyrrolidine cores in just a few steps. This principle is one of the key concepts in the design and development of this project.

With the ability to access the functionalised N-O containing heterocycles **90** and **96** through operationally simple procedures in only a few steps, the subsequent deoxygenative ring contraction provides a powerful tool for the convergent construction of these functionalised 3-pyrroline and pyrrolidine cores. Thus, all of the 1,2-oxazine and 1,2-oxazinane substrates **90** and **96** shown above were subjected to the optimised iridium-catalysed deoxygenative ring contraction reaction conditions described above (Section 2.1) in an attempt to synthesise a range of different cyclic tertiary amine products.

2.2.2. Scope of the Deoxygenative Ring Contraction of 1,2-Oxazines and 1,2-Oxazinanes

Using 1,2-oxazine and 1,2-oxazinane substrates **90** and **96**, the scope and tolerance of the deoxygenative ring contraction was explored, typically conducting the reactions on a 0.4 mmol scale with respect to the 1,2-oxazine/oxazinane. As shown in Scheme 55, using the optimised conditions, a number of 3-pyrroline products **91** were isolated from the corresponding 1,2-oxazine starting materials **90** without the requirement to exclude air or water from the reactions.

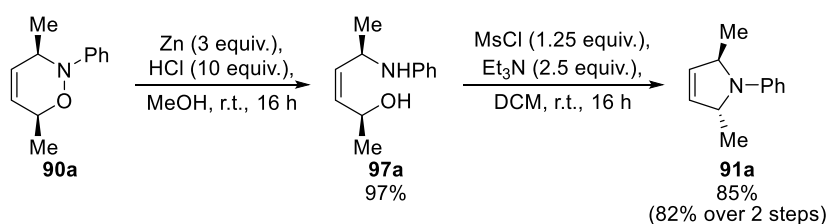


Scheme 55. Substrate scope of the deoxygenative ring contraction of 1,2-oxazines **90** to 3-pyrrolines **91**. Reactions were performed on a 0.4 mmol scale and all yields are isolated yields. ^aReaction performed on 0.65 mmol scale.

^bReaction performed on 0.75 mmol scale.

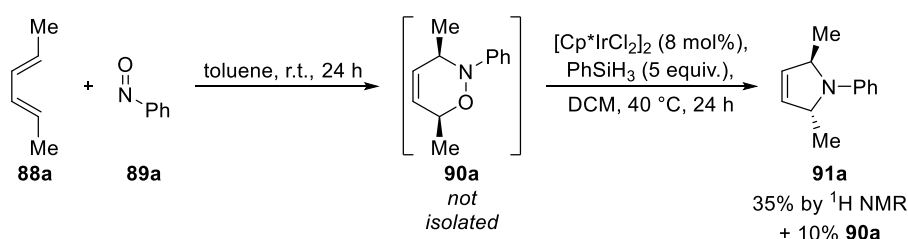
Starting with the model 3,6-*cis* 1,2-oxazine substrate **90a**, the deoxygenative ring contraction enabled the isolation of 3-pyrroline **91a** in 55% yield after inversion of configuration at the C-R⁴ carbon (*cf.* 60% ¹H NMR yield using the optimised conditions). The 2,5-*trans* relative configuration of the methyl substituents was later confirmed by comparing our data with an

authentic sample of the product obtained by a sequential 1,2-oxazine ring opening/ alcohol activation/ ring closure method from **90a** (Scheme 56) – similar to those seen in Section 1.5.



*Scheme 56. Alternative synthesis of 3-pyrroline **91a** via ring opening of 1,2-oxazine **90a** by a zinc-acid reduction followed by alcohol mesylation and amine cyclisation.*

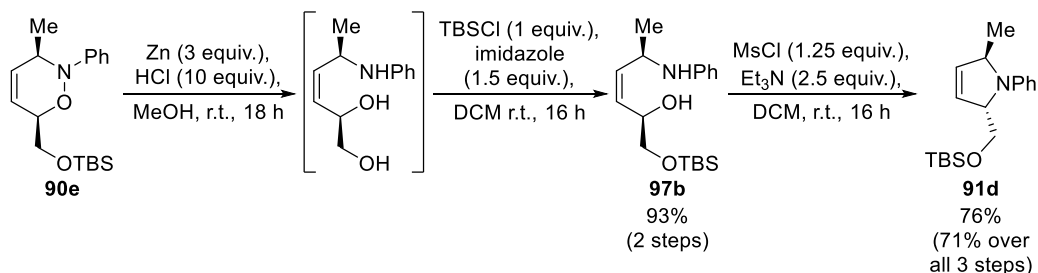
Gratifyingly, the reaction proved to be insensitive to scale, again allowing **91a** to be isolated in 55% yield on a 10 mmol scale. Furthermore, the [4+2] cycloaddition of 2,4-hexadiene **88a** and nitrosobenzene **89a** followed by the deoxygenative ring contraction of the resulting cycloadduct could be telescoped in a one-pot procedure, after a solvent swap from toluene to DCM (Scheme 57). However, after leaving the deoxygenative ring contraction step for 24 hours, 10% of 1,2-oxazine **90a** remained, giving **91a** in a ¹H NMR yield of only 35%.



*Scheme 57. Sequential one-pot nitroso Diels-Alder/ deoxygenative ring contraction to 3-pyrroline **91a**.*

Other structurally simple 1,2-oxazines are tolerated allowing the 2,5-*trans* diaryl-substituted 3-pyrroline **91b** and unsubstituted product **91c** to be obtained from **90b** and **90c** in 50% and 52% yields respectively (Scheme 55). As previously mentioned, the nitroso Diels-Alder between diene **88b** and nitrosobenzene gave a separable mixture of regioisomeric 1,2-oxazines **90e** and **90e'**. Interestingly when each of the regioisomers **90e** and **90e'** were subjected to the ring contraction the same 3-pyrroline product **91d** was observed in 33% and 45% yields respectively. This is only possible if the C-R⁴ carbon undergoes an inversion of configuration. As a result, obtaining mixtures of regioisomers from the cycloaddition step becomes inconsequential as subjecting that regioisomeric mixture to the deoxygenative ring contraction results in the

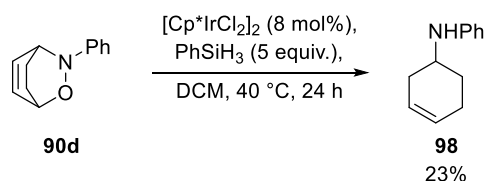
convergence to a single 3-pyrroline (or pyrrolidine) product. As displayed in Scheme 58 the analogous ring opening/ alcohol activation and ring closure sequence from 1,2-oxazine **90e** gave the same 3-pyrroline product **91d** in 71% over 3 steps.



*Scheme 58. Alternative synthesis of 3-pyrroline **91d** via ring opening of 1,2-oxazine **90e** by a zinc-acid reduction followed by secondary alcohol mesylation and amine cyclisation.*

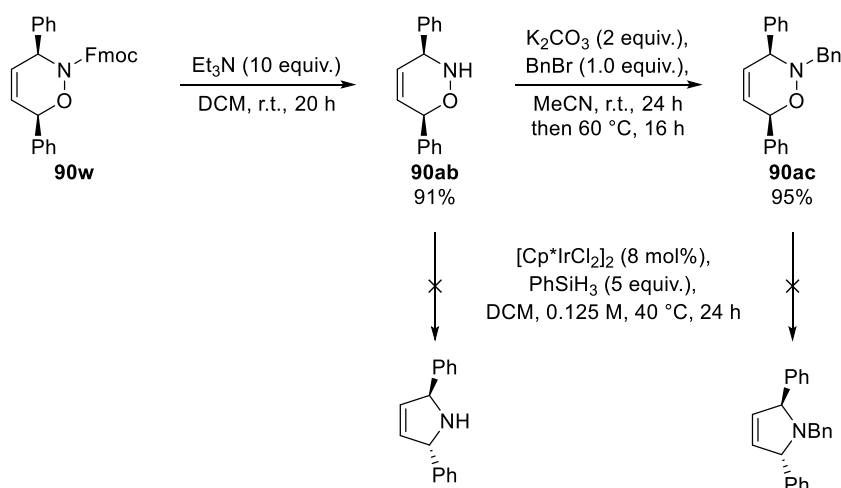
Both tetra- and tri-substituted alkenes can be tolerated in the reaction (**91e** to **91g**) although lower yields (19%, 35% and 40%) were obtained for these more electron-rich compounds due to decomposition during purification procedures. The successful synthesis of 3-pyrroline **91g** in two steps (16% overall) from the naturally occurring commercially available diene mycene highlights how the sequential cycloaddition/ deoxygenative ring contraction process can be used to expediently build up a number of novel natural product derivatives. A trisubstituted vinyl chloride was also tolerated in the reaction to yield **91h** in 34%, providing a valuable functional handle for further derivatisations.

Unsurprisingly however, 1,2-oxazines containing reducible functional groups such as amides, nitriles, esters and ketones (**90n** to **90q**) failed to give the ring contracted heterocycles, instead yielding mixtures of products in which the reduction of these functional groups had occurred. Similarly, the more structurally complex bicyclic 1,2-oxazines **90d** and **90i**, failed to form the ring contracted products. This is likely due to the greater rigidity and steric bulk of these structures which would hinder the cyclisation of the amine of the intermediate amino alcohol. Accordingly, only a small amount of deoxygenated ring opened product **98** was observed from 1,2-oxazine **90d** (Scheme 59), whilst no major product could be isolated from the reaction of 1,2-oxazine **90i**.



*Scheme 59. Attempted deoxygenative ring contraction of bicyclic 1,2-oxazine **90d**.*

During the exploration of the reaction scope, it was rapidly discovered that the deoxygenative ring contraction will only effectively proceed when the nitrogen atom of the 1,2-oxazine ring bears an aromatic substituent. Consequently, 1,2-oxazines **90v** to **90y** that possessed carbamate and amide protecting groups reacted poorly under the reaction conditions. Likewise, although complete consumption of the 1,2-oxazines was observed for sulfonamide substrates **90z** and **90aa**, analysis of the reaction ^1H NMR spectra suggested that **90z** resulted in the partial reduction of the nitro group with no further reaction occurring, whilst tosyl protected 1,2-oxazine **90aa** gave a more complex mixture in which no product could be extracted.



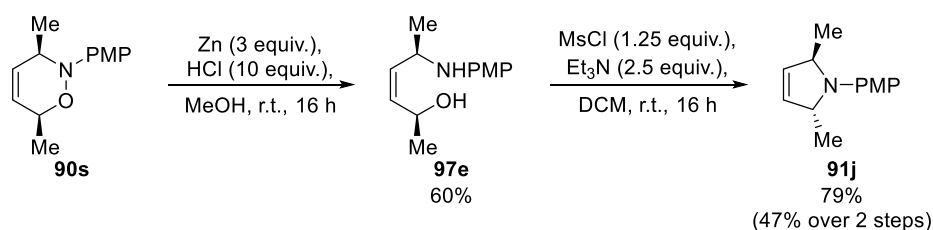
*Scheme 60. Deprotection of **90w** to **90ab** and re protection with a benzyl group to obtain 1,2-oxazine **90ac**.*

Subsequent attempted ring contraction of these 1,2-oxazines failed.

The deprotection of 1,2-oxazine **90w** yielded secondary amine **90ab**, which after reaction with benzyl bromide gave the benzyl protected 1,2-oxazine **90ac** (Scheme 60). Sadly, no reaction was observed when both the free secondary amine **90ab** and benzyl protected 1,2-oxazine **90ac** were subjected to the ring contraction, possibly indicating the existence of an inhibitory effect of substrates containing non-aromatic amines (the reduced piperine substrate **90m**, which

possesses an additional tertiary amine, similarly did not react under the ring contraction conditions).

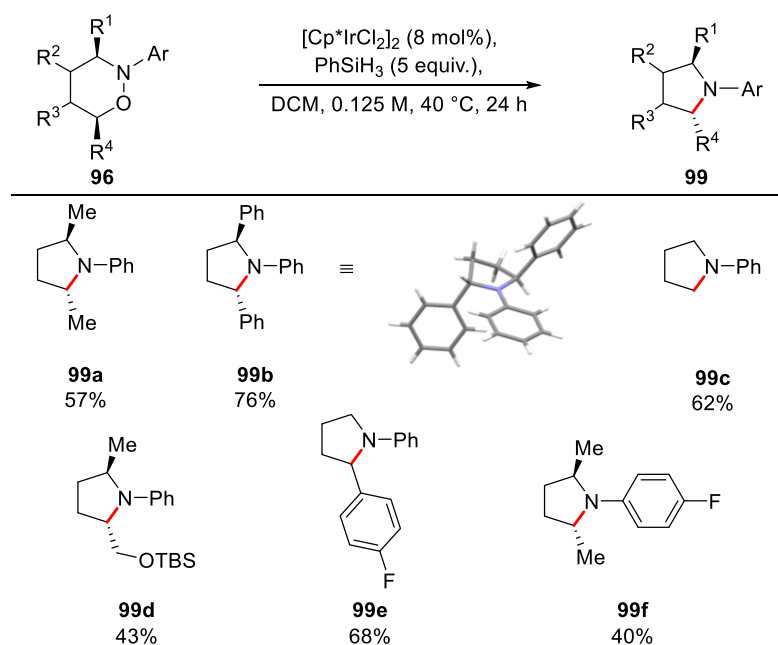
Despite the limiting requirement for an aryl group on the nitrogen of the 1,2-oxazine, alternative aromatic groups were tolerated in this position. **90r** underwent the deoxygenative ring contraction with a similar efficacy to **90a**, providing contracted **91i** in 53% yield (Scheme 55). More pleasingly, 1,2-oxazines **90s** and **90u** bearing a PMP-protected nitrogen could be contracted to the corresponding 3-pyrrolines **91j** and **91k** without significant depreciations in the yield. However, traces of the other diastereoisomers of these products were detected by ^1H NMR spectroscopy – presumably resulting from a competing $\text{S}_{\text{N}}1$ -type pathway (see Section 2.3 for a discussion on the proposed mechanism of the transformation). Despite the slightly lower isolated yield of 3-pyrroline **91j** vs. analogous **91a**, unlike the *N*-Ph compounds, **91j** has the capacity for *N*-deprotection under oxidative conditions to yield the free secondary amine. Furthermore, the obtained yield for the deoxygenative ring contraction of 1,2-oxazine **90s** to 3-pyrroline **91j** (49%) compares favourably to the yield acquired for the alternative ring opening/ alcohol activation/ ring closure sequence of 1,2-oxazine **90s** (47% over 2 steps) to get to the same product (Scheme 61).



*Scheme 61. Alternative synthesis of 3-pyrroline **91j** via ring opening of 1,2-oxazine **90s** by a zinc-acid reduction followed by alcohol mesylation and amine cyclisation.*

In addition to the successful acquisition of 3-pyrrolines, pyrrolidine heterocycles can be effectively synthesised using the deoxygenative ring contraction methodology (Scheme 62). Once again, simple aliphatic (**99a**) and aromatic (**99b**) substituents as well as unsubstituted rings (**99c**) were well tolerated giving the pyrrolidine products in good yields. The structure and *trans* relative configuration of the two phenyl substituents of pyrrolidine **99b** were unambiguously confirmed by X-ray crystallography, clearly highlighting the observed inversion of configuration. The pyrrolidine heterocycles were usually obtained in higher yields than their 3-pyrroline

analogues, this being attributed to the greater stability of the pyrrolidine products during handling and purification. 1,2-Oxazinanes containing a TBS-protected alcohol (**96d**) and electron-withdrawing aromatic substituents (**96e**) also smoothly underwent deoxygenative ring contraction to give the unsymmetrical pyrrolidines **99d** and **99e** in 43% and 68% yields respectively. Curiously, the 3-pyrroline analogue of **99e** could not be synthesised by the deoxygenative ring contraction due to the sluggish conversion of 1,2-oxazine **90f** into a complex mixture of products from which the 3-pyrroline could not be cleanly isolated. Finally, as observed in Scheme 62, functionalised aromatic groups on the 1,2-oxazinane nitrogen can also be tolerated in the ring contraction to the pyrrolidine product (**99f**).

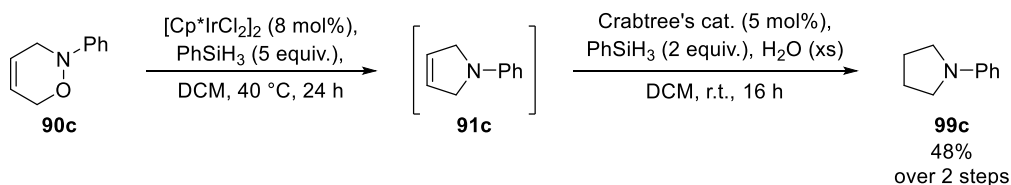


*Scheme 62. Substrate scope for the deoxygenative ring contraction of 1,2-oxazinanes **96** to pyrrolidines **99**. All reactions were performed on a 0.4 mmol scale and all yields are isolated yields.*

In many cases purification of the 3-pyrrolines **91** proved to be significantly more challenging than for the pyrrolidines. Consequently, after performing the deoxygenative ring contraction of 1,2-oxazines we hoped to employ a reductive work-up to remove the unsaturation from the resulting heterocycle, enhancing the stability of the products. Sadly, to the best of our knowledge no such protocol has been documented in the literature and so the introduction of an additional step for the olefin reduction was inevitable. We took inspiration for this transformation from a report by Wu and *et al.* in which unsaturated bonds were hydrogenated

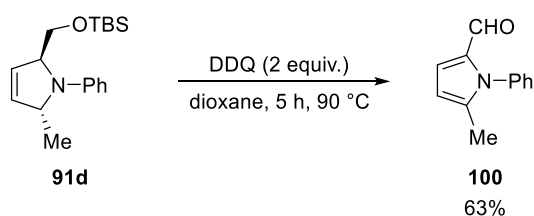
in a sealed tube using a $\text{Pd}(\text{OAc})_2$ precatalyst and H_2 gas generated *in situ* from the reaction between HBpin and H_2O .³⁰¹

Upon completion of the ring contraction, the excess PhSiH_3 remaining in the reaction mixture requires quenching before purification. However, we envisaged that the H_2 gas released during the quenching of this excess reagent with H_2O , MeOH or normal phase silica gel could be contained and, in combination with an appropriate hydrogenation catalyst, used to promote olefin reduction. As shown in Scheme 63, quenching the excess silane from the ring contraction step of 1,2-oxazine **90c** with H_2O in the presence of Crabtree's catalyst promoted the hydrogenation of 3-pyrroline **91c** to give the fully saturated pyrrolidine product **99c** in 48% over the two steps. The further addition of two equivalents of PhSiH_3 in the hydrogenation step ensured that there was sufficient H_2 gas present to facilitate the alkene hydrogenation. This process compares favourably with the alternative diimide reduction/ring contraction sequence used previously, boasting shorter reaction times and a comparable yield over two steps (*cf.* 52% over two steps for the diimide reduction/ring contraction route).



Scheme 63. Sequential deoxygenative ring contraction/alkene hydrogenation using PhSiH_3 as a source of H_2 .

The oxidation of a 3-pyrroline product to the corresponding pyrrole was also demonstrated. DDQ is a convenient reagent for the dehydrogenation of hydroaromatic carbocyclic and heterocyclic compounds. Consequently, DDQ was selected for the oxidation of 3-pyrroline **91d**. As shown in Scheme 64, subjecting **91d** to two equivalents of DDQ at 90 °C gave pyrrole **100** in 63% yield. After the initial oxidation of the 3-pyrroline ring to the pyrrole, the phenol by-product of the DDQ was sufficiently acidic to enable the deprotection of the silyl ether. The second equivalent of DDQ was then able to oxidise the primary alcohol to the aldehyde to give the observed pyrrole product **100**.



Scheme 64. Oxidation of 3-pyrroline 91d to pyrrole 100 using DDQ.

2.2.3. Studies Towards the Synthesis of (±)-DMDP Using the Deoxygenative Ring

Contraction as the Key Step

DMDP is a C₂ symmetric naturally occurring amino sugar first isolated in 1976 from *Derris elliptica*.^{302,303} This natural product has attracted much attention because of its interesting biological activity, particularly as a strong inhibitor of glucosidases. This alkaloid has been the synthetic target of many studies, despite its relatively simple structure, owing to the presence of the polyhydroxylated 2,3,4,5-tetrasubstituted pyrrolidine core with four stereogenic centres in an all *trans* arrangement.^{202,304,305}

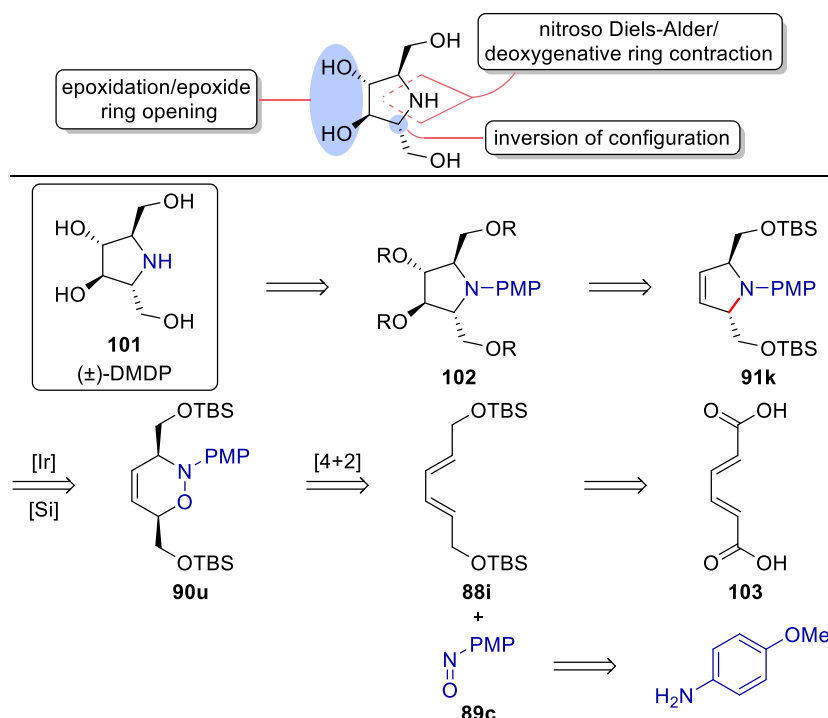
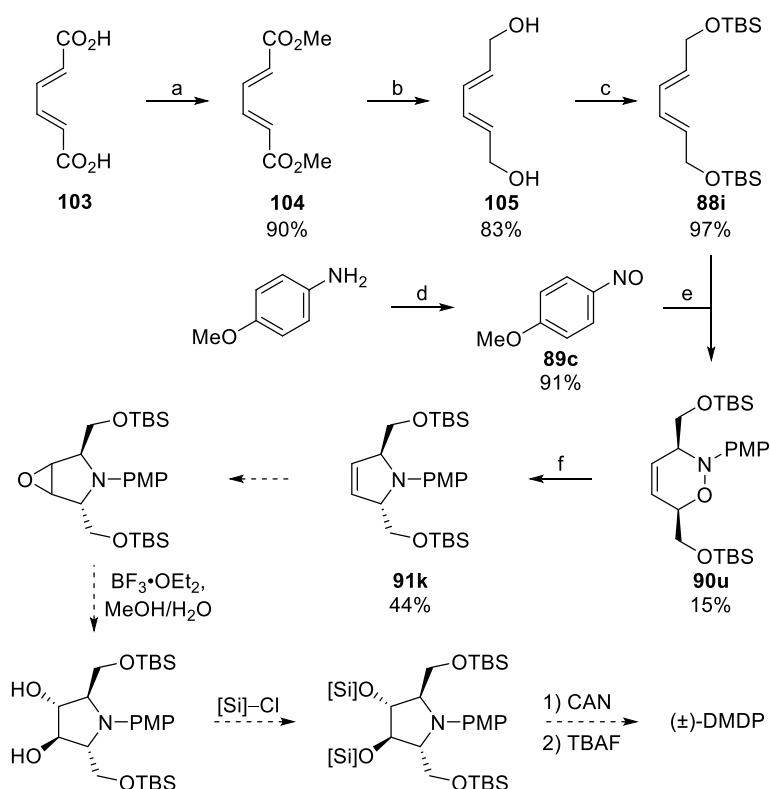


Figure 10. Retrosynthetic analysis of DMDP using the deoxygenative ring contraction as a key step.

DMDP was identified as a suitable target to demonstrate the synthetic utility of the iridium-catalysed deoxygenative ring contraction. The key retrosynthetic disconnections have been highlighted in Figure 10. The synthesis of (±)-DMDP **101** would involve the PMP deprotection of

polyhydroxylated pyrrolidine **102**, which in turn would be obtained from the *anti* dihydroxylation of 3-pyrroline **91k**. *Anti* dihydroxylation of the 3,4-olefin of 3-pyrrolines have often been achieved through epoxidation/ ring opening sequences (Section 1.3.2). Consequently, a similar strategy was considered to be appropriate in this case. In the key step, 2,5-*trans* disubstituted 3-pyrroline **91k** would be formed as a result of the deoxygenative ring contraction of unsymmetrical 3,6-*cis* 1,2-oxazine **90u**, obtained from a nitroso Diels-Alder reaction. As seen previously, the PMP nitroso compound **89c** can be synthesised from the corresponding aniline whilst the required *trans, trans* diene **88i** can be obtained from commercially available muconic acid by literature steps.



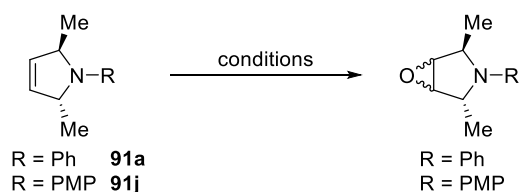
Scheme 65. Towards the synthesis of (±)-DMDP. a) H_2SO_4 (5 mol%), MeOH, 65 °C, 16 h, 90%. b) DIBAL-H (4.2 equiv.), DCM, 0 °C, 3.5 h, 83%. c) TBSCl (2.05 equiv.), imidazole (2.5 equiv.), DCM, r.t., 16 h, 97%. d) H_2O_2 (4.75 equiv.), $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (5 mol%), Bu_4NBr (1.5 mol%) DCM/hexane 1:1, r.t., 4.5 h, 91%. e) toluene, r.t., 24 h, 15%. f) $[\text{Cp}^*\text{IrCl}_2]_2$ (8 mol%), PhSiH_3 (5 equiv.), DCM, 40 °C, 24 h, 44%.

Scheme 65 shows our forward synthesis to the target. Our synthesis began with the esterification of commercially available *trans, trans* muconic acid **103**. Under standard Fischer esterification conditions, the diacid **103** was converted to diester **104** in 90% yield. Reduction of

104 to the diol **105** with four equivalents of DIBAL-H, followed by a double TBS protection gave the required nitroso Diels-Alder diene precursor **88i** in excellent yield. Despite the proceeding nitroso Diels-Alder between diene **88i** and nitroso **89c** going to completion, the [4+2] cycloadduct was only obtained in 15% yield. This was due to the very rapid decomposition of the 1,2-oxazine in contact with both basified silica gel and alumina making chromatographic purification challenging (decomposition occurred within 1 to 2 minutes of contact). However, we were pleased to find that our key step – the deoxygenative ring contraction of 1,2-oxazine **90u** – proceeded with a similar efficiency to similar substrates, giving 3-pyrroline **91k** in 44%. Furthermore, although some losses in the yield of **91k** can be attributed to decomposition during purification, the 3-pyrroline product showed greater stability than 1,2-oxazine **90u** during the purification process. Consequently, in this instance telescoping the cycloaddition and deoxygenative ring contraction steps is appropriate.

Sadly, the introduction of the 3,4-*trans* diol moiety proved problematic. Two 3-pyrrolines **91a** and **91j** were chosen as model substrates for the investigation into appropriate epoxidation conditions due to their simple structures and ease of accessibility. A summary of the epoxidation methods attempted is displayed in Table 14. Initially, common and practically simple epoxidation methods were explored. Both Jacobsen (Entry 1) and Shi (Entry 2) epoxidations of **91a** failed to give the desired product, the former yielding a complex mixture of products and the latter resulting in no conversion of the starting material.

In order to minimise the formation of unwanted side products such as the corresponding *N*-oxide the protection of the nitrogen lone pair was considered. Attempted protection with $\text{BF}_3 \cdot \text{OEt}_2$ or trifluoroacetic anhydride followed by epoxidation with *m*CPBA returned only the starting 3-pyrroline **91j** (Entries 3 and 4). In contrast, a procedure employed by Silverman and co-workers for the epoxidation of *N*-benzyl 3-pyrroline used H_2SO_4 to protonate the 3-pyrroline ring nitrogen to enable the epoxidation with *m*CPBA to occur without the formation of *N*-oxide side products.³⁰⁶ However, when this methodology was applied to *N*-phenyl 3-pyrroline **91a** no reaction occurred (Entry 5). In contrast, the PMP protected 3-pyrroline **91j** yielded a complex mixture of products under the reaction conditions in which the desired epoxide could not be clearly seen in the ^1H NMR spectrum of the crude reaction mixture (Entry 6).



Entry	R	Conditions
1	Ph	Jacobsen's catalyst (4 mol%), NaOCl (4 equiv.), NBu ₄ Cl (20 mol%), PhCl, 0 °C to r.t., 16 h
2	Ph	Shi catalyst (30 mol%), oxone (1.38 equiv.), K ₂ CO ₃ (5.8 equiv.), MeCN/Na ₂ B ₄ O ₇ •10H ₂ O-Na ₂ EDTA buffer (1.5:1), 0 °C to r.t., 17 h
3	PMP	1) BF ₃ •OEt ₂ (1.5 equiv.), DCM, -20 °C, 2 h 2) mCPBA (1.1 equiv.), 0 °C to r.t., 3 h
4	PMP	1) TFAA (1.1 equiv.), DCM, 0 °C, 1 h 2) mCPBA (1.2 equiv.), 0 °C to r.t., 4 h
5	Ph	H ₂ SO ₄ (1.2 equiv.), acetone/H ₂ O (4:1), 0 °C then mCPBA (1.3 equiv.), r.t., 5 h
6	PMP	H ₂ SO ₄ (1.2 equiv.), MeOH/H ₂ O (96:4), 0 °C then mCPBA (1.3 equiv.), r.t., 70 h
7	Ph	1) BF ₃ •OEt ₂ (1.0 equiv.), DCM, -78 °C to r.t., 1 h 2) Na ₂ CO ₃ (17 equiv.), trifluoroacetone (20 equiv.), oxone (17 equiv.), Na ₂ EDTA, MeCN, 0 °C, 2 h
8	Ph	1) BH ₃ •THF (1.1 equiv.), THF, -78 °C, 1 h 2) TFDO (xs), -78 °C, 3 h then r.t., 14 h
9	PMP	1) BCl ₃ •SMe ₂ (1 equiv.), DCM, r.t., 1.5 h 2) DMDO (1 equiv.), -78 °C, 10 min
10	PMP	NBS (1.5 equiv.), PPh ₃ (1 equiv.), MeCN/H ₂ O (99:1), 60 °C, 16 h
11	PMP	NIS (3 equiv.), THF/H ₂ O (7:2), 0 °C to r.t., 3 h
12	PMP	HClO ₄ (2.0 equiv.) THF/H ₂ O (7:2), 0 °C then NIS (3 equiv.), 0 °C, 1 h

Table 14. Attempted reaction conditions for the epoxidation of model 3-pyrroline substrates **91a** or **91j**.

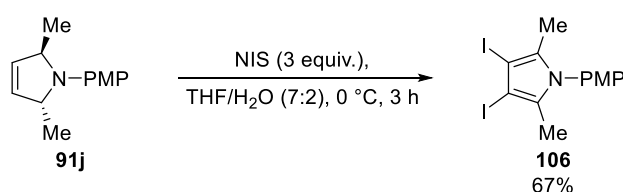
Donohoe *et al.* used conditions similar to Entry 7 for the epoxidation of an *N*-Boc 3-pyrroline in their synthesis of (+)-DGDP (a diastereoisomer of DMDP).³⁰⁷ This method relied on the *in situ* formation of methyl(trifluoromethyl)dioxirane (TFDO), an extremely potent electrophilic oxidant, from trifluoroacetone and oxone.³⁰⁸ Unfortunately, it is not commercially available or stable for extended periods of time and consequently needs to be formed in the reaction *in situ* or prepared as a solution in trifluoroacetone and stored at ≤ -20 °C before use. Due to the volatility of TFDO, its preparation can be tedious and challenging. However, despite seeing complete consumption of the starting material, when applied to 3-pyrroline **91a**, Donohoe's

conditions produced a complex mixture of polar products as judged by TLC analysis and ^1H NMR spectroscopy of the crude reaction mixture (Entry 7).

Protection of the amine of 3-pyrroline **91a** with $\text{BH}_3 \cdot \text{THF}$ was also attempted as the formation of pyrrolidine as well as other cyclic secondary and tertiary amine borane complexes have been characterised in the literature.^{309,310} In the case of 3-pyrroline **91a**, the possibility of a competing alkene hydroboration was noted, however these products were not obviously detected. Sadly, using an excess of a premade solution of TFDO in trifluoroacetone at $-78\text{ }^\circ\text{C}$ largely returned the starting 3-pyrroline **91a** after the work up (Entry 8) which could be on account of the competing evaporation of the TFDO even at the low reaction temperature thus removing the required oxidant for the epoxidation.

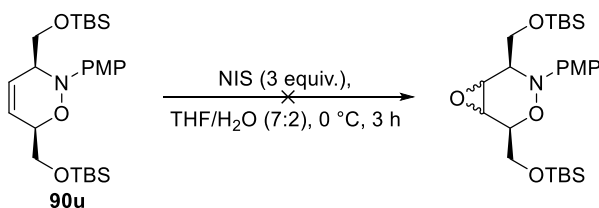
The milder and more practical oxidant dimethyldioxirane (DMDO)³¹¹ was equally unsuccessful in forming the desired epoxide from **91j**, instead yielding a mixture containing an unknown product (Entry 9). Thankfully, due to its higher boiling point, DMDO is a significantly easier oxidant to synthesise, handle and store than TFDO and its formation can be easily achieved from the reaction of acetone with oxone.³¹²

The final type of epoxidation attempted involved the initial formation of a halohydrin across the 3-pyrroline olefin. Ring closure of the halohydrin under basic conditions would then afford the epoxide. At first *N*-bromosuccinimide (NBS) was used in conjunction with PPh_3 as used by Hong and co-workers,³¹³ however, after heating at $60\text{ }^\circ\text{C}$ for 16 hours only the starting material was present (Entry 10). Exchanging NBS for *N*-iodosuccinimide (NIS) had a dramatic effect (Entry 11). The slow portion-wise addition of NIS to a solution of 3-pyrroline **91j** in $\text{THF}/\text{H}_2\text{O}$ gave the doubly iodinated pyrrole **106** as the major product in 67% yield (Scheme 66). Attempting to protect the nitrogen lone pair of **91j** with a proton using HClO_4 failed to mitigate the formation of the product, again yielding the pyrrole in 61% (Entry 12).



Scheme 66. Unexpected aromatisation and double iodination of 3-pyrroline **91j** to iodinated pyrrole **106**.

The failures in the epoxidation of 3-pyrrolines **91a** and **91j** prompted us to consider the reversal of the order of the deoxygenative ring contraction and epoxidation steps. However, this route is not optimal due to the possibility of forming two diastereomeric epoxides of the 1,2-oxazine where the diastereoselectivity could be difficult to control. The formation of the *trans* diol could result in similar issues, in which a lack of regioselectivity during the epoxide opening would ultimately result in the formation of undesired diastereoisomers of the natural product.



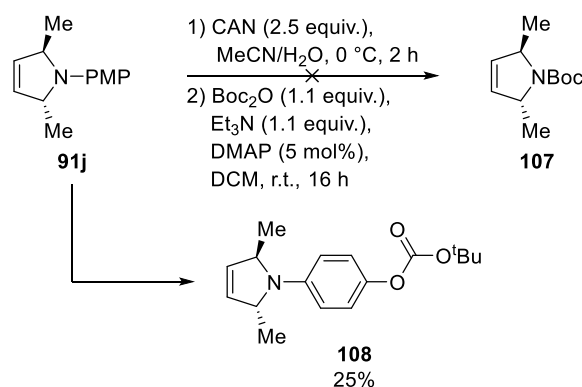
Scheme 67. Unsuccessful epoxidation of 1,2-oxazine **90u** via iodohydrin formation.

Despite this, we attempted the epoxidation of 1,2-oxazine **90u** using the NIS conditions described above, given that these conditions gave the cleanest reaction mixtures of any of the other oxidation methods tried. Sadly, the reaction of **90u** with a small excess of NIS (1.2 equiv.) in THF/H₂O resulted in no significant reaction being observed. Increasing the amount of NIS to three equivalents lead to the formation of a complex mixture of products as judged by ¹H NMR spectroscopy (Scheme 67). Similarly complex crude reaction mixtures were obtained when NIS was exchanged for I₂ or when 1,2-oxazine **90u** was replaced with the more stable substrate **90s** in combination with NIS.

Epoxidations of the 3,4-olefin of *N*-aryl 3-pyrrolines are very scarce in the literature. Typically, protecting groups such as amides, carbamates and sulfonamides are more often employed in these transformations. Due to the greater literature precedence of these protecting groups in the epoxidations of 3-pyrroline substrates, we hoped to exchange the PMP group required by the deoxygenative ring contraction for one of these more conventional nitrogen protecting groups prior to the epoxidation step.

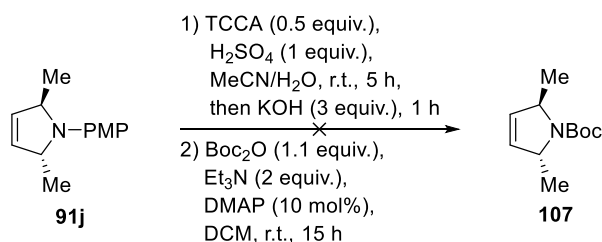
The PMP group is normally removed under oxidative conditions – most commonly using CAN, although other oxidants such as trichloroisocyanuric acid (TCCA) and H₅IO₆ to name a few have proven to be effective.^{314–316} Only traces of the desired deprotection occurred when 3-pyrroline **91j** was reacted with 1.2 equivalents of CAN in MeCN/H₂O, predominantly returning the starting

material after 4 hours. Fortunately, increasing the amount of CAN to 2.5 equivalents resulted in the complete consumption of **91j**. However, to minimise losses of the free secondary amine during purification due to its potential volatility, the crude reaction mixture was immediately subjected to reaction conditions for a Boc protection. However, instead of the desired *N*-Boc 3-pyrroline product **107**, only carbonate **108** was obtained because of **91j** demethylation and subsequent Boc protection of the revealed phenol (Scheme 68).



Scheme 68. Attempted PMP deprotection of **91j** with CAN and reprotection with Boc_2O .

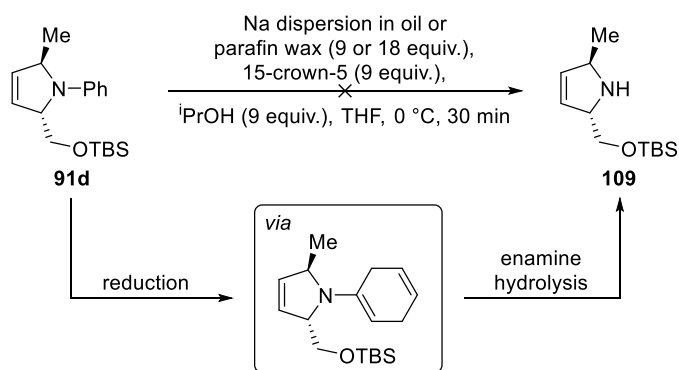
As with CAN, the reaction between 0.5 equivalents of TCCA and 3-pyrroline **91j** showed evidence of the deprotection of the PMP group. However, upon workup of the reaction very little crude material was obtained. Given that TCCA contains three equivalents of oxidising “Cl⁺”, only 0.5 molar equivalents of the reagent were used to ensure that a small excess was present in the reaction. Sadly, telescoping this deprotection step with a subsequent Boc protection step similarly resulted in the formation of carbonate **108**, with none of the desired *N*-Boc 3-pyrroline being isolated (Scheme 69). Finally, when the PMP deprotection of **91j** was attempted with H_5IO_6 a complex mixture was formed in which the only evidence for the occurrence of the desired reaction was the appearance of small signal in the mass spectrum of the crude reaction mixture that correlated to the mass of the free secondary amine.



Scheme 69. Attempted PMP deprotection of **91j** with TCCA and reprotection with Boc_2O .

The final line of enquiry for a usable *N*-deprotection of our 3-pyrroline ring contraction products **91** for use in our total synthesis of DMDP involved a Birch or Birch-like reduction. Using this type of reductive reaction on our *N*-aryl 3-pyrrolines would result in the partial reduction of the aromatic ring. The electron donating ability of the 3-pyrroline nitrogen into the aromatic ring would form the enamine regioisomer, which would liberate the secondary amine after hydrolysis.

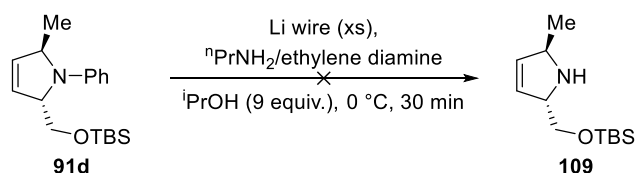
An and co-workers have developed a novel protocol for a practical and chemoselective ammonia-free Birch reduction mediated by bench-stable sodium dispersions and 15-crown-5 ether.²⁰⁰ The reduction of a broad range of aromatic and heteroaromatic compounds was demonstrated in excellent yields, although there were no examples of aniline substrates. Despite this, we decided to apply the methodology to the removal of the *N*-phenyl group of 3-pyrroline **91d**. Unfortunately, even when using new previously unopened containers of 15-crown-5 and sodium dispersion in oil or wax under inert and anhydrous conditions, the electride salt was not efficiently formed (denoted by an intense deep blue colour of the reaction mixture). As a result, very poor conversion of the starting material was observed (Scheme 70).



Scheme 70. Unsuccessful ammonia-free Birch reductions of 3-pyrroline **91d** to deprotected **109**.

The Benkeser reaction, like the Birch reduction, is a dissolving metal reduction used in the dearomatisation of aromatic and heteroaromatic compounds. The Benkeser reduction uses lithium metal in low molecular weight amine solvents such as ethyl- or *n*-propylamine (which are safer and more convenient alternatives than liquid ammonia). This reaction often furnishes the more extensively reduced products than those obtained under Birch conditions due to the greater reduction potential of lithium metal vs. sodium metal (-2.99 V for Li vs. -2.59 V for Na in

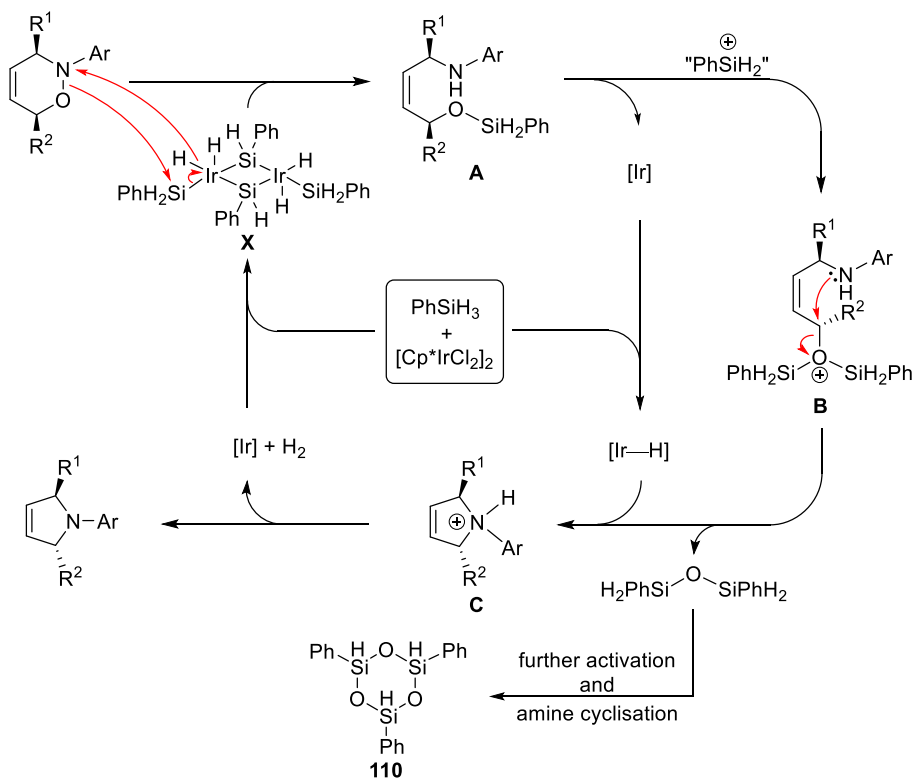
ammonia at $-50\text{ }^{\circ}\text{C}$).^{317–319} Pleasingly, the electride salt was easily formed by dissolving lithium wire (freshly cleaned in MeOH immediately before the reaction) in a 1:1 mixture of *n*-propylamine and ethylene diamine. Due to the greater reducing power of this system, 3-pyrroline **91d** formed a complex mixture that comprised of over-reduction products including the reduction of the 3-pyrroline olefin (Scheme 71).



Scheme 71. Attempted Benkeser reduction of 3-pyrroline **91d**.

Sadly, due to the difficulties encountered during the epoxidation and deprotection steps, further investigation into the total synthesis of DMDP was discontinued.

2.3. Mechanistic Insights



Scheme 72. Proposed mechanism for the iridium-catalysed deoxygenative ring contraction of 1,2-oxazines and 1,2-oxazinanes using PhSiH_3 as the terminal reductant. Cp^* ligands removed for clarity.

The proposed mechanism of the reductive ring contraction has been outlined in Scheme 72. Critical to this transformation is the reaction between PhSiH_3 and $[\text{Cp}^*\text{IrCl}_2]_2$ to form silylene bridged iridium dimer complexes such as **X**. Control deoxygenative ring contraction reactions conducted both in the absence of $[\text{Cp}^*\text{IrCl}_2]_2$ and/or PhSiH_3 have shown that the combination of the two reagents is essential for the observed reactivity. When either of these components were absent, no reaction was observed.

The oxidative addition of a Si-H bond across iridium results in complexes that can be considered to act as a source of both an $[\text{Ir}-\text{H}]$ and a silylium cation (e.g. PhSiH_2^+) and thus have been abbreviated as such in the mechanism for clarity. Similar active catalytic species have been proposed in iridium catalysed hydrosilylation reactions of carbonyls^{267,268,320} and alkynes.^{321,322} However, the exact speciation of the active catalytic component(s) participating in the deoxygenative ring contraction is likely more complicated (as suggested by ^1H NMR spectroscopy) and not currently fully understood.

As shown in Figure 11, the reaction of PhSiH_3 and $[\text{Cp}^*\text{IrCl}_2]_2$, both in the presence and absence of a 1,2-oxazine substrate, generated a number of signals in the -13 to -16 ppm region of the ^1H NMR spectra that are indicative of the presence of metal hydrides. Over the course of a few hours, the major signal at -13.48 ppm diminished slightly in intensity giving rise to multiple hydride signals around -15 to -16 ppm. These findings are in agreement with observations noted by Brookhart and co-workers in their iridium-catalysed reduction of secondary amides using diethylsilane, although their chemical shift values differ slightly due to the use of a different silane and iridium precatalyst.²⁶⁸

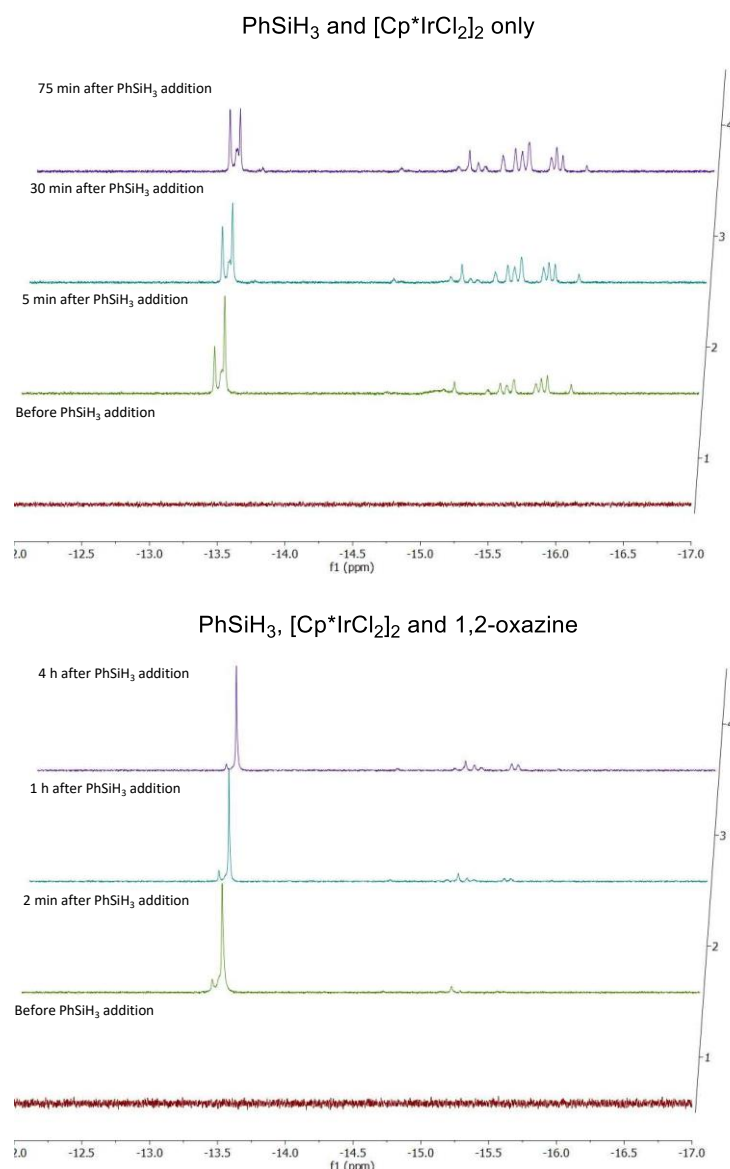
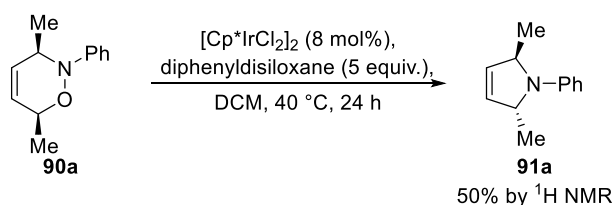


Figure 11. Stacked ¹H NMR spectra in the -12 to -17 ppm. region for: Top – the reaction between PhSiH₃ and [Cp*IrCl₂]₂; Bottom – the reaction between PhSiH₃, [Cp*IrCl₂]₂ and 1,2-oxazine **90a**.

We propose that the mechanism of the ring contraction begins with the oxygen atom of the 1,2-oxazine N-O bond being activated by a silylium ion generated from the reaction of PhSiH₃ and [Cp*IrCl₂]₂ (Scheme 72). Nucleophilic attack of the iridium hydride onto the nitrogen of the activated 1,2-oxazine cleaves the N-O bond generating an amino silyl ether intermediate, **A**. Further *O*-silylation of this amino silyl ether **A** by a silylium ion activates the alcohol towards intramolecular nucleophilic substitution of nitrogen leading to the observed inversion of configuration. Elimination of the siloxane leaving group from **B**, affords the protonated ring contracted heterocycle **C**. The initial diphenyldisiloxane leaving group is then amenable to

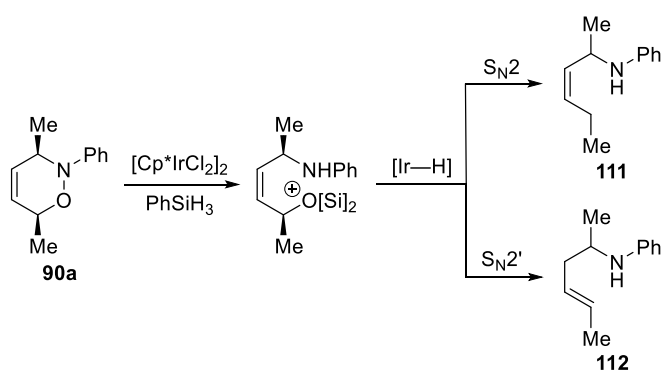
further activation by the iridium catalyst. Consequently, after further activation of oxygen with this silylium species and amine cyclisation, the observed major siloxane by-product **110** is obtained (as determined by ^1H and ^{29}Si NMR spectroscopy and mass spectrometry). This hypothesis was validated when diphenyldisiloxane was used in the reaction and proved to be a competent silane for the ring contraction, allowing 3-pyrroline **91a** to be obtained from **90a** in 50% yield as judged by ^1H NMR spectroscopy (Scheme 73). After cyclisation, the 3-pyrroline product is then formed upon deprotonation of the tertiary ammonium ion **C** by an iridium hydride, resulting in the evolution of hydrogen and regenerating the catalyst.



*Scheme 73. Deoxygenative ring contraction of 1,2-oxazine **90a** to 3-pyrroline **91a** using diphenyldisiloxane as the silane.*

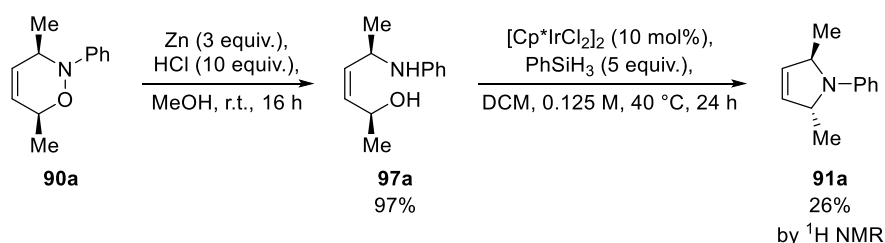
A number of additional observations support this proposed mechanism. Reaction monitoring by LC-MS and ^1H and ^{19}F NMR spectroscopy has shown the consumption of the 1,2-oxazine starting materials leading to the formation of amino alcohol-based intermediates after only a couple of hours. Immediately upon initiating the reaction only the 1,2-oxazine **90a** ($[\text{M}+\text{H}^+] = 190.2$ mu) was present in the mixture. After 2 hours most of the 1,2-oxazine had been consumed, being converted to the amino alcohol **97a** ($[\text{M}+\text{H}^+] = 192.2$ mu), amino silyl ether ($[\text{M}+\text{H}^+] = 298.2$ mu) and small quantities of the 3-pyrroline product **91a** ($[\text{M}+\text{H}^+] = 174.2$ mu). Over the following 8 hours these intermediates converted to the 3-pyrroline product **91a** until only traces of the starting material remained after this time. Interestingly, a mass signal, which could correlate to the acyclic deoxygenated amino alcohol products **111** and **112** was also observed ($[\text{M}+\text{H}^+] = 176.2$ mu). These products could form as a result of a competitive deoxygenative reduction by the $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ substitution of hydride to the activated amino alcohol intermediate (Scheme 74). This observation supports the formation of deoxygenated **98** witnessed during the attempted ring contraction of bicyclic 1,2-oxazine **90d**, owing to the more difficult cyclisation of the corresponding amino alcohol. These side products could provide an explanation for some of the

unaccounted mass in the ring contraction reactions that gave lower yields of the desired product.



Scheme 74. Reduction of the activated amino alcohol intermediate by $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ substitution of a hydride.

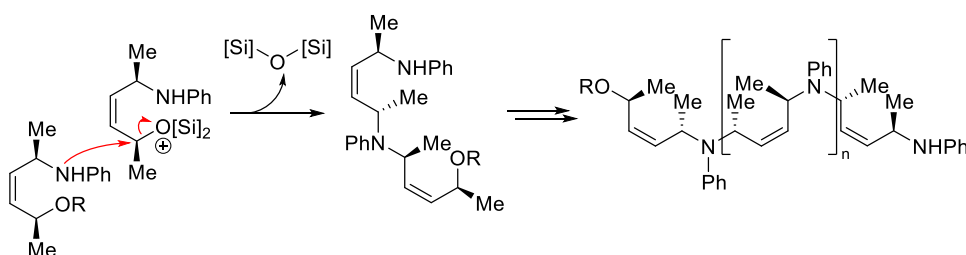
The successful cyclisation of the independently synthesised amino alcohol **97a** to the 3-pyrroline product **91a** under the reaction conditions provides further supporting evidence for the generation of this intermediate. Using the iridium-catalysed conditions, complete consumption of amino alcohol **97a** was observed and the corresponding cyclised 3-pyrroline product **91a** was generated in 26% yield (Scheme 75) as judged by ^1H NMR spectroscopy using methanesulfonylmethane as the internal standard. In this case the mechanism would involve the silylation of the alcohol with a silylium ion to form an intermediate such as **A** (Scheme 72). The alcohol would then be activated by a second silylation to form the leaving group, allowing the amine cyclisation to occur. However, as mentioned above (Scheme 74) the reduction of this activated intermediate could also be possible, although the presence of this product could not be determined from the ^1H NMR spectrum of the reaction mixture.



*Scheme 75. Cyclisation of amino alcohol **97a**, derived from 1,2-oxazine **90a**, to 3-pyrroline **91a** using the deoxygenative ring contraction conditions.*

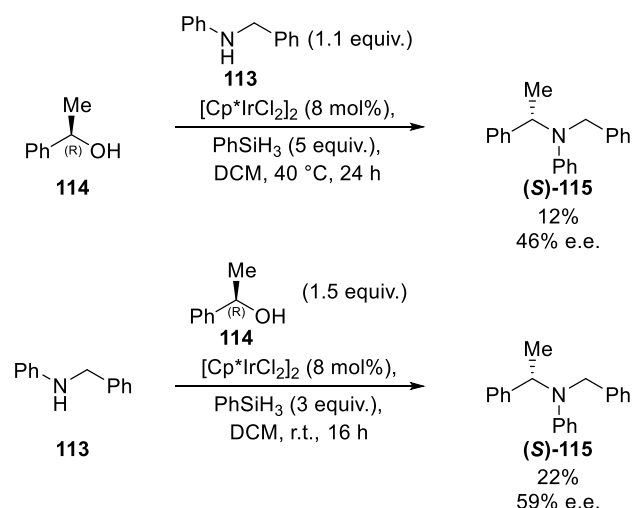
When the reaction was performed at significantly higher concentrations a decrease in the yield of the reaction was observed further suggesting the presence of these activated intermediates.

If the concentration of the reaction is too high, after the second activation of the alcohol, a competing polymerisation reaction could occur instead of cyclisation. This results from the amine of another molecule of the amino alcohol or amino silyl ether intermediate undergoing an intermolecular nucleophilic displacement on the activated alcohol to form oligomer and polymer chains (Scheme 76). The masses of side products of this nature have been observed by LC-MS and could also account for some of the mass balance (in addition to reduction products such as **111** or **112** – Scheme 74) in reactions where full consumption of the 1,2-oxazine or 1,2-oxazinane was observed but the desired ring contracted heterocycles were only isolated in poor or moderate yields.



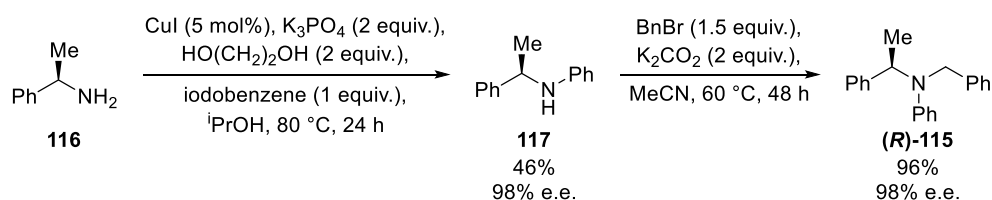
Scheme 76. Possible polymerisation side reaction of the activated amino alcohol intermediate.

Some evidence for the inversion of configuration of intermediate **B** to **C** has already been discussed in Section 2.2. This includes: (a) the comparison of our products obtained from the ring contraction to authentic samples made by an alternative method, (b) the ring contraction of 3,6-*cis* substituted regioisomers **90e** and **90e'** to give a single *trans* disubstituted 3-pyrroline product **91d**, and (c) the unambiguous X-ray crystal structure of the *trans* pyrrolidine **99b** derived from the *cis* 1,2-oxazinane **96b**. However, this inversion of configuration has also been demonstrated in a related intermolecular alkylation of amines with alcohols using our reaction conditions.



Scheme 77. Alkylation of *N*-benzylaniline **113** with enantioenriched (*R*)-1-phenylethanol **114** using the deoxygenative ring contraction reaction conditions.

As depicted in Scheme 77 the alkylation of *N*-benzylaniline **113** with enantioenriched (*R*)-1-phenylethanol **114** using PhSiH_3 and a catalytic quantity of $[\text{Cp}^*\text{IrCl}_2]_2$ proceeded in 12% yield to give tertiary amine (**S**)-**115** in 46% e.e. This inversion of configuration was verified using chiral HPLC by comparing our result against an independently synthesised enantioenriched sample of the tertiary amine product. Commercially available chiral primary amine **116** was arylated with iodobenzene using a literature procedure documented by Buchwald and co-workers to give secondary amine **117** (Scheme 78).³²³ Alkylation of this amine with benzyl bromide afforded the chiral tertiary amine product (**R**)-**115** in 96% yield and 98% e.e. (Scheme 78). Both the yield and enantiomeric excess for the iridium-catalysed reaction were increased when employing the amine as the limiting reagent with 1.5 equivalents of the chiral alcohol (Scheme 77 Bottom).



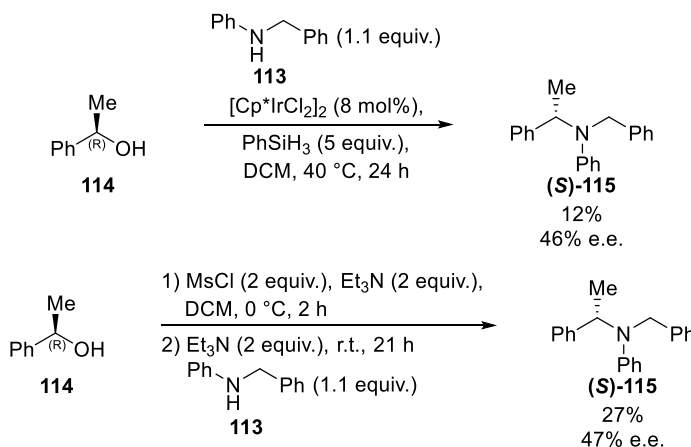
Scheme 78. Independent synthesis of an authentic enantioenriched sample of chiral tertiary amine (**R**)-**115** via known procedures.

Based on the mechanism for the ring contraction described above, the initial activation of the chiral alcohol **114** with silylium ions enhances the leaving group ability of the alcohol. This electrophilic intermediate can then undergo an $\text{S}_{\text{N}}2$ displacement reaction with the nucleophilic

amine, leading to the inversion of the chiral centre. However, the reduced e.e. obtained can be rationalised by considering a competing S_N1 pathway, which would result in a loss of the chiral information held in the alcohol starting material. The low yield of this transformation predominantly results from the stalling of the reaction after approximately 6 hours leading to the poor conversion of *N*-benzylaniline to the product. The exact reason for the stalling is not fully understood but possible catalyst poisoning by the amine/ (side)products and overly rapid activation and subsequent reduction of the alcohol by the catalyst/silane combination are likely possibilities.

2.4. Discovery of a New *N*-Alkylation of Amines Using Alcohols

As mentioned above (Section 2.3), during the course of our investigations into the mechanism of the deoxygenative ring contraction, a novel alkylation reaction was discovered. Subjecting a secondary aniline **113** to the deoxygenative ring contraction conditions in the presence of the chiral alcohol (*R*)-1-phenylethanol **114** yielded a small amount of the enantioenriched alkylated tertiary amine product (**S**)-**115** in 12% yield and 46% e.e. (Scheme 79 Top).



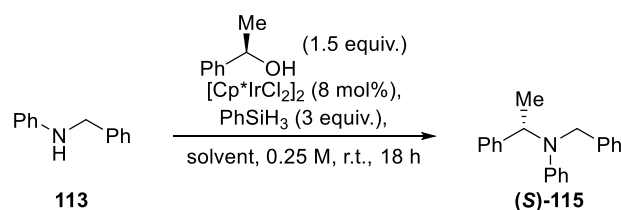
Scheme 79. Initial comparison of the alkylation of *N*-benzylaniline using our deoxygenative ring contraction conditions vs. mesylation conditions.

When the same reaction was carried out *via* the mesylation of the chiral alcohol followed by S_N2 displacement of the mesylate with the *N*-benzylaniline, a similar e.e. of 47% was obtained (Scheme 79 Bottom). This can be attributed to a competing S_N1 mechanism in which the stabilised benzylic secondary carbocation can form, eroding the optical purity of the alkylating

Results and Discussion

reagent before substitution by the amine occurs. Alternatively, the carbocation could be intercepted by Cl^- , again leading to the erosion of optical purity.

Based on this initial result we hoped to develop this reaction into an efficient and practical alkylation of secondary amines to acquire highly enantioenriched tertiary amines. It was quickly found that using an excess of the chiral alcohol led to an improved yield and enantioexcess for the reaction. Thus, this result formed the starting point for further investigations into this reaction. All screening reactions were conducted in conventional screw cap vials on a 0.25 mmol scale with respect to the *N*-benzylaniline starting material and the assay yields and enantioexcesses were determined by chiral SFC-MS using a calibration curve.



Entry	Solvent	Yield/ % ^a	% e.e. ^b
1	DCM	22	59
2 ^c	DCM	7	61
3	chloroform	11	68
4	DCE	15	46
5	chlorobenzene	18	66
6	fluorobenzene	19	66
7	trifluorotoluene	20	67
8	1-chlorobutane	20	71
9	MTBE	15	72
10	anisole	13	66
11	2-Me THF	9	37
12	propylene carbonate	18	66
13	sulfolane	21	26
14	hexane	10	75
15	toluene	9	69
16	Dowtherm A	15	71

^aYields are assay yields determined by chiral SFC-MS. ^bDetermined by chiral SFC-MS. ^c0.5 M reaction concentration.

Table 15. Solvent screening for the iridium-catalysed alkylation of amines with alcohols.

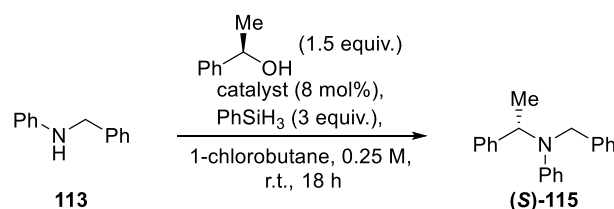
We began our investigation by screening a number of reaction solvents (Table 15). DCM is the solvent used in the deoxygenative ring contraction (detailed in Sections 2.1 to 2.3) and was able to furnish the tertiary amine product **(S)**-**115** in 22% yield and 59% e.e. (Entry 1). The low yield obtained for this reaction is due to the incomplete reaction of the *N*-benzylaniline starting material, which was present at 65% at the end of the reaction. Furthermore, in all of the future screening reactions outlined below the reaction failed to go to completion and considerable amounts of the starting secondary amine **113** were remaining after the reaction had ended.

Increasing the concentration was deleterious to the yield, possibly due to an increase in the rate of a competing reductive deoxygenation of the alcohol, thus removing the alkylating reagent from the reaction mixture (Entry 2). Both chloroform (Entry 3) and DCE (Entry 4) were less efficient at promoting the desired transformation, returning the product in 11% and 15% yields respectively. In contrast, chlorobenzene, fluorobenzene and trifluorotoluene gave similar yields to DCM but the e.e. values in these solvents were noticeably higher than for DCM (Entries 5-7). 1-Chlorobutane showed slight improvements over these other halogenated solvents, giving **(S)**-**115** in 20% yield and 71% e.e. (Entry 8). The reaction was less efficient in ethereal solvents, which was observed in the generally lower yields and e.e. values obtained in these cases (Entries 9-11). Propylene carbonate (Entry 12) showed comparable efficacy to the halogenated solvents (Entries 5-7) whilst the polar aprotic solvent sulfolane (Entry 13) – a popular substitute for DMSO – gave 21% of **(S)**-**115** (a comparable yield to DCM) but with a significantly reduced e.e. of 26%.

The polar aprotic solvents propylene carbonate (Entry 12) and sulfolane (Entry 13) gave comparable yields of **(S)**-**115** to DCM. However, whilst an e.e. of 66% was obtained in propylene carbonate, a disappointing e.e. of 26% was obtained using sulfolane as the solvent. On the other hand, non-polar solvents such as hexane, toluene and Dowtherm A (a eutectic mixture of 26% biphenyl and 74% diphenyl ether) offered lower yields of **(S)**-**115** but in higher enantioexcesses (Entries 14-16). The lower yields were attributed to the poor solubility of the starting materials and iridium catalyst in these solvents.

Polar solvents (Entries 4, 11 and 13) may give rise to lower e.e. values due to their greater ability to stabilise a carbocation that could form upon loss of the oxygen leaving group, thus possibly enabling a competing S_N1 pathway to occur. In contrast, more non-polar solvents (Entries 8, 9

and 14-16) would not be able to stabilise the positive charge from a developing carbocation and so an S_N2-type pathway that goes with inversion of configuration is more likely, leading to the generally higher enantiomeric excesses. 1-Chlorobutane was selected as the solvent going forward owing to a good balance in the yield and e.e. of **(S)**-115.



Entry	Catalyst	Yield/ % ^a	% e.e. ^b
1	[Cp*IrCl ₂] ₂	20	71
2	[Ir(COD)Cl] ₂	17	67
3 ^c	[Ir(COE) ₂ Cl] ₂	14	62
4	[Cp*RhCl ₂] ₂	7	78
5	[Ru(<i>p</i> -cymene)Cl ₂] ₂	5	55
6	[Cu(COD)Cl] ₂	0	0
7	Pd(OAc) ₂	0	0

^aYields are assay yields determined by chiral SFC-MS. ^bDetermined by chiral SFC-MS. ^c5 equivalents of chiral alcohol used.

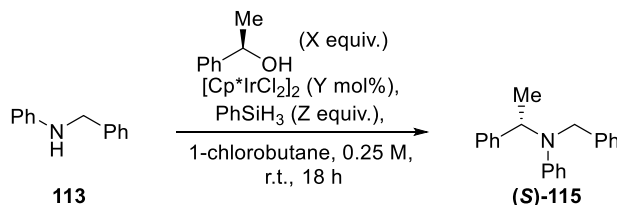
Table 16. Catalysts screened for the alkylation of *N*-benzylaniline with (*R*)-1-phenylethanol.

Next, a series of other catalysts were screened in the transformation (Table 16). These included [Cp*IrCl₂]₂, [Ir(COD)Cl]₂, [Ir(COE)₂Cl]₂, [Cp*RhCl₂]₂, [Ru(*p*-cymene)Cl₂]₂, [Cu(COD)Cl]₂ and Pd(OAc)₂. However, with the exception of [Ir(COD)Cl]₂ (Entry 2) which was of comparable efficacy to [Cp*IrCl₂]₂ (Entry 1), all of these other catalysts did not promote the alkylation reaction to a significant degree (Entries 3-7). Furthermore, since PhSiH₃ was one of only a few silanes found to successfully promote the deoxygenative ring contraction no other silanes have yet been screened in this reaction.

The most significant improvements in both the yield and e.e. of the reaction were observed when the stoichiometry of the reagents was altered (Table 17). From the initial result obtained in 1-chlorobutane in which **(S)**-115 was obtained in 20% yield and 71% e.e. (Entry 1), increasing the amount of the chiral alcohol to five equivalents gave small increases to both the yield and enantiomeric excess (Entry 2). Furthermore, the use of two additional equivalents of PhSiH₃ in tandem with the five equivalents of the alcohol gave **(S)**-115 in a 42% yield at the expense of a

Results and Discussion

small drop in the e.e. (Entry 3). Predictably, lowering the concentration of the reaction under these conditions resulted in a decrease in the yield of the desired tertiary amine product (Entry 4).



Entry	Alcohol equivalents X	[Cp*IrCl ₂] ₂ / mol%	Silane equivalents Z	Yield/ % ^a	% e.e. ^b
1	1.5	8	3	20	71
2	5	8	3	26	79
3	5	8	5	42	73
4 ^c	5	8	5	33	71
5	5	8	10	24	75
6	5	8	12	24	75
7	10	8	5	43	88
8	5	1	5	14	80
9	5	2	5	22	82
10	5	4	5	35	79
11	5	6	5	34	75
12	5	12	3	38	73
13	10	4	5	43	89
14	15	4	10	39	95

^aYields are assay yields determined by chiral SFC-MS. ^bDetermined by chiral SFC-MS. ^c0.125 M reaction concentration used.

Table 17. The effect of stoichiometry of the alcohol, silane and catalyst in the alkylation reaction of *N*-benzylaniline with (*R*)-1-phenylethanol.

Further increasing the amount of PhSiH₃ above five equivalents started to have a detrimental effect on the yield (Entries 5 and 6). It is likely that under these conditions the larger quantity of silane enables the reductive deoxygenation of the alcohol to occur to a greater extent. As a result, there would be less of the alcohol available to form the alkylating agent needed by the reaction, thus forming reduced quantities of tertiary amine (**(S)**-115).

Fortunately, returning to the use of five equivalents of PhSiH_3 and by further increasing the number of equivalents of the alcohol component to ten, 43% of the tertiary amine product was obtained in 88% e.e. (Entry 7), with 53% of unreacted *N*-benzylaniline remaining. With this promising result we next hoped to reduce the loading of the catalyst in the reaction. In combination with five equivalents of both PhSiH_3 and (*R*)-1-phenylethanol, the use of 1 mol% of the iridium catalyst (Entry 8) gave **(S)**-115 in a disappointing yield of 14% despite the greater enantiomeric excess relative to 8 mol% (1 mol% gave 80% e.e. vs. 8 mol% gave 73% e.e.). Doubling the quantity of the catalyst added to 2 mol% resulted in only a marginal increase in both the e.e. and yield of the reaction (Entry 9). Pleasingly however, when using 4 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$, **(S)**-115 was obtained in 35% yield and 79% e.e. (Entry 10). This result shows an increase in the e.e. of **(S)**-115 (relative to the use of 8 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$) at the expense of only a small portion of the yield. Further increases to the quantity of $[\text{Cp}^*\text{IrCl}_2]_2$ used to 6 mol% (Entry 11) and 12 mol% (Entry 12) offered no additional benefits to the reaction as **(S)**-115 was obtained in comparable yields of 34% and 38% respectively but with lower enantiomeric excesses.

By using 4 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$ and large excesses of (*R*)-1-phenylethanol, the yield and enantiomeric excess of the alkylation reaction of *N*-benzylaniline were greatly improved (Entries 13 and 14). With ten equivalents of the alcohol, the tertiary amine product could be obtained in modest yield and impressive enantiomeric excess (Entry 13). Despite this higher yield however, 52% of the *N*-benzylaniline starting material was still present after 18 hours. Pleasingly, this result is similar to that of Entry 7 (which used 8 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$ instead) indicating that higher quantities of the catalyst in the reaction aren't necessary. Upon further increasing the amount of alcohol and silane used in the reaction the alkylation product **(S)**-115 could be obtained in an acceptable yield but very high enantiopurity. Sadly, at present the disadvantage to these reaction conditions lies in the apparent requirement for large excesses of the chiral alcohol which are often expensive or require prior synthesis. Fortunately, some chiral alcohol derivatives are not prohibitively expensive and are available from commercial vendors.

Other factors were considered during this optimisation study including the order of addition of the reagents, the slow or portion-wise addition of the reagents to the reaction and the reaction

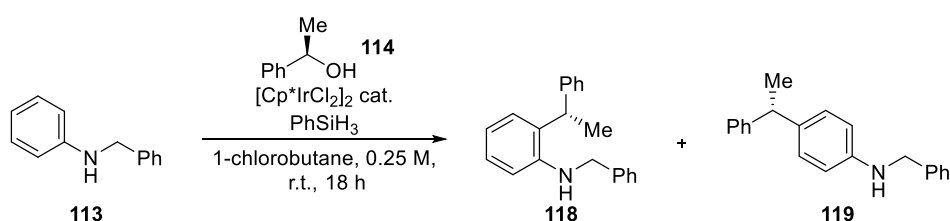
temperature. However, in all cases no further improvements to either the yield or e.e. were observed.

As mentioned above, significant quantities of the *N*-benzylaniline starting material were still present in the reaction mixture (in the order of 50-70%) after 18 hours. In order to gain an understanding of this observation, the alkylation reaction was monitored by SFC-MS by taking small aliquots of the reactions every hour. Interestingly the reaction progressed quickly in the first 2 hours after initiation before slowing down substantially over the next 4 hours. A final aliquot taken 23 hours after the previous showed that there was still a significant quantity of *N*-benzylaniline remaining in the mixture and that negligible change to the reaction composition had taken place during this time. This suggests that the reaction stalls after about 6 hours, preventing any further alkylation of the *N*-benzylaniline starting material to the tertiary amine product **(S)-115**.

The exact reason for this observed stalling is not currently known however, the poisoning of the active catalytic species by the amine starting material and/or products could be a possibility. Based on the observation of this stalling we repeated the reaction using our optimal conditions (Entry 13, Table 17) but after 5 hours added an additional five equivalents of PhSiH_3 and 4 mol% of $[\text{Cp}^*\text{IrCl}_2]_2$ and left for a further 16 hours. Although the yield after this time had improved marginally to give 49% of the desired tertiary amine **(S)-115**, the e.e. dropped to 80%. Additionally, 39% of the *N*-benzylaniline still remained unreacted in the reaction mixture. In this case, it is likely that after the first 5 hours the majority of the chiral alcohol had been consumed, either through the alkylation reaction or *via* a competitive deoxygenation. As such, the further addition of iridium catalyst and PhSiH_3 would not provide substantial increases to the yield of **(S)-115** as the key alkylating reagent had largely been consumed.

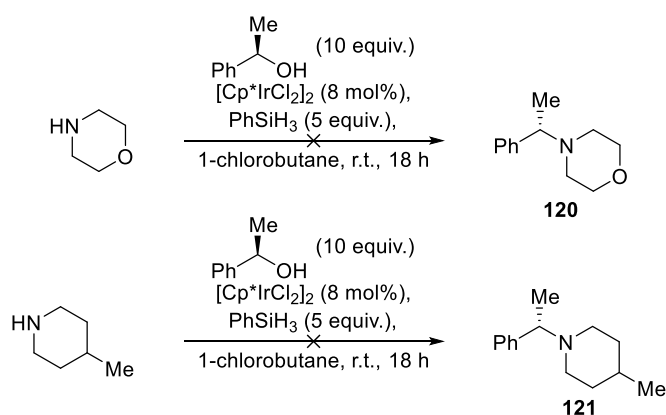
In the majority of the screening reactions described above, the considerable quantities of *N*-benzylaniline remaining at the end of the reaction accounted for the majority of the remaining mass balance. However, during the course of the optimisation of this reaction a few side products with the same mass as the desired product ($[\text{M}+\text{H}^+] = 288.2 \text{ mu}$) were observed in the SFC-MS chromatograms. Although not quantitatively analysed, these signals often indicated that similar e.e. values were obtained for these side products as for the desired product in that

reaction. Therefore, the structures of these products have been tentatively assigned as the *ortho* (**118**) and *para*-substitution (**119**) products of a competing S_EAr (Friedel-Crafts-like) reaction of the aniline ring of the starting secondary amine **113** (Scheme 80). Sadly though, to date these side products have not been successfully isolated from the reaction to validate the proposed structures.



Scheme 80. Possible S_EAr (Friedel-Crafts-like) side products **118** and **119** from the iridium-catalysed alkylation of *N*-benzylaniline **113** with (*R*)-1-phenylethanol **114**.

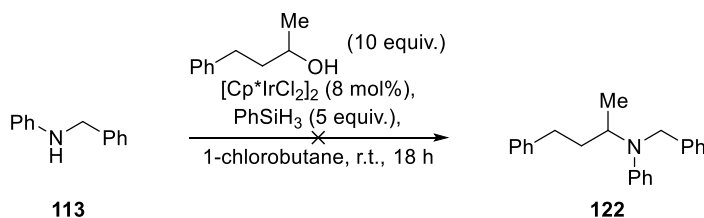
In addition to *N*-benzylaniline, two other secondary amines were considered for the iridium-catalysed alkylation reaction, namely morpholine and 4-methylpiperidine (Scheme 81). However, as observed for the iridium-catalysed deoxygenative ring contraction of 1,2-oxazines without *N*-aryl substituents, none of the tertiary amine products **120** or **121** were observed by SFC-MS of the crude reaction mixtures. The lack of any significant reaction occurring in these cases again indicates the possible inhibitory effects of more basic amine substrates towards the alkylation process possibly by poisoning the active catalytic species.



Scheme 81. Attempted use of additional amines in the iridium-catalysed alkylation reaction.

Likewise, when 1-phenylethanol was substituted with an analogous unactivated secondary alcohol, only traces of the desired product were detected by UPLC-MS (Scheme 82). With this

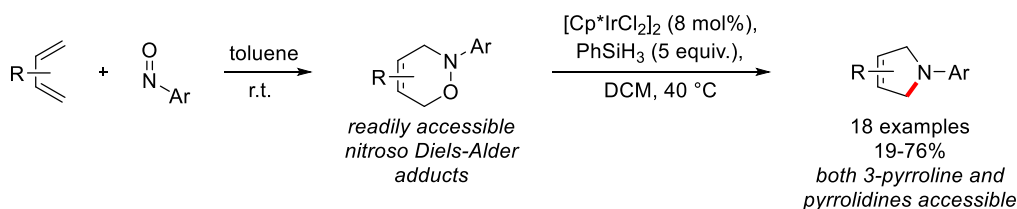
alcohol reaction partner the competing deoxygenation reaction may be more significant thus drastically reducing the quantity of the alkylating reagent available to react with *N*-benzylaniline. However, in this case, heating the reaction to improve the rate of the desired transformation could be beneficial.



Scheme 82. Alkylation of N-benzylaniline using an alternative alcohol.

The continued development of this alkylation reaction is being explored within the Denton group with the aim to further improve the yields initially discovered here and then apply those conditions to the synthesis of a number of chiral tertiary amines.

2.5. Conclusions and Future Work



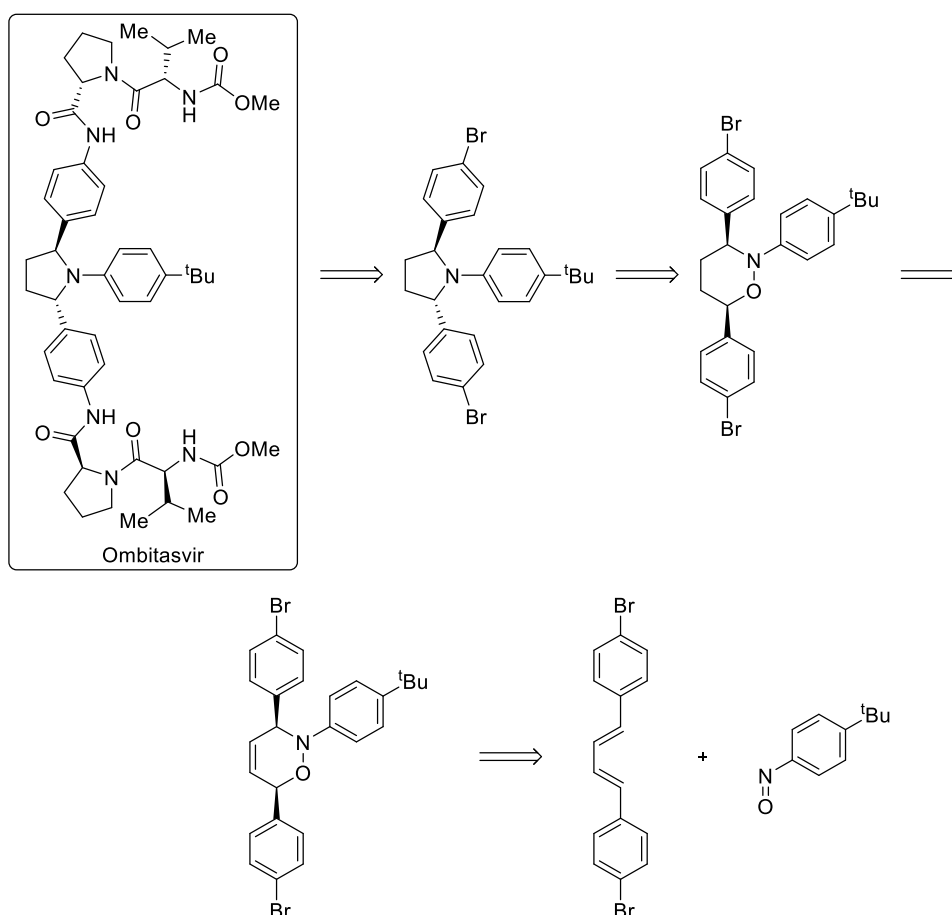
Scheme 83. Iridium-catalysed deoxygenative ring contraction of 1,2-oxazines and 1,2-oxazinanes using PhSiH₃ as the terminal reductant.

To conclude, a novel iridium-catalysed deoxygenative ring contraction of 1,2-oxazines and 1,2-oxazinanes using PhSiH₃ as the terminal reductant has been disclosed (Scheme 83). When paired with the nitroso Diels-Alder reaction the sequential [4+2] cycloaddition/ deoxygenative ring contraction protocol offers an expedient convergent synthesis of substituted 3-pyrroline and pyrrolidine architectures. A large number of reaction conditions were screened including various monomeric and dimeric metal catalysts, mono-, di- and trihydridic silanes as well as a number of halogenated and non-halogenated solvents. Ultimately however, catalytic quantities of [Cp*IrCl₂]₂ paired with PhSiH₃ in DCM proved to be the most effective and appropriate conditions tested.

The deoxygenative ring contraction of 1,2-oxazines enabled the isolation of an assortment of 3-pyrroline products in yields ranging from 19% to 55% exhibiting both structural and functional group tolerance. Furthermore, the reaction has been conducted on a 10 mmol scale without any appreciable losses in the yield. Likewise, pyrrolidines could be obtained from the corresponding 1,2-oxazinanes in typically better yields (40% to 76%) and possible reasons for the discrepancies between their yields have been outlined. The methodology developed here was then applied as the key step in the attempted total synthesis of the amino sugar ($\pm$)-DMDP. Despite the successful ring contraction to the required 3-pyrroline, the subsequent steps failed to advance the synthesis and so further investigations were ceased.

A plausible mechanism for the deoxygenative ring contraction has been proposed, supported by experimental and spectroscopic observations. Finally, from the investigation into this reaction mechanism a novel alkylation of secondary amines with chiral alcohols using our deoxygenative ring contraction reaction conditions has been discovered. Early optimisation studies of this reaction have improved both the yield and e.e. of the obtained tertiary amine product from 12% in 46% e.e. to 43% in 89% e.e. Further development of this reaction is still ongoing within the Denton group.

In the future, the scope of the deoxygenative ring contraction could be expanded to enable the synthesis of enantioenriched 3-pyrrolines and pyrrolidines. This would require the use of enantioselective syntheses of the 1,2-oxazine precursors which have been documented in the literature.^{324–326} Given the problems encountered during the total synthesis of ($\pm$)-DMDP, further screening of reaction conditions for the deprotection of one of the 3-pyrroline products would enable the possible completion of this sequence. To this end a ruthenium-catalysed reductive deamination of anilines published by Kakiuchi and co-workers could provide a means for the deprotection of the *N*-aryl 3-pyrroline products.³²⁷



Scheme 84. Key retrosynthetic disconnections of Ombitasvir using the deoxygenative ring contraction as a key step.

However, failing the deprotection, an alternative target of interest has been identified. Ombitasvir, an antiviral drug for the treatment of hepatitis C virus, is a 2,5 *trans* disubstituted *N*-aryl pyrrolidine which could be synthesised *via* the deoxygenative ring contraction of the corresponding 1,2-oxazinane. Some key retrosynthetic disconnections have been outlined in Scheme 84.

With respect to the alkylation reaction of amines with chiral alcohols, additional reaction conditions can be screened to improve on the modest yields currently seen. Upon finding acceptable conditions, the methodology could be applied to the synthesis of a number of chiral tertiary amine products. Furthermore, these conditions could be used in the cyclisation of amino alcohol substrates in order to access a number of cyclic amines.

3. Experimental

3.1. General Experimental Information

Reagents and anhydrous solvents were used throughout the below procedures as purchased without any further purification unless otherwise stated. Anhydrous solvents were obtained from towers or distilled and stored over an appropriate drying agent (4 Å molecular sieves or Na wire). $[\text{Cp}^*\text{IrCl}_2]_2$ was either purchased from Acros Organics and used without further purification or synthesised according to a literature procedure.³²⁸ 'Room temperature' varied between 15 °C and 30 °C. Reactions were carried out in oven- or flame-dried glassware and under an Ar or N₂ atmosphere unless otherwise indicated. The synthesis of 1,2-oxazines and all Ir-catalysed deoxygenative ring contraction reactions post-optimisation were carried out under an atmosphere of air in non-dried glassware and using Winchester grade solvent. Manipulations involving complex **92** were conducted in dry glassware using anhydrous degassed solvent under an atmosphere of N₂.

Analytical thin layer chromatography (TLC) was performed on Merck aluminium-backed silica gel 60 F254 plates and visualised by UV irradiation (254 nm) or by staining with a solution of potassium permanganate. Flash column chromatography was performed using pore 60 Å, 40-63 µm silica gel and where specified filtrations were carried out using non-washed diatomaceous earth (Celite®). NMR spectra were acquired with Bruker AV(III)400HD and Bruker AV(III)500HD spectrometers using CDCl₃ or C₆D₆ as a solvent, operating at 400 or 500 MHz for ¹H, 101 or 126 MHz for ¹³C, 128 MHz for ¹¹B, 376 MHz for ¹⁹F, 162 MHz for ³¹P and 79 MHz for ²⁹Si. Chemical shifts (δ) are reported in ppm relative to residual solvent signals: CDCl₃, 7.26 ppm for ¹H NMR and 77.0 ppm for ¹³C NMR; C₆D₆, 7.16 ppm for ¹H NMR and 128.1 ppm for ¹³C NMR. In all ¹H NMR spectra, multiplicity is indicated as follows: br s (broad singlet), s (singlet), d (doublet), t (triplet), m (multiplet), app. (apparent) *etc.* Coupling constant, *J*, values (in Hz), number of protons for each signal and assignments are also indicated. ¹³C, ¹⁹F, ²⁹Si and ³¹P NMR experiments were run with ¹H decoupling. Where possible full structural assignments were made with the aid of appropriate 2D NMR experiments (HSQC, HMBC, COSY and NOESY). Where appropriate proximal and distal isomers of 1,2-oxazines were assigned with the assistance of

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their 2D ^1H NOESY spectra. Mass spectra were obtained with a Bruker microTOF II using a positive (ESI+) or negative (ESI-) electrospray ionization technique. Obtained data are expressed in mass/charge (m/z) units. IR spectra were acquired on a Bruker Alpha spectrometer using an Alpha-P ATR sampling module. Melting points were measured in capillary tubes using a Gallenkamp melting point apparatus.

3.2. General Procedures

Deoxygenative Ring Contraction Reaction Optimisation Procedure

To a stirred solution of 1,2-oxazine (0.2 mmol) and catalyst (X mol%) (Section 2.1, Tables 1-6) in solvent (0.8 mL) (Section 2.1, Tables 7 and 8) was added silane (Y equiv.) (Section 2.1, Tables 10 and 11) and the mixture was heated at a given temperature (Section 2.1, Tables 7 and 8) for 24 h. The reaction mixture was cooled to room temperature and concentrated by approximately 50% [the reactions could not be concentrated to dryness due to formation of a sticky insoluble gel]. CDCl_3 (1 mL) and methanesulfonylmethane (1 equiv.) were added and the mixture was analysed by ^1H NMR spectroscopy.

General Procedure 1: Deoxygenative ring contraction

To a stirred solution of 1,2-oxazine or 1,2-oxazinane (1.0 equiv.) and $[\text{Cp}^*\text{IrCl}_2]_2$ (8 mol%) in DCM (0.125 M with respect to 1,2-oxazine) was added PhSiH_3 (5.0 equiv.) in one portion. The mixture was heated at 40 °C for 24 h before cooling to room temperature and adding silica (~2 g/ 0.4 mmol). The slurry was stirred at room temperature for 30 min or until fizzing had ceased and the solvent was removed *in vacuo*. Purification by column chromatography or preparative TLC gave the 3-pyrroline or pyrrolidine products.

General Procedure 2: Diimide reduction

To a stirred suspension of 1,2-oxazine (1.0 equiv.) and TsNHNH_2 (12 equiv.) in THF (0.1 M with respect to 1,2-oxazine) was added NaOAc (12 equiv.). The suspension was heated at reflux for 72-96 h. The reaction mixture was cooled to room temperature and diluted with EtOAc and NaOH (1 M aqueous solution). The aqueous layer was extracted with EtOAc three times and the

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combined organics were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography gave the 1,2-oxazinane products.

DMDO preparation:



To a vigorously stirred suspension of NaHCO_3 (24.0 g, 285 mmol) in H_2O (20 mL) at 0 °C was added acetone (30.0 mL, 405 mmol). The suspension was stirred at 0 °C for 15 min before the stirring was stopped and oxone (25.0 g, 40.6 mmol) was added in one portion. The stirring was then gradually increased until vigorous and continued for 15 min. The reaction flask was equipped with a splash guard then attached to a rotary evaporator with the bath at room temperature (see above image). The splash guard was cooled to -50 °C and a vacuum of ~200 mbar was maintained with rotation of 250 rpm for 15 min. After 15 min, the bath temperature was raised to 40 °C over 10 min. and upon reaching 40 °C the vacuum was released. The pale-yellow solution collected in the splash guard was dried over Na_2SO_4 and filtered to give a solution of DMDO in acetone (approximate volume of 25 mL of a 0.055 M solution).

The concentration of the solution was estimated as follows. Thioanisole (88.6 mg, 0.713 mmol) was dissolved in acetone- d_6 (1 mL) at 0 °C. The DMDO solution (2.0 mL) was added to 0.6 mL of the thioanisole solution at 0 °C and the mixture was stirred for 15 min before the resulting solution was analysed by ^1H NMR spectroscopy. Comparison of the integrations of the signals for the sulfoxide phenyl protons at δ 7.73-7.52 ppm vs. the thioanisole phenyl protons at δ 7.34-7.12 ppm allows for determination of the ratio of oxidized product to excess thioanisole. From this data, the concentration of the larger DMDO solution was calculated.

Experimental

TFDO preparation:



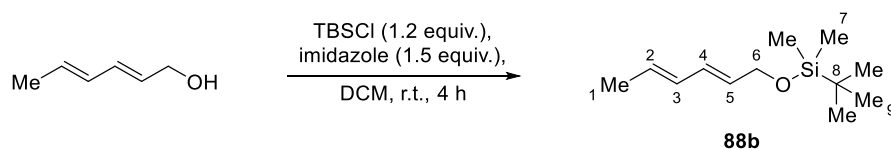
Prior to the reaction all glassware was rinsed with a 0.1 M aqueous solution of EDTA to remove any trace metal contaminants. The glassware was assembled and then wrapped in aluminium foil to protect the TFDO from the light (see above image). To a three-necked round bottomed flask attached by a hose connector to a condenser maintained at -78°C and receiving flask was added NaHCO_3 (26.0 g, 309 mmol) and H_2O (26 mL). The mixture was cooled to 0°C and oxone (48.0 g, 78.0 mmol) was added portionwise over 5 min to the vigorously stirred suspension during which time vigorous gas evolution was observed. Precooled (-20°C) trifluoroacetone (20.0 mL, 223 mmol) was added quickly in one portion and the pale-yellow solution of the methyl(trifluoromethyl)dioxirane (TFDO) in trifluoroacetone immediately started to collect in the receiving flask cooled to -78°C . The reaction was left stirring at 0°C for 30 min before tightly closing the receiving flask, wrapping it with aluminum foil and storing at -78°C to give a solution of TFDO in trifluoroacetone (approximate volume of 6.0 mL of a 0.2 M solution). Concentration determined as above.

Iridium-catalysed alkylation of amines with alcohols optimisation procedure.

To a suspension of *N*-benzylaniline (45.8 mg, 0.200 mmol) and catalyst (Section 2.4, Tables 16 and 17) in solvent (Section 2.4, Table 15, 0.25 M with respect to *N*-benzylaniline) was added (*R*)-1-phenylethanol (X equiv., Section 2.4, Table 17) immediately followed by PhSiH_3 (Y equiv., Section 2.4, Table 17) and the mixture was stirred at room temperature for 16 h. The mixture was quenched with MeOH (1 mL) and a measured aliquot was taken and diluted to 5 mL with IPA for sample analysis by SFC-MS.

3.3. Synthesis of Compounds

tert-Butyl(((2*E*,4*E*)-hexa-2,4-dien-1-yl)oxy)dimethylsilane **88b**.

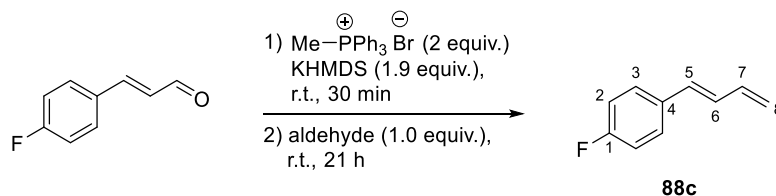


To a stirred suspension of *E,E*-2,4-hexadiene-1-ol (0.981 g, 10.0 mmol) and imidazole (1.02 g, 15.0 mmol) in DCM (5 mL) was added a solution of TBSCl (1.58 g, 10.5 mmol) in DCM (10 mL) over 30 min and the mixture was stirred at room temperature for 4 h. H₂O (15 mL) was added and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography using pentane as the eluent (*R*_f 0.13) gave the product, *tert*-butyl(((2*E*,4*E*)-hexa-2,4-dien-1-yl)oxy)dimethylsilane **88b** (1.93 g, 9.10 mmol, 91%), as a colourless oil.

IR v max (ATR)/ 3021, 2955, 2856, 1472, 1253, 1108 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 6.17 (1H, ddt, *J* 14.7, 10.2, 1.7 Hz, H-4), 6.05-6.04 (1H, m, H-3), 5.72-5.58 (2H, m, H-2 and H-5), 4.19 (2H, d, *J* 5.3 Hz, H-6), 1.75 (3H, d, *J* 6.7 Hz, H-1), 0.91 (9H, s, H-9), 0.07 (6H, s, H-7) ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 131.1 (C-3), 130.4 (C-4), 130.0 (C-2 or C-5), 129.1 (C-2 or C-5), 63.8 (C-6), 26.1 (C-9), 18.5 (C-8), 18.2 (C-1), -5.0 (C-7) ppm.

Data in agreement with the literature.³²⁹

(*E*)-1-(4-Fluorophenyl)-3-penten-2-one **88c**.



To a suspension of methyltriphenylphosphonium bromide (28.6 g, 80.1 mmol) in THF (400 mL) was added KHMDS (74.0 mL, 74.0 mmol of a 1.00 M solution in THF). The resulting bright yellow suspension was stirred for 30 min before 4-fluorocinnamaldehyde (5.25 mL, 40.1 mmol) was

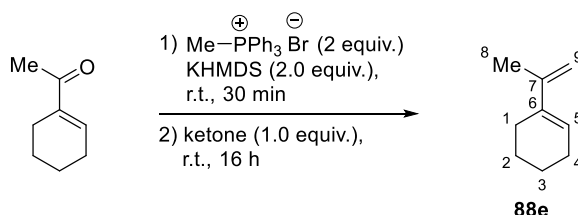
Experimental

added and left to stir at room temperature for 21 h. The mixture was concentrated to approx. 50 mL, pentane (200 mL) was added and the orange mixture was filtered through Celite®. The filtrate was collected and the solvent was removed *in vacuo*. The crude brown oil was purified by column chromatography using pentane (R_f 0.37) as the eluent to give the title compound, (*E*)-1-(buta-1,3-dien-1-yl)-4-fluorobenzene **88c** (5.42 g, 36.6 mmol, 92%), as a colourless oil.

IR ν max (ATR)/ 3093, 3065, 2891, 2872, 2829, 1598, 1507, 1494, 1216, 1154 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; C_6D_6) 6.95-6.90 (2H, m, H-3), 6.76-6.71 (2H, m, H-2), 6.48 (1H, dd, J 15.6, 10.4 Hz, H-6), 6.39-6.30 (1H, m, H-7), 6.22 (1H, d, J 15.6 Hz, H-5), 5.19 (1H, dd, J 16.9, 1.4 Hz, H-8'), 5.05 (1H, dd, J 10.3, 1.4 Hz, H-8) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; C_6D_6) 162.8 (d, J 247.0 Hz, C-1), 137.5 (C-7), 133.7 (d, J 3.3 Hz, C-4), 132.0 (C-5), 129.7 (d, J 2.4 Hz, C-6), 128.3 (d, J 7.8 Hz, H-3), 117.5 (C-8), 115.7 (d, J 21.7 Hz, H-2) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376 MHz; C_6D_6) -114.09 ppm.

Data in agreement with the literature.³³⁰

1-(Prop-1-en-2-yl)cyclohex-1-ene **88e**.



To a suspension of methyltriphenylphosphonium bromide (7.14 g, 20.0 mmol) in dry THF (100 mL) was added KHMDS (20.0 mL, 20.0 mmol of a 1.00 M solution in THF) over 30 min. The resulting bright yellow suspension was stirred for 30 min before 1-acetyl-1-cyclohexene (1.28 mL, 10.0 mmol) was added and left to stir at room temperature for 16 h. The solvent was removed *in vacuo* and pentane (50 mL) was added to the residue, the mixture was filtered through Celite® and the solvent was removed *in vacuo*. The pale-yellow oil was flushed through a silica plug using pentane to give the title compound, 1-(prop-1-en-2-yl)cyclohex-1-ene **88e** (0.915 g, 7.49 mmol, 75%), as a colourless oil.

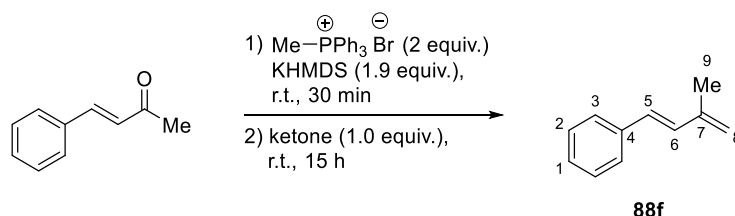
IR ν max (ATR)/ 3091, 2926, 2859, 1607, 1437, 918, 880 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 5.89 (1H, dd, J 4.1, 4.1 Hz, H-5), 4.95 (1H, brs, H-9), 4.83 (1H, brs, H-9'), 2.25-2.19 (2H, m, H-1), 2.18-

Experimental

2.12 (2H, m, H-4), 1.90 (3H, s, H-8), 1.71-1.65 (2H, m, H-2), 1.62-1.54 (2H, m, H-3) ppm.; $^{13}\text{C}\{^1\text{H}\}$ NMR δ_{C} (126 MHz; CDCl_3) 144.0 (C-6), 136.7 (C-7), 125.1 (C-5), 109.6 (C-9), 26.1 (C-4), 25.7 (C-1), 23.1 (C-2), 22.4 (C-3), 20.8 (C-8) ppm.

Data in agreement with the literature.³³¹

(E)-(3-Methylbuta-1,3-dien-1-yl)benzene **88f**.



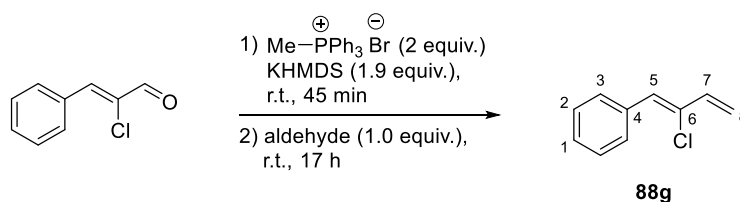
To a suspension of methyltriphenylphosphonium bromide (5.72 g, 16.0 mmol) in dry THF (70 mL) was added KHMDS (16.0 mL, 16.0 mmol of a 1.00 M solution in THF). The resulting bright yellow suspension was stirred for 30 min before 4-phenyl-3-buten-2-one (1.17 g, 8.00 mmol) was added and left to stir at room temperature for 15 h. The mixture was filtered through Celite® and the solvent was removed *in vacuo*. Pentane (50 mL) was added to the residue, the mixture was filtered through Celite® and the filtrate was washed with H_2O (15 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The pale-yellow oil was flushed through a silica plug using pentane as the eluent to give the title compound, (E)-(3-methylbuta-1,3-dien-1-yl)benzene **88f** (0.855 g, 5.92 mmol, 74%), as a colourless oil.

IR ν_{max} (ATR)/ 3080, 3025, 2972, 2947, 1604, 1493, 1445, 1376, 1216 cm^{-1} ; ^1H NMR δ_{H} (400 MHz; CDCl_3) 7.50-7.43 (2H, m, H-3), 7.35 (2H, dd, J 7.4, 7.4 Hz, H-2), 7.30-7.21 (1H, m, H-1), 6.92 (1H, d, J 16.2 Hz, H-6), 6.57 (1H, d, J 16.2 Hz, H-5), 5.15 (1H, s, H-8), 5.11 (1H, s, H-8'), 2.02 (3H, s, H-9) ppm.; $^{13}\text{C}\{^1\text{H}\}$ NMR δ_{C} (101 MHz; CDCl_3) 142.2 (C-7), 137.5 (C-4), 131.8 (C-6), 128.8 (C-5), 128.7 (C-2), 127.6 (C-1), 126.6 (C-3), 117.5 (C-8), 18.7 (C-9) ppm.

Data in agreement with the literature.³³²

Experimental

(Z)-(2-Chlorobuta-1,3-dien-1-yl)benzene **88g**.



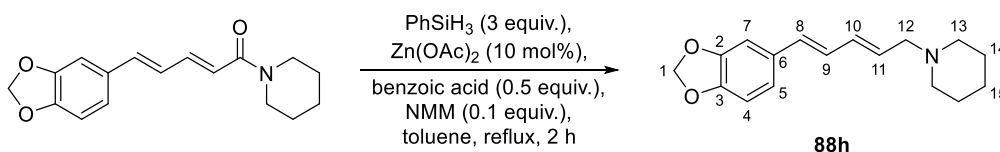
To a suspension of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol) in THF (40 mL) with was added KHMDS (10.0 mL, 10.0 mmol of a 1.00 M solution in THF). The resulting bright yellow suspension was stirred for 45 min before a solution of α -chlorocinnamaldehyde (0.932 g, 5.00 mmol) in THF (10 mL) was added and left to stir at room temperature for 17 h. The mixture was quenched with NH_4Cl (5 mL of a saturated aqueous solution) and the solvent was removed *in vacuo*. Pentane (100 mL) was added and the mixture was filtered through celite. The filtrate was collected and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography using pentane (R_f 0.37) as the eluent to give the title compound, (Z)-(2-chlorobuta-1,3-dien-1-yl)benzene **88g** (0.654 g, 3.97 mmol, 80%), as a colourless oil.

IR ν_{max} (ATR)/ 3055, 3020, 1619, 1604, 1490, 1446, 1276, 970 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.73-7.69 (2H, m, H-3), 7.41-7.35 (2H, m, H-2), 7.33-7.27 (1H, m, H-1), 6.68 (1H, s, H-5), 6.55 (1H, dd, J 16.5, 10.4 Hz, H-7), 5.76 (1H, d, J 16.5 Hz, H-8), 5.32 (1H, d, J 10.4 Hz, H-8') ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 136.0 (C-7), 134.9 (C-4), 131.7 (C-6), 131.5 (C-3), 129.8 (C-5), 128.4 (C-2), 128.3 (C-1), 117.1 (C-8) ppm.

Data in agreement with the literature.³³³

1-((2E,4E)-5-(Benzo[d][1,3]dioxol-5-yl)penta-2,4-dien-1-yl)piperidine **88h**.

Synthesised using a literature procedure.²⁶⁹



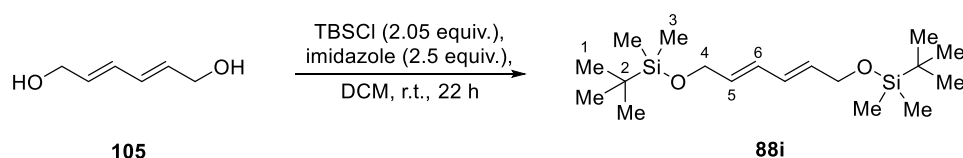
Experimental

To a stirred suspension of piperine (1.43 g, 5.01 mmol), Zn(OAc)₂ (92 mg, 0.50 mmol, 10 mol%) and benzoic acid (305 mg, 2.50 mmol) in toluene (5 mL) at reflux was added NMM (55 μ L, 0.50 mmol, 10 mol%) immediately followed by PhSiH₃ (1.85 mL, 15.0 mmol) and vigorous gas evolution was observed. The mixture was stirred at reflux for 2 h before cooling to room temperature, diluting with EtOAc (10 mL) and washing with HCl (2 x 15 mL of a 3 M aqueous solution). The combined aqueous layers were basified to pH 12 with NaOH (6 M aqueous solution) and extracted with DCM (4 x 20 mL). The combined organics were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give the product, 1-((2*E*,4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)penta-2,4-dien-1-yl)piperidine **88h** (0.900 g, 3.32 mmol, 66%), as an orange solid.

m.p. (EtOH) 79 – 81 °C; Lit m.p. 124 – 128 °C **IR** ν max (ATR)/ 3012, 2929, 2852, 2793, 1501, 1439, 1359, 1241 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 6.93 (1H, d, *J* 1.7 Hz, H-7), 6.81 (1H, dd, *J* 8.0, 1.7 Hz, H-5), 6.74 (1H, d, *J* 8.0 Hz, H-4), 6.61 (1H, dd, *J* 15.6, 10.4 Hz, H-9), 6.41 (1H, d, *J* 15.6 Hz, H-8), 6.27 (1H, dd, *J* 15.0, 10.4 Hz, H-10), 5.95 (2H, s, H-1), 5.83 (1H, ddd, *J* 15.0, 7.0, 7.0 Hz, H-11), 3.03 (2H, dd, *J* 7.0, 1.3 Hz, H-12), 2.58-2.20 (4H, m, H-13), 1.65-1.54 (4H, m, H-14), 1.49-1.39 (2H, m, H-15) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 148.2 (C-2), 147.3 (C-3), 133.4 (C-10), 132.0 (C-6), 131.5 (C-8), 130.9 (C-11), 127.2 (C-9), 121.3 (C-5), 108.5 (C-4), 105.6 (C-7), 101.2 (C-1), 61.8 (C-12), 54.7 (C-13), 26.1 (C-14), 24.5 (C-15) ppm.; **HRMS** *m/z* (ESI⁺): [M+Na⁺] calcd. for C₁₇H₂₂NO₂:272.1645, found: 272.1644.

Data in agreement with the literature.³³⁴

(6*E*,8*E*)-2,2,3,3,12,12,13,13-octamethyl-4,11-dioxo-3,12-disilatetradeca-6,8-diene **88i**.



To a stirred solution of **105** (2.51 g, 22.0 mmol) and imidazole (3.75 g, 55.0 mmol) in DCM (15 mL) was added a solution of TBSCl (6.80 g, 45.1 mmol) in DCM (20 mL) and the mixture was stirred at room temperature for 22 h. H₂O (20 mL) was added to the mixture and the aqueous

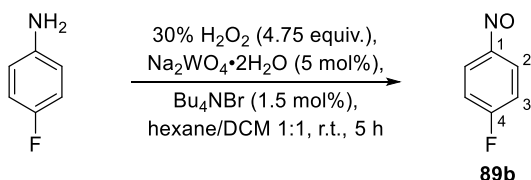
Experimental

layer was extracted with DCM (3 x 30 mL). The combined organics were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude mixture was flushed through a plug of silica using 2% Et_2O in pentane to give the product, (6*E*,8*E*)-2,2,3,3,12,12,13,13-octamethyl-4,11-dioxo-3,12-disilatetradeca-6,8-diene **88i** (7.17 g, 20.9 mmol, 97%), as a colourless solid.

m.p. 60 – 61 °C; **IR** ν_{max} (ATR)/ 2955, 2928, 2855, 1473, 1459, 1406, 1293, 1250 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 6.27-6.18 (2H, m, H-6), 5.78-5.67 (2H, m, H-5), 4.21 (4H, d, J 4.5 Hz, H-4), 0.91 (18H, s, H-1), 0.07 (12H, s, H-3) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 132.3 (C-5), 129.5 (C-6), 63.7 (C-4), 26.1 (C-1), 18.6 (C-2), -5.1 (C-3) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{18}\text{H}_{38}\text{O}_2\text{Si}_2\text{Na}$: 365.2303, found: 365.2294.

Data in agreement with the literature.³³⁵

1-Fluoro-4-nitrosobenzene **89b**.



To a suspension of 4-fluoroaniline (945 μL , 10.0 mmol), $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (165 mg, 0.500 mmol, 5 mol%) and Bu_4NBr (48.3 mg, 0.150 mmol, 1.5 mol%) in hexane/DCM 1:1 (50 mL) was added 30% w/w H_2O_2 (4.90 mL, 47.5 mmol) and the biphasic mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with H_2O (20 mL) and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organics were washed with HCl (2 x 50 mL of a 0.05 M aqueous solution), brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography using 15% DCM in pentane (R_f 0.20) as the eluent gave the title compound, 1-fluoro-4-nitrosobenzene **89b** (1.15 g, 9.19 mmol, 92%), as pale-green crystals.

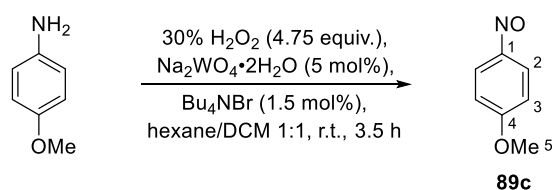
m.p. 43 – 44 °C, Lit m.p. 40 – 41 °C; **IR** ν_{max} (ATR)/ 3072, 3055, 1597, 1499, 1418, 1227 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 8.00-7.92 (2H, m, H-2), 7.31-7.24 (2H, m, H-3) ppm.; **^{13}C { ^1H } NMR** δ_{C}

Experimental

(126 MHz; CDCl₃) 167.0 (d, *J* 260.9 Hz, C-4), 163.7 (d, *J* 2.7 Hz, C-1), 124.1 (d, *J* 10.4 Hz, C-2), 116.5 (d, *J* 23.5 Hz, C-3) ppm.; **HRMS** *m/z* (ESI+): [M+Na⁺] calcd. for C₆H₄NOFNa: 148.0175, found: 148.0177.

Data in agreement with the literature.^{336,337}

1-Methoxy-4-nitrosobenzene **89c**.



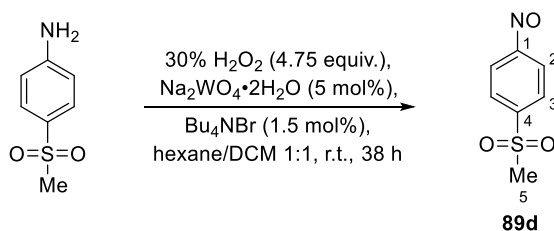
To a suspension of *p*-anisidine (1.85 g, 15.0 mmol), Na₂WO₄•2H₂O (248 mg, 0.752 mmol, 5 mol%) and Bu₄NBr (72 mg, 0.22 mmol, 1.5 mol%) in hexane/DCM 1:1 (80 mL) was added 30% w/w H₂O₂ (80 mL) and the biphasic mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with DCM (40 mL) and H₂O (20 mL) and the aqueous layer was extracted with DCM (4 x 40 mL). The combined organics were washed with HCl (2 x 50 mL of a 0.05 M aqueous solution), brine (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography using 30% DCM in pentane (*R_f* 0.20) as the eluent gave the title compound, 1-methoxy-4-nitrosobenzene **89c** (1.77 g, 12.9 mmol, 86%), as a blue oil.

IR *v* max (ATR)/ 3015, 2946, 2843, 1596, 1581, 1502, 1410, 1256, 1098 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.96-7.89 (2H, m, H-2), 7.07-6.93 (2H, m, H-3), 3.95 (3H, s, H-5) ppm.; **¹³C {¹H} NMR** δ_C (126 MHz; CDCl₃) 165.8 (C-4), 164.1 (C-2), 124.6 (C-1), 114.0 (C-3), 56.1 (C-5) ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₇H₈NO₂: 138.0555, found: 138.0544.

Data in agreement with the literature.³³⁸

Experimental

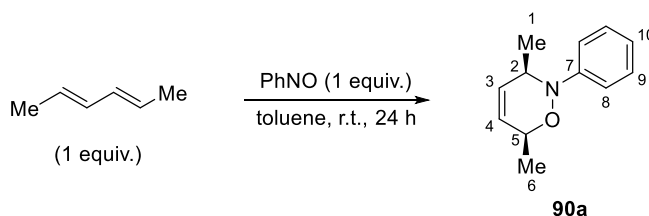
1-(Methylsulfonyl)-4-nitrosobenzene **89d**.



To a suspension of 4-(methylsulfonyl)aniline (3.42 g, 20.0 mmol), Na₂WO₄·2H₂O (330 mg, 1.00 mmol, 5 mol%) and Bu₄NBr (97.0 mg, 0.301 mmol, 1.5 mol%) in hexane/DCM 1:1 (100 mL) was added 30% w/w H₂O₂ (9.80 mL, 95.0 mmol) and the biphasic mixture was stirred at room temperature for 38 h. The reaction mixture was diluted with H₂O (25 mL) and the aqueous layer was extracted with DCM (4 x 30 mL). The combined organics were washed with HCl (2 x 50 mL of a 0.05 M aqueous solution), brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography using 50% EtOAc in pentane (*R_f* 0.31) as the eluent gave the title compound, 1-(methylsulfonyl)-4-nitrosobenzene **89d** (2.91 g, 15.7 mmol, 79%), as pale-green crystals.

m.p. (EtOAc) 143 – 144 °C; **IR** *v* max (ATR)/ 3106, 3011, 2926, 1524, 1363, 1348, 1297cm⁻¹; **¹H NMR** δ_H (500 MHz; CDCl₃) 8.46-8.40 (2H, m, H-2), 8.18-8.14 (2H, m, H-3), 3.12 (3H, s, H-5) ppm.; **¹³C {¹H} NMR** δ_C (126 MHz; CDCl₃) 151.0 (C-1), 146.1 (C-4), 129.1 (C-3), 124.8 (C-2), 44.5 (C-5) ppm.; **HRMS** *m/z* (ESI⁺): [M+Na⁺] calcd. for C₇H₇NO₃Na:208.0039, found:208.0046.

3,6-Dimethyl-2-phenyl-3,6-dihydro-2H-1,2-oxazine **90a**.



To a solution of nitrosobenzene (3.21 g, 30.0 mmol) in toluene (150 mL) was added 2,4-hexadiene (*ca.* 75% *trans*, *trans* isomer, 3.42 mL, 30.0 mmol). The blue solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude green/brown oil was purified by column chromatography using gradient elution (2% Et₂O in petrol to 5% Et₂O

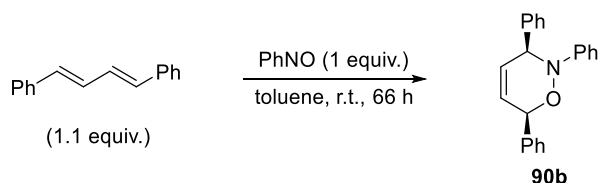
Experimental

in petrol, R_f 0.13) to give the product, 3,6-dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90a** (3.24 g, 17.1 mmol, 57%), as a pale-yellow oil.

IR ν max (ATR)/ 3037, 2976, 2930, 2866, 1597, 1491, 1452, 1255, 1092, 1034 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.32-7.26 (2H, m, H-9), 7.09-7.01 (2H, m, H-8), 6.95-6.89 (1H, m, H-10), 5.93 (1H, ddd, J 9.9, 4.8, 2.1 Hz, H-3), 5.76 (1H, ddd, J 9.9, 1.5, 1.5 Hz, H-4), 4.73-4.62 (1H, m, H-5), 4.20-4.08 (1H, m, H-2), 1.31 (3H, d, J 6.8 Hz, H-6), 1.11 (3H, d, J 6.5 Hz, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 148.9 (C-7), 130.2 (C-4), 129.1 (C-3), 128.9 (C-9), 121.1 (C-10), 115.7 (C-8), 73.6 (C-5), 54.5 (C-2), 19.0 (C-6), 14.5 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}$: 190.1226, found: 190.1233.

Data in agreement with the literature.³³⁹

2,3,6-Triphenyl-3,6-dihydro-2*H*-1,2-oxazine **90b**.



To a solution of nitrosobenzene (0.214 g, 2.00 mmol) in toluene (10 mL) was added *trans, trans*-1,4-diphenyl-1,3-butadiene (0.454 g, 2.20 mmol). The blue/green solution was stirred at room temperature for 66 h before removing the solvent *in vacuo*. The crude green oil was purified by column chromatography using 2% Et_2O in pentane (R_f 0.21) as the eluent to give 2,3,6-triphenyl-3,6-dihydro-2*H*-1,2-oxazine **90b** (0.591 g, 1.89 mmol, 94%), as a viscous pale-yellow oil that crystallised in the freezer.

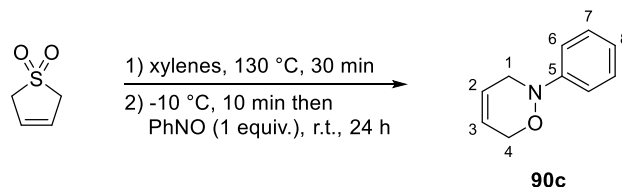
m.p. 77 – 78 °C, Lit m.p. 76 °C; **IR** ν max (ATR)/ 3085, 3061, 3027, 1597, 1491, 1451, 750, 692 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.59-7.51 (2H, m, PhCH), 7.49-7.36 (5H, m, PhCH), 7.29-7.13 (5H, m, PhCH), 7.04-6.97 (2H, m, PhCH), 6.87 (1H, t, J 7.3 Hz, PhCH), 6.22 (1H, ddd, J 10.0, 4.2, 2.0 Hz, CH=CH), 6.20-6.15 (1H, m, CH=CH), 5.70-5.64 (1H, m, OCH(Ph)CH=), 5.24-5.17 (1H, m, NCH(Ph)CH=) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 148.6 (PhC), 138.8 (PhC), 138.4 (PhC), 129.0 (PhCH), 128.8 (PhCH), 128.7 (PhCH), 128.6 (PhCH), 128.33 (PhCH), 128.28 (PhCH), 128.18

Experimental

(CH=CH), 127.6 (PhCH), 121.9 (PhCH), 117.0 (PhCH), 79.3 (OCH(Ph)CH=), 63.5 (NCH(Ph)CH=) ppm.; **HRMS** m/z (ESI+): $[M+H]^+$ calcd. for $C_{22}H_{20}NO$: 314.1539, found: 314.1539.

Data in agreement with the literature.^{237,340}

2-Phenyl-3,6-dihydro-2H-1,2-oxazine 90c.

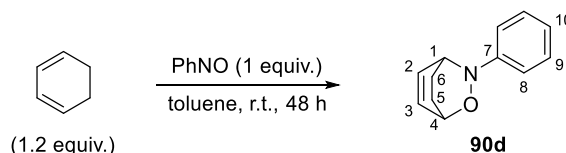


A solution of 3-sulfolene (355 mg, 3.00 mmol) in xylenes (3 mL) was heated at 130 °C for 30 min in a sealed tube. The solution was cooled to -10 °C for 10 min before nitrosobenzene (161 mg, 1.50 mmol) was added and the tube was quickly resealed. The mixture was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. Purification by column chromatography using 5% Et₂O in pentane (R_f 0.24) as the eluent gave the product, 2-phenyl-3,6-dihydro-2H-1,2-oxazine **90c** (241 mg, 1.49 mmol, 99%), as a colourless solid.

m.p. 60 – 61 °C, Lit m.p. 50 – 51 °C; **IR** ν max (ATR)/ 3039, 2937, 2881, 2835, 1559, 1486, 1429, 1355, 1284, 1216 cm^{-1} ; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.32 (2H, dd, J 8.2, 7.2 Hz, H-7), 7.14 (2H, d, J 8.2 Hz, H-6), 7.05-6.96 (1H, m, H-8), 6.02-5.93 (2H, m, H-2 and H-3), 4.56 (2H, d, J 2.7 Hz, H-4), 3.89-3.83 (2H, m, H-1) ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 150.7 (C-5), 128.9 (C-7), 126.3 (C-2/C-3), 123.3 (C-2/C-3), 122.5 (C-8), 116.0 (C-6), 69.2 (C-4), 52.5 (C-1) ppm.; **HRMS** m/z (ESI+): $[M+H]^+$ calcd. for $C_{10}H_{11}NO$: 162.0913, found: 162.0917.

Data in agreement with the literature.³⁴¹

3-Phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene 90d.



Experimental

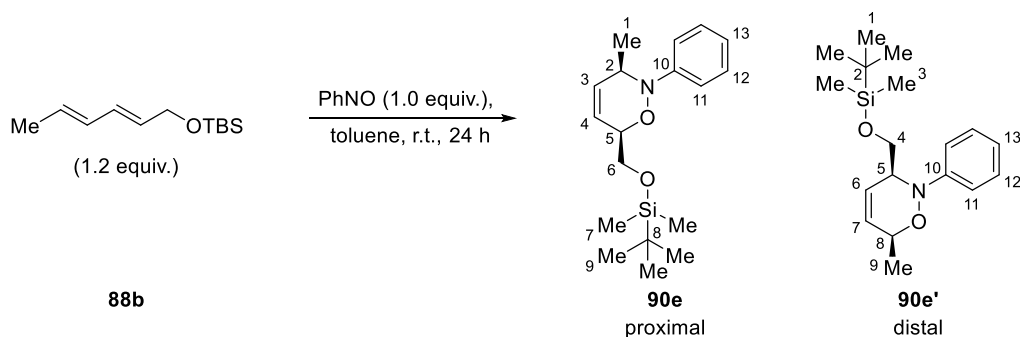
To a solution of nitrosobenzene (268 mg, 2.50 mmol) in toluene (12.5 mL) was added 1,3-cyclohexadiene (285 μ L, 3.00 mmol). The green/blue solution was stirred at room temperature for 48 h before the solvent was removed *in vacuo*. The crude brown solid was purified by column chromatography using 15% EtOAc in pentane as eluent (R_f 0.27) to give the product, 3-phenyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene **90d** (460 mg, 2.46 mmol, 98%), as colourless crystals.

m.p. 70 – 71 °C, Lit m.p. 65 – 66 °C; **IR** ν max (ATR)/ 3064, 3019, 2930, 2852, 1593, 1486, 1432, 1224, 955 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.25-7.16 (2H, m, H-9), 7.04-6.97 (2H, m, H-8), 6.95-6.90 (1H, m, H-10), 6.58 (1H, ddd, J 8.0, 5.9, 1.7 Hz, H-3), 6.15 (1H, ddd, J 8.0, 5.9, 1.5 Hz, H-2), 4.73-4.67 (1H, m, H-4), 4.47-4.39 (1H, m, H-1), 2.35-2.18 (2H, m, H-5' and H-6'), 1.68-1.52 (1H, m, H-6), 1.42-1.32 (1H, m, H-5) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 152.5 (C-7), 131.7 (C-3), 130.1 (C-2), 128.5 (C-9), 122.1 (C-10), 117.6 (C-8), 69.3 (C-4), 56.6 (C-1), 24.1 (C-5), 21.5 (C-6) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{Na}^+]$ calcd for $\text{C}_{16}\text{H}_{13}\text{NONa}$: 210.0889, found: 210.0889.

Data in agreement with the literature.^{300,342}

6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine 90e.
(proximal)

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-6-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine 90e'.
(distal)



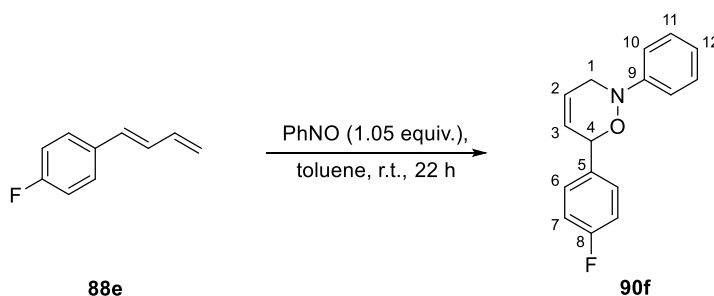
To solution of diene **88b** (1.02 g, 4.8 mmol) in toluene (20 mL) was added nitrosobenzene (0.428 g, 4.00 mmol). The mixture was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The resulting brown oil was purified by column chromatography using 2% Et_2O in pentane as the eluent to give the separable mixture of regioisomeric products 6-(((*tert*-

Experimental

butyldimethylsilyl)oxy)methyl)-3-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90e** (0.811 g, 2.54 mmol, 63%) and 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90e'** (0.247 g, 0.772 mmol, 19%) (*R_s* of 0.21 and 0.32 respectively), as pale-yellow oils.

IR ν max (ATR)/ 3039, 2954, 2928, 2857, 1598, 1491, 1471, 1361, 1253, 1125 cm^{-1} ; **¹H NMR** δ_{H} (400 MHz; CDCl_3) [Major regioisomer: proximal] 7.33-7.26 (2H, m, H-12), 7.12-7.04 (2H, m, H-11), 6.98-6.91 (1H, m, H-13), 6.02 (1H, ddd, *J* 10.0, 4.7, 2.2 Hz, H-3), 5.88-5.82 (1H, m, H-4), 4.68-4.60 (1H, m, H-5), 4.20-4.09 (1H, m, H-2), 3.84 (1H, dd, *J* 10.7, 6.5 Hz, H-6), 3.71 (1H, dd, *J* 10.7, 5.0 Hz, H-6'), 1.12 (3H, d, *J* 6.5 Hz, H-1), 0.94 (9H, s, H-9), 0.12 (3H, s, H-7), 0.11 (3H, s, H-7'); [Minor regioisomer: distal] 7.31-7.22 (2H, m, H-12), 7.08-7.01 (2H, m, H-11), 6.92-6.85 (1H, m, H-13), 6.10 (1H, ddd, *J* 10.2, 4.8, 2.2 Hz, H-6), 5.82 (1H, ddd, *J* 10.2, 1.5, 1.5 Hz, H-7), 4.62 – 4.51 (1H, m, H-8), 4.22-4.14 (1H, m, H-5), 3.90 (1H, dd, *J* 9.6, 5.7 Hz, H-4), 3.72 (1H, dd, *J* 9.6, 7.8 Hz, H-4'), 1.28 (3H, d, *J* 6.8 Hz, H-9), 0.86 (9H, s, H-1), 0.02 (3H, s, H-3), -0.02 (3H, s, H-3') ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; CDCl_3) [Major regioisomer: proximal] 148.9 (C-10), 130.8 (C-3), 128.9 (C-12), 126.1 (C-4), 121.5 (C-13), 116.2 (C-11), 78.5 (C-5), 64.4 (C-6), 54.9 (C-2), 26.0 (C-9), 18.5 (C-8), 14.8 (C-1), -5.1 (C-7), -5.2 (C-7'); [Minor regioisomer: distal] 148.4 (C-10), 131.2 (C-7), 129.0 (C-12), 125.6 (C-6), 120.8 (C-13), 115.0 (C-11), 71.4 (C-8), 63.7 (C-4), 58.7 (C-5), 26.0 (C-1), 19.0 (C-9), 18.4 (C-2), -5.2 (C-3), -5.4 (C-3') ppm.; **HRMS** *m/z* (ESI+): [*M*+*H*⁺] calcd. for $\text{C}_{18}\text{H}_{30}\text{NO}_2\text{Si}$: 320.2040, found: 320.2040.

6-(4-Fluorophenyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90f**.



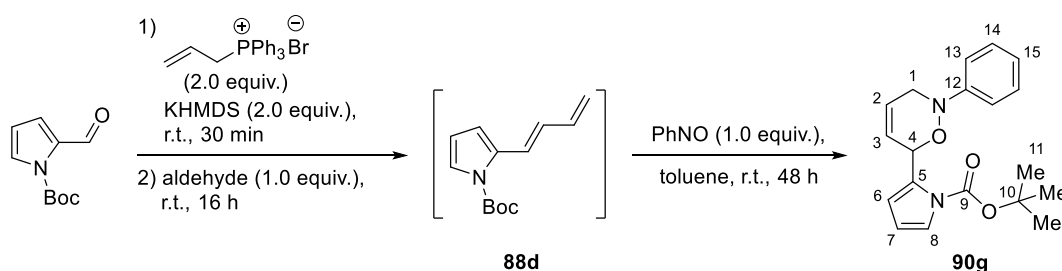
To a solution of **88e** (1.85 g, 12.5 mmol) in toluene (62 mL) was added nitrosobenzene (1.41 g, 13.2 mmol). The dark green suspension was stirred at room temperature for 22 h before the

Experimental

solvent was removed *in vacuo*. The crude brown oil was flushed through a silica plug using gradient elution of 100% pentane to 2% Et₂O in pentane to 4% Et₂O in pentane. The resulting yellow solid was purified by recrystallization from hot pentane to give the product, 6-(4-fluorophenyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90f** (1.92 g, 7.54 mmol, 60%), as colourless crystals.

m.p. 65 – 66 °C; **IR** ν max (ATR)/ cm⁻¹ 3179, 3064, 2993, 2944, 1598, 1507, 1436, 1216, 1040, 973; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.49-7.40 (2H, m, H-6), 7.30-7.24 (2H, m, H-11), 7.12-7.01 (4H, m, H-10 and H-7), 7.01-6.94 (1H, m, H-12), 6.19-6.12 (1H, m, H-2), 6.05 (1H, dddd, *J* 10.0, 2.1, 2.1, 2.0 Hz, H-3), 5.60-5.56 (1H, m, H-4), 4.02-3.85 (2H, m, H-1) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 162.9 (d, *J* 246.7 Hz, C-8), 150.4 (C-9), 134.9 (d, *J* 3.1 Hz, C-5), 130.2 (d, *J* 8.3 Hz, C-6), 128.9 (C-11), 128.8 (C-3), 124.3 (C-2), 122.4 (C-12), 115.9 (C-10), 115.4 (d, *J* 21.5 Hz, C-7), 79.3 (C-4), 51.7 (C-1) ppm.; **¹⁹F {¹H} NMR** δ _F (376 MHz; CDCl₃) -113.64 ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₆H₁₅FNO: 256.1138, found: 256.1130.

tert-Butyl 2-(2-phenyl-3,6-dihydro-2*H*-1,2-oxazin-6-yl)-1*H*-pyrrole-1-carboxylate **90g.**



To a suspension of allyltriphenylphosphonium bromide (6.13 g, 16.0 mmol) in THF (70 mL) was added KHMDS (16.0 mL, 16.0 mmol of a 1.00 M solution in THF) over 15 min. The resulting bright yellow suspension was stirred for 30 min before a solution of *tert*-butyl 2-formyl-1*H*-pyrrole-1-carboxylate (1.75 g, 8.00 mmol) in THF (10 mL) was added over 15 min and left to stir at room temperature for 16 h. To the dark red mixture was added NH₄Cl (30 mL of a saturated aqueous solution) and the aqueous was extracted with Et₂O (3 x 20 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Pentane (100 mL) and Et₂O (10 mL) were added to the residue, the mixture was filtered through celite

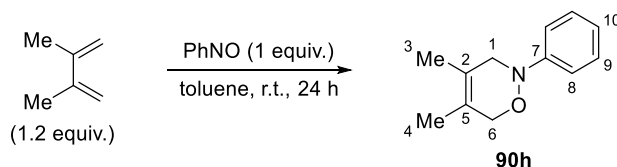
Experimental

and the solvent was removed *in vacuo*. The orange oil was flushed through a silica plug with 10% Et₂O in pentane and used immediately in the next step without purification.

To a solution of nitrosobenzene (375 mg, 3.50 mmol) in toluene (17.5 mL) was added diene **88d** (844 mg, 3.85 mmol). The blue solution was stirred at room temperature for 48 h before the solvent was removed *in vacuo*. The brown oil was purified by column chromatography using gradient elution (100% pentane to 1% Et₂O in pentane to 5% Et₂O in pentane (*R_f* 0.21)) as the eluent to give the product, *tert*-butyl 2-(2-phenyl-3,6-dihydro-2*H*-1,2-oxazin-6-yl)-1*H*-pyrrole-1-carboxylate **90g** (318 mg, 0.974 mmol, 28%), as a yellow oil.

IR ν max (ATR)/ 3050, 2979, 2933, 1736, 1598, 1489, 1369, 1121, 1064 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.34 (1H, dd, *J* 3.3, 1.8 Hz, H-8), 7.26-7.20 (2H, m, H-14), 7.06 (2H, d, *J* 8.1 Hz, H-13), 6.95-6.90 (1H, m, H-15), 6.31 (1H, dd, *J* 3.3, 1.8 Hz, H-6), 6.21-6.15 (2H, m, H-4 and H-2), 6.15-6.08 (2H, m, H-7 and H-3), 3.88 (2H, d, *J* 3.1 Hz, H-1), 1.64 (9H, s, H-11) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 150.6 (C-12), 149.3 (C-9), 132.0 (C-5), 128.7 (C-14), 127.7 (C-2), 124.5 (C-3), 123.2 (C-8), 121.9 (C-15), 115.7 (C-13), 115.5 (C-6), 110.1 (C-7), 84.2 (C-10), 72.4 (C-4), 51.2 (C-1), 28.1 (C-11) ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₁₉H₂₃N₂O₃: 327.1703, found: 327.1704.

4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90h**.



To a solution of nitrosobenzene (428 mg, 4.00 mmol) in toluene (20 mL) was added 2,3-dimethylbutadiene (500 μ L, 4.40 mmol). The blue solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude green/brown oil was purified by column chromatography using 20% DCM in pentane (*R_f* 0.11) as the eluent to give the product, 4,5-dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90h** (402 mg, 2.13 mmol, 53%), as colourless crystals.

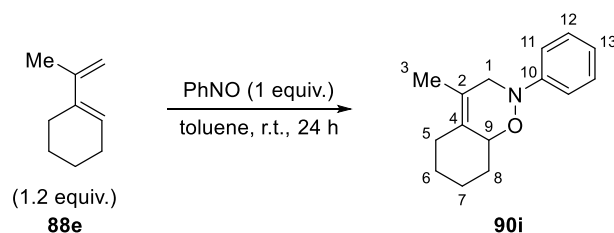
m.p. (EtOH) 42 – 44 °C, Lit. m.p. 39 – 40 °C; **IR** ν max (ATR)/ 3063, 2992, 2925, 2813, 1594, 1491, 1285, 1221 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.36-7.28 (2H, m, H-9), 7.18-7.12 (2H, m, H-8),

Experimental

7.03-6.98 (1H, m, H-10), 4.34 (2H, s, H-6), 3.68 (2H, s, H-1), 1.75 (3H, s, H-3), 1.66 (3H, s, H-4) ppm.; ^{13}C { ^1H } NMR δ_{C} (126 MHz; CDCl_3) 150.6 (C-7), 128.9 (C-9), 125.1 (C-5), 122.5 (C-2), 122.4 (C-10), 116.0 (C-8), 72.2 (C-6), 56.5 (C-1), 16.0 (C-4), 13.8 (C-3) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}$: 190.1232, found: 190.1227.

Data in agreement with the literature.^{237,270}

4-Methyl-2-phenyl-3,5,6,7,8,8a-hexahydro-2H-benzo[e][1,2]oxazine 90i.



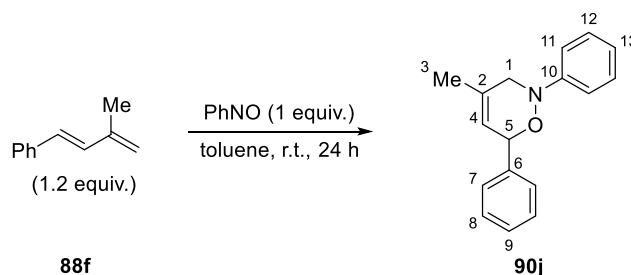
To a solution of nitrosobenzene (428 mg, 4.00 mmol) in toluene (20 mL) was added diene **88e** (586 mg, 4.80 mmol). The solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude material was purified by column chromatography using gradient elution (100% pentane to 2% Et_2O in pentane (R_f 0.13)) to give the product, 4-methyl-2-phenyl-3,5,6,7,8,8a-hexahydro-2H-benzo[e][1,2]oxazine **90i** (233 mg, 1.02 mmol, 25%), as a pale-yellow solid.

m.p. (MeOH) 51 – 52 °C, Lit m.p. 33 – 35 °C; **IR** ν_{max} (ATR)/ 3060, 3026, 2929, 2856, 1597, 1491, 1449, 1217 cm^{-1} ; ^1H NMR δ_{H} (400 MHz; CDCl_3) 7.33-7.27 (2H, m, H-12), 7.17-7.12 (2H, m, H-11), 7.00-6.94 (1H, m, H-13), 4.48-4.40 (1H, m, H-9), 3.71 (1H, d, J 15.1 Hz, H-1'), 3.66 (1H, d, J 15.1 Hz, H-1), 2.79-2.69 (1H, m, H-5), 2.19-2.07 (1H, m, H-8'), 1.96-1.66 (6H, m, H-3, 1 x H-5', H-6' and H-7'), 1.53-1.31 (2H, m, H-8 and H-7), 1.31-1.15 (1H, m, 1 x H-6) ppm.; ^{13}C { ^1H } NMR δ_{C} (101 MHz; CDCl_3) 150.6 (C-10), 132.3 (C-4), 128.9 (C-12), 122.2 (C-13), 120.4 (C-2), 116.0 (C-11), 78.4 (C-9), 56.7 (C-1), 31.8 (C-8), 26.9 (C-5), 26.6 (C-6), 24.4 (C-7), 15.9 (C-3) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{15}\text{H}_{20}\text{NO}$: 230.1539, found: 230.1533.

Data in agreement with the literature.³⁴³

Experimental

4-Methyl-2,6-diphenyl-3,6-dihydro-2H-1,2-oxazine 90j.

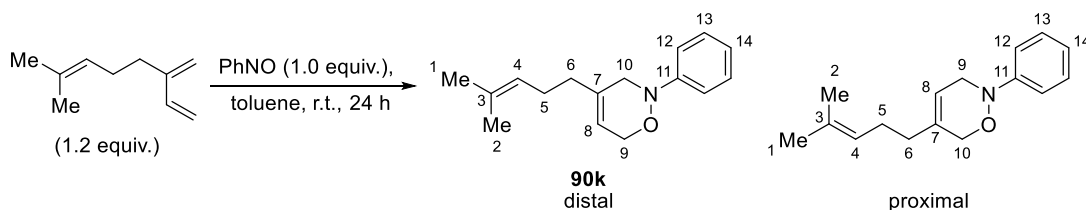


To a solution of nitrosobenzene (428 mg, 4.00 mmol) in toluene (20 mL) was added diene **88f** (634 mg, 4.40 mmol). The blue solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The brown oil was purified by column chromatography using gradient elution (100% pentane to 2% Et₂O in pentane to 5% Et₂O in pentane (*R_f* 0.24)) as the eluent to give the product, 4-methyl-2,6-diphenyl-3,6-dihydro-2H-1,2-oxazine **90j** (242 mg, 0.963 mmol, 24%), as a yellow oil.

IR ν max (ATR)/ 3057, 3029, 2978, 2914, 2814, 1598, 1489, 1452, 1374, 1219 cm⁻¹; **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.46 (2H, d, *J* 7.5 Hz, H-7), 7.42-7.27 (5H, m, H-8 and H-9 and H-12), 7.12 (2H, d, *J* 8.0 Hz, H-11), 7.00-6.94 (1H, m, H-13), 5.85-5.73 (1H, m, H-4), 5.58-5.51 (1H, m, H-5), 3.87-3.72 (2H, m, H-1), 1.91 (3H, s, H-3) ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; CDCl₃) 150.4 (C-10), 139.7 (C-6), 131.7 (C-2), 128.9 (PhCH), 128.5 (PhCH), 128.4 (PhCH), 128.2 (C-7), 123.1 (C-4), 122.3 (C-13), 116.0 (C-11), 79.4 (C-5), 55.5 (C-1), 20.5 (C-3) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₇H₁₈NO: 252.1382, found: 252.1383.

Data in agreement with the literature.³⁴⁴

4-(4-Methylpent-3-en-1-yl)-2-phenyl-3,6-dihydro-2H-1,2-oxazine 90k.



To a solution of nitrosobenzene (0.428 g, 4.00 mmol) in toluene (20 mL) was added myrcene (825 μ L, 4.80 mmol). The blue solution was stirred at room temperature for 24 h before the

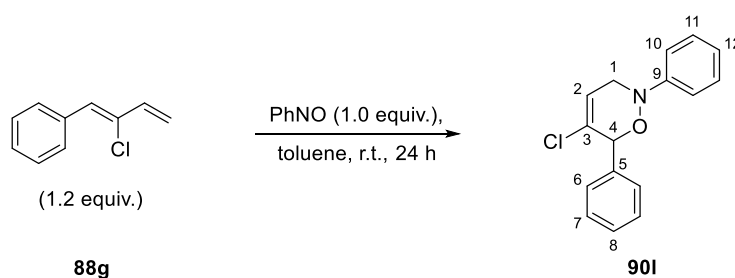
Experimental

solvent was removed *in vacuo*. The crude oil was purified by column chromatography using 2% Et₂O in pentane (*R_f* 0.20) as the eluent to give the product, 4-(4-methylpent-3-en-1-yl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine **90k** (81:19 inseparable mixture of distal:proximal isomers, 0.380 g, 1.56 mmol, 39%), as a yellow oil.

IR ν max (ATR)/ 3060, 3027, 2966, 2925, 1598, 1490, 1452, 1214 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.34-7.28 (2H, m, H-13) [Major and minor], 7.17-7.11 (2H, m, H-12) [Major and minor], 7.03-6.96 (1H, m, H-14) [Major and minor], 5.67-5.61 (1H, m, H-8) [Major and minor], 5.19-5.10 (1H, m, H-4) [Major and minor], 4.55-4.48 (2H, m, H-9) [Major], 4.46-4.42 (2H, m, H-10) [Minor], 3.86-3.80 (2H, m, H-9) [Minor], 3.76-3.71 (2H, m, H-10) [Major], 2.25-2.02 (4H, m, H-5 and H-6) [Major and minor], 1.71 (3H, s, H-1) [Major and Minor], 1.63 (3H, s, H-2) [Major], 1.62 (3H, s, H-2) [Minor] ppm.; **¹³C {¹H} NMR** δ _C (126 MHz; CDCl₃) [Some signals for the minor regioisomer were obscured by the major regioisomer signals] 150.6 (C-11) [Major], 137.6 (C_q) [Minor], 134.8 (C-7) [Major], 132.35 (C-3) [Major], 132.34 (C_q) [Minor], 128.94 (C-13) [Major], 128.92 (CH) [Minor], 123.73 (CH) [Minor], 123.71 (C-4) [Major], 122.44 (C-14) [Major], 122.39 (CH) [Minor], 119.4 (C-8) [Major], 116.6 (CH) [Minor], 116.07 (C-12) [Major], 115.98 (CH) [Minor], 71.40 (CH₂) [Minor], 68.70 (C-9) [Major], 55.28 (C-10) [Major], 52.17 (CH₂) [Minor], 34.6 (C-5/C-6 CH₂) [Major], 32.7 (CH₂) [Minor], 26.2 (C-5/C-6) [Major], 25.8 (C-1) [Major], 17.91 (C-2) [Major], 17.88 (CH₃) [Minor] ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₁₆H₂₂NO: 244.1696, found: 244.1694.

Data in agreement with the literature.³⁴⁵

5-Chloro-2,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine **90l**.



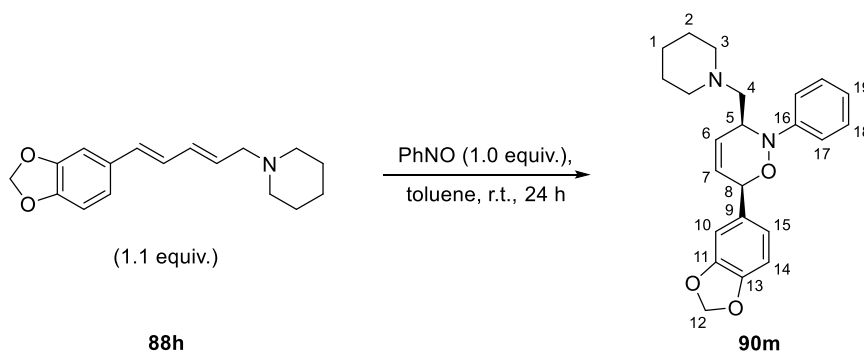
To a solution of nitrosobenzene (0.321 g, 3.00 mmol) in toluene (15 mL) was added diene **88g** (590 mg, 3.60 mmol). The blue solution was stirred at room temperature for 24 h before the

Experimental

solvent was removed *in vacuo*. The crude oil was purified by column chromatography using gradient elution (100% pentane to 10% Et₂O in pentane, *R_f* 0.34) to give the product, 5-chloro-2,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine **90l** (0.605 g, 2.23 mmol, 74%), as a pale-yellow solid.

m.p. (pentane) 90 – 91 °C; **IR** ν max (ATR)/ 3060, 2911, 2820, 1597, 1487, 1453, 1294 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.55-7.49 (2H, m, PhCH), 7.46-7.37 (3H, m, PhCH), 7.05-6.95 (3H, m, PhCH), 6.31 (1H, ddd, *J* 3.8, 3.8, 1.5 Hz, H-2), 5.53-5.46 (1H, m, H-4), 4.14-3.96 (2H, m, H-1) ppm.; **¹³C {¹H} NMR** δ _C (126 MHz; CDCl₃) 149.5 (C-9), 136.4 (C-5), 131.8 (C-3), 129.4 (PhCH), 129.2 (PhCH), 128.9 (PhCH), 128.5 (PhCH), 122.9 (PhCH), 122.3 (C-2), 116.3 (PhCH), 83.3 (C-4), 52.5 (C-1) ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₁₆H₁₅ClNO: 272.0837, found: 272.0839.

6-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenyl-3-(piperidin-1-ylmethyl)-3,6-dihydro-2*H*-1,2-oxazine **90m**.



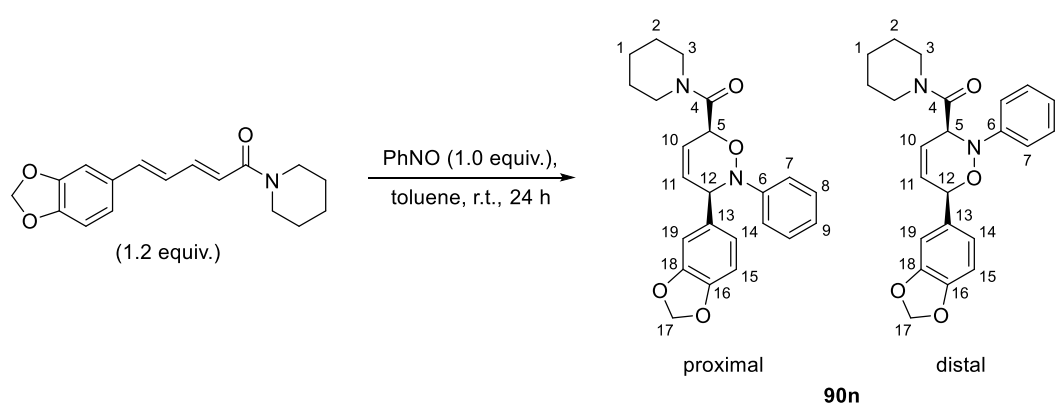
To a solution of **88h** (0.746 g, 2.75 mmol) in toluene (12.5 mL) was added nitrosobenzene (0.268 g, 2.50 mmol) and the mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography using 50% EtOAc in pentane (*R_f* 0.25) as the eluent to give 6-(benzo[*d*][1,3]dioxol-5-yl)-2-phenyl-3-(piperidin-1-ylmethyl)-3,6-dihydro-2*H*-1,2-oxazine **90m** (0.765 g, 2.02 mmol, 81%), as a brown oil.

IR ν max (ATR)/ 3038, 2933, 2852, 1596, 1502, 1441, 1244, 1099 cm⁻¹; **¹H NMR** δ _H (500 MHz; CDCl₃) 7.28 (2H, dd, *J* 8.7, 7.3 Hz, H-18), 7.08-7.04 (2H, m, H-17), 6.95-6.88 (3H, m, H-19 and H-14 and H-10), 6.81 (1H, d, *J* 7.8 Hz, H-15), 6.31 (1H, ddd, *J* 10.1, 5.0, 2.3 Hz, H-6), 5.98 (1H, d, *J* 1.5 Hz, H-12'), 5.97 (1H, d, *J* 1.5 Hz, H-12), 5.87 (1H, ddd, *J* 10.1, 1.4, 1.4 Hz, H-7), 5.35-5.31 (1H, m, H-8), 4.32 (1H, d, *J* 7.9 Hz, H-5), 2.77-2.64 (2H, m, H-4), 2.55-2.45 (2H, m, 2 x H-3'), 2.45-2.32

Experimental

(2H, m, 2 x H-3), 1.64-1.48 (4H, m, 2 x H-2), 1.44-1.36 (2H, m, H-1) ppm.; ^{13}C $\{^1\text{H}\}$ NMR δ_{C} (126 MHz; CDCl_3) 148.2 (C-16), 148.0 (C-11/C-13), 147.9 (C-11/C-13), 132.3 (C-9), 129.1 (C-18), 128.3 (C-7), 128.2 (C-6), 122.4 (C-10), 121.2 (C-19), 115.7 (C-17), 108.8 (C-14), 108.4 (C-15), 101.3 (C-12), 77.2 (C-8), 60.6 (C-4), 55.4 (C-5), 55.3 (C-3), 26.1 (C-2), 24.4 (C-1) ppm.; HRMS m/z (ESI $^{+}$): $[\text{M}+\text{H}^{+}]$ calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3$: 379.2016, found: 379.2016.

(3-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-3,6-dihydro-2H-1,2-oxazin-6-yl)(piperidin-1-yl)methanone (proximal) and **(6-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl)(piperidin-1-yl)methanone** (distal) **90n**.



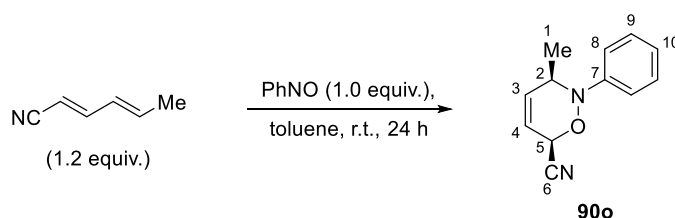
To a solution of nitrosobenzene (0.643 g, 6.00 mmol) in toluene (30 mL) was added piperine (2.05 mg, 7.20 mmol). The solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 20% EtOAc in pentane as the eluent (R_f 0.19) followed by trituration of the sticky yellow solid with 20% EtOAc in pentane to give a 75:25 proximal:distal inseparable mixture of regioisomers of the product, (3-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-3,6-dihydro-2H-1,2-oxazin-6-yl)(piperidin-1-yl)methanone and (6-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-3,6-dihydro-2H-1,2-oxazin-3-yl)(piperidin-1-yl)methanone **90n** (1.31 g, 3.34 mmol, 56%), as a white amorphous solid.

IR ν_{max} (ATR)/ 3055, 2926, 2858, 1647, 1595, 1487, 1437, 1250 cm^{-1} ; ^1H NMR δ_{H} (500 MHz; CDCl_3) Proximal isomer [Major]: 7.21-7.16 (2H, m, H-8), 6.99-6.96 (2H, m, H-7), 6.96-6.92 (1H, m, H-9), 6.82 (1H, d, J 1.7 Hz, H-19), 6.64 (1H, dd, J 8.0, 1.7 Hz, H-14), 6.59 (1H, d, J 8.0 Hz, H-15), 6.27 (1H, ddd, J 10.1, 1.9, 1.9 Hz, H-10), 6.08 (1H, ddd, J 10.1, 4.3, 2.1 Hz, H-11), 5.86 (1H, d, J 1.5 Hz, H-17'), 5.85 (1H, d, J 1.5 Hz, H-17), 5.33 (1H, dd, J 2.0, 2.0 Hz, H-5), 4.94-4.87 (1H, m, H-

Experimental

12), 3.71-3.49 (4H, m, 4 x H-3/H-3'), 1.66-1.46 (6H, m, 2 x H-1 and 4 x H-2/H-2'); Distal isomer [Minor] 7.34-7.30 (2H, m, H-8), 7.12-7.08 (2H, m, H-7), 7.05 (1H, d, *J* 1.7 Hz, H-19), 7.04-7.00 (1H, m, H-9), 6.96-6.92 (1H, m, H-14), 6.79 (1H, d, *J* 7.9 Hz, H-15), 6.17 (1H, ddd, *J* 10.2, 4.5, 2.2 Hz, H-10), 6.02 (1H, ddd, *J* 10.3, 1.9, 1.9 Hz, H-11), 5.95 (1H, d, *J* 1.5 Hz, H-17), 5.94 (1H, d, *J* 1.5 Hz, H-17), 5.18 (1H, dd, *J* 2.2, 2.2 Hz, H-12), 5.00 (1H, ddd, *J* 4.4, 2.1, 2.1 Hz, H-5), 3.52-3.30 (4H, m, 4 x H-3/H-3'), 1.54-1.35 (6H, m, 2 x H-1 and 4 x H-2/H-2') ppm.; $^{13}\text{C}\{^1\text{H}\}$ NMR δ_{C} (126 MHz; CDCl_3) Proximal isomer [Major] 165.94 (C-4), 148.83 (C-6), 147.38 (C-16 or C-18), 147.21 (C-16 or C-18), 130.95 (C-13), 128.61 (C-8), 128.17 (C-11), 125.13 (C-10), 123.31 (C-9), 123.28 (C-14), 118.50 (C-7), 110.20 (C-19), 107.69 (C-15), 100.97 (C-17), 75.86 (C-5), 65.66 (C-12), 47.02 (C-3 or C-3'), 43.43 (C-3 or C-3'), 26.73 (C-1 or C-2 or C-2'), 25.74 (C-1 or C-2 or C-2'), 24.67 (C-1 or C-2 or C-2'); Distal isomer [Minor] 167.11 (C-4), 148.04 (C-6), 147.91 (C-16 or C-18), 147.29 (C-16 or C-18), 132.11 (C-13), 129.62 (C-11), 129.27 (C-8), 122.77 (C-9), 122.69 (C-14), 122.66 (C-10), 117.12 (C-7), 109.45 (C-19), 108.27 (C-15), 101.22 (C-17), 75.40 (C-12), 58.39 (C-5), 46.98 (C-3 or C-3'), 43.88 (C-3 or C-3'), 26.45 (C-1 or C-2 or C-2'), 25.74 (C-1 or C-2 or C-2'), 24.63 (C-1 or C-2 or C-2') ppm.; HRMS *m/z* (ESI+): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{Na}$: 415.1628, found: 415.1626.

3-Methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine-6-carbonitrile **90o**.

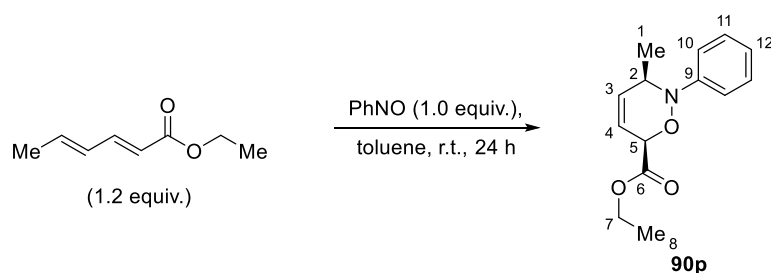


To a solution of nitrosobenzene (428 mg, 4.00 mmol) in toluene (20 mL) was added 2,4-hexadienenitrile (447 μL , 4.80 mmol). The green solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 5% EtOAc in pentane (R_f 0.19) as the eluent to give the product, 3-methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine-6-carbonitrile **90o** (358 mg, 1.79 mmol, 45%), as a yellow oil.

Experimental

IR v max (ATR)/ 3058, 2981, 2935, 2839, 1597, 1489, 1453, 1370, 1250 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3): 7.38 (2H, dd, J 8.5, 7.2 Hz, H-9), 7.33-7.28 (2H, m, H-8), 7.26-7.20 (1H, m, H-10), 6.08 (1H, ddd, J 9.8, 2.2, 2.2 Hz, H-3), 5.88 (1H, ddd, J 9.8, 3.5, 2.1 Hz, H-4), 5.16-5.09 (1H, m, H-5), 4.12-4.03 (1H, m, H-2), 1.09 (3H, d, J 6.8 Hz, H-1) ppm.; **^{13}C $\{^1\text{H}\}$ NMR** δ_{C} (101 MHz; CDCl_3) 147.3 (C-7), 134.7 (C-3), 129.1 (C-9), 126.6, (C-10) 122.7 (C-8), 120.5 (C-4), 116.9 (C-6), 66.1 (C-5), 56.6 (C-2), 16.9 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{ONa}$: 223.0842, found: 223.0845.

Ethyl-3-methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazine-6-carboxylate **90p**.

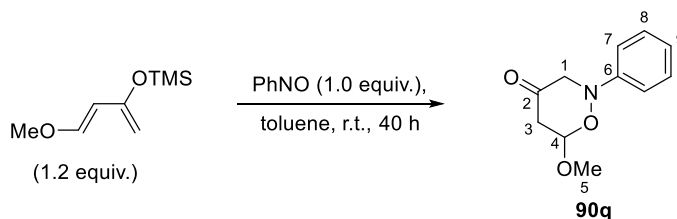


To a solution of nitrosobenzene (428 mg, 4.00 mmol) in toluene (20 mL) was added ethyl sorbate (705 μL , 4.80 mmol). The blue solution was stirred at room temperature for 24 h before the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 5% EtOAc in pentane (R_f 0.19) as the eluent to give the product, ethyl-3-methyl-2-phenyl-3,6-dihydro-2H-1,2-oxazine-6-carboxylate **90p** (883 mg, 3.57 mmol, 89%), as a yellow oil.

IR v max (ATR)/ 3057, 2980, 2933, 1753, 1733, 1597, 1491, 1368, 1186 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.38-7.28 (2H, m, H-11), 7.26-7.19 (2H, m, H-10), 7.11- 7.02 (1H, m, H-12), 6.08-6.00 (2H, m, H-3 and H-4), 5.04 (1H, d, J 2.3 Hz, H-5), 4.36-4.20 (2H, m, H-7), 4.13-4.05 (1H, m, H-2), 1.32 (3H, t, J 7.2 Hz, H-8), 1.11 (3H, d, J 6.6 Hz, H-1) ppm.; **^{13}C $\{^1\text{H}\}$ NMR** δ_{C} (101 MHz; CDCl_3) 169.2 (C-6), 148.2 (C-9), 132.0 (C-3), 128.9 (C-11), 123.8 (C-12), 123.3 (C-4), 119.1 (C-10), 76.6 (C-5), 61.4 (C-7), 55.4 (C-2), 15.8 (C-1), 14.3 (C-8) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_3$: 248.1281, found: 248.1279.

Experimental

6-Methoxy-2-phenyl-1,2-oxazinan-4-one **90q**.

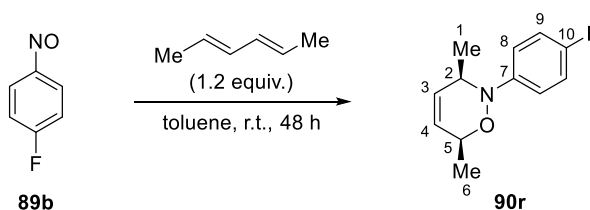


To a solution of nitrosobenzene (429 mg, 4.01 mmol) in toluene (20 mL) was added Danishefsky's diene (935 μ L, 4.80 mmol). The blue solution was stirred at room temperature for 40 h before the solvent was removed *in vacuo*. The crude pale-yellow oil was purified by column chromatography using gradient elution (5% EtOAc in pentane to 10% EtOAc in pentane, R_f 0.17) to give a clumpy white solid which, upon recrystallization from hot Et₂O, gave 6-methoxy-2-phenyl-1,2-oxazinan-4-one **90q** (328 mg, 1.58 mmol, 40%), as colourless crystals.

m.p. 90 – 91 °C, Lit m.p. 88 – 89 °C; **IR** ν max (ATR)/ 3045, 2961, 2911, 1726, 1597, 1492, 1405, 1207, 1103, 1060 cm^{-1} ; **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.39–7.30 (2H, m, H-8), 7.11 (2H, d, J 7.4 Hz, H-7), 7.11–7.03 (1H, m, H-9), 5.13 (1H, t, J 5.8 Hz, H-4), 4.07 (1H, d, J 16.8 Hz, H-1'), 3.79 (1H, d, J 16.8 Hz, H-1), 3.61 (3H, s, H-5), 2.92 (2H, d, J 5.8 Hz, H-3) ppm.; **¹³C NMR** δ_{C} (101 MHz; CDCl₃) 203.6 (C-2), 149.1 (C-6), 129.2 (C-8), 123.5 (C-9), 116.3 (C-7), 100.6 (C-4), 64.5 (C-1), 56.4 (C-5), 44.5 (C-3) ppm.; **HRMS** m/z (ESI+): $[M+H]^+$ calcd for C₁₁H₁₃NO₃Na: 230.0793, found: 230.0789.

Data in agreement with the literature.³⁴⁶

2-(4-Fluorophenyl)-3,6-dimethyl-3,6-dihydro-2H-1,2-oxazine **90r**.



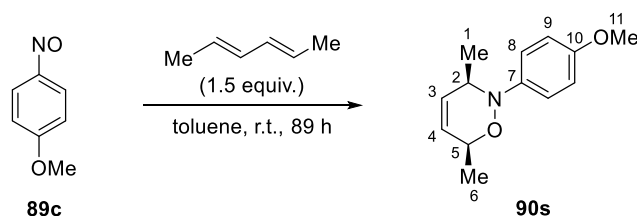
To a stirred solution of **89b** (500 mg, 4.00 mmol) in toluene (20 mL) was added 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 548 μ L, 4.80 mmol). The solution was stirred at room temperature for 48 h before the solvent was removed *in vacuo*. The crude material was purified by column chromatography using 3% Et₂O in pentane (R_f 0.21) as the eluent to give the product, 2-(4-

Experimental

fluorophenyl)-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine **90r** (622 mg, 3.00 mmol, 75%), as a pale-yellow oil.

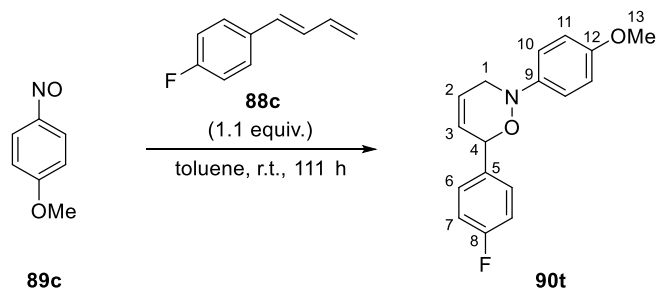
IR ν max (ATR)/ 3040, 2977, 2931, 2868, 1501, 1447, 1372, 1217, 1091 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.06-6.94 (4H, m, H-8 and H-9), 5.92 (1H, ddd, J 10.0, 4.7, 2.1 Hz, H-3), 5.76 (1H, ddd, J 10.0, 1.4, 1.4 Hz, H-4), 4.68-4.61 (1H, m, H-5), 4.07-4.00 (1H, m, H-2), 1.30 (3H, d, J 6.8 Hz, H-6), 1.07 (3H, d, J 6.5 Hz, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 158.2 (d, J 239.6 Hz, C-10), 145.2 (d, J 2.3 Hz, C-7), 130.2 (C-3), 129.1 (C-4), 117.7 (d, J 7.6 Hz, C-8), 115.4 (d, J 22.3 Hz, C-9), 73.7 (C-5), 55.3 (C-2), 19.1 (C-6), 14.4 (C-1) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376 MHz; CDCl_3) -123.03 ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{15}\text{NOF}$: 208.1132, found: 208.1130.

2-(4-Methoxyphenyl)-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine **90s**.



To a stirred solution of **89c** (1.37 g, 10.0 mmol) in toluene (50 mL) was added 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 1.71 mL, 15.0 mmol). The blue solution was stirred at room temperature for 89 h before the solvent was removed *in vacuo*. The crude product was flushed through a silica plug using 5% Et_2O in pentane (R_f 0.14) to give the product, 2-(4-methoxyphenyl)-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine **90s** (2.10 g, 9.58 mmol, 96%) as a green oil.

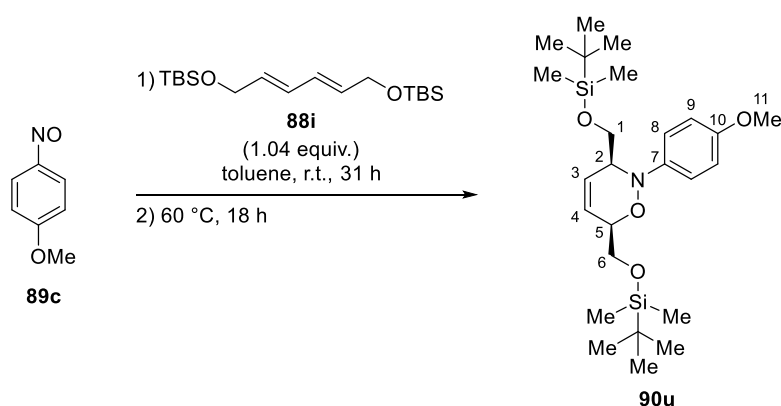
IR ν max (ATR)/ 3038, 2975, 2931, 1594, 1504, 1442, 1238, 1034 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.08-6.96 (2H, m, H-9), 6.91-6.81 (2H, m, H-8), 5.91 (1H, ddd, J 10.0, 4.5, 2.1 Hz, H-3), 5.76 (1H, ddd, J 10.0, 1.6, 1.6 Hz, H-4), 4.64-4.56 (1H, m, H-5), 4.04-3.95 (1H, m, H-2), 3.78 (3H, s, H-11), 1.30 (3H, d, J 6.7 Hz, H-6), 1.06 (3H, d, J 6.5 Hz, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 155.1 (C-10), 142.7 (C-7), 130.2 (C-4), 129.3 (C-3), 118.9 (C-9), 114.2 (C-8), 73.4 (C-5), 55.7 (C-11), 55.5 (C-2), 19.2 (C-6), 14.9 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{13}\text{H}_{18}\text{NO}_2$: 220.1338, found: 220.1337.

6-(4-Fluorophenyl)-2-(4-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine 90t.

To a stirred solution of **89c** (241 mg, 1.75 mmol) in toluene (9 mL) was added diene **88c** (287 mg, 1.93 mmol). The blue mixture was stirred at room temperature for 111 h before the solvent was removed *in vacuo*. The resulting brown solid was flushed through a plug of silica using 50% Et₂O in pentane to 100% Et₂O as the eluent. The solvent was removed *in vacuo* and the crude solid was purified by recrystallization from Et₂O to give the product, 6-(4-fluorophenyl)-2-(4-methoxyphenyl)-3,6-dihydro-2H-1,2-oxazine **90t** (162 mg, 0.568 mmol, 32%), as off-white crystals.

m.p. (Et₂O) 94 – 96 °C; **IR** ν max (ATR)/ 3045, 2874, 2809, 1608, 1506, 1245, 1213, 968, 820 cm⁻¹; **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.46-7.39 (2H, m, H-7), 7.09-7.00 (4H, m, H-10 and H-6), 6.86-6.80 (2H, m, H-11), 6.17-6.11 (1H, m, H-2), 6.03 (1H, dddd, *J* 10.1, 2.1, 2.1, 2.1 Hz, H-3), 5.60-5.54 (1H, m, H-4), 3.89-3.79 (2H, m, H-1), 3.77 (3H, s, H-13) ppm.; **¹³C {¹H} NMR** δ_{C} (126 MHz; CDCl₃) 162.9 (d, *J* 246.6 Hz, C-8), 155.9 (C-12), 144.1 (C-9), 135.1 (d, *J* 3.2 Hz, C-5), 130.2 (d, *J* 8.2 Hz, C-6), 128.9 (C-3), 124.5 (C-2), 118.7 (C-10), 115.4 (d, *J* 21.5 Hz, C-7), 114.2 (C-11), 79.4 (C-4), 55.7 (C-13), 52.6 (C-1) ppm.; **¹⁹F {¹H} NMR** δ_{F} (376 MHz; CDCl₃) -113.81 ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₁₇H₁₇FO₂: 286.1238, found: 286.1238.

3,6-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-1,2-oxazine 90u.



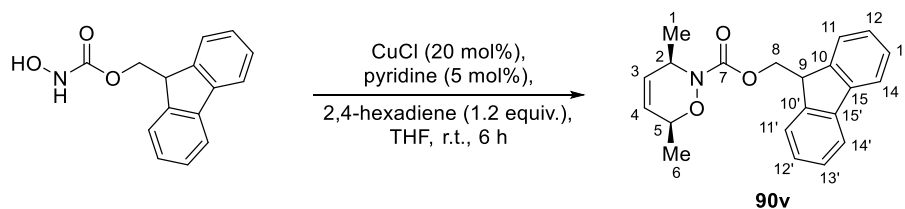
To a solution of 1-methoxy-4-nitrosobenzene **89c** (2.74 g, 20.0 mmol) in toluene (100 mL) was added diene **88i** (7.09 g, 20.7 mmol). The blue solution was stirred at room temperature for 31 h before heating the mixture at 60 °C for 18 h. After this time the solvent was removed *in vacuo* and the crude mixture was purified by column chromatography on basic alumina using 5% EtOAc in pentane as the eluent (R_f 0.34) to give the product, 3,6-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-1,2-oxazine **90u** (1.48 g, 3.04 mmol, 15%), as a pale-yellow oil.

IR ν max (ATR)/ 3045, 2953, 2929, 2856, 1506, 1463, 1245 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.09-7.02 (2H, m, H-8), 6.86-6.81 (2H, m, H-9), 6.16 (1H, ddd, J 10.3, 4.3, 2.1 Hz, H-3), 5.89 (1H, ddd, J 10.3, 1.8, 1.8 Hz, H-4), 4.41-4.34 (1H, m, H-5), 4.06-3.98 (1H, m, H-2), 3.86-3.79 (2H, m, H-1), 3.78 (3H, s, H-11), 3.70-3.60 (2H, m, H-6), 0.90 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.85 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.07 (6H, s, $\text{Si}(\text{CH}_3)_2\text{tBu}$), 0.00 (3H, s, $\text{Si}(\text{CH}_3)(\text{CH}_3')\text{tBu}$), -0.03 (3H, s, $\text{Si}(\text{CH}_3)(\text{CH}_3')\text{tBu}$) ppm.; **^{13}C $\{^1\text{H}\}$ NMR** δ_{C} (101 MHz; CDCl_3) 155.2 (C-10), 141.9 (C-7), 127.1 (C-3/C-4), 127.0 (C-3/C-4), 119.0 (C-8), 114.1 (C-9), 75.5 (C-5), 64.4 (C-1/C-6), 63.7 (C-1/C-6), 59.9 (C-2), 55.5 (C-11), 25.90 ($\text{C}(\text{CH}_3)_3$), 25.88 ($\text{C}(\text{CH}_3)_3$), 18.4 ($\text{C}(\text{CH}_3)_3$), 18.3 ($\text{C}(\text{CH}_3)_3$), -5.25 ($\text{Si}'(\text{CH}_3)(\text{CH}_3')\text{tBu}$), -5.31 ($\text{Si}'(\text{CH}_3)(\text{CH}_3')\text{tBu}$), -5.34 ($\text{Si}(\text{CH}_3)(\text{CH}_3')\text{tBu}$), -5.5 ($\text{Si}(\text{CH}_3)(\text{CH}_3')\text{tBu}$) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{25}\text{H}_{46}\text{NO}_4\text{Si}_2$: 480.2960, found: 480.2959.

Experimental

(9*H*-Fluoren-9-yl)methyl-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate **90v**.

Synthesised using a literature procedure.³⁰⁰

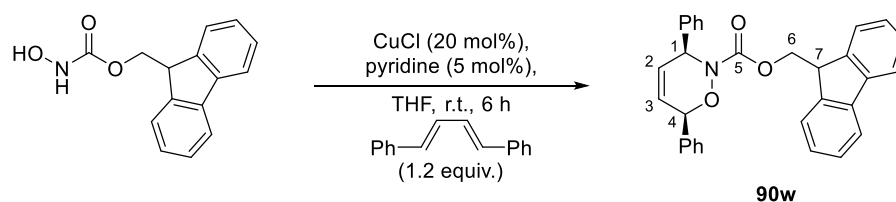


To a solution of 9-fluorenylmethyl *N*-hydroxycarbamate (511 mg, 2.00 mmol), CuCl (39.6 mg, 0.400 mmol, 20 mol%) and pyridine (8 μ L, 100 μ mol, 5 mol%) in THF (20 mL) was added 2,4-hexadiene (*ca.* 75% *trans*, *trans* isomer, 278 μ L, 2.40 mmol). The dark green suspension was stirred at room temperature for 6 h before diluting with EtOAc (20 mL) and quenching with Na₂EDTA (25 mL of a 4x10⁻⁴ M aqueous solution). The blue biphasic mixture was stirred at room temperature for 30 min until no colour remained in the organic layer. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and solvent removed *in vacuo*. The crude green oil was purified by column chromatography using 10% EtOAc in pentane (*R_f* 0.21) as the eluent to give (9*H*-fluoren-9-yl)methyl-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate **90v** (0.615 g, 4.31 mmol, 92%), as a colourless oil.

IR ν max (ATR)/ 3066, 3040, 2977, 2931, 1698, 1449, 1415, 1303, 1117 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.78 (2H, d, *J* 7.5 Hz, H-14/H'14'), 7.67 (1H, d, *J* 7.3 Hz, H-11), 7.63 (1H, d, *J* 7.4 Hz, H-11'), 7.45-7.38 (2H, m, H-13/H-13'), 7.33 (2H, t, *J* 7.3 Hz, H-12/H-12'), 5.83-5.74 (1H, m, H-4/H-3), 5.70-5.65 (1H, m, H-4/H-3), 4.62-4.40 (4H, m, H-2 and H-5 and H-8), 4.29 (1H, t, *J* 7.1 Hz, H-9), 1.30 (6H, m, H-1 and H-6) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) [Some carbon signals overlapped] 154.8 (C-7), 144.1 (C-15), 143.7 (C-15'), 141.49 (C-10), 141.45 (C-10'), 128.8 (C-3/C-4), 127.85 (C-3/C-4), 127.83 (C-13), 127.2 (C-12), 127.1 (C-12'), 125.4 (C-11), 125.2 (C-11'), 120.1 (C-14), 74.0 (C-5), 67.6 (C-8), 50.0 (C-2), 47.3 (C-9), 18.9 (C-6), 18.3 (C-1) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₂₁H₂₂NO₃: 336.1594, found:336.1591.

(9H-Fluoren-9-yl)methyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate 90w.

Synthesised using a literature procedure.³⁰⁰



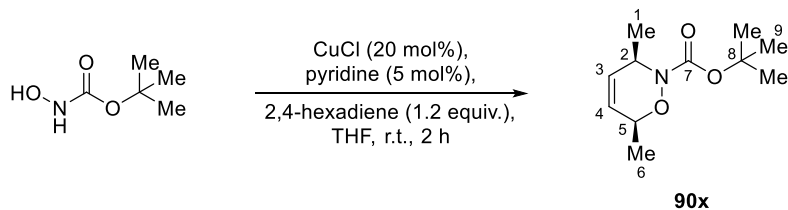
To a solution of 9-fluorenylmethyl *N*-hydroxycarbamate (638 mg, 2.50 mmol), CuCl (49.6 mg, 0.501 mmol, 20 mol%) and pyridine (10 μ L, 0.10 mmol, 5 mol%) in THF (25 mL) was added *trans,trans*-1,4-diphenyl-1,3-butadiene (618 mg, 3.00 mmol). The dark green suspension was stirred at room temperature for 16 h before diluting with EtOAc (25 mL) and quenching with an aqueous solution of Na₂EDTA (25 mL of a 4x10⁻⁴ M solution). The blue biphasic mixture was stirred at room temperature for 30 min until no colour remained in the organic layer. The aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and solvent removed *in vacuo*. The crude oil was purified by column chromatography using gradient elution (100% pentane to 10% EtOAc in pentane (*R_f* 0.14) as the eluent) to give (9H-fluoren-9-yl)methyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine-2-carboxylate **90w** (1.07 g, 2.33 mmol, 93%), as colourless crystals.

m.p. 62 – 64 °C; **IR** ν max (ATR)/ 3064, 3031, 2951, 1698, 1450, 1414, 1273 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.76 (2H, d, *J* 7.6 Hz, ArCH), 7.63 (1H, d, *J* 7.5 Hz, ArCH), 7.57 (1H, d, *J* 7.5 Hz, ArCH), 7.53-7.45 (2H, m, ArCH), 7.44-7.30 (10H, m, ArCH), 7.28-7.22 (2H, m, ArCH), 6.18-6.11 (1H, m, H-2/H-3), 6.11-6.05 (1H, m, H-2/H-3), 5.57 (1H, s, H-4/H-1), 5.52 (1H, s, H-4/H-1), 4.59 (1H, dd, *J* 10.6, 6.6 Hz, H-6), 4.52 (1H, dd, *J* 10.6, 7.3 Hz, H-6'), 4.26 (1H, t, *J* 6.9 Hz, H-7) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 154.8 (C-5), 144.0 (ArC), 143.6 (ArC), 141.5 (ArC), 141.5 (ArC), 138.8 (ArC), 137.0 (ArC), 129.3 (ArCH), 128.9 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 128.10 (ArCH), 128.06 (ArCH), 127.92 (ArCH), 127.90 (ArCH), 127.85 (C-2/C-3), 127.3 (ArCH), 127.2 (C-2/C-3), 125.5 (ArCH), 125.3 (ArCH), 120.1 (ArCH), 79.9 (C-4), 67.6 (C-6), 57.0 (C-1), 47.3 (C-7) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₃₁H₂₆NO₃: 460.1907, found: 460.1912.

Experimental

***tert*-Butyl-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate **90x**.**

Synthesised using a literature procedure.³⁰⁰



To a solution of *tert*-butyl hydroxycarbamate (1.00 g, 7.51 mmol), CuCl (0.149 g, 1.51 mmol, 20 mol%) and pyridine (30 μ L, 0.37 mmol, 5 mol%) in THF (75 mL) was added 2,4-hexadiene (*ca.* 75% *trans*, *trans* isomer, 1.03 mL, 9.04 mmol). The dark green suspension was stirred at room temperature for 2 h before diluting with EtOAc (50 mL) and quenching with a solution of citric acid (50 mL of a 0.1 M aqueous solution). The blue biphasic mixture was stirred at room temperature for 30 min until no colour remained in the organic layer. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and solvent removed *in vacuo*. The crude green oil was purified by column chromatography using 10% EtOAc in pentane (*R_f* 0.39) as the eluent to give *tert*-butyl-3,6-dimethyl-3,6-dihydro-2*H*-1,2-oxazine-2-carboxylate **90x** (0.918 g, 4.31 mmol, 57%, 96:4 d.r.), as a colourless oil.

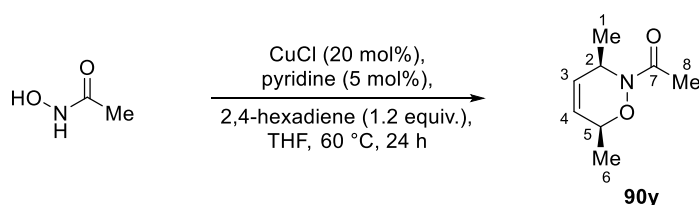
IR ν max (ATR)/ 2977, 2933, 2872, 1722, 1695, 1365, 1307, 1116 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 5.80-5.70 (1H, m, H-3), 5.69-5.65 (1H, m, H-4), 4.66-4.54 (1H, m, H-5), 4.47-4.34 (1H, m, H-2), 1.48 (9H, d, *J* 1.4 Hz, H-9), 1.29 (3H, dd, *J* 6.6, 1.0 Hz, H-1), 1.24 (3H, dd, *J* 6.8, 1.1 Hz, H-6) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 154.4 (C-7), 129.0 (C-4), 128.1 (C-3), 81.3 (C-8), 73.5 (C-5), 50.2 (C-2), 28.5 (C-9), 18.9 (C-6), 18.2 (C-1) ppm.; **HRMS** *m/z* (ESI⁺): [M+Na⁺] calcd. for C₁₁H₁₉NONa: 236.1257, found: 236.1256.

Data in agreement with the literature.³⁴⁷

1-(3,6-Dimethyl-3,6-dihydro-2*H*-1,2-oxazin-2-yl)ethan-1-one **90y.**

Synthesised using a literature procedure.³⁰⁰

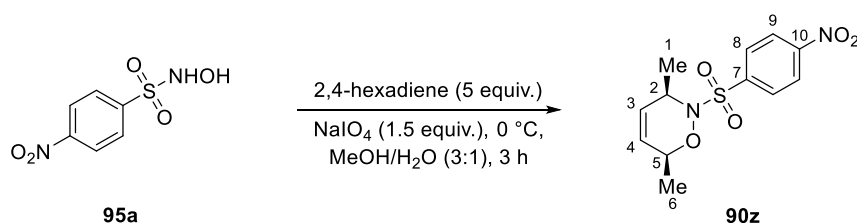
Experimental



To a solution of acetohydroxamic acid (375 mg, 5.00 mmol), CuCl (99.0 mg, 1.00 mmol, 20 mol%) and pyridine (20 μ L, 0.25 mmol, 5 mol%) in THF (50 mL) was added 2,4-hexadiene (*ca.* 75% *trans*, *trans* isomer, 685 μ L, 6.00 mmol). The dark green suspension was stirred at 60 °C for 24 h before diluting with EtOAc (30 mL) and quenching with a solution of Na₂EDTA (30 mL of a 4x10⁻⁴ M aqueous solution). The blue biphasic mixture was stirred at room temperature for 30 min until no colour remained in the organic layer. The remaining copper residue was removed by filtration under gravity. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over MgSO₄, filtered and solvent removed *in vacuo*. The crude product was purified by column chromatography using 25% EtOAc in pentane (*R_f* 0.15) as the eluent to give 1-(3,6-dimethyl-3,6-dihydro-2H-1,2-oxazin-2-yl)ethan-1-one **90y** (410 mg, 2.64 mmol, 53%), as a colourless oil.

IR v max (ATR)/ 3043, 2979, 2932, 1664, 1645, 1409, 1385, 1202, 1092 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 5.80-5.71 (1H, m, H-4), 5.65 (1H, d, *J* 10.2 Hz, H-3), 4.84-4.70 (1H, m, H-2), 4.59-4.47 (1H, m, H-5), 2.10 (3H, s, H-8), 1.30-1.21 (6H, m, H-1 and H-6) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 168.9 (C-7), 128.2 (C-3/C-4), 128.1 (C-3/C-4), 75.4 (C-5), 46.9 (C-2), 20.2 (C-8), 18.9 (C-1/C-6), 18.0 (C-1/C-6) ppm.; **HRMS** *m/z* (ESI+): [M+Na⁺] calcd for C₈H₁₃NO₂Na: 178.0838, found: 178.0845.

3,6-Dimethyl-2-((4-nitrophenyl)sulfonyl)-3,6-dihydro-2H-1,2-oxazine 90z.

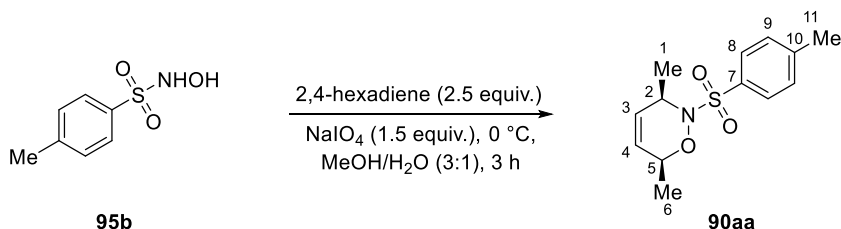


Experimental

To a stirred suspension of **95a** (218 mg, 1.00 mmol) and NaIO₄ (216 mg, 1.00 mmol) in MeOH/H₂O 3:1 (8 mL) was added 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 340 μ L, 3.00 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h before adding another portion of NaIO₄ (104 mg, 0.500 mmol) and 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 230 μ L, 2.00 mmol) followed by stirring for a further 45 min. The mixture was warmed to room temperature and diluted with H₂O (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with H₂O (10 mL), Na₂S₂O₃ (10 mL of a saturated aqueous solution), brine and dried over MgSO₄ before filtering and removing the solvent *in vacuo*. The crude product was purified by column chromatography using gradient elution (10% EtOAc in pentane to 20% EtOAc in pentane, R_f 0.28) to give the product, 3,6-dimethyl-2-((4-nitrophenyl)sulfonyl)-3,6-dihydro-2H-1,2-oxazine **90z** (162 mg, 0.544 mmol, 54%), as a white solid.

m.p. (EtOH) 125 – 127 °C; **IR** ν max (ATR)/ 3018, 3042, 2981, 2935, 1531, 1351, 1170, 1090 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 8.41-8.33 (2H, m, H-8), 8.20-8.12 (2H, m, H-9), 5.79 (1H, ddd, *J* 10.2, 4.6, 2.0 Hz, H-3), 5.66 (1H, ddd, *J* 10.2, 1.7 Hz, H-4), 4.63-4.54 (1H, m, H-5), 4.48-4.39 (1H, m, H-2), 1.32 (3H, d, *J* 6.7 Hz, H-1), 1.20 (3H, d, *J* 6.7 Hz, H-6) ppm.; **¹³C {¹H} NMR** δ _C (126 MHz; CDCl₃) 150.6 (C-10), 144.0 (C-7), 129.9 (C-9), 128.8 (C-4), 127.7 (C-3), 124.2 (C-8), 75.7 (C-5), 51.7 (C-2), 18.9 (C-6), 18.1 (C-1) ppm.; **HRMS** *m/z* (ESI⁺): [M+Na⁺] calcd. for C₁₂H₁₂N₂O₅S₁Na: 321.0516, found: 321.0512.

3,6-Dimethyl-2-tosyl-3,6-dihydro-2H-1,2-oxazine **90aa**.



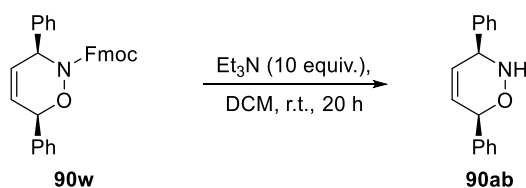
To a stirred suspension of **95b** (374 mg, 2.00 mmol) and NaIO₄ (427 mg, 2.00 mmol) in MeOH/H₂O 3:1 (16 mL) was added 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 285 μ L, 2.50 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h before adding another portion of NaIO₄ (211 mg, 1.00 mmol) and 2,4-hexadiene (*ca.* 75% *trans, trans* isomer, 285 μ L, 2.50 mmol)

Experimental

followed by stirring for a further 1 h. The mixture was warmed to room temperature and diluted with H₂O (15 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with H₂O (10 mL), Na₂S₂O₃ (10 mL of a saturated aqueous solution), brine and dried over MgSO₄ before filtering and removing the solvent *in vacuo*. The crude product was purified by column chromatography using 10% EtOAc in pentane (*R_f* 0.18) as the eluent to give the product, 3,6-dimethyl-2-tosyl-3,6-dihydro-2*H*-1,2-oxazine **90aa** (179 mg, 0.671 mmol, 34%), as a viscous pale-yellow oil.

IR v max (ATR)/ 3041, 2979, 2932, 1631, 1451, 1339, 1118 cm⁻¹; **¹H NMR** δ_H (500 MHz; CDCl₃) 7.86-7.81 (2H, m, H-8), 7.33-7.28 (2H, m, H-9), 5.76 (1H, ddd, *J* 10.2, 4.6, 2.1 Hz, H-3), 5.62 (1H, ddd, *J* 10.2, 2.0, 1.5 Hz, H-4), 4.56-4.49 (1H, m, H-5), 4.41-4.33 (1H, m, H-2), 2.44 (3H, s, H-11), 1.34 (3H, dd, *J* 6.6, 0.8 Hz, H-1), 1.17 (3H, dd, *J* 6.8, 0.7 Hz, H-6) ppm.; **¹³C {¹H} NMR** δ_C (126 MHz; CDCl₃) 144.4 (C-10), 135.2 (C-7), 129.5 (C-9), 128.9 (C-4), 128.7 (C-8), 128.0 (C-3), 75.1 (C-5), 51.6 (C-2), 21.8 (C-11), 18.9 (C-6), 18.1 (C-1) ppm.; **HRMS** *m/z* (ESI+): [M+H⁺] calcd. for C₁₃H₁₈NO₃S: 268.1002, found: 268.1002.

3,6-Diphenyl-3,6-dihydro-2*H*-1,2-oxazine **90ab**.



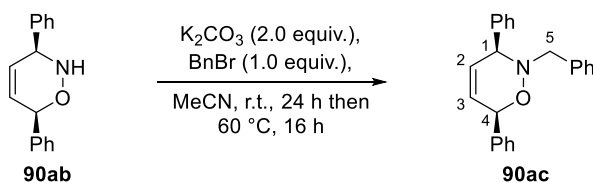
To a solution of **90w** (970 mg, 2.11 mmol) in DCM (8 mL) was added Et₃N (2.95 mL, 21.1 mmol) and the mixture was stirred at room temperature for 20 h. The solvent was removed *in vacuo* and the crude oil was purified by column chromatography using gradient elution (10% EtOAc in pentane to 25% EtOAc in pentane (*R_f* 0.24)) to give 3,6-diphenyl-3,6-dihydro-2*H*-1,2-oxazine **90ab** (454 mg, 1.91 mmol, 91%), as a viscous pale-yellow oil that solidified in the freezer.

m.p. (EtOAc) 50 – 51 °C; **IR** v max (ATR)/ 3284, 3030, 3005, 2978, 1491, 1452, 1258 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.58-7.31 (10H, m, ArH), 6.26 (2H, d, *J* 1.9 Hz, CH=CH), 5.41 (1H, d, *J* 2.6 Hz, OCH(Ph)), 5.23 (1H, brs, NH), 4.81-4.73 (1H, m, NHCH(Ph)) ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 139.7 (NHCH(PhC)), 139.2 (OCH(PhC)), 128.7 (sp²CH), 128.6 (sp²CH), 128.4 (sp²CH),

Experimental

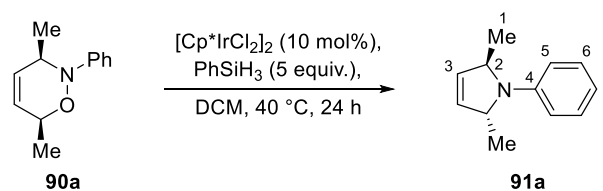
128.34 (sp²CH), 128.33 (sp²CH), 128.28 (sp²CH), 128.1 (sp²CH), 128.0 (sp²CH), 77.3 (OCH(Ph)), 59.7 (NHCH(Ph)) ppm.; **HRMS** m/z (ESI+): [M+H⁺] calcd. for C₁₆H₁₆NO: 238.1226, found: 238.1224.

2-Benzyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine 90ac.

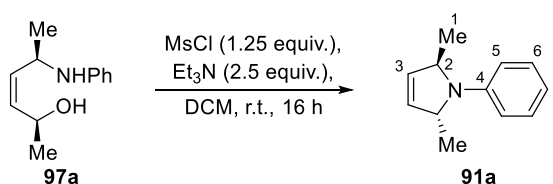


To a stirred suspension of **90ab** (179 mg, 0.750 mmol) and K₂CO₃ (207 mg, 1.50 mmol) in MeCN (3 mL) was added benzyl bromide (89 µL, 0.75 mmol) and the mixture was stirred at room temperature for 24 h. TLC analysis of the reaction indicated the starting material had not been consumed and so the reaction was heated at 60 °C for 16 h. The mixture was cooled to room temperature and diluted with H₂O (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography using gradient elution (100% pentane to 2% Et₂O in pentane (R_f 0.15)) to give the product, 2-benzyl-3,6-diphenyl-3,6-dihydro-2H-1,2-oxazine **90ac** (234 mg, 0.715 mmol, 95%), as a colourless solid.

m.p. (EtOH) 81 – 83 °C; **IR** v max (ATR)/ 3059, 3032, 2913, 2808, 1493, 1452, 1257 cm⁻¹; **¹H NMR** δ_H (500 MHz; CD₃CN) 7.50-7.46 (2H, m, PhCH), 7.42-7.37 (2H, m, PhCH), 7.37-7.30 (6H, m, PhCH), 7.17-7.09 (3H, m, PhCH), 7.06-6.98 (2H, m, PhCH), 6.15 (1H, ddd, *J* 10.0, 2.8, 2.3 Hz, H-3), 6.00 (1H, ddd, *J* 10.0, 3.0, 2.3 Hz, H-2), 5.36-5.29 (1H, m, H-4), 4.49-4.45 (1H, m, H-1), 3.69-3.55 (2H, m, H-5) ppm.; **¹³C {¹H} NMR** δ_C (126 MHz; CD₃CN) [Some carbon signals overlapped] 140.9 (PhC), 140.2 (PhC), 139.2 (PhCH), 130.2 (C-2), 130.1 (PhCH), 129.4 (PhCH), 129.3 (PhCH), 129.2 (PhCH), 129.1 (PhCH), 128.9 (PhCH), 128.8 (PhCH), 128.7 (PhCH), 128.0 (C-3), 127.5 (PhCH), 79.0 (C-4), 67.4 (C-1), 59.6 (C-5) ppm.; **HRMS** m/z (ESI+): [M+H⁺] calcd. for C₂₃H₂₂NO: 328.1696, found: 328.1698.

2,5-Dimethyl-1-phenyl-2,5-dihydro-1H-pyrrole 91a.Via Ir-catalysed deoxygenative ring contraction:

To a suspension of 1,2-oxazine **90a** (123 mg, 0.650 mmol) and $[\text{Cp}^*\text{IrCl}_2]_2$ (51 mg, 65 μmol , 10 mol%) in DCM (5.2 mL) was added PhSiH_3 (400 μL , 3.25 mmol) and the mixture was heated at 40 $^\circ\text{C}$ for 24 h. The pale-yellow reaction mixture was cooled to room temperature, silica (~2 g) was added and the slurry was stirred for 30 min at room temperature. The mixture was purified by column chromatography using 10% DCM in pentane (R_f 0.20) as the eluent to give the product, 2,5-dimethyl-1-phenyl-2,5-dihydro-1H-pyrrole **91a** (62 mg, 0.36 mmol, 55%), as an off-white solid.

Via 1,2-oxazine ring opening/alcohol mesylation/cyclisation sequence:

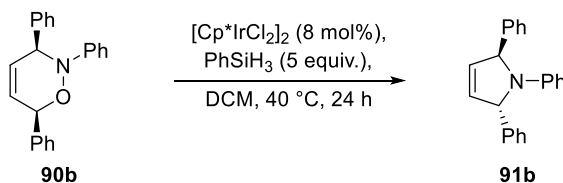
The amino alcohol **97a** was obtained from 1,2-oxazine **90a** (*vide infra*). To a stirred solution of amino alcohol **97a** (0.144 g, 0.760 mmol) and Et_3N (0.265 mL, 1.90 mmol) in DCM (7.6 mL) at 0 $^\circ\text{C}$ was added mesyl chloride (74.0 μL , 0.950 mmol) dropwise over 15 min. The resulting mixture was allowed to warm to room temperature and stirred for 16 h before diluting with DCM (10 mL) and H_2O (10 mL). The aqueous phase was extracted with DCM (3 x 10 mL) and the combined organics were dried over MgSO_4 , filtered and the solvent removed *in vacuo*. Purification by column chromatography using 10% DCM in pentane (R_f 0.26) as the eluent gave the product, 2,5-dimethyl-1-phenyl-2,5-dihydro-1H-pyrrole **91a** (0.112 g, 0.646 mmol, 85%), as a colourless oil that solidified in the freezer.

m.p. (EtOH) 38 – 39 $^\circ\text{C}$; **IR** ν max (ATR)/ 3055, 3031, 2975, 2820, 1594, 1498, 1453, 1352, 1183, 1168 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.26-7.21 (2H, m, H-6), 6.70-6.64 (3H, m, H-5 and H-7),

Experimental

5.82-5.78 (2H, m, H-3), 4.80-4.71 (2H, m, H-2), 1.25-1.20 (6H, m, H-1) ppm.; ^{13}C $\{^1\text{H}\}$ NMR δ_{C} (126 MHz; CDCl_3) 144.8 (C-4), 131.1 (C-3), 129.0 (C-6), 115.6 (PhCH), 114.8 (PhCH), 59.7 (C-2), 18.8 (C-1) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{16}\text{N}$: 174.1283, found: 174.1277.

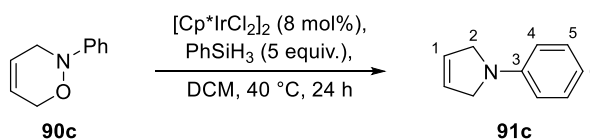
1,2,5-Triphenyl-2,5-dihydro-1H-pyrrole **91b**.



Prepared according to general procedure 1, using 1,2-oxazine **90b** (125 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 2% Et_2O in pentane (R_f 0.18)) to give the product, 1,2,5-triphenyl-2,5-dihydro-1H-pyrrole **91b** (60 mg, 0.20 mmol, 51%), as a colourless solid.

m.p. (EtOH) 188 – 189 °C; **IR** ν_{max} (ATR)/ 3080, 3019, 2922, 2825, 1594, 1500, 1346, 1157 cm^{-1} ; ^1H NMR δ_{H} (400 MHz; $(\text{CD}_3)_2\text{CO}$) 7.38-7.26 (8H, m, PhH), 7.20 (2H, tt, J 7.2, 1.4 Hz PhH), 6.92-6.82 (2H, m, PhH), 6.51-6.43 (2H, m, PhH), 6.39 (1H, tt, J 7.3, 1.1 Hz, $\text{NPhH}_{\text{para}}$), 6.02-5.97 (2H, m, NCH(Ph)), 5.97-5.92 (2H, m, CH=CH) ppm.; ^{13}C $\{^1\text{H}\}$ NMR δ_{C} (101 MHz; C_6D_6) 144.1(PhC), 142.5 (PhCN), 130.6 (CH=CH), 129.02 (PhCH), 128.95 (PhCH), 128.4 (PhCH), 126.9 (PhCH), 116.6 (PhCH), 114.8 (PhCH), 70.7 (PhCH(NPh)) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{22}\text{H}_{20}\text{N}$: 298.1596, found: 298.1587.

1-Phenyl-2,5-dihydro-1H-pyrrole **91c**.



Prepared according to general procedure 1, using 1,2-oxazine **90c** (64.6 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane

Experimental

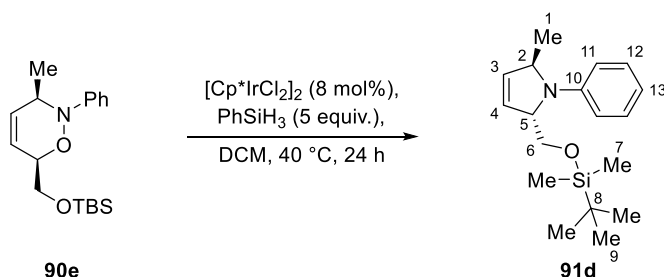
to 1% Et₂O in pentane (*R_f* 0.13)) to give the product, 1-phenyl-2,5-dihydro-1*H*-pyrrole **91c** (29.9 mg, 0.206 mmol, 52%), as a white solid.

m.p. (EtOH) 97 – 98 °C, Lit m.p. 101 – 104 °C; **IR** ν max (ATR)/ 3078, 3040, 2963, 2822, 1595, 1505, 1466, 1360, 1184 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.34-7.20 (2H, m, H-5), 6.72-6.66 (1H, m, H-6), 6.60-6.48 (2H, m, H-4), 5.96 (2H, s, H-1), 4.12 (4H, s, H-2) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 147.2 (C-3), 129.5 (C-5), 126.5 (C-1), 115.7 (C-6), 111.3 (C-4), 54.5 (C-2) ppm.; **HRMS** *m/z* (ESI+): [2M+H⁺] calcd. for C₂₀H₂₃N₂:291.1861, found:291.1852.

Data in agreement with the literature.³⁴⁸

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91d**.

Via Ir-catalysed deoxygenative ring contraction of 1,2-oxazine **90e**:



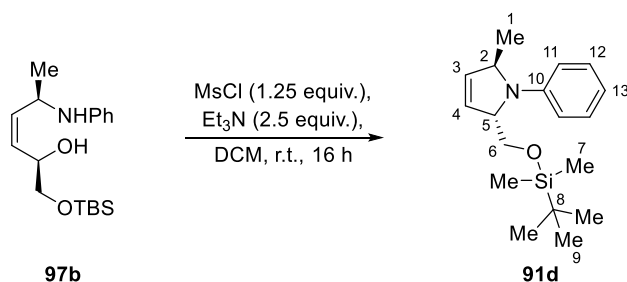
Prepared according to general procedure 1, using 1,2-oxazine **90e** (128 mg, 0.400 mmol). The crude product was purified by column chromatography using 100% pentane (*R_f* 0.20) as the eluent to give the product, 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91d** (54.8 mg, 0.181 mmol, 45%, 95:5 d.r.), as a pale-yellow oil.

Via Ir-catalysed deoxygenative ring contraction of 1,2-oxazine **90e'**:

Prepared according to general procedure 1, using 1,2-oxazine **90e'** (128 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 1% Et₂O in pentane (*R_f* 0.20)) to give the product, 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91d** (39.7 mg, 0.131 mmol, 33%), as a pale-yellow oil.

Experimental

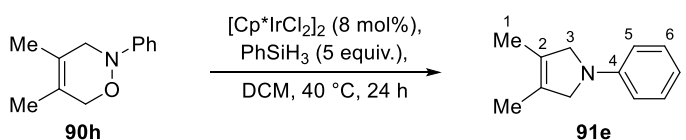
Via 1,2-oxazine ring opening/alcohol mesylation/cyclisation sequence:



The amino alcohol **97b** was obtained from 1,2-oxazine **90e** (*vide infra*). To a stirred solution of amino alcohol **97b** (3.67 g, 11.4 mmol) and Et₃N (3.97 mL, 28.5 mmol) in DCM (114 mL) at 0 °C was added mesyl chloride (1.10 mL, 14.3 mmol) dropwise over 15 min. The resulting mixture was allowed to warm to room temperature and stirred for 16 h before diluting with DCM (50 mL) and H₂O (50 mL). The aqueous was extracted with DCM (3 x 30 mL) and the combined organics were dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by column chromatography using 3% Et₂O in pentane (*R_f* 0.27) as the eluent gave the product, 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91d** (2.62 g, 8.63 mmol, 76%) as a pale-yellow oil.

IR v max (ATR)/ 3068, 2955, 2927, 2856, 1596, 1498, 1471, 1352, 1252, 1100 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.24-7.20 (2H, m, H-12), 6.72-6.64 (3H, m, H-11 and H-13), 6.02-5.95 (1H, m, H-4), 5.91-5.82 (1H, m, H-3), 4.77-4.68 (2H, m, H-2 and H-5), 3.94 (1H, dd, *J* 9.8, 2.6 Hz, H-6), 3.42 (1H, dd, *J* 9.8, 7.1 Hz, H-6'), 1.21 (3H, d, *J* 5.8 Hz, H-1), 0.87 (9H, s, H-9), -0.02 (3H, s, H-7), -0.07 (3H, s, H-7') ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 144.9 (C-10), 132.6 (C-3), 129.0 (C-12), 128.3 (C-4), 116.0 (C-13), 114.9 (C-11), 66.0 (C-5), 63.5 (C-6), 60.5 (C-2), 26.0 (C-9), 18.8 (C-1), 18.3 (C-8), -5.3 (C-7), -5.4 (C-7') ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₈H₃₀NOSi: 304.2097, found: 304.2091.

3,4-Dimethyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91e**.



Experimental

Prepared according to general procedure 1, using 1,2-oxazine **90h** (75.5 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 5% DCM in pentane to 10% DCM in pentane (R_f 0.15)) to give the product, 3,4-dimethyl-1-phenyl-2,5-dihydro-1*H*-pyrrole **91e** (12.9 mg, 75.0 μ mol, 19%), as an off white solid.

m.p. (EtOH) 108 – 110 °C, Lit m.p. 114 – 115 °C; **IR** ν max (ATR)/ 3063, 2968, 2915, 2850, 1613, 1591, 1505, 1467, 1378, 1251 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.26-7.21 (2H, m, H-6), 6.69-6.63 (1H, m, H-7), 6.51 (2H, d, J 8.2 Hz, H-5), 3.99 (4H, s, H-3), 1.73 (6H, s, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 147.3 (C-4), 129.4 (C-6), 127.1 (C-2), 115.3 (C-7), 111.0 (C-5), 59.2 (C-3), 11.6 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{16}\text{N}$: 174.1277, found: 174.1260.

Data in agreement with the literature.³⁴⁹

4-Methyl-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole **91f**.

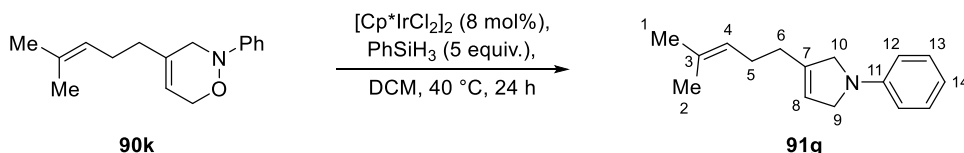


Prepared according to general procedure 1, using 1,2-oxazine **90j** (101 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 1% Et_2O in pentane (R_f 0.27)) to give the title compound, 4-methyl-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole **91f** (33.0 mg, 0.140 mmol, 35%), as a colourless solid.

m.p. (EtOH) 67 – 69 °C; **IR** ν max (ATR)/ 3084, 3062, 2960, 2914, 2819, 1598, 1505, 1371, 1343 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.32-7.27 (4H, m, H-6 and H-7), 7.24-7.18 (1H, m, H-8), 7.16-7.11 (2H, m, H-12), 6.65-6.61 (1H, m, H-13), 6.51-6.46 (2H, m, H-11), 5.51-5.48 (1H, m, H-3), 5.38-5.33 (1H, m, H-4), 4.40-4.32 (1H, m, H-9'), 4.19-4.10 (1H, m, H-9), 1.88-1.83 (3H, m, H-1) ppm.; **^{13}C NMR** δ_{C} (126 MHz; CDCl_3) 146.6 (C-10), 143.3 (C-5), 134.0 (C-2), 129.2 (C-12), 128.9 (C-7), 127.1 (C-8), 126.7 (C-3), 126.2 (C-6), 116.0 (C-13), 112.2 (C-11), 70.4 (C-4), 59.7 (C-9), 14.4 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{17}\text{H}_{18}\text{N}$: 236.1439, found: 236.1435.

Experimental

3-(4-Methylpent-3-en-1-yl)-1-phenyl-2,5-dihydro-1*H*-pyrrole **91g**.



Prepared according to general procedure 1, using 1,2-oxazine **90k** (91.4 mg, 0.400 mmol). The crude product was purified by preparative TLC using 1% Et₂O in pentane as the eluent followed by a trituration of the residue at -20 °C with cold EtOH to give the product, 3-(4-methylpent-3-en-1-yl)-1-phenyl-2,5-dihydro-1*H*-pyrrole **91g** (42.7 mg, 0.188 mmol, 47%), as a colourless oil that solidified in the freezer.

IR ν max (ATR)/ 3060, 2966, 2924, 1599, 1507, 1474, 1377 cm^{-1} ; **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.25-7.21 (2H, m, H-13), 6.69-6.65 (1H, m, H-14), 6.54-6.50 (2H, m, H-12), 5.60-5.53 (1H, m, H-8), 5.18-5.09 (1H, m, H-4), 4.11-4.04 (2H, m, H-9), 4.04-3.98 (2H, m, H-10), 2.26-2.16 (4H, m, H-5 and H-6), 1.71 (3H, s, H-1), 1.63 (3H, s, H-3) ppm.; **¹³C {¹H} NMR** δ_{C} (126 MHz; CDCl₃) 147.4 (C-11), 140.4 (C-7), 132.3 (C-2), 129.4 (C-13), 123.8 (C-4), 119.2 (C-8), 115.5 (C-14), 111.1 (C-12), 56.7 (C-10), 54.9 (C-9), 29.4 (CH₂), 26.4 (CH₂), 25.9 (C-1), 17.9 (C-3) ppm.; **HRMS** m/z (ESI⁺): [M+H⁺] calcd. for C₁₆H₂₂N: 228.1752, found:228.1746.

3-Chloro-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole **91h**.

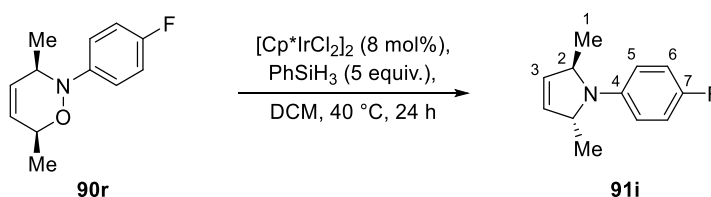


Prepared according to general procedure 1, using 1,2-oxazine **90l** (108 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (1% Et₂O in pentane to 2% Et₂O in pentane to 5% Et₂O in pentane (R_f 0.37), followed by trituration of the resulting solid in cold EtOH to give the product, 3-chloro-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole **91h** (34.3 mg, 0.134 mmol, 34%), as a colourless solid.

Experimental

m.p. 127 – 128 °C; **IR** ν max (ATR)/ 3058, 3025, 2924, 2832, 1596, 1503, 1429 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.39-7.32 (4H, m, H-6 and H-7), 7.31-7.27 (1H, m, H-8), 7.17-7.12 (2H, m, H-11), 6.69-6.65 (1H, m, H-12), 6.52-6.46 (2H, m, H-10), 5.98 (1H, dd, J 2.1, 2.1 Hz, H-2), 5.24 (1H, ddd, J 6.6, 3.3, 1.7 Hz, H-4), 4.52 (1H, ddd, J 13.8, 6.6, 2.1 Hz, H-1), 4.27 (1H, ddd, J 13.8, 3.3, 2.1 Hz, H-1') ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 146.0 (C-9), 140.1 (C-5), 132.6 (C-3), 129.3 (C-11), 128.8 (C-7), 128.2 (C-8), 127.3 (C-6), 120.9 (C-2), 116.9 (C-12), 112.0 (C-10), 71.4 (C-4), 54.9 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{15}\text{N}^{35}\text{Cl}$: 256.0888, found: 256.0887.

1-(4-Fluorophenyl)-2,5-dimethyl-2,5-dihydro-1H-pyrrole **91i**.



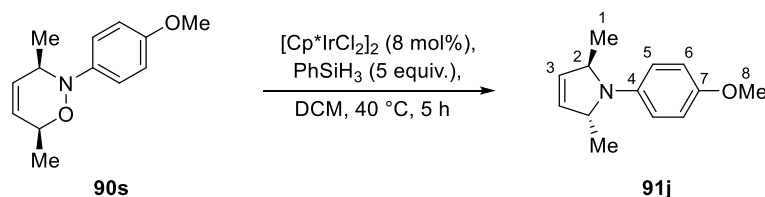
Prepared according to general procedure 1, using 1,2-oxazine **90r** (82.9 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 2% Et_2O in pentane R_f 0.27) to give the title compound, 1-(4-fluorophenyl)-2,5-dimethyl-2,5-dihydro-1H-pyrrole **91i** (40.3 mg, 0.211 mmol, 53%), as a colourless solid.

m.p. (EtOH) 76 – 78 °C; **IR** ν max (ATR)/ 3055, 2968, 2926, 1509, 1449, 1307, 1209 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 6.96-6.90 (2H, m, ArCH), 6.59-6.54 (2H, m, ArCH), 5.79 (2H, s, H-3), 4.72-4.66 (2H, m, H-2), 1.20-1.17 (6H, m, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 154.9 (d, J 234.1 Hz, C-7), 141.3 (d, J 1.8 Hz, C-4), 131.1 (C-3), 115.45 (d, J 22.1 Hz, C-6), 115.44 (d, J 7.3 Hz, C-5), 60.0 (C-2), 18.6 (C-1) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376 MHz; CDCl_3) -130.31 ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{15}\text{FN}$: 192.1189, found: 192.1182.

Experimental

1-(4-Methoxyphenyl)-2,5-dimethyl-2,5-dihydro-1H-pyrrole **91j**.

Via Ir-catalysed deoxygenative ring contraction:



To a stirred suspension of 1,2-oxazine **90s** (88.1 mg, 0.402 mmol) and $[\text{Cp}^*\text{IrCl}_2]_2$ (25.8 mg, 32.3 μmol , 8 mol%) in DCM (3.2 mL) was added PhSiH_3 (248 μL , 2.00 mmol) and the mixture was stirred at 40 °C for 5 h. The resulting solution was cooled to room temperature and stirred over silica for 25 min in preparation for column chromatography. The solvent was removed *in vacuo* and purification by column chromatography using 25% DCM in pentane as eluent (R_f 0.11) gave the title compound, 1-(4-methoxyphenyl)-2,5-dimethyl-2,5-dihydro-1H-pyrrole **91j** (40 mg, 0.20 mmol, 49%, 90:10 d.r.), as a yellow oil.

Via 1,2-oxazine ring opening/alcohol mesylation/cyclisation sequence:



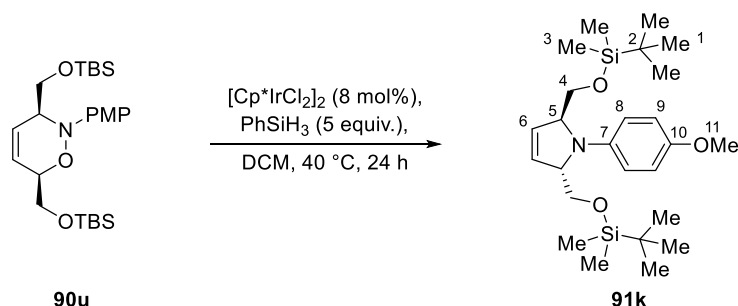
The amino alcohol **97c** was obtained from 1,2-oxazine **90s** (*vide infra*). To a stirred solution of amino alcohol **97c** (438 mg, 1.98 mmol) and Et_3N (0.690 mL, 4.95 mmol) in DCM (20 mL) at 0 °C was added mesyl chloride (0.192 mL, 2.48 mmol) dropwise over 10 min. The resulting mixture was allowed to warm to room temperature and stirred for 16 h before diluting with DCM (20 mL) and H_2O (20 mL). The aqueous was extracted with DCM (3 x 20 mL) and the combined organics were dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude product was flushed through a plug of silica using 10% Et_2O in pentane to give the product, 1-(4-methoxyphenyl)-2,5-dimethyl-2,5-dihydro-1H-pyrrole **91j** (318 mg, 0.156 mmol, 79%), as a pale-yellow oil.

IR ν max (ATR)/ 3068, 2965, 2925, 2830, 1507, 1464, 1348, 1236, 1040 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 6.89-6.80 (2H, m, H-5), 6.67-6.58 (2H, m, H-6), 5.79 (2H, s, H-3), 4.75-4.64 (2H, m,

Experimental

H-2), 3.77 (3H, s, H-8), 1.18 (6H, d, J 5.5 Hz, H-1) ppm.; ^{13}C { ^1H } NMR δ_{C} (101 MHz; CDCl_3) 150.8 (C-7), 139.3 (C-4), 131.3 (C-3), 115.9 (C-6), 114.8 (C-5), 59.9 (C-2), 55.9 (C-8), 18.7 (C-1) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{13}\text{H}_{18}\text{NO}$: 204.1383, found: 204.1384.

2,5-Bis(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole **91k**.

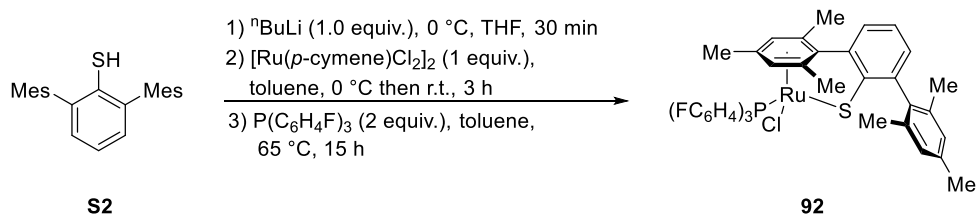


To a stirred suspension of 1,2-oxazine **90u** (383 mg, 0.800 mmol) and $[\text{Cp}^*\text{IrCl}_2]_2$ (51.1 mg, 64.0 μmol , 8 mol%) in DCM (6.4 mL) was added PhSiH_3 (495 μL , 4.00 mmol) and the mixture was heated at 40 °C for 24 h. The pale-yellow reaction mixture was cooled to room temperature and H_2O (100 μL) was added. The mixture was then flushed through a silica plug with DCM (150 mL) and the solvent was removed *in vacuo*. Purification by column chromatography 2% Et_2O in pentane (R_f 0.22) as the eluent gave the product, 2,5-bis(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole **91k** (127 mg, 0.274 mmol, 34%, 94:6 d.r.), as a yellow oil.

IR ν max (ATR)/ 3043, 2953, 2928, 2856, 1510, 1463, 1241 cm^{-1} ; ^1H NMR δ_{H} (500 MHz; CDCl_3) 6.84-6.78 (2H, m, H-8), 6.71-6.65 (2H, m, H-9), 6.05-6.01 (2H, m, H-6), 4.67-4.62 (2H, m, H-5), 3.89-3.83 (2H, m, 2 x H-4), 3.76 (3H, s, H-11), 3.43-3.37 (2H, m, 2 x H-4'), 0.85 (18H, s, H-1), -0.04 (6H, s, 2 x H-3), -0.08 (6H, s, 2 x H-3') ppm.; ^{13}C { ^1H } NMR δ_{C} (126 MHz; CDCl_3) 151.3 (C-10), 139.3 (C-7), 130.0 (C-6), 116.1 (C-9), 114.8 (C-8), 67.1 (C-5), 63.5 (C-4), 55.9 (C-11), 26.0 (C-1), 18.4 (C-2), -5.28 (C-3), -5.34 (C-3') ppm.; HRMS m/z (ESI+): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{25}\text{H}_{45}\text{NO}_3\text{Si}_2\text{Na}$: 486.2830, found: 486.2822.

Experimental

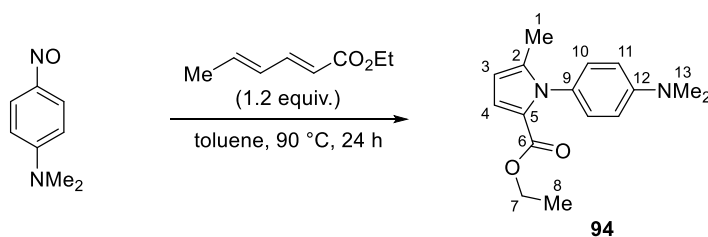
[2,6- η^6 : η^1 -Bis(2,4,6-trimethylphenyl)phenylthiolato]chlorido[tris(4-fluorophenyl)-phosphine]-ruthenium(II) **92**.



To a solution of thiol **S2** (243 mg, 0.702 mmol) in THF (7 mL) was added *n*-BuLi (0.35 mL, 0.70 mmol of a 2.0 M solution in hexane) dropwise over 30 min at 0 °C. The solution was stirred at 0 °C for 2 h before being added dropwise over 30 min to a solution [Ru(*p*-cymene)Cl₂]₂ (214 mg, 0.349 mmol) in THF (7 mL) at 0 °C. The mixture was warmed to room temperature slowly over 3 h before the solvent was removed *in vacuo*. The brown solid was suspended in toluene (7 mL) and the brown mixture was filtered under inert atmosphere. Toluene (7 mL) and P(*p*-FC₆H₄)₃ (222 mg, 0.702 mmol) were added and the suspension was heated at 65 °C for 15 h. The mixture was cooled to room temperature and the toluene was removed *in vacuo*. The crude brown solid was triturated in cold pentane/toluene (1:2) and filtered to give the product, [2,6- η^6 : η^1 -bis(2,4,6-trimethylphenyl)phenylthiolato]chlorido[tris(4-fluorophenyl)-phosphine]-ruthenium(II) **92** (418 mg, 0.551 mmol, 75%), as dark red crystals.

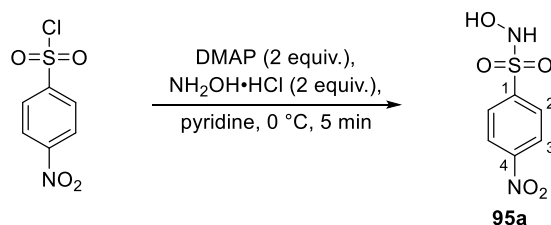
m.p. decomposed >250 °C **IR** ν max (ATR)/ 3655, 3037, 2955, 1588, 1496, 1393, 1226, 1160, 1092 cm⁻¹; **¹H NMR** δ_{H} (400 MHz; C₆D₆) 7.59-7.49 (6H, m, ArCH), 6.99-6.95 (3H, m, ArCH), 6.86-6.82 (1H, m, ArCH), 6.76 (1H, s, ArCH), 6.64-6.56 (7H, m, ArCH), 5.07 (1H, s, ArCH), 3.40 (1H, d, *J* 4.9 Hz, CH₃), 2.39 (3H, s, CH₃), 2.26 (3H, s, CH₃), 2.16 (3H, s, CH₃), 2.12 (3H, d, *J* 3.6 Hz, CH₃), 1.44 (3H, s, CH₃), 1.16 (3H, s, CH₃) ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; C₆D₆) [Due to peak splitting from heteronuclei, peak assignments could not be made and so all visible signals have been listed]: 165.39, 165.37, 162.89, 162.87, 160.32, 160.27, 142.9, 137.7, 137.1, 136.8, 136.7, 136.6, 136.3, 135.7, 135.4, 129.9, 128.8, 128.4, 126.2, 122.1, 115.4, 115.3, 115.2, 115.1, 113.3, 113.2, 97.4, 97.32, 97.27, 97.2, 97.1, 87.9, 83.9, 21.2, 20.9, 18.5, 16.94, 16.92, 16.7 ppm.; **¹⁹F {¹H} NMR** δ_{F} (376 MHz; C₆D₆) -109.68 ppm.; **³¹P {¹H} NMR** δ_{P} (162 MHz; C₆D₆) 27.4 ppm.; **HRMS** *m/z* (ESI⁺): [M – Cl]⁺ calcd. for C₄₂H₃₇F₃PRuS: 763.1349, found: 763.1341.

Data in agreement with the literature.⁸³

Ethyl-1-(4-(dimethylamino)phenyl)-5-methyl-1H-pyrrole-2-carboxylate 94.

To a stirred solution of *N,N*-dimethyl-4-nitrosoaniline (600 mg, 4.00 mmol) in toluene (20 mL) was added ethyl sorbate (0.70 mL, 4.8 mmol) and the mixture was heated at 90 °C for 24 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography using 15% EtOAc in pentane (R_f 0.15) to give the product, ethyl-1-(4-(dimethylamino)phenyl)-5-methyl-1H-pyrrole-2-carboxylate **94** (46.5 mg, 0.251 mmol, 63%), as an orange crystalline solid.

m.p. (EtOAc) 112 – 113 °C; **IR** ν max (ATR)/ 3111, 2981, 2897, 1698, 1611, 1522, 1479, 1343 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.08-7.01 (2H, m, H-10), 6.99 (1H, d, J 3.8 Hz, H-4), 6.78-6.70 (2H, m, H-11), 6.01 (1H, d, J 3.8 Hz, H-3), 4.11 (2H, q, J 7.1 Hz, H-7), 3.00 (6H, s, H-13), 2.03 (3H, s, H-1), 1.19 (3H, t, J 7.1 Hz, H-8) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 160.7 (C-6), 150.0 (C-12), 138.2 (C-2), 128.3 (C-10), 128.2 (C-9), 123.7 (C-5), 117.4 (C-4), 112.0 (C-11), 107.6 (C-3), 59.4 (C-7), 40.6 (C-13), 14.5 (C-1), 13.1 (C-8) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}_2$: 273.1603, found: 273.1588.

***N*-Hydroxy-4-nitrobenzenesulfonamide 95a.**

To a solution of hydroxylamine hydrochloride (208 mg, 3.00 mmol) and DMAP (367 mg, 3.00 mmol) in pyridine (15 mL) at 0 °C was added 4-nitrobenzenesulfonyl chloride (332 mg, 1.50 mmol). The mixture was allowed to warm to room temperature and stirred for 5 min. The

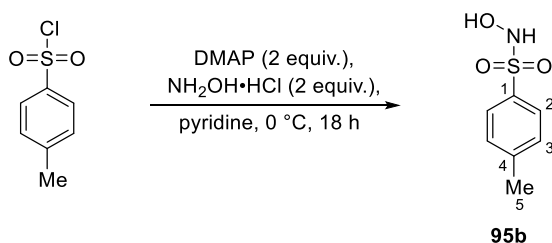
Experimental

reaction mixture was then diluted with EtOAc (50 mL) and HCl (50 mL of a 1 M aqueous solution) and the organic layer was washed with HCl (20 mL of a 1 M aqueous solution), brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography using 30% EtOAc in pentane (R_f 0.12) as the eluent followed by recrystallization from Et_2O /pentane gave the title compound, *N*-hydroxy-4-nitrobenzenesulfonamide **95a** (242 mg, 1.11 mmol, 74%), as pale-yellow crystals.

m.p. (Et_2O /pentane) Decomposed $>190^\circ\text{C}$, Lit m.p. decomposed $>168^\circ\text{C}$; **IR** ν_{max} (ATR)/ 3416, 3108, 1642, 1521, 1353, 1198 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; DMSO) 8.22–8.18 (2H, m, H-3), 7.85–7.81 (2H, m, H-2) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; DMSO) 154.3 (C-4), 147.3 (C-1), 126.9 (C-2), 123.4 (C-3) ppm.; **HRMS** m/z (ESI-): $[\text{M}]^-$ calcd. for $\text{C}_6\text{H}_5\text{N}_2\text{O}_5\text{S}$: 216.9925, found: 216.9926.

Data in agreement with the literature.³⁵⁰

N-Hydroxy-4-methylbenzenesulfonamide **95b**.



To a solution of hydroxylamine hydrochloride (2.78 g, 40.0 mmol) and DMAP (4.89 g, 40.0 mmol) in pyridine (12.5 mL) at 0°C was added tosyl chloride (3.81 g, 20.0 mmol) portionwise over 30 min. The mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then diluted with EtOAc (25 mL) and HCl (20 mL of a 1 M aqueous solution) and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organics were washed with HCl (2 x 20 mL of a 1 M aqueous solution), brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by recrystallization from DCM/pentane gave the title compound, *N*-hydroxy-4-methylbenzenesulfonamide **95b** (1.44 g, 7.70 mmol, 39%), as colourless crystals.

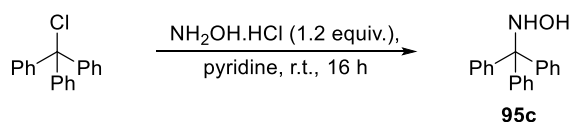
m.p. (DCM/pentane) $144 - 145^\circ\text{C}$, Lit m.p. $148 - 149^\circ\text{C}$; **IR** ν_{max} (ATR)/ 3393, 3225, 3086, 2688, 1591, 1443, 1305 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; DMSO) 9.54 (1H, br s, OH), 9.48 (1H, br s, NH),

Experimental

7.75-7.70 (2H, m, H-3), 7.42 (2H, d, *J* 8.2 Hz, H-2), 2.39 (3H, s, H-5) ppm.; ^{13}C { ^1H } NMR δ_{C} (126 MHz; DMSO) 143.6 (C-4), 134.5 (C-1), 129.4 (C-2), 128.2 (C-3), 21.1 (C-5) ppm.; HRMS *m/z* (ESI+): [M+Na⁺] calcd. for C₇H₉NO₃Na:210.0195, found:210.0190.

Data in agreement with the literature.^{351,352}

N-Tritylhydroxylamine **95c**.



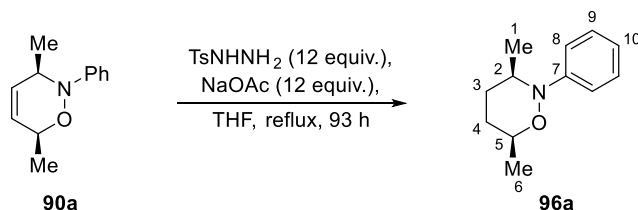
To a solution of trityl chloride (5.58 g, 20.0 mmol) in pyridine (20 mL) was added a suspension of hydroxylamine hydrochloride (1.67 g, 24.0 mmol) in pyridine (20 mL) over 5 min. The mixture was stirred at room temperature for 16 h before H₂O (50 mL) was added and the mixture of trityl alcohol and *N*-tritylhydroxylamine was filtered. The crude solid was purified by column chromatography using 20% EtOAc in pentane as the eluent (*R_f* 0.24) followed by recrystallisation from 10% EtOAc in hexane to give the title compound, *N*-tritylhydroxylamine **95c** (1.38.g, 5.01 mmol, 25%), as colourless crystals.

m.p. (EtOAc/hexane) 135 – 137 °C, Lit m.p. 132 – 134 °C; **IR** ν max (ATR)/ 3250, 3166, 3056, 1486, 1444, 1408, 1000 cm⁻¹; ^1H NMR δ_{H} (500 MHz; CDCl₃) 7.41-7.38 (6H, m, PhCH_{ortho}), 7.34-7.30 (6H, m, PhCH_{meta}), 7.29-7.25 (3H, m, PhCH_{para}) ppm.; ^{13}C { ^1H } NMR δ_{C} (126 MHz; CDCl₃) 143.9 ((PhC)₃C), 129.1 (PhCH_{ortho}), 128.2 (PhCH_{meta}), 127.2 (PhCH_{para}), 74.7 ((Ph)₃C) ppm.; HRMS *m/z* (ESI+): [M+Na⁺] calcd. for C₁₉H₁₇NONa:298.1202, found: 298.1201.

Data in agreement with the literature.³⁵³

Experimental

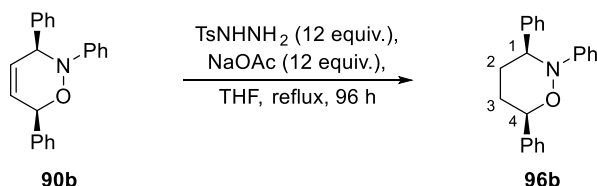
3,6-Dimethyl-2-phenyl-1,2-oxazinane **96a**.



Prepared according to general procedure 2, using 1,2-oxazine **90a** (0.479 g, 2.53 mmol) and heating for 93 h. The crude product was purified by column chromatography using 5% Et₂O in pentane as the eluent (*R_f* 0.21) to give the title compound, 3,6-dimethyl-2-phenyl-1,2-oxazinane **96a** (0.437 g, 2.29 mmol, 91%), as a colourless oil.

IR ν max (ATR)/ 3036, 2971, 2934, 1596, 1489, 1451, 1370, 1260, 1130, 1041 cm⁻¹; **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.29-7.23 (2H, m, H-9), 7.05-6.97 (2H, m, H-8), 6.90-6.85 (1H, m, H-10), 4.03 (1H, dqd, *J* 10.7, 6.3, 2.7 Hz, H-5), 3.94 (1H, qdd, *J* 6.6, 5.0, 2.0 Hz, H-2), 2.15 (1H, dddd, *J* 12.8, 12.8, 5.0, 5.0 Hz, H-3), 1.77-1.50 (3H, m, H-3' and 2 x H-4), 1.27 (3H, d, *J* 6.3 Hz, H-6), 1.11 (3H, d, *J* 6.6 Hz, H-1) ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; CDCl₃) 149.7 (C-7), 128.9 (C-9), 120.6 (C-10), 115.1 (C-8), 75.8 (C-5), 53.3 (C-2), 29.0 (C-3), 27.8 (C-4), 20.3 (C-6), 11.7 (C-1) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₂H₁₈NO: 192.1383, found: 192.1385.

2,3,6-Triphenyl-1,2-oxazinane **96b**.



Prepared according to general procedure 2, using 1,2-oxazine **90b** (0.390 g, 1.25 mmol) and heating for 96 h. The crude product was purified by column chromatography using 2% Et₂O in pentane (*R_f* 0.15) as the eluent to give the product, 2,3,6-triphenyl-1,2-oxazinane **96b** (0.372 g, 1.18 mmol, 95%), as a colourless oil.

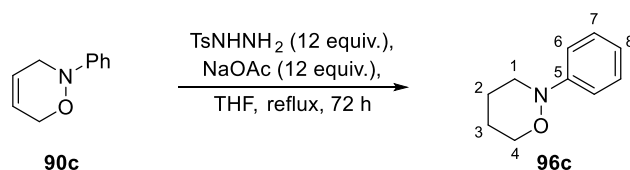
IR ν max (ATR)/ 3059, 3028, 2947, 2921, 1597, 1450, 1358 cm⁻¹; **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.59-7.53 (2H, m, PhCH), 7.46-7.37 (4H, m, PhCH), 7.37-7.27 (3H, m, PhCH), 7.25-7.17 (3H, m,

Experimental

PhCH), 7.07-7.00 (2H, m, PhCH_{ortho}), 6.83 (1H, dddd, *J* 7.3, 7.3, 1.1, 1.1 Hz, NPhCH_{para}), 5.15 (1H, dd, *J* 5.4, 2.8 Hz, H-1), 5.05 (1H, dd, *J* 11.2, 2.7 Hz, H-4), 2.54 (1H, dddd, *J* 13.2, 13.2, 5.4, 4.4 Hz, H-2'), 2.27 (1H, dddd, *J* 13.2, 4.0, 2.8, 2.8 Hz, H-2), 2.01-1.92 (1H, m, H-3), 1.84 (1H, dddd, *J* 13.3, 4.5, 3.1, 3.1 Hz, H-3') ppm.; ¹³C {¹H} NMR δ_c (126 MHz; CDCl₃) 149.1 (NPhC), 140.9 (PhC), 140.4 (PhC), 129.1 (PhCH), 128.6 (PhCH), 128.5 (PhCH), 128.3 (PhCH), 128.1 (PhCH), 126.7 (PhCH), 126.6 (PhCH), 120.3 (PhCH), 114.4 (PhCH), 80.7 (C-4), 58.9 (C-1), 29.9 (C-2), 27.4 (C-3) ppm.; HRMS *m/z* (ESI+): [M+H⁺] calcd. for C₂₂H₂₂NO: 316.1696, found: 316.1690.

Data in agreement with the literature.³⁵⁴

2-Phenyl-1,2-oxazinane **96c**.



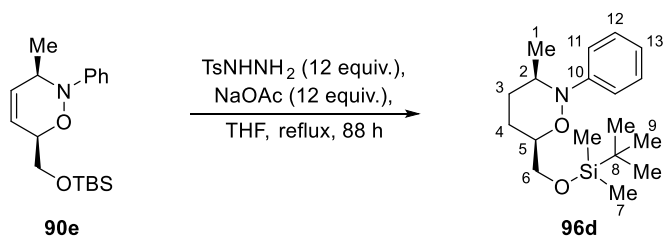
Prepared according to general procedure 2, using 1,2-oxazine **90c** (0.322 g, 2.00 mmol) and heating for 72 h. The crude product was purified by column chromatography using 4% Et₂O in pentane (*R_f* 0.20) as the eluent to give the title compound, 2-phenyl-1,2-oxazinane **96c** (0.278 g, 1.70 mmol, 85%), as a colourless oil.

IR ν max (ATR)/ 3027, 2942, 1597, 1489, 1453, 1251, 1211 cm⁻¹; ¹H NMR δ_H (400 MHz; CDCl₃) 7.29 (2H, m, H-7), 7.12-7.06 (2H, m, H-6), 7.00-6.95 (1H, m, H-8), 4.16-4.12 (2H, m, H-4), 3.40-3.34 (2H, m, H-1), 1.97-1.89 (2H, m, H-2), 1.75-1.68 (2H, m, H-3) ppm.; ¹³C {¹H} NMR δ_c (101 MHz; CDCl₃) 151.2 (C-5), 128.9 (C-7), 122.2 (C-8), 116.1 (C-6), 70.7 (C-4), 54.5 (C-1), 25.0 (C-3), 23.7 (C-2) ppm.; HRMS *m/z* (ESI+): [M+H⁺] calcd. for C₁₀H₁₄NO 164.1075; found: 164.1070.

Data in agreement with the literature.³⁵⁵

Experimental

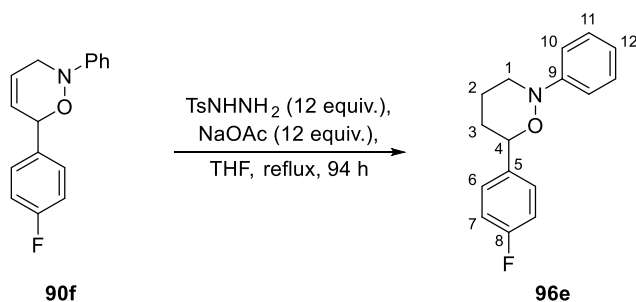
6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methyl-2-phenyl-1,2-oxazinane **96d**.



Prepared according to general procedure 2, using 1,2-oxazine **90e** (0.381 g, 1.20 mmol) and heating for 88 h. The crude product was purified by column chromatography using gradient elution (100% pentane to 1% Et_2O in pentane to 2% Et_2O in pentane (R_f 0.16)) to give the title compound, 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-2-phenyl-1,2-oxazinane **96d** (0.289 g, 0.899 mmol, 75%), as a colourless oil.

IR ν max (ATR)/ 3026, 2951, 2929, 2856, 1598, 1490, 1471, 1462, 1253 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.29-7.22 (2H, m, H-12), 7.07-6.98 (2H, m, H-11), 6.90-6.86 (1H, m, H-13), 4.08-3.99 (1H, m, H-5), 3.99-3.91 (1H, m, H-2), 3.77 (1H, dd, J 11.0, 6.0 Hz, H-6), 3.67 (1H, dd, J 11.0, 4.3 Hz, H-6'), 2.22-2.07 (1H, m, H-4), 1.80-1.66 (2H, m, H-3 and H-4'), 1.57-1.48 (1H, m, H-3'), 1.12 (3H, d, J 6.6 Hz, H-1), 0.93 (9H, s, H-9), 0.10 (6H, s, H-7) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 149.5 (C-10), 128.9 (C-12), 120.7 (C-13), 115.3 (C-11), 80.2 (C-5), 65.4 (C-6), 53.5 (C-2), 28.4 (C-4), 26.0 (C-9), 22.0 (C-3), 18.5 (C-8), 12.0 (C-1), -5.1 (C-7), -5.2 (C-7') ppm.; **HRMS** m/z (ESI⁺): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{18}\text{H}_{31}\text{NO}_2\text{SiNa}$: 344.2016, found: 344.2013.

6-(4-Fluorophenyl)-2-phenyl-1,2-oxazinane **96e**.



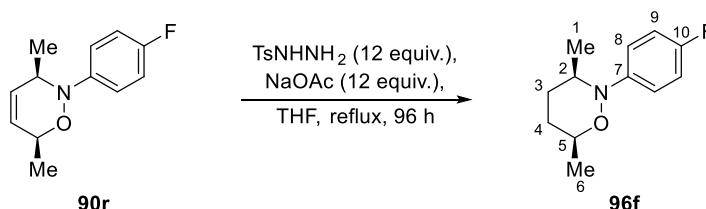
Prepared according to general procedure 2, using 1,2-oxazine **90f** (0.510 g, 2.00 mmol) and heating for 94 h. The crude product was purified by column chromatography using 5% Et_2O in

Experimental

pentane (R_f 0.16) as the eluent to give the title compound, 6-(4-fluorophenyl)-2-phenyl-1,2-oxazinane **96e** (494 mg, 1.92 mmol, 96%), as a colourless oil.

IR ν max (ATR)/ 3061, 3039, 2943, 2878, 1597, 1510, 1489, 1221, 1157 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.44-7.37 (2H, m, H-6), 7.29 (2H, dd, J 8.7, 7.2 Hz, H-11), 7.15-7.10 (2H, m, H-10), 7.09-7.03 (2H, m, H-7), 7.01-6.94 (1H, m, H-12), 4.98 (1H, dd, J 11.3, 2.1 Hz, H-4), 3.81-3.68 (1H, m, H-1), 3.13 (1H, ddd, J 12.2, 12.2, 2.7 Hz, H-1'), 2.22-2.08 (1H, m, H-3), 2.06-1.95 (2H, m, H-2' and H-3'), 1.85-1.71 (1H, m, H-2) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 162.5 (d, J 246.0 Hz, C-8), 151.0 (C-9), 136.9 (d, J 3.3 Hz, C-5), 129.0 (C-11), 128.3 (d, J 8.1 Hz, C-6), 122.3 (C-12), 116.1 (C-10), 115.4 (d, J 21.3 Hz, C-7), 80.6 (C-4), 53.4 (C-1), 31.7 (C-2), 24.1 (C-3) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376 MHz; CDCl_3) -114.53 ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{16}\text{H}_{17}\text{FNO}$: 258.1294, found: 258.1287.

2-(4-Fluorophenyl)-3,6-dimethyl-1,2-oxazinane **96f**.



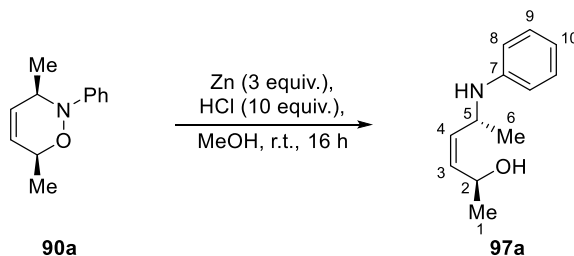
Prepared according to general procedure 2, using 1,2-oxazine **90r** (0.311 g, 1.50 mmol) and heating for 96 h. The crude product was purified by column chromatography using 5% Et₂O in pentane (R_f 0.24) as the eluent to give the product, 2-(4-fluorophenyl)-3,6-dimethyl-1,2-oxazinane **96f** (0.315 g, 1.50 mmol, 100%), as a colourless oil.

IR ν max (ATR)/ 3050, 2972, 2935, 1501, 1447, 1344, 1223, 1041 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 6.99-6.91 (4H, m, H-8 and H-9), 4.02 (1H, dqd, J 10.2, 6.3, 3.0 Hz, H-5), 3.82 (1H, qdd, J 6.6, 4.9, 2.2 Hz, H-2), 2.15 (1H, dddd, J 13.0, 12.9, 5.2, 5.2 Hz, H-3), 1.71 (1H, dddd, J 13.0, 4.6, 2.5, 2.5 Hz, H-3'), 1.64-1.50 (2H, m, H-4 and H-4'), 1.26 (3H, d, J 6.3 Hz, H-6), 1.06 (3H, d, J 6.6 Hz, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 157.8 (d, J 238.8 Hz, C-10), 146.1 (d, J 2.3 Hz, C-7), 116.9 (d, J 7.7 Hz, C-8), 115.4 (d, J 22.0 Hz, C-9), 76.1 (C-5), 54.3 (C-2), 29.2 (C-3), 27.6 (C-

Experimental

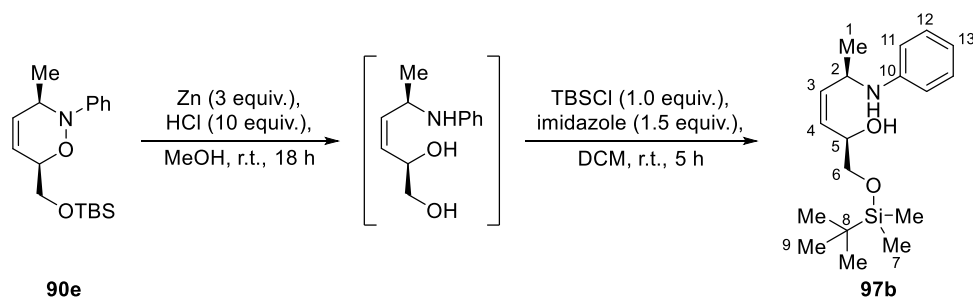
4), 20.3 (C-6), 11.3 (C-1) ppm.; ^{19}F $\{^1\text{H}\}$ NMR δ_{F} (376 MHz; CDCl_3) -124.05 ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{17}\text{NOF}$: 210.1289, found: 210.1292.

(Z)-5-(Phenylamino)hex-3-en-2-ol **97a**.



To a suspension of **90a** (188 mg, 0.995 mmol) and zinc powder (197 mg, 3.01 mmol) in MeOH (10 mL) was added HCl (3.3 mL, 10 mmol of a 3.0 M aqueous solution) over 5 min with stirring. The resulting colourless solution was stirred at room temperature for 16 h before neutralising the mixture with NaHCO_3 (15 mL of a saturated aqueous solution). The aqueous mixture was extracted with EtOAc (3 x 15 mL) and the combined organics were washed with brine, dried over MgSO_4 , and filtered. The filtrate was collected and the solvent was removed *in vacuo* to give a pale-yellow oil. Purification by column chromatography using 14% EtOAc and 1% Et_3N in petrol (R_f 0.17) as the eluent gave the product, (Z)-5-(phenylamino)hex-3-en-2-ol **97a** (185 mg, 0.968 mmol, 97%), as a colourless oil.

IR ν_{max} (ATR)/ 3355, 3011, 2967, 2925, 1600, 1500, 1316, 1254, 1076 cm^{-1} ; ^1H NMR δ_{H} (500 MHz; CDCl_3) 7.23-7.16 (2H, m, H-9), 6.76-6.71 (1H, m, H-10), 6.69-6.63 (2H, m, H-8), 5.48 (1H, ddd, J 11.0, 8.7, 1.2 Hz, H-3), 5.30 (1H, ddd, J 11.0, 8.6, 1.1 Hz, H-4), 4.77-4.68 (1H, m, H-2), 4.31 (1H, dqd, J 7.7, 6.5, 1.2 Hz, H-5), 2.98 (1H, br s, OH/NH), 1.27 (6H, d, J 6.5 Hz, H-1 and H-6) ppm.; ^{13}C NMR δ_{C} (126 MHz; CDCl_3) 147.2 (C-7), 134.7 (C-3), 134.3 (C-4), 129.3 (C-9), 118.3 (C-10), 114.4 (C-8), 63.8 (C-2), 47.0 (C-5), 23.6 (CH_3), 22.2 (CH_3) ppm.; HRMS m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{12}\text{H}_{18}\text{NO}$: 192.1388, found: 192.1383.

(Z)-1-((*tert*-butyldimethylsilyl)oxy)-5-(phenylamino)hex-3-en-2-ol 97b.

To a suspension of 1,2-oxazine **90e** (4.00 g, 12.5 mmol) and Zn powder (2.45 g, 37.5 mmol) in MeOH (125 mL) was added HCl (41.7 mL, 125 mmol of a 3.00 M aqueous solution) over 15 min. The mixture was stirred at room temperature for 18 h before neutralising with NaHCO₃ (100 mL) and diluting with H₂O (150 mL). The aqueous mixture was extracted with EtOAc (3 x 200 mL) and the combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude product was carried through to the next step without further purification.

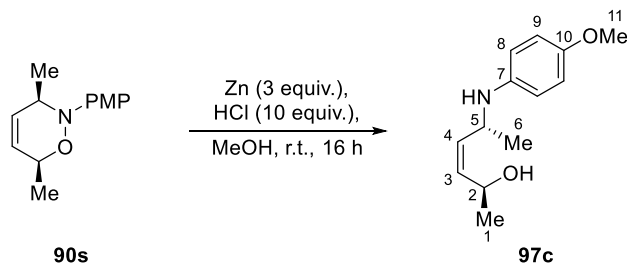
To a solution of the crude alcohol (assuming 12.5 mmol) and imidazole (1.28 g, 18.75 mmol) in DCM (10 mL) was added a solution of TBSCl (1.88 g, 12.5 mmol) in DCM (20 mL) over 10 min. The mixture was stirred at room temperature for 5 h before diluting with H₂O (20 mL) and extracting the aqueous phase with DCM (3 x 25 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography using 10% EtOAc in pentane (*R_f* 0.13) as the eluent to give the title compound, (Z)-1-((*tert*-butyldimethylsilyl)oxy)-5-(phenylamino)hex-3-en-2-ol **97b** (3.76 g, 11.7 mmol, 94% over 2 steps), as a pale-yellow oil.

IR ν max (ATR)/ 3373, 3052, 2954, 2928, 1601, 1502, 1471, 1316, 1252 cm⁻¹; **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.20-7.15 (2H, m, H-12), 6.73-6.69 (1H, m, H-13), 6.67-6.62 (2H, m, H-11), 5.52-5.38 (2H, m, H-3 and H-4), 4.62 (1H, dd, *J* 7.8, 3.9 Hz, H-5), 4.35-4.27 (1H, m, H-2), 3.59 (1H, dd, *J* 10.0, 3.9 Hz, H-6), 3.49 (1H, dd, *J* 10.0, 7.8 Hz, H-6'), 1.30 (3H, d, *J* 6.6 Hz, H-1), 0.93 (9H, s, H-9), 0.10 (6H, s, H-7) ppm.; **¹³C {¹H} NMR** δ_{C} (126 MHz; CDCl₃) 147.4 (C-10), 138.1 (C-4), 129.4 (C-12), 128.8 (C-3), 117.9 (C-13), 113.8 (C-11), 68.7 (C-5), 67.1 (C-6), 47.2 (C-2), 26.0 (C-9), 22.8 (C-1), 18.5 (C-

Experimental

8), -5.16 (C-7), -5.23 (C-7') ppm.; **HRMS** m/z (ESI+): $[M+Na]^+$ calcd. for $C_{18}H_{31}NO_2SiNa$: 344.2016, found:344.2020.

(Z)-5-((4-Methoxyphenyl)amino)hex-3-en-2-ol **97c**.



To a suspension of 1,2-oxazine **90s** (0.719 g, 3.28 mmol) and Zn powder (0.643 g, 9.83 mmol) in MeOH (33 mL) was added HCl (10.9 mL, 32.8 mmol of a 3.00 M aqueous solution) over 5 min. The mixture was stirred at room temperature for 16 h before neutralising with $NaHCO_3$ (15 mL of a saturated aqueous solution) and diluting with H_2O (10 mL). The aqueous mixture was extracted with EtOAc (3 x 20 mL) and the combined organics were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography using 30% EtOAc in pentane (R_f 0.11) as the eluent to give the title compound, (Z)-5-((4-methoxyphenyl)amino)hex-3-en-2-ol **97c** (438 mg, 1.98 mmol, 60%), as a brown oil.

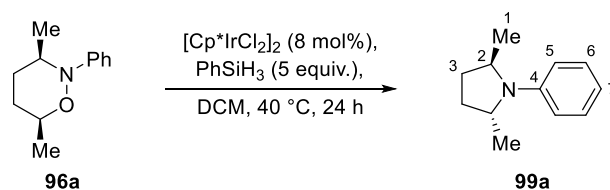
IR ν max (ATR)/ 3348, 2967, 2928, 1510, 1464, 1233 cm^{-1} ; **^1H NMR** δ_H (500 MHz; $CDCl_3$) 6.78-6.74 (2H, m, H-8), 6.65-6.61 (2H, m, H-9), 5.45 (1H, ddd, J 11.0, 8.5, 1.2 Hz, H-3), 5.26 (1H, ddd, J 11.0, 8.5, 1.2 Hz, H-4), 4.69-4.60 (1H, m, H-2), 4.24-4.15 (1H, m, H-5), 3.71 (3H, s, H-11), 2.98 (2H, br s, NH and OH), 1.23 (3H, d, J 3.8 Hz, H-1), 1.21 (3H, d, J 4.1 Hz, H-6) ppm.; **^{13}C { ^1H } NMR** δ_C (126 MHz; $CDCl_3$) 152.9 (C-10), 141.1 (C-7), 135.0 (C-3), 134.5 (C-4), 116.5 (C-9), 114.8 (C-8), 63.7 (C-2), 55.7 (C-11), 48.3 (C-5), 23.5 (C-1), 22.1 (C-6) ppm.; **HRMS** m/z (ESI+): $[M+H]^+$ calcd. for $C_{13}H_{20}NO_2$: 222.1489, found:222.1489.

***N*-(Cyclohex-3-en-1-yl)aniline **98**.**

To a stirred suspension of 1,2-oxazine **90d** (88.1 mg, 0.402 mmol) and $[\text{Cp}^*\text{IrCl}_2]_2$ (25.8 mg, 32.2 μmol , 8 mol%) in DCM (3.2 mL) was added PhSiH_3 (248 μL , 2.00 mmol) and the mixture was stirred at 40 °C for 5 h. The resulting solution was cooled to room temperature and stirred over silica for 30 min in preparation for column chromatography. The solvent was removed *in vacuo* and purification by column chromatography using 1% Et_2O in pentane as eluent (R_f 0.11) followed by preparative TLC using 10% Et_2O in pentane (R_f 0.29) gave *N*-(cyclohex-3-en-1-yl)aniline **98** (15.9 mg, 91.8 μmol , 23%), as a yellow oil.

$^1\text{H NMR}$ δ_{H} (400 MHz; CDCl_3) 7.20-7.13 (2H, m, H-9), 6.71-6.66 (1H, m, H-10), 6.65-6.60 (2H, m, H-8), 5.76-5.69 (1H, m, H-3), 5.69-5.63 (1H, m, H-2), 3.69-3.57 (1H, m, H-6), 2.56-2.43 (1H, m, H-1), 2.22-2.10 (2H, m, H-4 and H-4'), 2.07-1.87 (2H, m, H-1' and H-5'), 1.58 (1H, dddd, J 12.6, 9.3, 7.2, 7.2 Hz, H-5) ppm.; $^{13}\text{C NMR}$ δ_{C} (101 MHz; CDCl_3) 147.5 (C-7), 129.4 (C-9), 127.2 (C-3), 125.0 (C-2), 117.2 (C-10), 113.4 (C-8), 48.0 (C-6), 32.5 (C-1), 28.3 (C-5), 24.0 (C-4) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd for $\text{C}_{12}\text{H}_{16}\text{N}$:174.1283, found:174.1276.

Data in agreement with the literature.³⁵⁶

2,5-Dimethyl-1-phenylpyrrolidine **99a.**

Prepared according to general procedure 1, using 1,2-oxazinane **96a** (76.5 mg, 0.400 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane

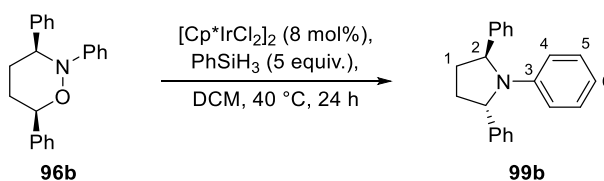
Experimental

to 5% DCM in pentane R_f 0.14) to give the title compound, 2,5-dimethyl-1-phenylpyrrolidine **99a** (40 mg, 0.23 mmol, 57%), as a yellow oil.

IR ν max (ATR)/ 3060, 2961, 2925, 1595, 1498, 1350, 1160 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.23-7.17 (2H, m, H-6), 6.62-6.56 (3H, m, H-5 and H-7), 4.06-3.95 (2H, m, H-2), 2.32-2.14 (2H, m, 2 x H-3'), 1.74-1.57 (2H, m, 2 x H-3), 1.11 (6H, dd, J 6.3, 1.1 Hz, H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 145.4 (C-4), 129.2 (C-6), 114.7 (C-7), 113.4 (C-5), 52.8 (C-2), 30.5 (C-3), 18.3 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{18}\text{N}$: 176.1434, found: 176.1442.

Data in agreement with the literature.³⁵⁷

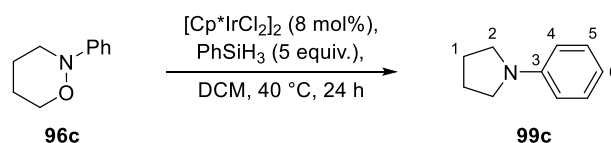
1,2,5-Triphenylpyrrolidine **99b**.



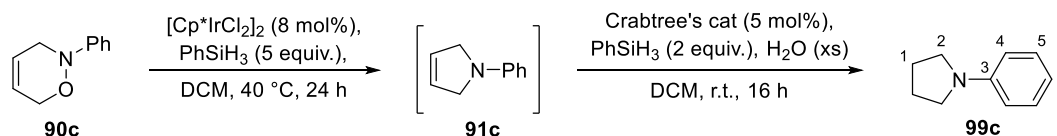
Prepared according to general procedure 1, using 1,2-oxazinane **96b** (126 mg, 0.400 mmol). The crude product was purified by column chromatography using 0.5% Et_2O in pentane (R_f 0.10) as the eluent to give the title compound, 1,2,5-triphenylpyrrolidine **99b** (91.2 mg, 0.305 mmol, 76%), as colourless crystals.

m.p. (EtOH) 204 – 205 $^{\circ}\text{C}$; **IR** ν max (ATR)/ 3082, 3061, 2983, 1594, 1570, 1357 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 7.33-7.28 (4H, m, PhCH), 7.25-7.18 (6H, m, PhCH), 7.02-6.97 (2H, m, H-5), 6.55-6.51 (1H, m, H-6), 6.35-6.31 (2H, m, H-4), 5.24-5.15 (2H, m, H-2), 2.61-2.50 (2H, m, 2 x H-1/H-1'), 1.89-1.75 (2H, m, 2 x H-1/H-1') ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 145.0 (C-3), 144.0 (PhC), 128.9 (C-5), 128.6 (PhCH), 126.8 (PhCH), 126.3 (PhCH), 115.7 (C-6), 114.0 (C-4), 63.2 (C-2), 32.5 (C-1) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{22}\text{H}_{22}\text{N}$: 300.1747, found: 300.1740.

Data in agreement with the literature.³⁵⁸

1-Phenylpyrrolidine 99c.Via deoxygenative ring contraction of 1,2-oxazinane 96c.

Prepared according to general procedure 1, using 1,2-oxazinane **96c** (65.2 mg, 0.399 mmol). The crude product was purified by column chromatography using gradient elution (100% pentane to 1% Et₂O in pentane *R_f* 0.13) to give the title compound, 1-phenylpyrrolidine **99c** (36.7 mg, 0.249 mmol, 62%), as a pale-yellow oil.

Via deoxygenative ring contraction of 1,2-oxazine 90c followed by *in situ* 3-pyrroline reduction

To a stirred suspension of 1,2-oxazine **90c** (64.9 mg, 0.400 mmol) and [Cp*IrCl₂]₂ (25.5 mg, 32.0 μmol, 8 mol%) in DCM (3.2 mL) was added PhSiH₃ (248 μL, 2.00 mmol) and the mixture was heated at 40 °C in a sealed tube for 24 h. The mixture was then cooled to room temperature and H₂O (106 μL, 6.00 mmol) and PhSiH₃ (99.0 μL, 0.800 mmol) were added with vigorous stirring immediately followed by Crabtree's catalyst (16.1 mg, 5 mol%) and the vial was resealed after 10 s. The mixture was stirred at room temperature for 16 h and MgSO₄ was added and the suspension filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using gradient elution (1% Et₂O in pentane to 3% Et₂O in pentane to 5% Et₂O in pentane *R_f* 0.45) to give the title compound, 1-phenylpyrrolidine **99c** (28.2 mg, 0.192 mmol, 48%), as a pale-yellow oil.

IR v max (ATR)/ 3090, 3026, 2965, 2828, 1608, 1593, 1504, 1485, 1365 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.26-7.21 (2H, m, H-5), 6.69-6.64 (1H, m, H-6), 6.58 (2H, d, *J* 8.1 Hz, H-4), 3.32-3.27 (4H, m, H-2), 2.06-1.95 (4H, m, H-1) ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 148.1 (C-3), 129.3 (C-5), 115.5 (C-6), 111.8 (C-4), 47.7 (C-2), 25.6 (C-1) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₀H₁₄N: 148.1121, found: 148.1116.

Experimental

Data in agreement with the literature.³⁵⁹

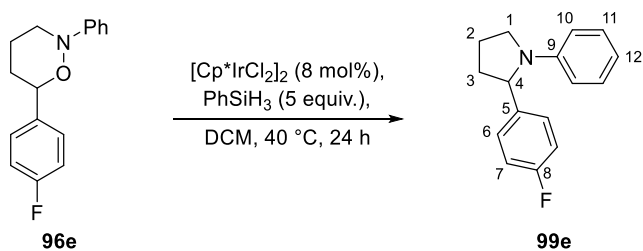
2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenylpyrrolidine **99d**.



Prepared according to general procedure 1, using 1,2-oxazinane **96d** (129 mg, 0.400 mmol). The crude product was purified by column chromatography using 1% Et₂O in pentane (*R_f* 0.25) as the eluent to give the title compound, 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-methyl-1-phenylpyrrolidine **99d** (52.6 mg, 0.172 mmol, 43%), as a colourless oil.

IR ν max (ATR)/ 3025, 2955, 2927, 1597, 1499, 1354 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.23-7.15 (2H, m, H-12), 6.65-6.57 (3H, m, H-11 and H-13), 4.07-3.97 (1H, m, H-2), 3.93-3.86 (1H, m, H-5), 3.73 (1H, dd, *J* 10.0, 3.3 Hz, H-6), 3.26 (1H, dd, *J* 10.0, 8.6 Hz, H-6'), 2.23-1.99 (3H, m, H-3 and H-3' and H-4), 1.68-1.57 (1H, m, H-4'), 1.10 (3H, d, *J* 6.2 Hz, H-1), 0.90 (9H, s, H-9), 0.04 (3H, s, H-7), 0.01 (3H, s, H-7') ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 145.8 (C-10), 129.6 (C-12), 115.4 (PhCH), 113.8 (PhCH), 62.1 (C-6), 59.4 (C-5), 53.4 (C-2), 30.7 (C-4), 26.4 (C-9), 26.3 (C-3), 18.8 (C-8), 18.2 (C-1), -4.8 (C-7), -4.9 (C-7') ppm.; **HRMS** *m/z* (ESI+): [M+H]⁺ calcd. for C₁₈H₃₂NOSi:306.2248, found:306.2251.

2-(4-Fluorophenyl)-1-phenylpyrrolidine **99e**.



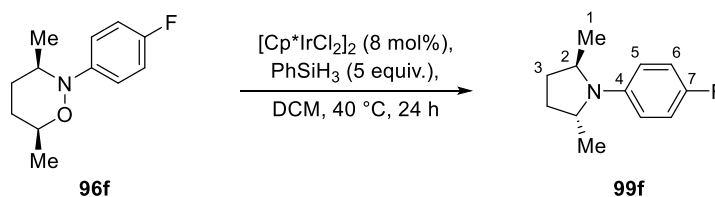
Experimental

Prepared according to general procedure 1, using 1,2-oxazinane **96e** (103 mg, 0.400 mmol). The crude product was purified by column chromatography using 5% DCM in pentane (R_f 0.18) as the eluent to give the title compound, 2-(4-fluorophenyl)-1-phenylpyrrolidine **99e** (66 mg, 0.27 mmol, 68%), as a colourless oil.

IR ν max (ATR)/ 3061, 2969, 2872, 2836, 1596, 1502, 1358, 1217, 1152 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.22-7.11 (4H, m, H-7 and H-11), 7.03-6.92 (2H, m, H-6), 6.68-6.62 (1H, m, H-12), 6.48 (2H, dd, J 8.2 Hz, H-10), 4.70 (1H, dd, J 8.4, 1.6 Hz, H-4), 3.74-3.67 (1H, m, H-1), 3.40 (1H, ddd, J 8.4, 8.4, 8.4 Hz, H-1'), 2.45-2.31 (1H, m, H-3'), 2.09-1.95 (2H, m, H-2 and H-2'), 1.94-1.86 (1H, m, H-3) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 161.8 (d, J 244.2 Hz, C-8), 147.2 (C-9), 140.4 (d, J 3.1 Hz, C-5), 129.2 (C-11), 127.5 (d, J 7.9 Hz, C-6), 116.1 (C-12), 115.4 (d, J 21.3 Hz, C-7), 112.5 (C-10), 62.5 (C-4), 49.2 (C-1), 36.3 (C-3), 23.2 (C-2) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376 MHz; CDCl_3) -116.75 ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{16}\text{H}_{17}\text{FN}$: 242.1340, found: 242.1341.

Data in agreement with the literature.³⁶⁰

1-(4-Fluorophenyl)-2,5-dimethylpyrrolidine **99f**.



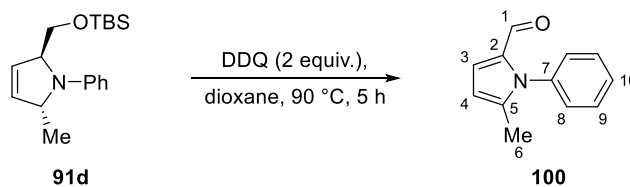
Prepared according to general procedure 1, using 1,2-oxazinane **96f** (83.7 mg, 0.400 mmol). The crude product was purified by column chromatography using 10% DCM in pentane (R_f 0.15) as the eluent to give the title compound, 1-(4-fluorophenyl)-2,5-dimethylpyrrolidine **99f** (31.2 mg, 0.161 mmol, 40%), as pale-yellow crystals.

m.p. (CHCl_3) 68 – 70 $^{\circ}\text{C}$; **IR** ν max (ATR)/ 3057, 2966, 2948, 1609, 1508, 1465, 1339, 1203 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 6.95-6.88 (2H, m, H-6), 6.52-6.46 (2H, m, H-5), 3.99-3.89 (2H, m, H-2), 2.30-2.15 (2H, m, 2 x H-3'), 1.69-1.57 (2H, m, 2 x H-3), 1.07 (6H, d, J 6.2 Hz, 2 x H-1) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 154.4 (d, J 233.1 Hz, C-7), 142.1 (d, J 1.7 Hz, C-4), 115.6 (d, J 21.9 Hz, C-6), 114.1 (d, J 7.0 Hz, C-5), 53.2 (C-2), 30.6 (C-3), 18.2 (C-1) ppm.; **^{19}F { ^1H } NMR** δ_{F} (376

Experimental

MHz; CDCl_3) -131.59 ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{17}\text{NF}$: 194.1340, found: 194.1336.

5-Methyl-1-phenylpyrrole-2-carbaldehyde **100**.

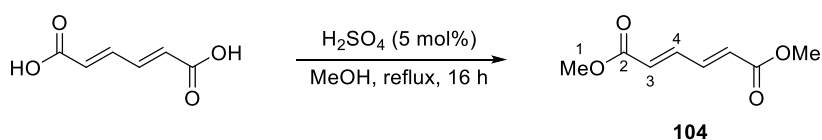


To a stirred solution of **91d** (121 mg, 0.400 mmol) in dioxane (4 mL) was added DDQ (182 mg, 0.800 mmol) and the mixture was heated at 90 °C for 5 h. The mixture was cooled to room temperature and diluted with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude oil was purified by column chromatography using gradient elution (10% Et_2O in pentane to 20% Et_2O in pentane (R_f 0.15)) to give the product, 5-methyl-1-phenylpyrrole-2-carbaldehyde **100** (46.5 mg, 0.251 mmol, 63%), as pale-yellow crystals.

m.p. (EtOAc) 96 – 97 °C, Lit. m.p. 93 – 94 °C; **IR** ν_{max} (ATR)/ 3096, 3056, 2921, 2848, 1640, 1597, 1417, 1338, 1283 cm^{-1} ; **^1H NMR** δ_{H} (500 MHz; CDCl_3) 9.32 (1H, s, H-1), 7.52–7.46 (3H, m, PhCH), 7.29–7.23 (2H, m, PhCH), 7.06 (1H, d, J 4.0 Hz, H-3), 6.18 (1H, d, J 4.0 Hz, H-4), 2.10 (3H, s, H-6) ppm.; **^{13}C { ^1H } NMR** δ_{C} (126 MHz; CDCl_3) 178.3 (C-1), 140.0 (H-5), 137.5 (C-7), 133.6 (C-2), 129.3 (PhCH), 128.8 (PhCH), 127.9 (PhCH), 121.4 (C-3), 110.3 (C-4), 12.8 (C-6) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{12}\text{NO}$: 186.0913, found: 186.0909.

Data in agreement with the literature.³⁶¹

Dimethyl (2E,4E)-hexa-2,4-dienedioate **104**.



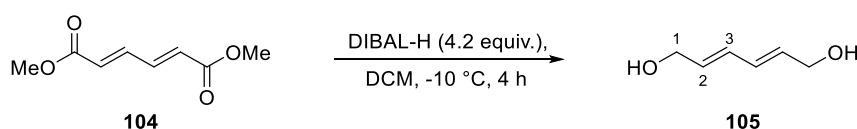
Experimental

To a stirred suspension of *trans,trans*-muconic acid (4.26 g, 30.0 mmol) in MeOH (37.5 mL) was added H₂SO₄ (87 μ L, 1.5 mmol, 5 mol% of an 18 M solution) and the mixture was heated at reflux for 16 h. The mixture was cooled to room temperature and the white solid was filtered, washed with MeOH (10 mL) and H₂O (10 mL) to give the product, dimethyl (2*E*,4*E*)-hexa-2,4-dienedioate **104** (4.62 g, 27.2 mmol, 91%), as a colourless solid.

m.p. 158 – 159 °C, Lit m.p. 158.5 – 159.5 °C; **IR** ν max (ATR)/ 3042, 3004, 2955, 2850, 1697, 1598, 1435, 1311 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.38-7.27 (2H, m, H-4), 6.27-6.14 (2H, m, H-3), 3.78 (6H, s, H-1) ppm.; **¹³C {¹H} NMR** δ _C (101 MHz; CDCl₃) 166.5 (C-2), 141.1 (C-4), 128.2 (C-3), 52.1 (C-1) ppm.; **HRMS** m/z (ESI⁺): [M+Na⁺] calcd. for C₈H₁₀O₄Na: 193.0471, found: 193.0477.

Data in agreement with the literature.^{362,363}

(2*E*,4*E*)-Hexa-2,4-diene-1,6-diol **105**.



To a stirred solution of **104** (4.59 g, 27.0 mmol) in dry DCM (108 mL) was added DIBAL-H (114 mL, 114 mmol of a 1.00 M solution in hexane) dropwise over 75 min at -10 °C. The mixture was stirred at -10 °C for 4 h before the reaction was quenched with EtOAc (50 mL). The reaction mixture was added portion wise to a vigorously stirred mixture of Rochelle salt (80 mL of a saturated aqueous solution) and DCM (100 mL) and the biphasic mixture was left to stir until the gelatinous mixture became homogenous. The layers were separated and the aqueous layer was extracted with DCM (4 x 100 mL) followed by EtOAc (3 x 75 mL). The EtOAc extractions were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo*. The extraction process was repeated until negligible quantities of solid were obtained. The product, (2*E*,4*E*)-hexa-2,4-diene-1,6-diol **105** (2.54 g, 22.3 mmol, 83%), was obtained after evaporation of the solvent as a colourless solid.

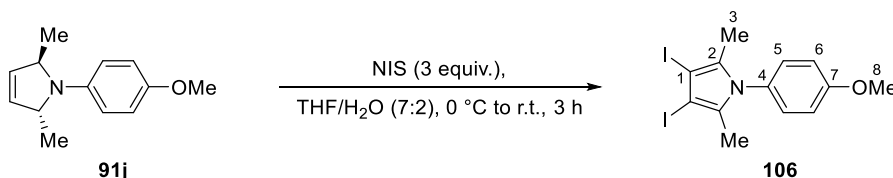
m.p. 106 – 107 °C, Lit m.p. 105.5 – 106.5 °C; **IR** ν max (ATR)/ 3271, 3174, 3023, 2927, 1447, 1390, 1071 cm⁻¹; **¹H NMR** δ _H (500 MHz; DMSO-*d*₆) 6.21-6.13 (2H, m, H-3), 5.77-5.68 (2H, m, H-2), 4.71

Experimental

(2H, t, J 5.4 Hz, OH), 3.97 (4H, dd, J 5.2, 5.2 Hz, H-1) ppm.; ^{13}C { ^1H } NMR δ_{C} (126 MHz; DMSO- d_6) 133.2 (C-2), 128.8 (C-3), 61.1 (C-1) ppm.; HRMS m/z (ESI+): $[2\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{12}\text{H}_{20}\text{O}_4\text{Na}$: 251.1259, found: 251.1249.

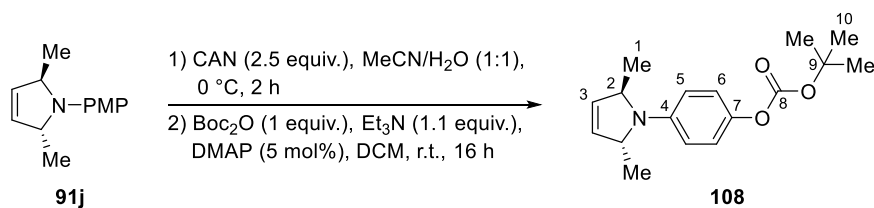
Data in agreement with the literature.^{363,364}

3,4-Diiodo-1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole **106**.



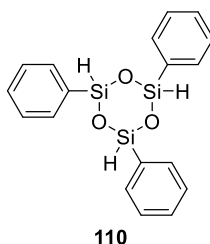
To a stirred suspension of 3-pyrroline **91j** (2.18 g, 10.7 mmol) in THF/H₂O 7:2 (112 mL) was added NIS (7.24 g, 32.2 mmol) portion wise over 25 min at 0 °C. After completion of the addition the mixture was stirred at room temperature for 3 h before quenching the reaction with Na₂SO₃ (20 mL of a saturated aqueous solution) and adding EtOAc (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organics were washed with brine, dried over MgSO₄, filtered and the solvent removed *in vacuo*. The crude residue was flushed through a silica plug using 10% Et₂O in pentane to give the product, 3,4-diiodo-1-(4-methoxyphenyl)-2,5-dimethyl-1H-pyrrole **106** (3.27 g, 7.22 mmol, 67%), as brown crystals.

m.p. (Et₂O) 137 – 138 °C; **IR** ν max (ATR)/ 3064, 2958, 2925, 1584, 1507, 1460, 1392, 1243 cm⁻¹; ^1H NMR δ_{H} (500 MHz; CDCl₃) 7.08-7.03 (2H, m, H-6), 6.99-6.95 (2H, m, H-5), 3.86 (3H, s, H-8), 2.10 (6H, s, H-3) ppm.; ^{13}C { ^1H } NMR δ_{C} (101 MHz; CDCl₃) 159.7 (C-7), 132.5 (C-2), 131.8 (C-4), 129.1 (C-6), 114.7 (C-5), 73.5 (C-1), 55.7 (C-8), 15.3 (C-3) ppm.; HRMS m/z (APCI): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{12}\text{H}_{14}\text{I}_2\text{NO}$: 453.9159, found: 453.9156.

***tert*-Butyl (4-(2,5-dimethyl-2,5-dihydro-1*H*-pyrrol-1-yl)phenyl) carbonate **108**.**

To a stirred solution of CAN (685 mg, 1.25 mmol) in H₂O (5 mL) at 0 °C was added a solution of **91j** (101 mg, 0.500 mmol) in MeCN (5 mL) dropwise over 15 min. The mixture was stirred at 0 °C for 2 h before adding Na₂S₂O₃ (5 mL of a saturated aqueous solution) and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resulting green residue was suspended in DCM (10 mL) and Boc₂O (114 mg, 0.500 mmol), DMAP (3.5 mg, 5 mol%) and Et₃N (76.5 μL, 0.550 mmol) were added and the mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography using 5% Et₂O in pentane as the eluent to give, *tert*-butyl (4-(2,5-dimethyl-2,5-dihydro-1*H*-pyrrol-1-yl)phenyl) carbonate **108** (36.9 mg, 0.128 mmol, 25%) as a yellow oil.

IR ν max (ATR)/ 3072, 3050, 2977, 2927, 1751, 1609, 1509, 1254, 1142 cm⁻¹; **¹H NMR** δ_{H} (500 MHz; CDCl₃) 7.04-6.97 (2H, m, ArCH), 6.62-6.56 (2H, m, ArCH), 5.78 (2H, s, H-3), 4.75-4.66 (2H, m, H-2), 1.55 (9H, s, H-10), 1.21-1.18 (6H, m, H-1) ppm.; **¹³C NMR** δ_{C} (126 MHz; CDCl₃) 153.0 (C-8), 142.7 (ArC), 141.3 (ArC), 131.0 (C-3), 121.6 (ArCH), 114.9 (ArCH), 83.1 (C-9), 59.9 (C-2), 27.9 (C-10), 18.8 (C-2) ppm.; **HRMS** m/z (ESI⁺): [M+H⁺] calcd for C₁₇H₂₄NO₃: 290.1756, found: 290.1747.

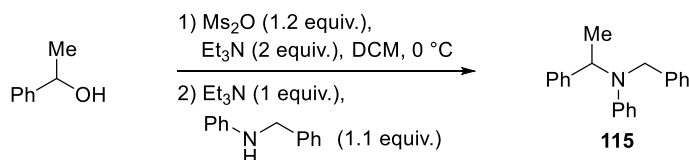
2,4,6-Triphenyl-1,3,5,2,4,6-trioxatrisilinane **110.**

Isolated as a by-product from the Ir-catalysed deoxygenative ring contraction.

Experimental

IR v max (ATR)/ 3068, 3050, 3013, 2132, 1428, 1121 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.63-7.58 (6H, m, $\text{PhCH}_{\text{ortho}}$), 7.46-7.34 (9H, m, $\text{PhCH}_{\text{meta}}$ and $\text{PhCH}_{\text{para}}$), 4.93 (3H, s, SiH) ppm.; **^{13}C { ^1H }** **NMR** δ_{C} (101 MHz; CDCl_3) 135.8 ($\text{PhCH}_{\text{ortho}}$), 131.6 (PhCSi), 130.0 ($\text{PhCH}_{\text{para}}$), 128.3 ($\text{PhCH}_{\text{meta}}$) ppm.; **^{29}Si { ^1H }** **NMR** δ_{Si} (79 MHz, CDCl_3) -33.29 ppm.; **HRMS** m/z (APCI): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{Si}_3$: 367.0637, found: 367.0607.

N-Benzyl-*N*-(1-phenylethyl)aniline **115**.



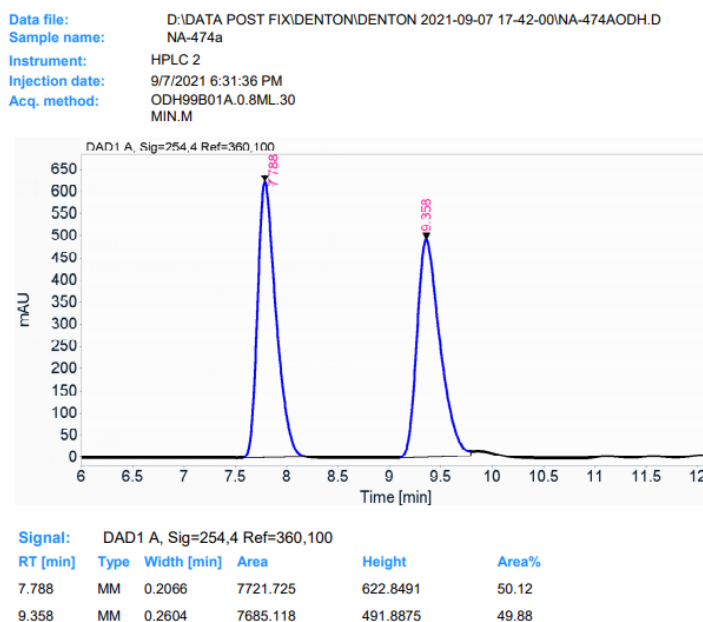
To a stirred solution of 1-phenylethanol (621 mg, 5.08 mmol) and Et_3N (1.40 mL, 10.0 mmol) in DCM (15 mL) was added a solution of Ms_2O (1.05 g, 6.00 mmol) in DCM (5 mL) over 15 min and the resulting mixture was stirred at room temperature for 1 h. A solution of *N*-benzylaniline (1.01g, 5.50 mmol) in DCM (5 mL) was added and the mixture was stirred at room temperature for 17 h. The reaction was diluted with H_2O (15 mL) and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organics were washed with brine, dried over MgSO_4 , filtered and the solvent removed *in vacuo*. Purification by column chromatography using 5% DCM in heptane (R_f 0.18) as the eluent gave the product, *N*-benzyl-*N*-(1-phenylethyl)aniline **115** (587 mg, 2.04 mmol, 41%), as a colourless sticky viscous oil.

IR v max (ATR)/ 3082, 3022, 2982, 1595, 1502, 1444, 1254 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.35-7.30 (4H, m, PhCH), 7.28-7.21 (5H, m, PhCH), 7.21-7.12 (3H, m, PhCH), 6.79-6.74 (2H, m, $\text{NPhCH}_{\text{ortho}}$), 6.73-6.68 (1H, m, $\text{NPhCH}_{\text{para}}$), 5.28 (1H, q, J 7.0 Hz, CHCH_3), 4.52 (1H, d, J 17.5 Hz, $\text{NCHH}'\text{Ph}$), 4.44 (1H, d, J 17.5 Hz, $\text{NCHH}'\text{Ph}$), 1.60 (3H, d, J 7.0 Hz, CHCH_3) ppm.; **^{13}C { ^1H }** **NMR** δ_{C} (101 MHz; CDCl_3) 149.4 (NPhC), 143.0 (PhCH), 140.3 (PhCH), 129.2 (PhCH), 128.7 (PhCH), 128.5 (PhCH), 127.04 (PhCH), 127.01 (PhCH), 126.58 (PhCH), 126.55 (PhCH), 117.3 ($\text{NPhCH}_{\text{para}}$), 114.3 ($\text{NPhCH}_{\text{ortho}}$), 57.2 (NCHCH_3), 50.5 (NCH_2), 18.9 (NCHCH_3) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{Na}^+]$ calcd. for $\text{C}_{21}\text{H}_{22}\text{N}$: 288.1747, found: 288.1749.

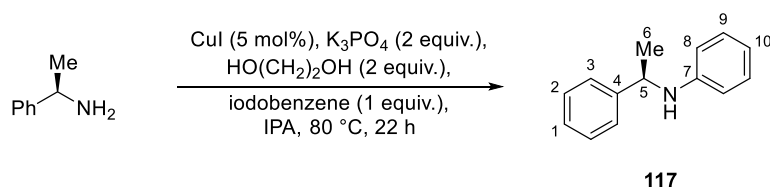
Data in agreement with the literature.³⁶⁵

Experimental

HPLC trace of the racemic tertiary amine **115**.



(*R*)-*N*-(1-Phenylethyl)aniline **117**.



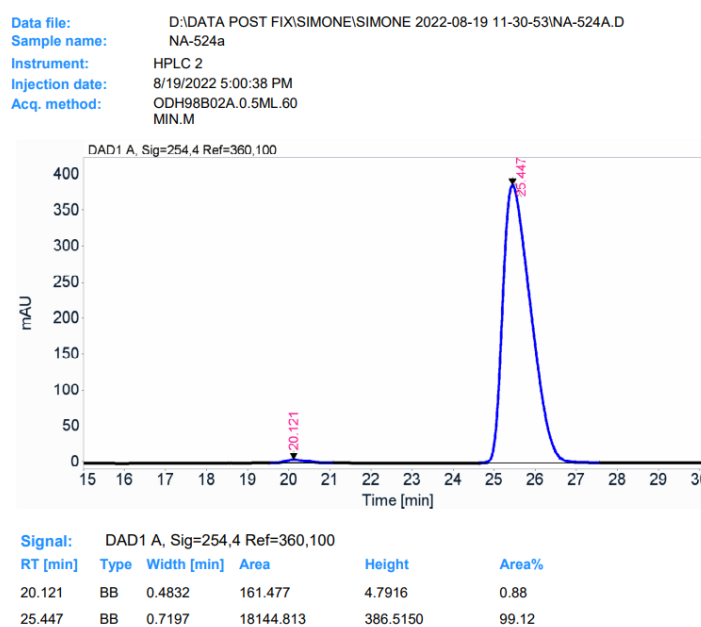
To a stirred mixture of CuI (19.1 mg, 0.100 mmol, 5 mol%), K₃PO₄ (849 mg, 4.00 mmol), ethylene glycol (225 μ L, 4.00 mmol) and iodobenzene (225 μ L, 2.00 mmol) in IPA (2 mL) was added (*R*)- α -methylbenzylamine (305 μ L, 2.40 mmol) and the yellow suspension was stirred at 80°C for 22 h. The mixture was cooled to room temperature and diluted with H₂O (5 mL) and EtOAc (5 mL). The layers were separated, the organic layer was washed with NH₄OH (2 mL of a 28% NH₃ solution in H₂O) and the aqueous layers were then extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by column chromatography using 5% EtOAc in pentane as the eluent (*R_f* 0.30) gave the product, (*R*)-*N*-(1-phenylethyl)aniline **117** (181 mg, 0.917 mmol, 46%), as a pale-yellow solid. A sample of the racemic amine was synthesised using the same procedure in 32% isolated yield.

Experimental

m.p. (CHCl₃) 50 – 51 °C; **IR** ν max (ATR)/ 3411, 3052, 3022, 2966, 1599, 1502, 1449, 1315 cm⁻¹; **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.43-7.37 (2H, m, H-3), 7.37-7.31 (2H, m, H-2), 7.29-7.21 (1H, m, H-1), 7.15-7.08 (2H, m, H-9), 6.71-6.64 (1H, m, H-10), 6.54 (2H, d, *J* 8.0 Hz, H-8), 4.51 (1H, q, *J* 6.7 Hz, H-5), 4.04 (1H, br s, NH), 1.54 (3H, dd, *J* 6.7, 1.4 Hz, H-6) ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; CDCl₃) 147.4 (C-7), 145.4 (C-4), 129.2 (C-9), 128.8 (C-2), 127.0 (C-1), 126.0 (C-3), 117.4 (C-10), 113.4 (C-8), 53.6 (C-5), 25.2 (C-6) ppm.; **HRMS** *m/z* (ESI⁺): [M+H⁺] calcd. for C₁₄H₁₆N: 198.1277, found: 198.1270.; **Specific Rotation** [α]_D²⁵ = -4.396 (*c* = 1.001, CHCl₃); **HPLC analysis** (OD-H, 2.0% ⁱPrOH/isohexane, 0.5 mL/min) indicated 98% e.e.: *t*_R (minor) = 20.121 min, *t*_R (major) = 25.447 min.

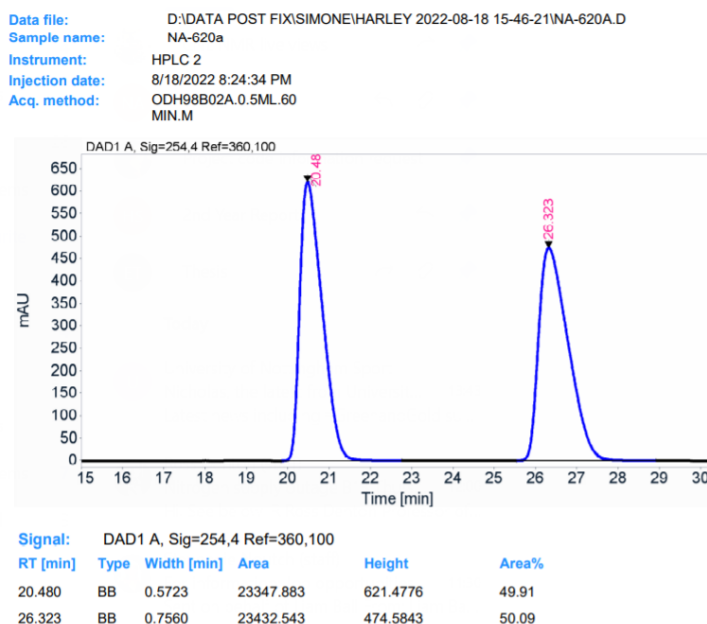
Data in agreement with the literature.³⁶⁶

HPLC trace of the enantioenriched secondary amine **117**.

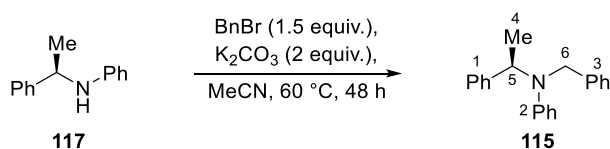


HPLC trace of the racemic secondary amine **117**.

Experimental



(*R*)-*N*-Benzyl-*N*-(1-phenylethyl)aniline **115**.



To a stirred mixture of **117** (98.4 mg, 0.500 mmol) and K₂CO₃ (138 mg, 1.00 mmol) in MeCN (2 mL) was added benzylbromide (59.5 μL, 0.500 mmol) and the mixture was heated at 60 °C for 24 h. After this time a further portion of benzyl bromide (29.5 μL, 0.250 mmol) was added and the mixture was continued to be heated at 60 °C for 24 h. The mixture was then cooled to room temperature and diluted with H₂O (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by column chromatography using 2% Et₂O in pentane as the eluent (*R_f* 0.37), followed by recrystallization of the pale-yellow solid from hot MeOH, gave the product, (*R*)-*N*-benzyl-*N*-(1-phenylethyl)aniline **115** (138 mg, 0.480 mmol, 96%), as colourless crystals.

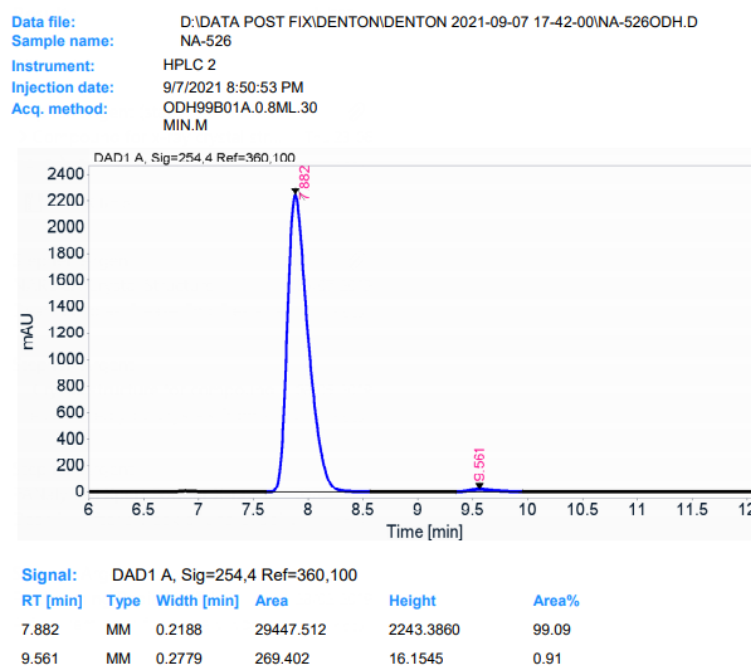
m.p. (MeOH) 67 – 68 °C; **IR** ν max (ATR)/ 3082, 3023, 2982, 1595, 1501, 1453, 1390 cm⁻¹; **¹H NMR** δ _H (400 MHz; CDCl₃) 7.36-7.28 (4H, m, PhCH), 7.28-7.22 (5H, m, PhCH), 7.21-7.11 (3H, m, PhCH), 6.80-6.73 (2H, m, Ph²CH_{ortho}), 6.73-6.68 (1H, m, Ph²CH_{para}), 5.28 (1H, q, *J* 7.0 Hz, H-5), 4.52

Experimental

(1H, d, J 17.4 Hz, H-6'), 4.44 (1H, d, J 17.4 Hz, H-6), 1.60 (3H, d, J 7.0 Hz, H-4) ppm.; ^{13}C { ^1H } NMR δ_{C} (101 MHz; CDCl_3) 149.4 (NPh ^{2} C), 143.0 (Ph ^{2} C), 140.3 (Ph ^{3} C), 129.2 (PhCH), 128.7 (PhCH), 128.5 (PhCH), 127.04 (PhCH), 127.01 (PhCH), 126.58 (PhCH), 126.55 (PhCH), 117.3 (Ph ^{2} CH $_{\text{para}}$), 114.3 (Ph ^{2} CH $_{\text{ortho}}$), 57.2 (C-5), 50.5 (C-6), 18.9 (C-4) ppm.; **HRMS** m/z (ESI+): $[\text{M}+\text{H}^+]$ calcd. for $\text{C}_{21}\text{H}_{22}\text{N}$: 288.1747, found: 288.1748.; **Specific Rotation** $[\alpha]_{\text{D}}^{25} = 121.578$ ($c = 1.001$, CHCl_3); **HPLC analysis** (OD-H, 1.0% i PrOH/isohexanes, 0.8 mL/min) indicated 98% e.e.: t_{R} (major) = 7.882 min, t_{R} (minor) = 9.561 min.

Data in agreement with the literature.³⁶⁷

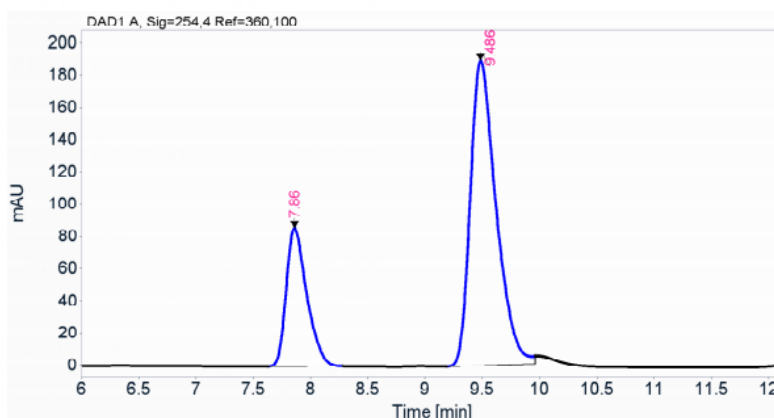
HPLC trace of independently synthesised authentic sample of *R* enantiomer of tertiary amine product **115**.



HPLC trace for synthesis of tertiary amine **115** *via* mesylation with enantioenriched (*R*)-1-phenylethanol.

Experimental

Data file: D:\DATA POST FIX\IDENTON\IDENTON 2021-09-07 17-42-00\NA-476AODH.D
 Sample name: NA-476a
 Instrument: HPLC 2
 Injection date: 9/7/2021 7:18:02 PM
 Acq. method: ODH99B01A.0.8ML.30 MIN.M

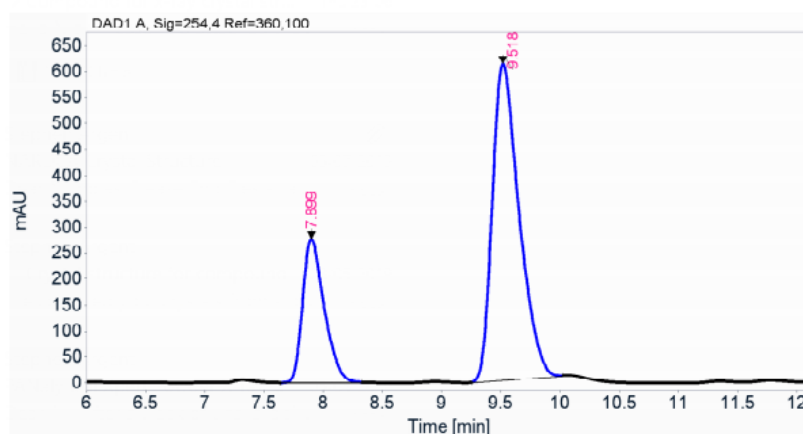


Signal: DAD1 A, Sig=254,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.860	MM	0.2085	1074.750	85.9060	26.63
9.486	MM	0.2611	2961.469	189.0183	73.37

HPLC trace for the synthesis of tertiary amine **115** via Ir-catalysed coupling using enantioenriched (*R*)-1-phenylethanol.

Data file: D:\DATA POST FIX\IDENTON\IDENTON 2021-09-07 17-42-00\NA-478AODH.D
 Sample name: NA-478a
 Instrument: HPLC 2
 Injection date: 9/7/2021 8:04:27 PM
 Acq. method: ODH99B01A.0.8ML.30 MIN.M

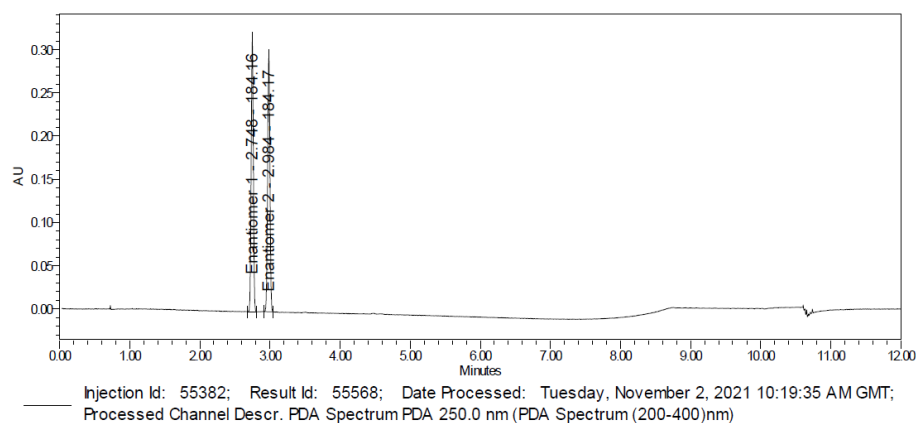


Signal: DAD1 A, Sig=254,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
7.899	MM	0.2118	3533.947	278.1456	26.86
9.518	MM	0.2626	9622.903	610.8208	73.14

SFC trace of the racemic tertiary amine product **115**.

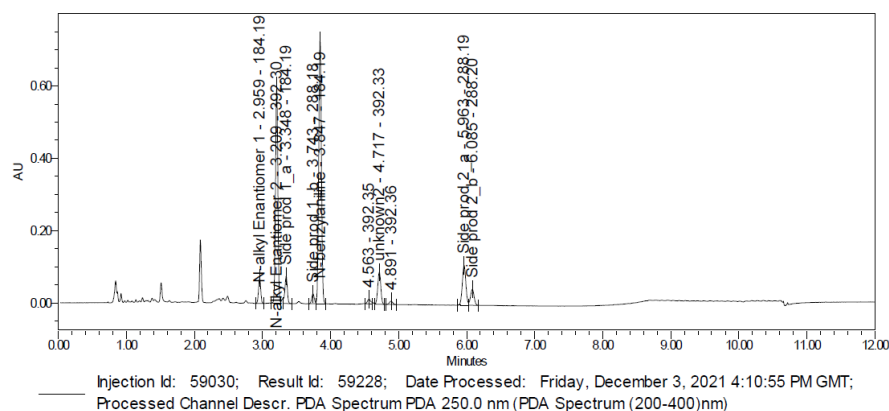
Experimental



Peak Results

	Peak Name	RT	% Area	Area (μV·sec)	Height (μV)	Channel
1	Enantiomer 1	2.748	50.007	678625.069	313550	PDA Spectrum
2	Enantiomer 2	2.984	49.993	678427.209	294102	PDA Spectrum

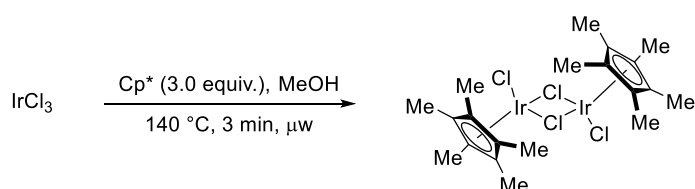
Example SFC trace from the reaction mixture of Ir-catalysed coupling using enantioenriched (*R*)-1-phenylethanol with *N*-benzylaniline.



Peak Results

	Peak Name	RT	% Area	Area (μV·sec)	Height (μV)	Channel
1	Unknown	2.730				PDA Spectrum
2	N-alkyl Enantiomer 1	2.959	3.208	157987.485	69697	PDA Spectrum
3	N-alkyl Enantiomer 2	3.209	30.032	1438875.806	601879	PDA Spectrum
4	Side prod 1_a	3.348	4.040	193546.033	75148	PDA Spectrum
5	Side prod 1_b	3.743	1.506	72149.833	27427	PDA Spectrum
6	N-benzylaniline	3.847	42.032	2013758.833	728861	PDA Spectrum

Bis[dichloro(pentamethylcyclopentadienyl)iridium(III)].



Experimental

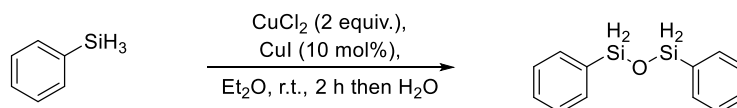
To a suspension of $\text{IrCl}_3 \cdot x\text{H}_2\text{O}$ (448 mg, 1.50 mmol) in MeOH (14 mL) was added pentamethylcyclopentadiene (705 μL , 4.50 mmol). The green suspension was heated in the microwave at 140 °C for 3 min. The resulting red suspension was filtered and washed with cold MeOH (3 mL) and pentane (3 mL) to give the product, bis[dichloro(pentamethylcyclopentadienyl)iridium(III)] (371 mg, 0.466 mmol, 62%), as an orange microcrystalline powder.

m.p. decomposed >200 °C; **IR** ν_{max} (ATR)/ 2983, 2965, 2911, 1447, 1372, 1032 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 1.59 (30H, s, CH_3) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 86.4 (C- CH_3), 9.5 (CH_3) ppm.; **HRMS** m/z (ESI+): Fragmentation of molecular ion: $[\text{Cp}^*\text{IrCl}]$ calcd. for $\text{C}_{10}\text{H}_{15}^{193}\text{Ir}^{35}\text{Cl}_2$: 363.0502, found: 363.0483.

Data in agreement with the literature.³²⁸

Diphenyldisiloxane.

Synthesised according to literature procedure.³⁶⁸



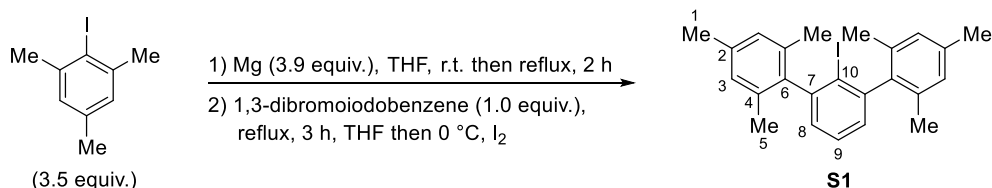
To a stirred suspension of CuCl_2 (5.38 g, 40.0 mmol), CuI (380 mg, 2.00 mmol, 10 mol%) and 4 Å molecular sieves in Et_2O (30 mL) was added PhSiH_3 (2.16 mL, 20 mmol) and the mixture stirred at room temperature for 2 h. The mixture was diluted with Et_2O (10 mL) and filtered through Celite® onto crushed ice (25 g). The layers were separated and the organic layer was washed with H_2O (2 x 30 mL), brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by distillation gave the product, diphenyldisiloxane (0.858 g, 3.72 mmol, 37%), as a colourless oil.

b.p. 90 – 93 °C at 3.0 mbar; **IR** ν_{max} (ATR)/ 3070, 3052, 2145, 1591, 1428, 1122, 1062 cm^{-1} ; **^1H NMR** δ_{H} (400 MHz; CDCl_3) 7.68-7.63 (4H, m, PhCH), 7.50-7.40 (6H, m, PhCH), 5.20 (1H, s, SiH_2) ppm.; **^{13}C { ^1H } NMR** δ_{C} (101 MHz; CDCl_3) 134.2 (PhCH), 133.8 (PhCSi), 130.7 (PhCH), 128.5 (PhCH) ppm.; **^{29}Si { ^1H } NMR** δ_{Si} (79 MHz; CDCl_3) -25.4 ppm.

Experimental

Data in agreement with the literature.^{368,369}

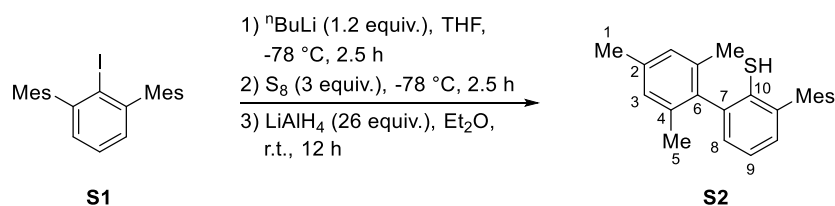
2'-Iodo-2,2'',4,4'',6,6''-hexamethyl-1,1':3',1''-terphenyl **S1**.



To a stirred suspension of magnesium turnings (0.261 g, 10.7 mmol) and a single crystal of iodine in degassed THF (8 mL) was added a solution of bromomesitylene (1.5 mL, 9.8 mmol) in degassed THF (1.5 mL) dropwise over 40 min at room temperature. The mixture was heated at reflux for 2.5 h before cooling to room temperature and adding a solution of 1,3-dibromoiodobenzene (0.989 g, 2.75 mmol) in degassed THF (1.5 mL) dropwise over 20 min. The mixture was then heated at reflux for 4 h, cooled to 0 °C and a solution of I₂ (1.09 g, 4.30 mmol) in degassed THF (3 mL) was added. The resulting brown suspension was stirred at 0 °C for 20 min then at room temperature for 10 min. The reaction mixture was washed with Na₂SO₃ (20 mL of a saturated aqueous solution) and the aqueous was extracted with Et₂O (3 x 20 mL). The combined organics were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resultant sludgy white solid was heated in MeOH (50 mL) at 60 °C for 10 min and filtered to give the product, 2'-iodo-2,2'',4,4'',6,6''-hexamethyl-1,1':3',1''-terphenyl **S1** (690 mg, 1.57 mmol, 57%), as an amorphous colourless solid.

m.p. 216 – 218 °C, Lit. m.p. 212 – 214 °C; **IR** v max (ATR)/ 3003, 2943, 2851, 1439, 1378, 1013, 850, 801, 737 cm⁻¹; **¹H NMR** δ_H (400 MHz; CDCl₃) 7.46 (1H, t, *J* 7.5 Hz, H-9), 7.08 (2H, d, *J* 7.5 Hz, H-8), 6.96 (4H, s, H-3), 2.35 (6H, s, H-1), 1.98 (12 H, s, H-5) ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; CDCl₃) 147.3 (C-7), 142.2 (C-6), 137.4 (C-4), 135.5 (C-2), 129.0 (C-9), 128.2 (C-3), 127.9 (C-8), 107.8 (C-10), 21.4 (C-1), 20.4 (C-5) ppm.; **HRMS** m/z (ESI+): [M+H⁺] calcd. for C₂₄H₂₆I: 441.1074, found: 441.1065.

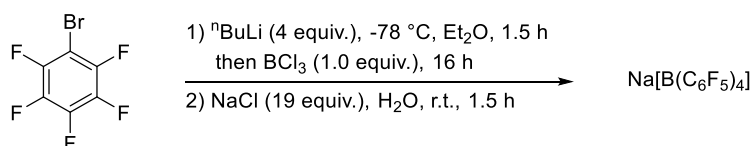
Data in agreement with the literature.³⁷⁰

2,2'',4,4'',6,6''-Hexamethyl-[1,1':3',1''-terphenyl]-2'-thiol **S2.**

To a stirred solution of **S1** (4.90 g, 11.1 mmol) in THF (80 mL) at -78 °C was added *n*-BuLi (6.60 mL, 13.2 mmol of a 2.0 M solution in hexane) dropwise over 30 min. The pale-yellow solution was stirred at -78 °C for 2.5 h before sulfur (1.06 g, 33.1 mmol) was added. The resulting red solution was stirred at -78 °C for 2.5 h then was added dropwise over 30 min to a suspension of LiAlH₄ (9.81 g, 285 mmol) in Et₂O (100 mL) at -78 °C. During this addition toxic H₂S gas is given off. This suspension was allowed to slowly warm to room temperature over 12 h, diluted with Et₂O and HCl (80 mL of a 3 M aqueous solution) was added dropwise over 9 h. The aqueous was extracted with Et₂O (3 x 100 mL) and the combined organics were dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by recrystallization from hot EtOAc gave the product, 2,2'',4,4'',6,6''-hexamethyl-[1,1':3',1''-terphenyl]-2'-thiol **S2** (1.81 g, 5.23 mmol, 47%), as colourless needles.

m.p. (EtOAc) 197 – 199 °C, Lit. m.p. 192 – 194 °C; **IR** ν max (ATR)/ 3000, 2988, 2913, 2853, 1741, 1452, 1391, 1375, 1246, 1034 cm⁻¹; **¹H NMR** δ_{H} (400 MHz; CDCl₃) 7.23 (1H, t, *J* 7.6 Hz, H-9), 7.03 (2H, d, *J* 7.6 Hz, H-8), 6.98 (4H, s, H-3), 3.02 (1H, s, SH), 2.34 (6H, s, H-1), 2.02 (12H, s, H-5) ppm.; **¹³C {¹H} NMR** δ_{C} (101 MHz; CDCl₃) 139.0 (ArC), 137.5 (ArC), 136.4 (ArC), 132.9 (ArC), 128.6 (C-3), 128.4 (C-8), 128.2 (C-10), 125.3 (C-9), 21.3 (C-1), 20.1 (C-5) ppm.; **HRMS** *m/z* (ESI⁺): [M+Na⁺] calcd. for C₂₄H₂₆SNa: 369.1653, found: 369.1657.

Data in agreement with the literature.³⁷¹

Sodium tetrakis(perfluorophenyl)borate **S3**

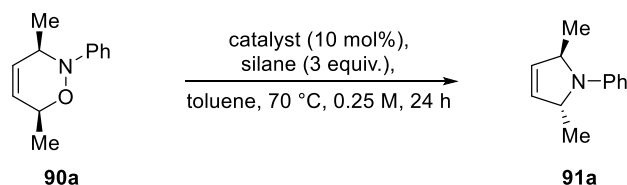
Experimental

To a stirred solution of pentafluorophenyl bromide (2.05 mL, 16.5 mmol) in Et₂O (4 mL) at –78 °C was added *n*-BuLi (7.0 mL, 14 mmol of a 2.0 M solution in hexane) dropwise. The yellow solution was stirred at –78 °C for 1.5 h before BCl₃ (3.5 mL, 3.5 mmol of a 1.0 M solution in heptane) was added dropwise over 20 min. The resulting white suspension was allowed to slowly warm to room temperature over 16 h and NaCl (3.84 g, 65.8 mmol) and H₂O (23 mL) were added. The biphasic mixture was stirred vigorously for 1 h and the organic layer was washed with brine (15 mL), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The sticky yellow solid was sonicated in pentane for 30 min, filtered and dried *in vacuo* to give the product, sodium tetrakis(perfluorophenyl)borate **S3** (1.96 g, 2.79 mmol, 80%), as a colourless powder.

m.p. decomposed >200 °C; **IR** ν max (ATR)/ 3700, 3631, 1647, 1620, 1515, 1455, 1082, 972 cm⁻¹; **¹¹B NMR** δ_B (128 MHz; DMSO-d₆) -16.73 ppm.; **¹³C {¹H} NMR** δ_C (101 MHz; DMSO-d₆) 147.6 (d, J_{C-F} 240.4 Hz, ArCF_{ortho}), 137.2 (br d, J_{C-F} 246.1 Hz, ArCF), 134.4 (br d, J_{C-F} 244.8 Hz, ArCF), 123.5 (br s, ArCB⁻Ar₃) ppm.; **¹⁹F {¹H} NMR** δ_F (376 MHz; DMSO-d₆) -132.40 (d, J_{C-F} 12.1 Hz, ArCF_{ortho}), -161.28 (t, J_{C-F} 21.6 Hz, ArCF_{para}), -165.89 (dd, J_{C-F} 20.8 Hz, ArCF_{meta}) ppm.; **HRMS** m/z (ESI⁻): [M⁻] calcd for C₂₄F₂₀B: 678.9779, found: 678.9779.

Data in agreement with the literature.⁸⁶

3.4. Supplementary Data



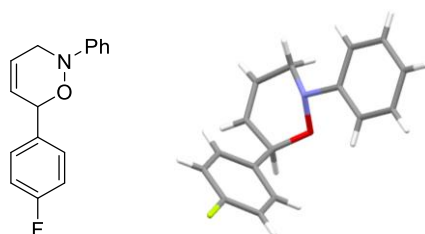
Experimental

Catalyst	PhSiH ₃		Et ₃ SiH		Et ₂ SiH ₂		(EtO) ₃ SiH		TMDS		Ph ₃ SiH	
	91a/ % ^a	90a/ % ^a	91a/ % ^a	90a/ % ^a	91a/ % ^a	90a/ % ^a	91a/ % ^a	90a/ % ^a	91a/ % ^a	90a/ % ^a	91a/ % ^a	90a/ % ^a
[Ir(COD)Cl] ₂	36	0	0	0	0	0	0	0	0	0	N/A	N/A
(Ph ₃ P) ₂ ReOCl ₃	0	50	0	47	0	52	4	31	0	54	N/A	N/A
(PPh ₃) ₃ RhCl	1	12	0	0	0	0	0	0	0	0	N/A	N/A
Fe ₃ (CO) ₁₂	4	0	0	- ^b	0	- ^b	0	0	0	- ^b	N/A	N/A
IrCl ₃	8	67	0	95	0	94	0	96	0	24	N/A	N/A
[(ppy) ₂ Ir-μ-Cl] ₂	32	0	0	- ^b	0	27	0	46	0	41	N/A	N/A
InBr ₃	0	64	0	63	0	60	0	70	0	100	N/A	N/A
[Cp*Ir] ₂	35	0	0	0	0	43	0	44	0	0	N/A	N/A
[Rh(cod)Cl] ₂	21	23	0	0	0	54	0	17	0	0	N/A	N/A
B(C ₆ F ₅) ₃	0	0	0	0	0	0	0	70	0	0	N/A	N/A
Co(acac) ₃ / DPEPhos	0	0	0	91	0	85	0	0	0	50	N/A	N/A
Cu(acac) ₃ / BINAP	0	92	0	70	0	94	0	99	0	98	N/A	N/A
Crabtree's Catalyst	26	41	0	0	0	89	0	2	0	87	N/A	N/A
[Ir(cod)(OMe)] ₂	15	0	0	19	0	90	0	0	- ^b	- ^b	N/A	N/A
[Ru(<i>p</i> -cymene)Cl ₂] ₂	28	10	0	37	0	36	0	29	0	78	0	57

^aYield determined by ¹H NMR spectroscopy using MSM as the internal standard. ^bUnable to determine NMR yield.

Supplement 1. All results for catalysts, in which more than one silane was trialled, tested during the reaction optimisation of the deoxygenative ring contraction of 91a.

Crystal Data and Structural Refinement for 90f.

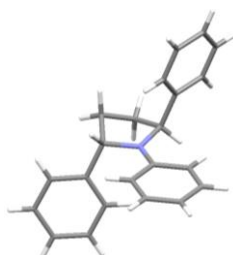
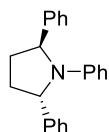


Empirical formula	C ₁₆ H ₁₄ FNO
Formula weight	255.28
Temperature/K	120(2)
Crystal system	monoclinic
Space group	P2 ₁ /n
a/Å	5.55250(10)
b/Å	11.6962(2)
c/Å	19.2020(3)
α/°	90
β/°	96.7260(10)
γ/°	90
Volume/Å ³	1238.46(4)
Z	4
ρ _{calc} /g/cm ³	1.369
μ/mm ⁻¹	0.782
F(000)	536.0
Crystal size/mm ³	0.319 × 0.255 × 0.076
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.87 to 145.77
Index ranges	-6 ≤ h ≤ 6, -14 ≤ k ≤ 13, -17 ≤ l ≤ 23

Experimental

Reflections collected	8315
Independent reflections	2424 [$R_{\text{int}} = 0.0196$, $R_{\text{sigma}} = 0.0174$]
Data/restraints/parameters	2424/0/172
Goodness-of-fit on F^2	1.059
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0364$, $wR_2 = 0.0936$
Final R indexes [all data]	$R_1 = 0.0380$, $wR_2 = 0.0950$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.25/-0.21

Crystal Data and Structural Refinement for **99b**.



Empirical formula	$C_{22}H_{21}N$
Formula weight	299.40
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1/n$
$a/\text{\AA}$	5.94130(10)
$b/\text{\AA}$	16.3011(3)
$c/\text{\AA}$	16.8056(3)
$\alpha/^\circ$	90
$\beta/^\circ$	98.536(2)
$\gamma/^\circ$	90
Volume/ $\text{\AA}^3$	1609.59(5)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.235
μ/mm^{-1}	0.538
$F(000)$	640.0
Crystal size/ mm^3	$0.36 \times 0.04 \times 0.02$
Radiation	$\text{Cu K}\alpha$ ($\lambda = 1.54184$)
2θ range for data collection/ $^\circ$	7.596 to 144.68
Index ranges	$-7 \leq h \leq 7$, $-20 \leq k \leq 20$, $-20 \leq l \leq 20$
Reflections collected	26086
Independent reflections	3156 [$R_{\text{int}} = 0.0350$, $R_{\text{sigma}} = 0.0163$]
Data/restraints/parameters	3156/0/208
Goodness-of-fit on F^2	1.041
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0351$, $wR_2 = 0.0906$
Final R indexes [all data]	$R_1 = 0.0403$, $wR_2 = 0.0943$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.22/-0.17

4. References

- 1 L. Advincula de Araújo, F. Addor and P. M. B. G. M. Campos, *An. Bras. Dermatol.*, 2016, **91**, 331–335.
- 2 P. Lotfi-Kamran and H. Sarbazi-Azad, *Dark Silicon and the History of Computing*, Elsevier Inc., Tehran, 1st edn., 2018, vol. 110.
- 3 F. S. Kipping, *Proc. Chem. Soc.*, 1904, **20**, 14–15.
- 4 F. S. Kipping, *Proc. R. Soc. A*, 1936, **159**, 139–148.
- 5 R. West and T. J. Barton, *J. Chem. Educ.*, 1980, **57**, 165–169.
- 6 N. R. Thomas, *Silicon*, 2011, **2**, 187–193.
- 7 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190–6191.
- 8 S. E. Denmark, R. P. Hammer, E. J. Weber and K. L. Habermas, *J. Org. Chem.*, 1987, **52**, 165–168.
- 9 M. Lalonde and T. H. Chan, *Synthesis*, 1985, **59**, 817–845.
- 10 T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, **2**, 1011–1014.
- 11 T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503–7509.
- 12 J. Xu, A. E. Krajewski, Y. Niu, G. S. M. Kiruba and J. K. Lee, *Chem. Sci.*, 2019, **10**, 8002–8008.
- 13 G. L. Larson and R. J. Liberatore, *Org. Process Res. Dev.*, 2021, **25**, 1719–1787.
- 14 A. Postigo, S. Kopsov, C. Ferreri and C. Chatgililoglu, *Org. Lett.*, 2007, **9**, 5159–5162.
- 15 C. Chatgililoglu and J. Lalevée, *Molecules*, 2012, **17**, 527–555.
- 16 M. Kira, M. Kobayashi and H. Sakurai, *Tetrahedron Lett.*, 1987, **28**, 4081–4084.
- 17 Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918–920.
- 18 S. E. Denmark, R. C. Smith, W. T. T. Chang and J. M. Muhuhi, *J. Am. Chem. Soc.*, 2009, **131**, 3104–3118.
- 19 D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780–784.
- 20 L. Frances van Staden, D. Gravestock and D. J. Ager, *Chem. Soc. Rev.*, 2002, **31**, 195–200.
- 21 K. Tamao, N. Ishida and M. Kumada, *J. Org. Chem.*, 1983, **48**, 2120–2122.
- 22 I. Fleming, R. Henning and H. E. Plaut, *J. Chem. Soc. Chem. Commun.*, 1984, 29–31.
- 23 B. Cordero, V. Gómez, A. E. Platero-Prats, M. Revés, J. Echeverría, E. Cremades, F. Barragán and S. Alvarez, *Dalton Trans.*, 2008, 2832–2838.
- 24 R. Walsh, *Acc. Chem. Res.*, 1981, **14**, 246–252.
- 25 J. I. Musher, *Angew. Chem. Int. Ed.*, 1969, **8**, 54–68.
- 26 W. B. Jensen, *J. Chem. Educ.*, 2006, **83**, 1751–1752.
- 27 R. J. Gillespie and E. A. Robinson, *Inorg. Chem.*, 1995, **34**, 978–979.
- 28 H. Bürger, *Angew. Chem. Int. Ed.*, 1973, **12**, 474–486.
- 29 B. T. Luke, J. A. Poole, M. B. Krogh-Jespersen, Y. Apeloig, J. Chandrasekhar and P. Von Rague Schleyer, *J. Am. Chem. Soc.*, 1986, **108**, 260–269.

References

- 30 E. Magnusson, *J. Am. Chem. Soc.*, 1990, **112**, 7940–7951.
- 31 T. B. Brill, *J. Chem. Educ.*, 1973, **50**, 392–396.
- 32 C. A. Ramsden, *Chem. Soc. Rev.*, 1994, **23**, 111–118.
- 33 R. J. Hach and R. E. Rundle, *J. Am. Chem. Soc.*, 1951, **73**, 4321–4324.
- 34 R. E. Rundle, *J. Am. Chem. Soc.*, 1947, **69**, 1327–1331.
- 35 R. E. Rundle, *J. Phys. Chem.*, 1957, **61**, 45–50.
- 36 R. E. Rundle, *J. Am. Chem. Soc.*, 1963, **85**, 112–113.
- 37 G. C. Pimentel, *J. Chem. Phys.*, 1951, **19**, 446–448.
- 38 G. A. Landrum, N. Goldberg and R. Hoffmann, *J. Chem. Soc. Dalt. Trans.*, 1997, 3605–3613.
- 39 S. Rendler and M. Oestreich, *Synthesis*, 2005, 1727–1747.
- 40 W. Von E. Doering, M. Saunders, H. G. Boyton, H. W. Earhart, W. E. F., W. R. Edwards and G. Laber, *Tetrahedron*, 1958, **4**, 178–185.
- 41 S. Hollenstein and T. Laube, *J. Am. Chem. Soc.*, 1993, **115**, 7240–7245.
- 42 L. Olsson, C. H. Ottosson and D. Cremer, *J. Am. Chem. Soc.*, 1995, **117**, 7460–7479.
- 43 J. Belzner, *Angew. Chem. Int. Ed.*, 1997, **36**, 1277–1280.
- 44 J. B. Lambert and S. Zhang, *J. Chem. Soc. Chem. Commun.*, 1993, 383–384.
- 45 H. F. T. Klare and M. Oestreich, *Dalton Trans.*, 2010, **39**, 9176–9184.
- 46 H. F. T. Klare, L. Albers, L. Süsse, S. Keess, T. Müller and M. Oestreich, *Chem. Rev.*, 2021, **121**, 5889–5985.
- 47 Y. Nagai, *Org. Prep. Proced. Int.*, 1980, **12**, 13–48.
- 48 E. Farber, *Chymia*, 1962, **8**, 165–180.
- 49 H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567–607.
- 50 J. Boyer, R. J. P. Corriu, R. Perz and C. Reye, *Tetrahedron*, 1981, **37**, 2165–2171.
- 51 Y. Kobayashi, E. Takahisa, M. Nakano and K. Watatani, *Tetrahedron*, 1997, **53**, 1627–1634.
- 52 M. Fujita and T. Hiyama, *J. Am. Chem. Soc.*, 1984, **106**, 4629–4630.
- 53 S. Kohra, H. Hayashida, Y. Tominaga and A. Hosomi, *Tetrahedron Lett.*, 1988, **29**, 89–92.
- 54 J. Jiang, L. Xiao and Y. L. Li, *Synlett*, 2020, **32**, 291–294.
- 55 F. A. Carey and H. S. Tremper, *J. Am. Chem. Soc.*, 1968, **90**, 2578–2583.
- 56 V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 6179–6186.
- 57 T. Krachko, V. Lyaskovskyy, M. Lutz, K. Lammertsma and J. C. Slootweg, *Zeitschrift fuer Anorg. und Allg. Chemie*, 2017, **643**, 916–921.
- 58 J. M. Kanabus-Kaminska, J. A. Hawari and D. Griller, *J. Am. Chem. Soc.*, 1987, **109**, 5267–5268.
- 59 C. Chatgililoglu, D. Griller and M. Lesage, *J. Org. Chem.*, 1988, **53**, 3641–3642.
- 60 C. Chatgililoglu, *Chem. Rev.*, 1995, **95**, 1229–1251.

References

- 61 C. Chatgililoglu, C. Ferreri, Y. Landais and V. I. Timokhin, *Chem. Rev.*, 2018, **118**, 6516–6572.
- 62 D. Lloyd and C. S. Bennett, *J. Org. Chem.*, 2014, **79**, 9826–9829.
- 63 A. Odedra, K. Geyer, T. Gustafsson, R. Gilmour and P. H. Seeberger, *Chem. Commun.*, 2008, 3025–3027.
- 64 S. Rendler and M. Oestreich, in *Modern Reduction Methods*, eds. P. G. Anderson and I. J. Munslow, Wiley-VCH, Weinheim, 1st Ed., 2008, pp. 183–207.
- 65 Z. Lin, *Chem. Soc. Rev.*, 2002, **31**, 239–245.
- 66 G. S. McGrady, P. Sirsch, N. P. Chatterton, A. Ostermann, C. Gatt, S. Altmannshofer, V. Herz, G. Eickerling and W. Scherer, *Inorg. Chem.*, 2009, **48**, 1588–1598.
- 67 R. H. Crabtree, *Angew. Chem. Int. Ed.*, 1993, **32**, 789–805.
- 68 D. V. Gutsulyak, S. F. Vyboishchikov and G. I. Nikonov, *J. Am. Chem. Soc.*, 2010, **132**, 5950–5951.
- 69 X. L. Luo and R. H. Crabtree, *J. Am. Chem. Soc.*, 1989, **111**, 2527–2535.
- 70 S. N. Blackburn, R. N. Haszeldine, R. V. Parish and J. H. Setchfield, *J. Organomet. Chem.*, 1980, **192**, 329–338.
- 71 J. Y. Corey and J. Braddock-Wilking, *Chem. Rev.*, 1999, **99**, 175–292.
- 72 R. Malacea, R. Poli and E. Manoury, *Coord. Chem. Rev.*, 2010, **254**, 729–752.
- 73 K. Riener, M. P. Högerl, P. Gigler and F. E. Kühn, *ACS Catal.*, 2012, **2**, 613–621.
- 74 I. Ojima, M. Nihonyanagi and Y. Nagai, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 3722–3722.
- 75 I. Ojima, M. Nihonyanagi and Y. Nagai, *J. Chem. Soc. Chem. Commun.*, 1972, 938–938.
- 76 Y. Nishibayashi, K. Segawa, H. Takada, K. Ohe and S. Uemura, *Chem. Commun.*, 1996, 847–848.
- 77 R. Kuwano, T. Uemura, M. Saitoh and Y. Ito, *Tetrahedron Lett.*, 1999, **40**, 1327–1330.
- 78 Y. Ohki, Y. Takikawa, H. Sadohara, C. Kesenheimer, B. Engendahl, E. Kapatina and K. Tatsumi, *Chem. - Asian J.*, 2008, **3**, 1625–1635.
- 79 E. A. LaPierre, W. E. Piers, D. M. Spasyuk and D. W. Bi, *Chem. Commun.*, 2016, **52**, 1361–1364.
- 80 T. Higashi, S. Kusumoto and K. Nozaki, *Chem. Rev.*, 2019, **119**, 10393–10402.
- 81 K. D. Hesp, R. McDonald, M. J. Ferguson and M. Stradiotto, *J. Am. Chem. Soc.*, 2008, **130**, 16394–16406.
- 82 H. F. T. Klare, M. Oestreich, J. I. Ito, H. Nishiyama, Y. Ohki and K. Tatsumi, *J. Am. Chem. Soc.*, 2011, **133**, 3312–3315.
- 83 T. Stahl, H. F. T. Klare and M. Oestreich, *J. Am. Chem. Soc.*, 2013, **135**, 1248–1251.
- 84 C. D. F. Königs, H. F. T. Klare and M. Oestreich, *Angew. Chem. Int. Ed.*, 2013, **52**, 10076–10079.
- 85 L. Omann and M. Oestreich, *Angew. Chem. Int. Ed.*, 2015, **54**, 10276–10279.
- 86 L. Omann and M. Oestreich, *Organometallics*, 2017, **36**, 767–776.
- 87 R. D. Taylor, M. Maccoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.

References

- 88 G. Li Petri, M. V. Raimondi, V. Spanò, R. Holl, P. Barraja and A. Montalbano, *Top. Curr. Chem.*, 2021, **379**, 1–46.
- 89 World Health Organization, *World Health Organisation Model List of Essential Medicines - 22nd List, 2021*, World Health Organisation, Geneva, 22nd List., 2021.
- 90 Z. Fang, Y. Song, P. Zhan, Q. Zhang and X. Liu, *Future Med. Chem.*, 2014, **6**, 885–901.
- 91 M. W. Harrold and R. M. Zavod, in *Basic Concepts in Medicinal Chemistry*, 1st Ed., 2013, pp. 1–36.
- 92 B. List, *Tetrahedron*, 2003, **58**, 5573–5590.
- 93 D. Enders and T. Gasperi, *Chem. Commun.*, 2007, 88–90.
- 94 N. M. Hilmy Elnagdi and N. S. Al-Hokbany, *Molecules*, 2012, **17**, 4300–4312.
- 95 U. Eder, G. Sauer and R. Wiechert, *Angew. Chem. Int. Ed.*, 1971, **10**, 496–497.
- 96 M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2005, **44**, 794–797.
- 97 Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem. Int. Ed.*, 2005, **44**, 4212–4215.
- 98 P. G. Bulger, in *Comprehensive Chirality*, eds. E. M. Carreira and H. Yamamoto, Elsevier Ltd., 1st Ed., 2012, vol. 9, pp. 228–252.
- 99 H. Gotoh and Y. Hayashi, *Org. Lett.*, 2007, **9**, 2859–2862.
- 100 K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem. Commun.*, 2006, 66–68.
- 101 C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 2039–2049.
- 102 Y. Yamamoto, N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 5962–5963.
- 103 P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2007, **46**, 1983–1987.
- 104 M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964–6965.
- 105 D. B. Ramachary and R. Mondal, *Tetrahedron Lett.*, 2006, **47**, 7689–7693.
- 106 M. Marigo, T. Schulte, J. Franzén and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711.
- 107 J. Tang, D. Q. Xu, A. B. Xia, Y. F. Wang, J. R. Jiang, S. P. Luo and Z. Y. Xu, *Adv. Synth. Catal.*, 2010, **352**, 2121–2126.
- 108 A. Erkkila, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416–5470.
- 109 G. Stork, *J. Am. Chem. Soc.*, 1954, **76**, 2029–2030.
- 110 S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471–5569.
- 111 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
- 112 O. Tokuda, T. Kano, W. G. Gao, T. Ikemoto and K. Maruoka, *Org. Lett.*, 2005, **7**, 5103–5105.
- 113 B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336–9337.
- 114 B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423–2425.

References

- 115 P. Melchiorre and K. A. Jørgensen, *J. Org. Chem.*, 2003, **68**, 4151–4157.
- 116 T. Yang, A. Ferrali, L. Campbell and D. J. Dixon, *Chem. Commun.*, 2008, 2923–2925.
- 117 S. Afewerki, P. Breistein, K. Pirttilä, L. Deiana, P. Dziedzic, I. Ibrahim and A. Córdova, *Chem. - Eur. J.*, 2011, **17**, 8784–8788.
- 118 A. Vega-Peñaloza, S. Paria, M. Bonchio, L. Dell'Amico and X. Companyó, *ACS Catal.*, 2019, **9**, 6058–6072.
- 119 J. J. Zhao, H. H. Zhang, X. Shen and S. Yu, *Org. Lett.*, 2019, **21**, 913–916.
- 120 C. R. Müller, I. Meiners and P. Domínguez de María, *RSC Adv.*, 2014, **4**, 46097–46101.
- 121 G. Rulli, N. Duangdee, W. Hummel, A. Berkessel and H. Gröger, *Eur. J. Org. Chem.*, 2017, 812–817.
- 122 O. H. Hankovszky, K. Hideg, I. Bodi and L. Frank, *J. Med. Chem.*, 1986, **29**, 1138–1152.
- 123 H. Wu, V. Coble, O. Vasalatiy, R. E. Swenson, M. C. Krishna and J. B. Mitchell, *Tetrahedron Lett.*, 2014, **55**, 5570–5571.
- 124 Y. Lee, H. Huang and L. M. Sayre, *J. Am. Chem. Soc.*, 1996, **118**, 7241–7242.
- 125 Y. Lee, K. Q. Ling, X. Lu, R. B. Silverman, E. M. Shepard, D. M. Dooley and L. M. Sayre, *J. Am. Chem. Soc.*, 2002, **124**, 12135–12143.
- 126 C. H. Williams and J. Lawson, *Biochem. J.*, 1998, **336**, 63–67.
- 127 I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801–1839.
- 128 M. Sai and S. Matsubara, *Org. Lett.*, 2011, **13**, 4676–4679.
- 129 H. Ahankar, A. Ramazani, K. Ślepokura, T. Lis and S. W. Joo, *Green Chem.*, 2016, **18**, 3582–3593.
- 130 T. J. Donohoe, H. O. Sintim, L. Sisangia, K. W. Ace, P. M. Guyo, A. Cowley and J. D. Harling, *Chem. - Eur. J.*, 2005, **11**, 4227–4238.
- 131 T. J. Donohoe and H. O. Sintim, *Org. Lett.*, 2004, **6**, 2003–2006.
- 132 G. Poli, *Tetrahedron Lett.*, 1989, **30**, 7385–7388.
- 133 A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner and A. A. Thomas, *J. Am. Chem. Soc.*, 1997, **119**, 9907–9908.
- 134 E. A. Severino and C. R. D. Correia, *Org. Lett.*, 2000, **2**, 3039–3042.
- 135 S. G. Davies, K. Iwamoto, C. A. P. Smethurst, A. D. Smith and H. Rodriguez-Solla, *Synlett*, 2002, **2**, 1146–1148.
- 136 P. Gkizis, N. G. Argyropoulos and E. Coutouli-Argyropoulou, *Tetrahedron*, 2013, **69**, 8921–8928.
- 137 L. M. Young, W. J. Geldenhuys, O. C. Domingo, S. F. Malan and C. J. Van Der Schyf, *Arch. Pharm. (Weinheim)*, 2016, **349**, 252–267.
- 138 V. Santhanam, P. Pant, B. Jayaram and N. G. Ramesh, *Org. Biomol. Chem.*, 2019, **17**, 1130–1140.
- 139 R. K. Dieter, N. Chen and R. T. Watson, *Tetrahedron*, 2005, **61**, 3221–3230.
- 140 A. Dondoni, P. P. Giovannini and D. Perrone, *J. Org. Chem.*, 2002, **67**, 7203–7214.
- 141 D. Wei, C. Netkaew and C. Darcel, *Adv. Synth. Catal.*, 2019, **361**, 1781–1786.

References

- 142 K. Fujita, T. Fujii and R. Yamaguchi, *Org. Lett.*, 2004, **6**, 3525–3528.
- 143 M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774.
- 144 A. Noole, T. Pehk, I. Järving, M. Lopp and T. Kanger, *Tetrahedron Asymmetry*, 2012, **23**, 188–198.
- 145 M. G. Vinogradov, O. V. Turova and S. G. Zlotin, *Org. Biomol. Chem.*, 2019, **17**, 3670–3708.
- 146 Z. F. Zhang, Z.-H. Gao, C.-L. Zhang and S. Ye, *Tetrahedron*, 2021, **94**, 132337.
- 147 Y.-X. Song and D.-M. Du, *Adv. Synth. Catal.*, 2021, **363**, 4667–4694.
- 148 C. Enkisch and C. Schneider, *Eur. J. Org. Chem.*, 2009, 5549–5564.
- 149 W. N. Olmstead, Z. Margolin and F. G. Bordwell, *J. Org. Chem.*, 1980, **45**, 3295–3299.
- 150 A. Barco, S. Benetti, A. Casolari, G. Piero Pollini and G. Spalluto, *Tetrahedron Lett.*, 1990, **31**, 3039–3042.
- 151 H. Li, L. Zu, H. Xie, J. Wang and W. Wang, *Chem. Commun.*, 2008, 5636–5638.
- 152 B.-L. Zhao, Y. Lin, H.-H. Yan and D.-M. Du, *Org. Biomol. Chem.*, 2015, **13**, 11351–11361.
- 153 S. Mukhopadhyay and S. C. Pan, *Org. Biomol. Chem.*, 2018, **16**, 9349–9353.
- 154 A. Padwa, Y.-Y. Chen, W. Dent and H. Nimmesgern, *J. Org. Chem.*, 1985, **50**, 4006–4014.
- 155 I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2809.
- 156 G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484–4517.
- 157 V. L. Mykhalchuk, V. S. Yarmolchuk, R. O. Doroschuk, A. A. Tolmachev and O. O. Grygorenko, *Eur. J. Org. Chem.*, 2018, 2870–2876.
- 158 X. Zhang, M. Liu, D. Zhan, M. Kaur, J. P. Jasinski and W. Zhang, *New J. Chem.*, 2022, **46**, 3866–3870.
- 159 A. R. Haight, A. E. Bailey, W. S. Baker, M. H. Cain, R. R. Copp, J. A. DeMattei, K. L. Ford, R. F. Henry, M. C. Hsu, R. F. Keyes, S. A. King, M. A. McLaughlin, L. M. Melcher, W. R. Nadler, P. A. Oliver, S. I. Parekh, H. H. Patel, L. S. Seif, M. A. Staeger, G. S. Wayne, S. J. Wittenberger and W. Zhang, *Org. Process Res. Dev.*, 2004, **8**, 897–902.
- 160 J. Hartung, S. N. Greszler, R. C. Klix and J. M. Kallemeyn, *Org. Process Res. Dev.*, 2019, **23**, 2532–2537.
- 161 R. Yamada, Y. Adachi, S. Yokoshima and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2016, **55**, 6067–6070.
- 162 P. DeShong, D. A. Kell and D. R. Sidler, *J. Org. Chem.*, 1985, **50**, 2309–2315.
- 163 K. Yamazaki, P. Gabriel, G. Di Carmine, J. Pedroni, M. Farizyan, T. A. Hamlin and D. J. Dixon, *ACS Catal.*, 2021, **11**, 7489–7497.
- 164 M. Rueping, D. Leonori and T. Poisson, *Chem. Commun.*, 2011, **47**, 9615–9617.
- 165 R. Kumar and P. Banerjee, *J. Org. Chem.*, 2021, **86**, 16104–16113.
- 166 J. Caruano, G. G. Muccioli and R. Robiette, *Org. Biomol. Chem.*, 2016, **14**, 10134–10156.
- 167 C. J. Collins, M. Lanz and B. Singaram, *Tetrahedron Lett.*, 1999, **40**, 3673–3676.
- 168 A. R. Katritzky, B. Rachwal and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 3993–4001.

References

- 169 A. R. Katritzky, B. Rachwal, S. Rachwal and K. A. Abboud, *J. Org. Chem.*, 1996, **61**, 3117–3126.
- 170 R. Kuwano, M. Takahashi and Y. Ito, *Tetrahedron Lett.*, 1998, **39**, 1017–1020.
- 171 W. Yao, H. Fang, Q. He, D. Peng, G. Liu and Z. Huang, *J. Org. Chem.*, 2019, **84**, 6084–6093.
- 172 V. Bhajammanavar, S. Mallik and M. Baidya, *Org. Biomol. Chem.*, 2019, **17**, 1740–1743.
- 173 K. Satoh, A. Imura, A. Miyadera, K. Kanai and Y. Yukimoto, *Chem. Pharm. Bull.*, 1998, **46**, 587–590.
- 174 P. Szcześniak, S. Stecko, O. Staszewska-Krajewska and B. Furman, *Tetrahedron*, 2014, **70**, 1880–1888.
- 175 P. Szcześniak, E. Maziarz, S. Stecko and B. Furman, *J. Org. Chem.*, 2015, **80**, 3621–3633.
- 176 L. H. Andrews and S. M. McElvain, *J. Am. Chem. Soc.*, 1929, **51**, 887–892.
- 177 G. G. Evans, *J. Am. Chem. Soc.*, 1951, **73**, 5230–5234.
- 178 J. M. Bobbitt, L. H. Amundsen and R. I. Steiner, *J. Org. Chem.*, 1960, **25**, 2230–2231.
- 179 N. S. Medran, A. La-Venia and S. A. Testero, *RSC Adv.*, 2019, **9**, 6804–6844.
- 180 V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2008, **73**, 7417–7419.
- 181 R. A. Walsh and A. T. Bottini, *J. Org. Chem.*, 1970, **35**, 1086–1092.
- 182 T. Shioiri and T. Aoyama, *J. Synth. Org. Chem. Japan*, 1996, **54**, 918–928.
- 183 H. Ogawa, T. Aoyama and T. Shioiri, *Heterocycles*, 1996, **42**, 75–82.
- 184 H. Ogawa, T. Aoyama and T. Shioiri, *Heterocycles*, 1996, **27**, 1996.
- 185 M. P. Green, J. C. Prodger, A. E. Sherlock and C. J. Hayes, *Org. Lett.*, 2001, **3**, 3377–3379.
- 186 M. P. Green, J. C. Prodger and C. J. Hayes, *Tetrahedron Lett.*, 2002, **43**, 6609–6611.
- 187 H. Ohno, Y. Kadoh, N. Fujii and T. Tanaka, *Org. Lett.*, 2006, **8**, 947–950.
- 188 T. Shibata, S. Kadowaki and K. Takagi, *Heterocycles*, 2002, **57**, 2261–2266.
- 189 R. K. Dieter and H. Yu, *Org. Lett.*, 2001, **3**, 3855–3858.
- 190 M. O. Amombo, A. Hausherr and H. U. Reissig, *Synlett*, 1999, 1871–1874.
- 191 R. K. Dieter, N. Chen and V. K. Gore, *J. Org. Chem.*, 2006, **71**, 8755–8760.
- 192 K. Amiri, H. Khosravi, S. Balalaie, F. Golmohammadi, M. U. Anwar and A. Al-Harrasi, *Org. Biomol. Chem.*, 2019, **17**, 8858–8870.
- 193 G. Makov, *J. Phys. Chem.*, 1996, **99**, 9337–9339.
- 194 L. Knorr and P. Rabe, *Berichte der Dtsch. Chem. Gesellschaft*, 1901, **34**, 3491–3502.
- 195 D. M. Ketcha, K. P. Carpenter and Q. Zhou, *J. Org. Chem.*, 1991, **56**, 1318–1320.
- 196 B. S. Gourlay, J. H. Ryan and J. A. Smith, *Beilstein J. Org. Chem.*, 2008, **4**, 1–5.
- 197 H. T. You, A. C. Grosse, J. K. Howard, C. J. T. Hyland, J. Just, P. P. Molesworth and J. A. Smith, *Org. Biomol. Chem.*, 2011, **9**, 3948–3953.
- 198 Y. Ohta, M. Onoshima, M. Tamura, R. Tanaka, Y. Morimoto, K. Yoshihara and T. Kinoshita, *J. Heterocycl. Chem.*, 1998, **35**, 461–465.
- 199 J. T. Kim and V. Gevorgyan, *J. Org. Chem.*, 2005, **70**, 2054–2059.

References

- 200 P. Lei, Y. Ding, X. Zhang, A. Adijiang, H. Li, Y. Ling and J. An, *Org. Lett.*, 2018, **20**, 3439–3442.
- 201 F. R. Cordell and J. E. Boggs, *J. Mol. Struct. THEOCHEM*, 1981, **85**, 163–178.
- 202 T. J. Donohoe, C. E. Headley, R. P. C. Cousins and A. Cowley, *Org. Lett.*, 2003, **5**, 999–1002.
- 203 N. Fukuda, K. Sasaki, T. V. R. S. Sastry, M. Kanai and M. Shibasaki, *J. Org. Chem.*, 2006, **71**, 1220–1225.
- 204 T. J. Donohoe and R. E. Thomas, *Chem. Rec.*, 2007, **7**, 180–190.
- 205 T. J. Donohoe and P. M. Guyo, *J. Org. Chem.*, 1996, **61**, 7664–7665.
- 206 T. J. Donohoe, P. M. Guyo and M. Helliwell, *Tetrahedron Lett.*, 1999, **40**, 435–438.
- 207 T. J. Donohoe, P. M. Guyo, R. L. Beddoes and M. Helliwell, *J. Chem. Soc. Perkin Trans. 1*, 1998, 667–676.
- 208 T. J. Donohoe, C. L. Rigby, R. E. Thomas, W. F. Nieuwenhuys, F. L. Bhatti, A. R. Cowley, G. Bhalay and I. D. Linney, *J. Org. Chem.*, 2006, **71**, 6298–6301.
- 209 T. J. Donohoe, G. C. Freestone, C. E. Headley, C. L. Rigby, R. P. C. Cousins and G. Bhalay, *Org. Lett.*, 2004, **6**, 3055–3058.
- 210 T. J. Donohoe, R. R. Harji and R. P. C. Cousins, *Tetrahedron Lett.*, 2000, **41**, 1327–1330.
- 211 T. J. Donohoe and D. House, *J. Org. Chem.*, 2002, **67**, 5015–5018.
- 212 A. E. Favorskii, *J. Russ. Phys. Chem. Soc.*, 1894, **26**, 559.
- 213 N. Tsuchida, S. Yamazaki and S. Yamabe, *Org. Biomol. Chem.*, 2008, **6**, 3109–3117.
- 214 L. Wolff, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129–195.
- 215 L. Horner and E. Spietschka, *Chem. Ber.*, 1955, **88**, 934–939.
- 216 R. D. Bach and H. B. Schlegel, *J. Phys. Chem. A*, 2021, **125**, 5014–5021.
- 217 S. Kumarn, D. M. Shaw, D. A. Longbottom and S. V. Ley, *Org. Lett.*, 2005, **7**, 4189–4191.
- 218 V. Dekaris, R. Pulz, A. Al-Harrasi, D. Lentz and H. U. Reissig, *Eur. J. Org. Chem.*, 2011, 3210–3219.
- 219 G. Calvet, N. Blanchard and C. Kouklovsky, *Synthesis*, 2005, 3346–3354.
- 220 R. Pulz, T. Watanabe, W. Schade and H. U. Reissig, *Synlett*, 2000, 983–986.
- 221 R. Zimmer, B. Orschel, S. Scherer and H. U. Reissig, *Synthesis*, 2002, 1553–1563.
- 222 H. U. Reissig, K. Homann, F. Hiller and R. Zimmer, *Synthesis*, 2007, 2681–2689.
- 223 R. Zimmer, M. Collas, R. Czerwonka, U. Hain and H. U. Reissig, *Synthesis*, 2008, 237–244.
- 224 R. Zimmer, M. Buchholz, M. Collas, J. Angermann, K. Homann and H. U. Reissig, *Eur. J. Org. Chem.*, 2010, 4111–4121.
- 225 R. Pulz, A. Al-Harrasi and H. U. Reissig, *Org. Lett.*, 2002, **4**, 2353–2355.
- 226 R. Pulz, W. Schade and H. U. Reissig, *Synlett*, 2003, 405–407.
- 227 T. Pecchioli, F. Cardona, H. U. Reissig, R. Zimmer and A. Goti, *J. Org. Chem.*, 2017, **82**, 5835–5844.
- 228 C. Parmeggiani, F. Cardona, L. Giusti, H. U. Reissig and A. Goti, *Chem. - Eur. J.*, 2013, **19**,

References

- 10595–10604.
- 229 I. S. Young, J. L. Williams and M. A. Kerr, *Org. Lett.*, 2005, **7**, 953–955.
- 230 I. S. Young and M. A. Kerr, *J. Am. Chem. Soc.*, 2007, **129**, 1465–1469.
- 231 J. Firl, *Chem. Ber.*, 1968, **101**, 218–225.
- 232 P. Scheiner, O. L. Chapman and J. D. Lassila, *J. Org. Chem.*, 1969, **34**, 813–816.
- 233 R. S. Givens, D. J. Choo, M. S. N., R. P. Stitt and B. Matuszewski, *Tetrahedron Lett.*, 1982, **23**, 1327–1330.
- 234 W. J. Humenny, P. Kyriacou, K. Sapeta, A. Karadeolian and M. A. Kerr, *Angew. Chem. Int. Ed.*, 2012, **51**, 11088–11091.
- 235 K. Sapeta and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 8597–8599.
- 236 I. Shimizu and J. Tsuji, *J. Am. Chem. Soc.*, 1982, **104**, 5844–5846.
- 237 N. Yasukawa, M. Kuwata, T. Imai, Y. Monguchi, H. Sajiki and Y. Sawama, *Green Chem.*, 2018, **20**, 4409–4413.
- 238 F. Tripoteau, L. Eberlin, M. A. Fox, B. Carboni and A. Whiting, *Chem. Commun.*, 2013, **49**, 5414–5416.
- 239 L. Eberlin, B. Carboni and A. Whiting, *J. Org. Chem.*, 2015, **80**, 6574–6583.
- 240 B. François, L. Eberlin, F. Berrée, A. Whiting and B. Carboni, *J. Org. Chem.*, 2020, **85**, 5173–5182.
- 241 L. Eberlin, A. Macé, A. S. Batsanov, B. Carboni and A. Whiting, *ChemistrySelect*, 2018, **3**, 4557–4561.
- 242 R. J. Lee, M. R. Lindley, G. J. Pritchard and M. C. Kimber, *Chem. Commun.*, 2017, **53**, 6327–6330.
- 243 R. D. Bach and H. B. Schlegel, *J. Phys. Chem. A*, 2020, **124**, 4742–4751.
- 244 P. B. Dervan and C. R. Jones, *J. Org. Chem.*, 1979, **44**, 2116–2122.
- 245 B. W. Greatrex and D. K. Taylor, *J. Org. Chem.*, 2004, **69**, 2577–2579.
- 246 T. V. Robinson, D. S. Pedersen, D. K. Taylor and E. R. T. Tiekink, *J. Org. Chem.*, 2009, **74**, 5093–5096.
- 247 L. Kong, M. Rao, J. Ou, J. Yin, W. Lu, M. Liu, X. Pang and S. Gao, *Org. Biomol. Chem.*, 2014, **12**, 7591–7597.
- 248 J. Xu, E. J. E. Caro-Diaz, M. H. Lacoske, C. I. Hung, C. Jamora and E. A. Theodorakis, *Chem. Sci.*, 2012, **3**, 3378–3386.
- 249 J. Yin, L. Kong, C. Wang, Y. Shi, S. Cai and S. Gao, *Chem. - Eur. J.*, 2013, **19**, 13040–13046.
- 250 J. Yin and S. Gao, *Synlett*, 2014, **25**, 1–7.
- 251 R. A. Alonso, G. D. Vite, R. E. McDevitt and B. Fraser-Reid, *J. Org. Chem.*, 1992, **57**, 573–584.
- 252 E. J. Verner and T. Cohen, *J. Am. Chem. Soc.*, 1992, **114**, 375–377.
- 253 H. Redlich, *Angew. Chem. Int. Ed.*, 1994, **33**, 1345–1347.
- 254 H. Ito, Y. Motoki, T. Taguchi and Y. Hanzawa, *J. Am. Chem. Soc.*, 1993, **115**, 8835–8836.

References

- 255 Y. Hanzawa, I. Hisanaka and T. Taguchi, *Synlett*, 1995, 299–305.
- 256 L. A. Paquette and N. Cunière, *Org. Lett.*, 2002, **4**, 1927–1929.
- 257 D. A. Paquette, R. M. Arbit, J. Funel and S. Bolshakov, *Synthesis*, 2002, 2105–2109.
- 258 L. A. Paquette, Z. Tian, C. K. Seekamp and T. Wang, *Helv. Chim. Acta*, 2005, **88**, 1185–1198.
- 259 L. A. Paquette, X. Peng and J. Yang, *Angew. Chem. Int. Ed.*, 2007, **46**, 7817–7819.
- 260 L. A. Paquette, X. Peng, J. Yang and H. J. Kang, *J. Org. Chem.*, 2008, **73**, 4548–4558.
- 261 E. Thornton, University of Nottingham, 2019.
- 262 A. Zanobini, M. Gensini, J. Magull, D. Vidović, S. I. Kozhushkov, A. Brandi and A. De Meijere, *Eur. J. Org. Chem.*, 2004, 4158–4166.
- 263 A. Zanobini, A. Brandi and A. De Meijere, *Eur. J. Org. Chem.*, 2006, 1251–1255.
- 264 S. Diethelm and E. M. Carreira, *J. Am. Chem. Soc.*, 2015, **137**, 6084–6096.
- 265 T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366–5412.
- 266 J. W. Kelly, N. L. Eskew and S. A. Evans, *J. Org. Chem.*, 1986, **51**, 95–97.
- 267 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–1858.
- 268 C. Cheng and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 11304–11307.
- 269 E. L. Stoll, T. Tongue, K. G. Andrews, D. Valette, D. J. Hirst and R. M. Denton, *Chem. Sci.*, 2020, **11**, 9494–9500.
- 270 O. Wichterle, *Collect. Czechoslov. Chem. Commun.*, 1947, **12**, 292–304.
- 271 A. Y. Khalimon, K. A. Gudun and D. Hayrapetyan, *Catalysis*, 2019, **9**, 490–516.
- 272 N. C. Mamillapalli and G. Sekar, *Chem. Commun.*, 2014, **50**, 7881–7884.
- 273 B. J. Simmons, M. Hoffmann, J. Hwang, M. K. Jackl and N. K. Garg, *Org. Lett.*, 2017, **19**, 1910–1913.
- 274 D. W. Lee and J. Yun, *Tetrahedron Lett.*, 2004, **45**, 5415–5417.
- 275 S. Das, B. Join, K. Junge and M. Beller, *Chem. Commun.*, 2012, **48**, 2683–2685.
- 276 P. Q. Huang, Q. W. Lang and Y. R. Wang, *J. Org. Chem.*, 2016, **81**, 4235–4243.
- 277 A. Nurseit, J. Janabel, K. A. Gudun, A. Kassymbek, M. Segizbayev, T. M. Seilkhanov and A. Y. Khalimon, *ChemCatChem*, 2019, **11**, 790–798.
- 278 S. Zhou, K. Junge, D. Addis, S. Das and M. Beller, *Angew. Chem. Int. Ed.*, 2009, **48**, 9507–9510.
- 279 S. Das, B. Wendt, K. Möller, K. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2012, **51**, 1662–1666.
- 280 N. Sakai, T. Moriya and T. Konakahara, *J. Org. Chem.*, 2007, **72**, 5920–5922.
- 281 R. G. De Noronha, C. C. Romão and A. C. Fernandes, *J. Org. Chem.*, 2009, **74**, 6960–6964.
- 282 B. Chatterjee and C. Gunanathan, *Chem. Commun.*, 2014, **50**, 888–890.
- 283 B. H. Lipshutz, A. Lower and K. Noson, *Org. Lett.*, 2002, **4**, 4045–4048.
- 284 Y. Tsuchiya, H. Uchimura, K. Kobayashi and H. Nishiyama, *Synlett*, 2004, 2099–2102.

References

- 285 T. Dumszlaff, B. Yang, A. Maghsoumi, G. Velpula, K. S. Mali, C. Castiglioni, S. De Feyter, M. Tommasini, A. Narita, X. Feng and K. Müllen, *J. Am. Chem. Soc.*, 2016, **138**, 4726–4729.
- 286 EP2133357A1, 2009, 14.
- 287 O. Martínez-Ferraté, B. Chatterjee, C. Werlé and W. Leitner, *Catal. Sci. Technol.*, 2019, **9**, 6370–6378.
- 288 R. G. de Noronha, C. C. Romão and A. C. Fernandes, *Tetrahedron Lett.*, 2010, **51**, 1048–1051.
- 289 P. T. K. Lee and L. Rosenberg, *Dalton Trans.*, 2017, **46**, 8818–8826.
- 290 F. G. Fontaine and D. Zargarian, *J. Am. Chem. Soc.*, 2004, **126**, 8786–8794.
- 291 N. Mucha, PhD Thesis, University of Vermont, 2015.
- 292 V. Magne, Postdoctoral Report, University of Nottingham, 2020.
- 293 A. Feigl, I. Chiorescu, K. Deller, S. U. H. Heidsieck, M. R. Buchner, V. Karttunen, A. Bockholt, A. Genest, N. Rösch and B. Rieger, *Chem. - Eur. J.*, 2013, **19**, 12526–12536.
- 294 B. Yang, W. Lin, V. Krchnak and M. J. Miller, *Tetrahedron Lett.*, 2009, **50**, 5879–5883.
- 295 P. Zuman and B. Shah, *Chem. Rev.*, 1994, **94**, 1621–1641.
- 296 R. Jurok, J. Hodačová, V. Eigner, H. Dvořáková, V. Setnička and R. Cibulka, *Eur. J. Org. Chem.*, 2013, 7724–7738.
- 297 T. E. Sample and L. F. Hatch, *J. Chem. Educ.*, 1968, **45**, 55–56.
- 298 B. G. Gowenlock and G. B. Richter-Addo, *Chem. Rev.*, 2004, **104**, 3315–3340.
- 299 M. G. Memeo and P. Quadrelli, *Chem. Rev.*, 2017, **117**, 2108–2200.
- 300 C. P. Frazier, A. Bugarin, J. R. Engelking and J. Read de Alaniz, *Org. Lett.*, 2012, **14**, 3620–3623.
- 301 Y. Wang, X. Cao, L. Zhao, C. Pi, J. Ji, X. Cui and Y. Wu, *Adv. Synth. Catal.*, 2020, **362**, 4119–4129.
- 302 A. Welter, J. Jadot, G. Dardenne, M. Marlier and J. Casimir, *Phytochemistry*, 1976, **15**, 747–749.
- 303 N. Asano, A. Kato, M. Miyauchi, H. Kizu, Y. Kameda, A. A. Watson, R. J. Nash and G. W. J. Fleet, *J. Nat. Prod.*, 1998, **61**, 625–628.
- 304 B. M. Trost, D. B. Horne and M. J. Woltering, *Chem. - Eur. J.*, 2006, **12**, 6607–6620.
- 305 E. L. Tsou, Y. T. Yeh, P. H. Liang and W. C. Cheng, *Tetrahedron*, 2009, **65**, 93–100.
- 306 H. Ji, B. Z. Stanton, J. Igarashi, H. Li, P. Martíásek, L. J. Roman, T. L. Poulos and R. B. Silverman, *J. Am. Chem. Soc.*, 2008, **130**, 3900–3914.
- 307 T. J. Donohoe, M. D. Cheeseman, T. J. C. O’Riordan and J. A. Kershaw, *Org. Biomol. Chem.*, 2008, **6**, 3896–3898.
- 308 R. Mello, M. Fiorentino, O. Sciacovelli and R. Curci, *J. Org. Chem.*, 1988, **53**, 3890–3891.
- 309 A. M. Ja’o, D. A. Wann, C. D. Rankine, J. P. F. Nunes, J. C. Guillemin and S. L. Masters, *Struct. Chem.*, 2021, **32**, 205–213.
- 310 A. Zhdanko, B. A. van der Worp and S. Lemaire, *Eur. J. Org. Chem.*, 2022, **e202200130**, 1–11.

References

- 311 R. D. Bach, O. Dmitrenko, W. Adam and S. Schambony, *J. Am. Chem. Soc.*, 2003, **125**, 924–934.
- 312 D. F. Taber, P. W. DeMatteo and R. A. Hassan, *Org. Synth.*, 2013, **90**, 350–357.
- 313 J. Ouyang, R. Yan and R. Hong, *Angew. Chem. Int. Ed.*, 2015, **54**, 10940–10943.
- 314 D. Uraguchi, D. Nakashima and T. Ooi, *J. Am. Chem. Soc.*, 2009, **131**, 7242–7243.
- 315 J. M. M. Verkade, L. J. C. van Hemert, P. J. L. . M. Quaedflieg, P. L. Alsters, F. L. van Delft and F. P. J. T. Rutjes, *Tetrahedron Lett.*, 2006, **47**, 8109–8113.
- 316 C. Vaxelaire, F. Souquet, M.-I. Lannou, J. Ardisson and J. Royer, *Eur. J. Org. Chem.*, 2009, 3138–3140.
- 317 H. Kwart and R. A. Conley, *J. Org. Chem.*, 1973, **38**, 2011–2016.
- 318 R. A. Benkeser, F. G. Belmonte and J. Kang, *J. Org. Chem.*, 1983, **48**, 2796–2802.
- 319 K. Briner, *e-EROS Encycl. Reagents Org. Synth.*, 1995, 3003–3007.
- 320 C. Cheng and M. Brookhart, *Angew. Chem. Int. Ed.*, 2012, **51**, 9422–9424.
- 321 V. S. Sridevi, Y. F. Wai and K. L. Weng, *Organometallics*, 2007, **26**, 1157–1160.
- 322 X. Xie, X. Zhang, W. Gao, C. Meng, X. Wang and S. Ding, *Commun. Chem.*, 2019, **2**, 4–11.
- 323 F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581–584.
- 324 S. Kumarn, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2006, 3211–3213.
- 325 H. Lin, Y. Tan, X. W. Sun and G. Q. Lin, *Org. Lett.*, 2012, **14**, 3818–3821.
- 326 M. Zhang, X. Di, M. Zhang and J. Zhang, *Chinese J. Chem.*, 2018, **36**, 519–525.
- 327 T. Koreeda, T. Kochi and F. Kakiuchi, *J. Organomet. Chem.*, 2013, **741–742**, 148–152.
- 328 J. Tönnemann, J. Risse, Z. Grote, R. Scopelliti and K. Severin, *Eur. J. Inorg. Chem.*, 2013, 4558–4562.
- 329 I. Giménez-Nueno, J. Guasch, I. Funes-Ardoiz, F. Maseras, M. I. Matheu, S. Castellón and Y. Díaz, *Chem. - Eur. J.*, 2019, **25**, 12628–12635.
- 330 N. Yasukawa, H. Yokoyama, M. Masuda, Y. Monguchi, H. Sajiki and Y. Sawama, *Green Chem.*, 2018, **20**, 1213–1217.
- 331 K. Duvvuri, K. R. Dewese, M. M. Parsutkar, S. M. Jing, M. M. Mehta, J. C. Gallucci and T. V. RajanBabu, *J. Am. Chem. Soc.*, 2019, **141**, 7365–7375.
- 332 R. A. Fernandes, P. Kumar, A. Bhowmik and D. A. Gorge, *Org. Lett.*, 2022, **24**, 3435–3439.
- 333 E. S. Krijnen, H. Zuilhof and G. Lodder, *J. Org. Chem.*, 1994, **59**, 8139–8150.
- 334 A. Schöffmann, L. Wimmer, D. Goldmann, S. Khom, J. Hintersteiner, I. Baburin, T. Schwarz, M. Hintersteiner, P. Pakfeifer, M. Oufir, M. Hamburger, T. Erker, G. F. Ecker, M. D. Mihovilovic and S. Hering, *J. Med. Chem.*, 2014, **57**, 5602–5619.
- 335 A. Krasovskiy, A. Tishkov, V. del Amo, H. Mayr and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 5010–5014.
- 336 D. A. Fletcher, B. G. Gowenlock and K. G. Orrell, *J. Chem. Soc. Perkin Trans. 2*, 1997, 2201–2205.
- 337 C. Kohlmeyer, M. Klüppel and G. Hilt, *J. Org. Chem.*, 2018, **83**, 3915–3920.

References

- 338 S. Fountoulaki, P. L. Gkizis, T. S. Symeonidis, E. Kaminioti, A. Karina, I. Tamiolakis, G. S. Armatas and I. N. Lykakis, *Adv. Synth. Catal.*, 2016, **358**, 1500–1508.
- 339 S. Murru and R. S. Srivastava, *Eur. J. Org. Chem.*, 2014, 2174–2181.
- 340 O. Wichterle and S. Svastal, *Collect. Czechoslov. Chem. Commun.*, 1951, **16**, 33–41.
- 341 A. Maquestiau, Y. Van Haverbeke, R. Flammang and C. De Meyer, *Bull. des Chim. Belges*, 1974, **83**, 139–146.
- 342 J. Roth-Barton and J. M. White, *Aust. J. Chem.*, 2009, **62**, 1695–1698.
- 343 S. Kumarn, A. J. Oelke, D. M. Shaw, D. A. Longbottom and S. V. Ley, *Org. Biomol. Chem.*, 2007, **5**, 2678–2689.
- 344 C.-M. Ting, Y.-L. Hsu and R.-S. Liu, *Chem. Commun.*, 2012, **48**, 6577–6579.
- 345 F. Ragaini, S. Cenini, D. Brignoli, M. Gasperini and E. Gallo, *J. Org. Chem.*, 2003, **68**, 460–466.
- 346 K. F. McClure and S. J. Danishefsky, *J. Org. Chem.*, 1991, **56**, 850–853.
- 347 A. Defoin, M. Joubert, J.-M. Heuchel, C. Strehler and J. Streith, *Synthesis*, 2000, 1719–1726.
- 348 P. D. Brown and A. L. Lawrence, *Angew. Chem. Int. Ed.*, 2016, **55**, 8421–8425.
- 349 R. Lukeš and J. Trojánek, *Collect. Czechoslov. Chem. Commun.*, 1957, **22**, 569–574.
- 350 K. Aizawa, H. Nakagawa, K. Matsuo, K. Kawai, N. Ieda, T. Suzuki and N. Miyata, *Bioorganic Med. Chem. Lett.*, 2013, **23**, 2340–2343.
- 351 M. Fujimoto and M. Sakai, *Chem. Pharm. Bull.*, 1965, **13**, 248–252.
- 352 S.-M. Yang, B. Lagu and L. J. Wilson, *J. Org. Chem.*, 2007, **72**, 8123–8126.
- 353 M. L. Canle, W. Clegg, I. Demirtas, M. R. J. Elsegood, J. Haider, H. Maskill and P. C. Miatt, *J. Chem. Soc. Perkin Trans. 2*, 2001, 1742–1747.
- 354 J. B. Shaum, D. J. Fisher, M. M. Sroda, L. Limon and J. Read de Alaniz, *Chem. Sci.*, 2018, **9**, 8748–8752.
- 355 C. Degrand, P.-L. Compagnon, G. Belot and D. Jacquin, *J. Org. Chem.*, 1980, **45**, 1189–1196.
- 356 Y. Becker, A. Eisenstadt and Y. Shvo, *Tetrahedron*, 1978, **34**, 799–806.
- 357 C. Boga, F. Manescalchi and D. Savoia, *Tetrahedron*, 1994, **50**, 4709–4722.
- 358 M. Periasamy, M. Seenivasaperumal and V. D. Rao, *Synthesis*, 2003, 2507–2510.
- 359 B. Y. Park, M. T. Pirnot and S. L. Buchwald, *J. Org. Chem.*, 2020, **85**, 3234–3244.
- 360 L. R. E. Pantaine, J. A. Milligan, J. K. Matsui, C. B. Kelly and G. A. Molander, *Org. Lett.*, 2019, **21**, 2317–2321.
- 361 A. Defoin, G. Geffroy, D. Le Nouen, D. Spileers and J. Streith, *Helv. Chim. Acta*, 1989, **72**, 1199–1215.
- 362 H. Shimasaki, H. Kagechika, H. Fukasawa, E. Kawachi and K. Shudo, *Chem. Pharm. Bull.*, 1995, **43**, 100–107.
- 363 Y. Huang, M. Fañanás-Mastral, A. J. Minnaard and B. L. Feringa, *Chem. Commun.*, 2013, **49**, 3309–3311.
- 364 E. B. Bates, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1954, 1854–1860.

References

- 365 N. Yoshikai, A. Mieczkowski, A. Matsumoto, L. Ilies and E. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 5568–5569.
- 366 J. Hermeke, M. Mewald and M. Oestreich, *J. Am. Chem. Soc.*, 2013, **135**, 17537–17546.
- 367 S. Ichikawa, S. Zhu and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2018, **57**, 8714–8718.
- 368 J. A. Buonomo, C. G. Eiden and C. C. Aldrich, *Synthesis*, 2018, **50**, 278–281.
- 369 D. C. Lenstra, J. J. Wolf and J. Mecinović, *J. Org. Chem.*, 2019, **84**, 6536–6545.
- 370 C. Gerdes, W. Saak, D. Haase and T. Müller, *J. Am. Chem. Soc.*, 2013, **135**, 10353–10361.
- 371 O. Mallow, M. A. Khanfar, M. Malischewski, P. Finke, M. Hesse, E. Lork, T. Augenstein, F. Breher, J. R. Harmer, N. V. Vasilieva, A. Zibarev, A. S. Bogomyakov, K. Seppelt and J. Beckmann, *Chem. Sci.*, 2015, **6**, 497–504.