

The Versatile Chemistry of Azidoalkyl Enol Ethers and their Equivalents

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“Do not ask for a lighter load, but rather a stronger back” – Unknown

Abstract

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This thesis describes the synthesis and intramolecular cycloaddition products of azides tethered to olefins bearing a heteroatom in an attempt to access a proposed triazolium intermediate **77**.

Chapter 1 covers the synthesis and reactivity of simple di- and trisubstituted azidoalkyl enol ethers. These substrates were found to provide isolable 1,2,3-triazoline products, but displayed a propensity to aromatise to 1,2,3-triazoles upon ionisation. Difficulties in synthesising fully-substituted azidoalkyl enol ethers have precluded a detailed study in this project, though a bias towards α-alkoxy imine formation was suggested.

Chapter 2 covers the chemistry of azidoalkyl vinyl bromides. Simple vinyl bromide substrates were found to yield 1-azadienes upon thermolysis, presumably *via* the dehydrobromination of an α-bromo imine intermediate *in situ*.

In Chapter 3, a brief diversity-oriented synthesis (DOS) campaign was undertaken to demonstrate the potent reactivity of 1-azadiene substrates. 1-Azadienes were found to be versatile intermediates, and a small DOS library was built by exploiting several key reactivity modes.

In Chapter 4, two miscellaneous routes towards the desired triazolium intermediate are discussed, and finally an Appendix chapter deals with an attempted total synthesis of salinosporamide C.

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I would also like to thank the Eli Lilly and the EPSRC for their generous support of this work.

Abbreviations

°	degrees
Å	ångström, 10^{-10} m
ACD	Advanced Chemistry Development, Inc.
Ac	acetyl
AIBN	azobisisobutyronitrile
ATMM	azatrimethylenemethane
aq	aqueous
BMDA	bromomagnesium diisopropylamine
Bn	benzyl
BrettPhos	a commercially available generation 1 Buchwald pre-catalyst (structure in Scheme 116)
BRSM	based on recovered starting material
BSA	(bistrimethylsilyl)acetamide
Bu	butyl
°C	degrees Celsius
cat.	catalytic amount, catalyst
CI	chemical ionisation
CIPE	complexity-induced proximity effect
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CuAAC	copper(I)-catalysed azide-alkyne cycloaddition
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOS	diversity-oriented synthesis
DPPA	diphenyl phosphoryl azide
d.r.	diastereomeric ratio
eq.	equivalent
ESI	electrospray ionisation
Et	ethyl
et al.	and others
EVE	ethyl vinyl ether
FETFE	fluoroelastomer with tetrafluoroethylene additives
FI	field ionisation
FMO	frontier molecular orbital
g	gram
GC	gas chromatography
h	hour
hal	halogen
HMBC	heteronuclear multiple-bond correlation
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high-resolution mass-spectrometry
HSAB	hard/soft acid base
HSQC	heteronuclear single-quantum coherence
hν	(ultraviolet) irradiation
Hz	hertz
i-	iso-
IAOV	intramolecular azide-olefin cycloaddition
IAVBC	intramolecular azide-vinyl bromide cycloaddition
in situ	in place
in vitro	in glass
in vivo	within the living
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry

J	coupling constant
JC	Johnson–Claisen
KHMDS	potassium *bis*-(trimethylsilyl)amide
L	litre
LCMS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LHMDS	lithium *bis*-(trimethylsilyl)amide
lit.	literature value
LUMO	lowest unoccupied molecular orbital
M	mole/litre
m/z	mass/charge ratio
Me	methyl
mg	milligram
MHz	megahertz
min	minutes
mL	millilitre
mmol	millimole
mol	mole
M.p.	melting point
MS	mass spectrometry
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PMDTA	*N*,*N*,*N*′,*N*′,*N*′′-pentamethyldiethylenetriamine
ppm	parts-per-million
Pr	propyl
p-TSA	4-toluenesulfonic acid
PTFE	polytetrafluoroethylene
pyr	pyridine
RBF	round-bottom flask
R_f	retention factor

rt	room temperature
RuAAC	rhuthenium(II)-catalysed azide-alkyne cycloaddition
RuPhos	a commercially available generation 2 Buchwald pre-catalyst
s-	sec-
sat.	saturated
SM	starting material
SPhos	a commercially available generation 2 Buchwald pre-catalyst
t-	tertiary-
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCNE	tetracyanoethylene
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UV	ultraviolet
µW	microwave irradiation
vice versa	with position turned
vide infra	see below
vide supra	see above
vs.	versus
v/v	volume-to-volume ratio
w/w	weight-to-weight ratio
XPhos	a commercially available generation 2 Buchwald pre-catalyst (structure in Scheme 114)

1 Introduction

This introduction will review the synthesis of nitrogen-containing heterocycles, focusing on organic azides as the nitrogen source. After a brief overview of azide reactivity, attention will shift to the 1,3-dipolar cycloadditions of organic azides onto alkyne, allene and alkene dipolarophiles. This will lead into previous work from the Robertson group, and conclude with the aims of this research project.

1.1 Nitrogen-containing heterocycles: an overview

Nitrogen-containing heterocycles are one of the most prevalent and ubiquitous classes of compounds found within the field of organic chemistry. These heterocycles are essential for our existence,[1,2] with many of the molecules of life including DNA,[3–6] haemoglobin,[7,8] alkaloids,[9,10] and countless naturally derived products embedding nitrogen atoms within their cyclic frameworks.

It is not surprising that natural or Nature-inspired molecules are often the starting point for identifying bio-active compounds, yet almost all fully synthetic drugs contain a heterocyclic motif.[11] Over 50% of all known organic chemicals[11,12] and over 90% of new drugs[12] contain a heterocyclic unit, with small molecule nitrogen-containing heterocycles accounting for *ca.* 43% of the top 200 selling US pharmaceuticals in 2012.[13]

Beyond pharmaceuticals, agrochemicals,[14] and materials science, nitrogen-containing heterocycles find extensive use in chemical methodology as bases,[15] ligands,[16,17] organocatalysts,[18–20] and as targets within total synthesis.[21–23]

Clearly the importance of nitrogen-containing heterocycles cannot be overstated, and their synthesis continues to be a central area of study. The field is constantly striving for new methods of constructing these essential building blocks and, since the rise of sp^2–sp^2 cross-coupling reactions, methodology relating to non-aromatic nitrogen-

containing heterocycles is of paramount importance.[24–26] One incredibly versatile nitrogen source is that of organic azides (hereafter "azides"), and their application towards the synthesis of nitrogen-containing heterocycles is described below.

1.2 Azide chemistry: history, synthesis, and selected reactivity

The first published account of azide chemistry appeared in 1864 with the discovery of phenyl azide by Griess[27] and continued with the eponymous rearrangement by Curtius in 1890.[28] In the 150 years since, the field has exploded metaphorically speaking, with azides adopting a key role in chemistry, medicine, materials science, and the interfaces between.[29–35]

Organic azides, R–N_3, can be represented by several polar mesomeric forms (Figure 1). The central nitrogen holds a formal positive charge, while the negative charge is shared between the two end nitrogens. The R–N–N_2 and RN–N–N bond angles are on average ~115.2 ° and ~172.5 ° respectively (calculated for methylazide[36]) giving an essentially linear structure with sp^2 hybridisation at the internal nitrogen.

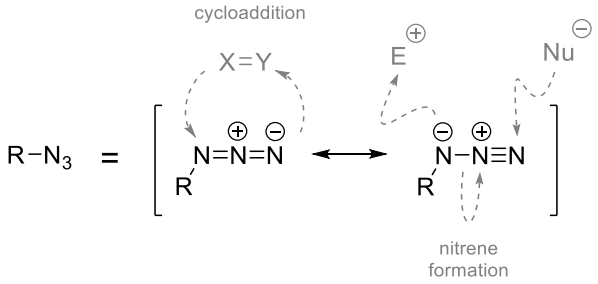


Figure 1: Azide structure, major contributing resonance forms, and general reactivity.

Alkyl azides are most conveniently prepared through S_N2 displacement of a suitable leaving group with an anionic azide ion source, which is commonly NaN_3 (Figure 2).[30] The linear structure of this anion, and ability to distribute the counterion solvation sphere towards the rear of the molecule, allows it to circumvent steric hindrance.[37]

Additional methods of synthesis include Mitsunobu[38–40] or Appel[41] type transformations from alcohols, 1,4 addition of N_3^- to activated unsaturated bonds,[42,43] and 1,2-addition of XN_3 across non-activated unsaturated bonds.[44–46] In 2014, Hartwig reported an iron–catalysed azidation of tertiary C–H bonds which is suitable for late-stage functionalization.[47] Acyl azides, most famous for their Curtius rearrangement chemistry, are derived from carboxylic acids[48,49] or their derivatives.[50] For aryl azide synthesis, both diazonium salt chemistry[51,52] and S_NAr reactions[53–55] have proven successful. A variety of methods are depicted in Figure 2.

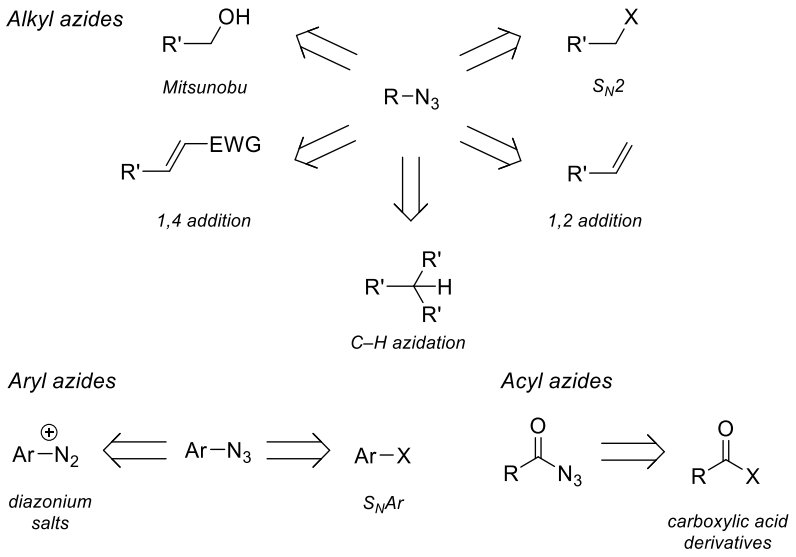
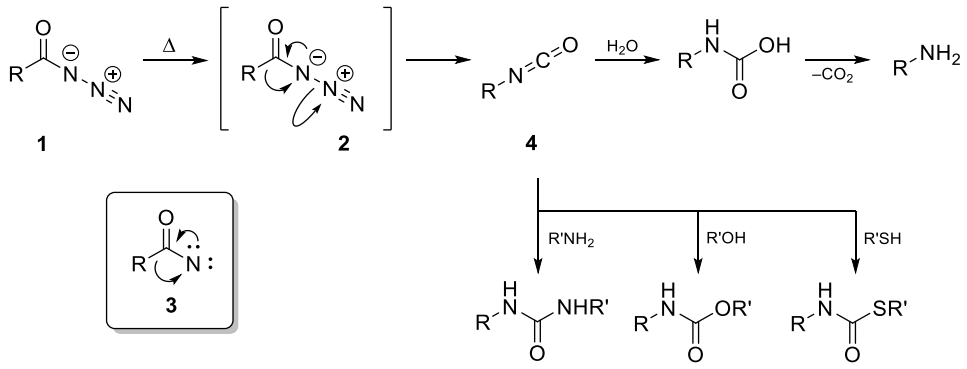


Figure 2: Example starting materials for azide synthesis.

The diverse reactivity of azides is summarised in the many excellent reviews of the subject.[29–35] Here, discussion is confined to relevant highlights. The varied reactivity of azides can be inferred from the functional groups major contributing resonance forms (Figure 1). In general, azides react with electrophiles at the internal nitrogen and nucleophiles at the terminal nitrogen. Additionally, azides serve as convenient nitrene or nitrenoid precursors due to their ease of introduction, and cleavage of the $N–N_2$ bond to liberate nitrogen gas, the release of which is often the driving force of azide reactions.

The Curtius rearrangement is a classical reaction for the synthesis of isocyanates and amine derivatives *via* the decomposition of acyl azides **1** (Scheme 1).[28,56] The thermal rearrangement can be explained as a concerted process **2** with no true nitrene intermediate **3** (Scheme 1).[57–59] Typically, thermolysis of an acyl azide in an inert solvent leads to cleavage of the RC(O)N–N_2 bond, with alkyl group C to N migration, and entropically favourable release of nitrogen gas to provide the isocyanate **4**. The reaction may proceed under purely thermal conditions or may be catalysed by either Lewis or Brønsted acids. While the thermal Curtius rearrangement is generally believed to be a concerted process, the photochemical alternative may well proceed *via* a discrete nitrene intermediate **3**. This can lead to side products resulting from nitrene-trapping reactions (typically C–H insertion).[29,60]



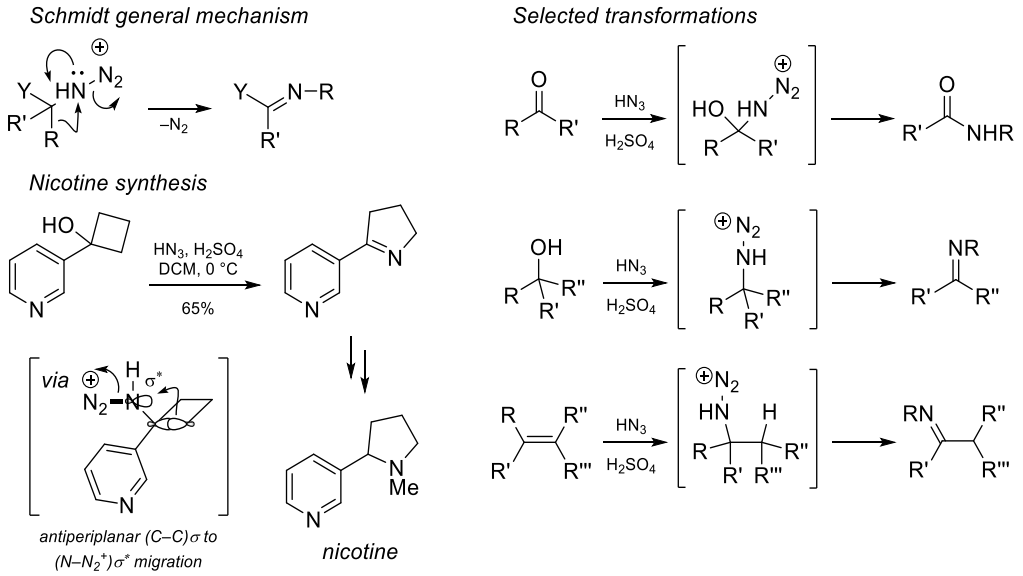
Scheme 1: Curtius rearrangement, mechanism, and derivatives.

The classical Curtius reaction achieves the replacement of a carboxyl group with an amino group. When formed in the presence of water, the isocyanate is trapped to form a carbamic acid that decarboxylates to yield a primary amine (Scheme 1).[61] Although the isocyanate can be isolated, in modern usage the intermediate is typically intercepted with nucleophiles to yield amines as above,[62] as well as ureas,[63] thiocarbamates,[64] and carbamates. For example, Curtius rearrangements performed in the presence of *tert*-butyl or benzyl alcohol provide Boc[65] and Cbz[66] protected amines

respectively. The Curtius rearrangement has found extensive use in total synthesis for the formation of nitrogen-containing heterocycles,[67–69] including Robertson's 2011 synthesis of NP25302.[70]

Closely related to the Curtius rearrangement are both the Schmidt reaction[29,30,61,71] and Aubé's extensions[72–74] (with credit to Boyer[75,76]) using alkyl azides. The Schmidt reaction is an all-encompassing term for the reaction of azide in mineral acid with carbocations or carbonyl compounds to provide amines and their derivatives (Scheme 2). The azide is typically generated *in situ* through protonation of a suitable XN_3 surrogate (commonly NaN_3). A Schmidt rearrangement may also be used more generally to describe any transformation that involves the C to N alkyl migration of an R group (with the R group antiperiplanar to the leaving N_2) and the liberation of nitrogen gas. As with the Curtius rearrangement, the loss of nitrogen provides a powerful driving force, making the reaction irreversible.

While the classical Schmidt reaction of carboxylic acids follows a similar mechanism to the more frequently used Curtius rearrangement (albeit with protonated intermediates) to provide amines, the reaction can also use pro-electrophiles such as ketones,[77,78] alkenes,[77,79] and alcohols.[77,80] The reaction of ketones proceeds with formal insertion of nitrogen between the RC(O)–R bond to provide amides, while both alkenes and alcohols can give rise to imines, which are either isolated, tautomerised, or hydrolysed. Aldehydes may also provide nitriles as well as formamides during Schmidt rearrangement. A plausible mechanism for the Schmidt reaction is shown in Scheme 2, along with general examples and a synthetic application *en route* to nicotine.[81]

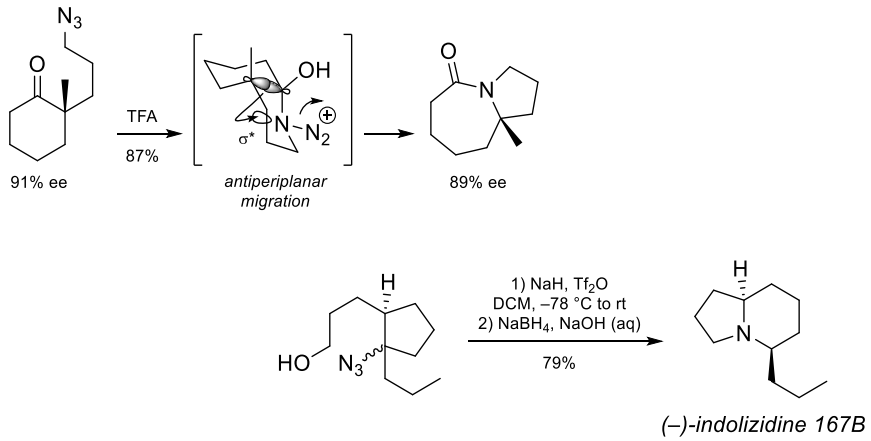


Scheme 2: The Schmidt reaction: mechanism and examples.

Conceptually, alkyl azides can react with electrophiles to provide rearrangement products in a Schmidt-style process. Despite the superficial similarities between HN_3 and RN_3, early attempts in this field met with failure.[82] Boyer had limited success with the rearrangement of alkyl azides and aromatic aldehydes in the 1950s,[75,76] but it was Aubé in the 1990s who harnessed the synthetic utility of the azidoalkyl Schmidt reaction as a method of producing diverse nitrogen-containing heterocycles (Scheme 3).

Aubé first reported the intramolecular variant of the Schmidt reaction in 1991,[73] which has since become a convenient means for the production of polycyclic ring systems with nitrogen at the ring fusion. By tethering the alkyl azide to a pro-electrophile, the benefit of intramolecularity allows this reaction to occur with either Lewis or Brønsted acid activation, under remarkably mild conditions with high selectivity.[77,83–86] The intramolecular Schmidt reaction is broad in scope, generally high yielding, and proceeds with retention of stereochemistry. Perhaps the greatest restriction is that the azide and electrophile must be linked by a 4–5 carbon tether to achieve high yields, but this is compensated by a high tolerance of ketone ring size (4–12).[87] Azidoalkyl Schmidt reactions have found extensive use in total synthesis,[88–93] and

the intramolecular Schmidt,[87] along with a key step from the total synthesis of (–)-indolizidine 167B[89] are shown in Scheme 3. The total synthesis features a non-acidic variation of the Schmidt reaction, whereby the primary alcohol is converted to an excellent leaving group that promptes intramolecular azide attack.

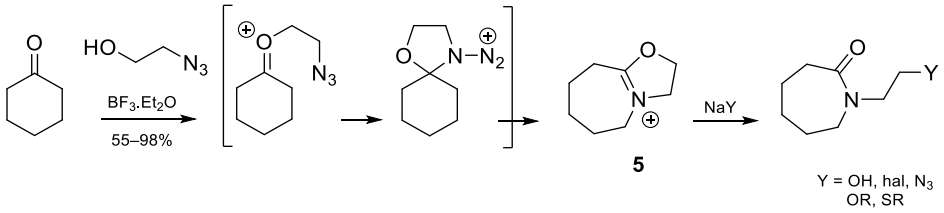


Scheme 3: The intramolecular Schmidt,[87] and the total synthesis of (–)-indolizidine 167B.[89]

While the intramolecular azidoalkyl Schmidt reaction is highly applicable, the intermolecular variant suffers from many drawbacks. The known examples are often poorly site selective, poor yielding, and highly limited by steric hindrance and ring size (with 5-membered ketones being especially problematic). Thus the methodology is only synthetically useful for a fairly restricted set of compounds, requiring strong pre-activation of the electrophile with Lewis acids to encourage nucleophilic azide attack.[74,94] This is likely due to the relative weak nucleophilicity of alkyl azides compared to the free azide. Alkyl substitution may encumber the slender shape of N_3^- (*vide supra*), while the strong acid activation required risks decomposition of the azide along with self-condensation of the electrophile prior to attack.

The problem of intermolecularity can be addressed by using hydroxyalkyl azides, which achieve a tethered intermediate to effect a formal Schmidt rearrangement with ketones (Scheme 4). Dubbed the "Boyer reaction" by Aubé in honour of its initial

discovery,[75] 1,2- or 1,3-hydroxyalkyl azides were found to react with aldehydes under acidic conditions to afford oxonium ions, which were readily intercepted by the tethered azide to form an azidohydrin derivative. This can rearrange with loss of nitrogen to produce oxazolines and dihydrooxazines. Aubé discovered that when ketones were used, the resulting iminium ether **5** could be opened with a nucleophile, most commonly OH^-, to yield amides.[72,77,95] In contrast to the intermolecular azidoalkyl Schmidt reaction with ketones, the range of ring-sizes tolerated by the Boyer reaction is broad (4–7), the yields high, and the reaction may even be performed asymmetrically.



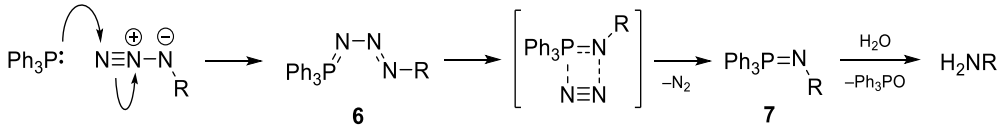
Scheme 4: The Boyer reaction.[96]

Both the Curtius and Schmidt rearrangements can yield primary amines either by rearrangement of carboxylic acid derivatives or the hydrolysis of ketone-derived amides. Complementary to this, azides themselves are often employed as primary amine surrogates in synthesis due to their stereo- and regioselective introduction and reduction. There are numerous methods of azide reduction available,[29,30] several of which are discussed below.

Pending compatible functional groups, azides can be readily reduced by catalytic hydrogenation over Pt, Pd, or Ni, often in excellent yields.[97] The reduction is presumed to proceed *via* a triazene intermediate, $RN{=}N{-}NH_2$.[98] Additionally, one may use classical hydride reducing agents such as $LiAlH_4$[99] and $NaBH_4$,[100,101] though more exotic borohydride reagents[102–105] and borane reducing agents[106] can show improved reactivity and selectivity. There are many metals and metal complexes that can effect

azide reduction by electron transfer processes, including but not limited to Sm^{2+},[107] In^{3+},[108] Fe^{2+},[109] and Zn^{0}.[110]

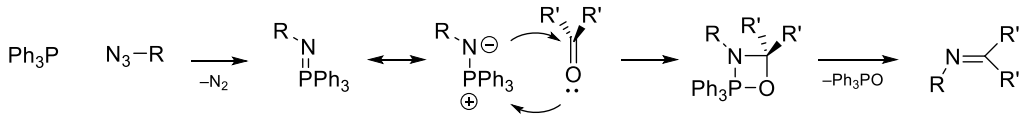
The reduction of azides using phosphines (most often triphenylphosphine) to primary amines, the Staudinger reduction, is one of the mildest and most chemoselective reactions available for this transformation (Scheme 5). First discovered in 1919, by Herman Staudinger,[111] the reaction exploits the electrophilicity of alkyl azides at the terminal nitrogen, Figure 1. The reaction can be broken down into two phases; first, nucleophilic attack of the phosphorus onto the terminal nitrogen to form a phosphazide adduct **6**. This adduct decomposes *via* a four-membered ring transition state with entropically favourable loss of nitrogen to yield an iminophosphorane **7**.[112] Second, hydrolysis of this phosphorane provides the primary amine and corresponding phosphine oxide, the driving force being the formation of a strong oxygen-phosphorus double bond (Scheme 5). The Staudinger reaction has been the reduction of choice in numerous total syntheses of nitrogen-containing heterocycles because of its mild nature,[113–115] although the downside is of course the stoichiometric production of triphenylphosphine oxide, an atom-inefficient by-product.



Scheme 5: The Staudinger reduction.[111]

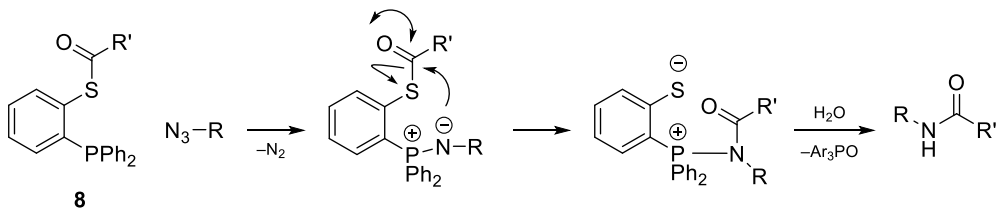
The iminophosphorane produced in the Staudinger reduction is itself a useful and isolable intermediate and is classified as a superbase due to the highly electron-rich nitrogen.[116] Azide-derived iminophosphoranes react with aldehydes, ketones, and even carboxylic acid derivatives to produce imines in a process known as the aza-Wittig reaction (Scheme 6).[117] The intramolecular variation of this transformation is of

particular merit for the formation of nitrogen heterocycles and is a key step in many total syntheses for this reason.[118–120]



Scheme 6: The aza-Wittig reacton.[117]

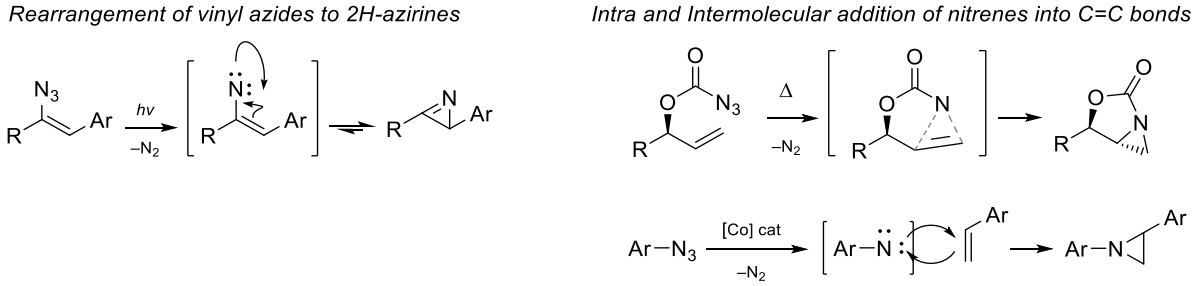
Another reaction that exploits the iminophosphorane intermediate is the Staudinger ligation, a highly selective method for the preparation of bioconjugates.[121] Azides are described as bioorthogonal as they are absent in almost all naturally occurring compounds and can react selectively within living organisms without interfering with native biochemical processes. Exploiting the room temperature reaction between an azide and a phosphine featuring an acyl trap in close proximity **8**, the resulting iminophosphorane can react intramolecularly to form a stable amide bond, outcompeting hydrolysis even within the aqueous environment of a human cell (Scheme 7). The Staudinger ligation has been described as a gift to biology;[122] by tethering an ester-appended phosphine to a biological anchor, the ligation reaction can allow the linkage of carbohydrates, peptides, probes, and numerous other functionalities to cells within living systems. Though initially retaining a phosphine oxide within the link, the process has evolved to a "traceless" ligation whereby the phosphine is cleaved during the amide forming process.[123]



8

Scheme 7: The traceless Staudinger ligation.[123]

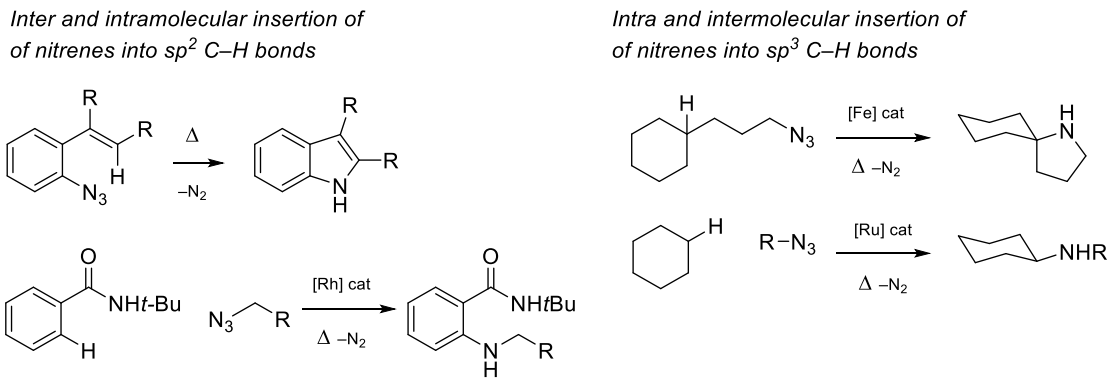
Azides may decompose with loss of nitrogen to form nitrenes that can react in modes analogous to carbenes by inserting into both π- and σ-bonds, often as a means to construct nitrogen-containing heterocycles. Consider, to start, an example where the azide and π-bond are in the closest proximity: the rearrangement of vinyl azides into 2*H*-azirines (Scheme 8). 2*H*-Azirines are highly strained cyclic imines that find extensive use as reactive intermediates within synthesis, including the Neber rearrangement to α-amino ketones.[124] Vinyl azides can be decomposed thermally or photolytically to vinyl nitrenes, which undergo a (reversible) insertion/rearrangement to yield the 2*H*-azirine which then often reacts further *in situ*.[125–128] While vinyl azides rearrange to form an unsaturated ring, azide-derived nitrenes may also insert into remote C=C π-bonds as a means to construct saturated aziridine systems. This insertion may occur in an intra-[129] or intermolecular fashion,[130] under photolytic,[131] thermal,[129] or metal-catalysed conditions (Scheme 8).[132]



Scheme 8: Addition of azide-derived nitrenes and nitrenoids into π-bonds.[128–130]

Perhaps the most remarkable reaction of azide-derived nitrenes is the ability to insert into both sp^2 and sp^3 C–H σ-bonds. The selective conversion of C–H bonds to C–N bonds represents a landmark in organic synthesis, effectively streamlining the construction of nitrogenous targets and eliminating the need for divergent pre-functionalisation of substrates.[31,133,134] Thanks to the chemistry of alkyl azides, the synthetic community is moving closer towards reaching this goal. *Ortho*-aryl or alkenyl

aryl azides can rearrange to indoles *via* a formal intramolecular sp^2 C–H insertion, otherwise known as the Sundberg cyclisaton (Scheme 9).[135,136] With the aid of a suitable directing group, the direct intermolecular C–H amination of arenes using alkyl azides has been reported under rhodium catalysis.[137] Moving from sp^2 to sp^3 centres, the task becomes even greater, as the large number and inert nature of aliphatic C–H bonds renders both selectivity and reactivity very challenging, especially in the presence of more labile functionalities. In 2013, Betley and Hennessy reported the iron-catalyzed direct amination of both activated and unactivated C–H bonds, relying on the azide tether length to dictate regioselectivity and even reporting high ee's for asymmetric cases.[134,138] Even without the benefit of intramolecularity, chemists have begun to utilise the intermolecular amination of unactivated sp^3 C–H bonds, with[139] and without[140,141] directing groups by exploiting the high reactivity of metallo-azido adducts. Though the field is in its infancy, methodology such as this would allow the late-stage functionalisation of hydrocarbon skeletons as a biomimetic strategy in total synthesis. The amination of sp^2,[135–137] and sp^3 C–H bonds[138,140] are demonstrated in Scheme 9.



Scheme 9: Insertion of azide derived nitrenes and nitrenoids into σ-bonds.[135–138,140]

This discussion has omitted many classes of azide reactivity in the interest of clarity, and for more information one can consult the many reviews on the subject.[29–35] Arguably the most important application of azide chemistry is in 1,3-dipolar

cycloaddition with unsaturated hydrocarbons as a means to construct nitrogen-containing heterocycles. Three classes of this transformation are discussed in Section **1.3**.

1.3 Alkyl azide 1,3-dipolar cycloadditions: Pericyclic annulations with alkynes, allenes and alkenes

1.3.1 Alkyne-azide cycloadditions

In 2001 Sharpless introduced the term "click chemistry" to describe modular reactions of a certain calibre: those that are known to be highly practical, reliable, and applicable.[142] Taking inspiration from Nature, the principle of click chemistry is to rapidly explore chemical space by joining together small units (usually) through heteroatom linkages with the aim of identifying "drug-like" molecules. To make complex structures through a handful of simple processes parallels the strategy prevalent in biosynthesis. To qualify, would-be reactions must strive for near-perfection: be high-yielding, run with either no solvent or a benign solvent, and generate only inoffensive by-products that can be removed by methods other than chromatography.[143] In other words, components must simply *click* together regardless of how each piece is decorated, much like Velcro joining two straps. Click chemistry serves as a guiding principle in the quest for function over structure, and is restricted to molecules that are easy to make.

Reactions that attain the title of *near-perfection* usually possess a highly exothermic thermodynamic driving force (>20 kcal mol^{-1}) and are essentially spring-loaded to produce a single product. Reactions that reach this standard include the nucleophilic ring-opening of strained heterocycles (e.g. epoxides, aziridines), carbonyl chemistry of the non-aldol type (e.g. formation of hydrazones), addition reactions across

unsaturated bonds (e.g. dihydroxylation and thiol Michael additions), the Staudinger ligation (*vide supra*) and, most importantly, cycloadditions across unsaturated bonds by 1,3-dipolar species to produce 5-membered rings.[142–144] At the top of his list Sharpless placed the (3+2) Huisgen reaction between azides and terminal alkynes as the premier example of click chemistry (Figure 3).

Although the reaction between azides and acetylenes was discovered in the 1900s by Dimroth,[143] it was Huisgen in 1960s who developed the reaction that would come to bear his name.[144] The thermal Huisgen reaction unites azides with alkynes to yield 1,2,3-triazoles **9** in an exothermic reaction exceeding 45 kcal mol^{-1}.[147] Both azides and alkynes are easy to install, highly energetic, and are passive towards many functional groups yet possess an amazing mutual affinity. This means that both functionalities can be installed at a convenient synthetic point and remain untouched through numerous subsequent transformations. In addition, azides and alkynes are inert towards oxygen, biological molecules, and aqueous conditions within living cells. Thus the Huisgen reaction allows the modular linkage of two components in a high yielding, widely applicable reaction that is tolerant of functionality and generates no waste products. As the name suggests, the thermal Huisgen requires elevated temperatures to unite both components due to the kinetic stability of azides, and therefore the reaction can be quite sluggish, requiring several hours of heating to reach completion. The rate of reaction is often dependent on the nature of the alkyne, with strained internal, activated, or terminal alkynes reacting faster than unactivated and unstrained internal cases.

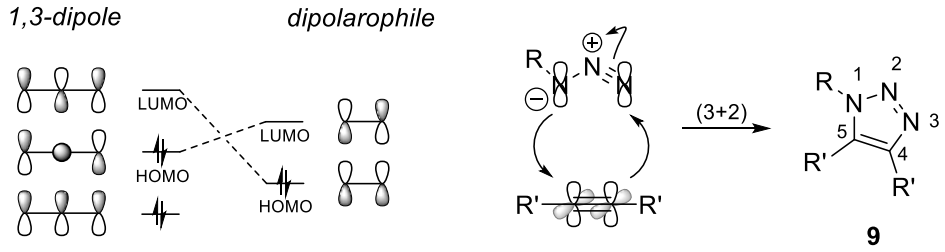


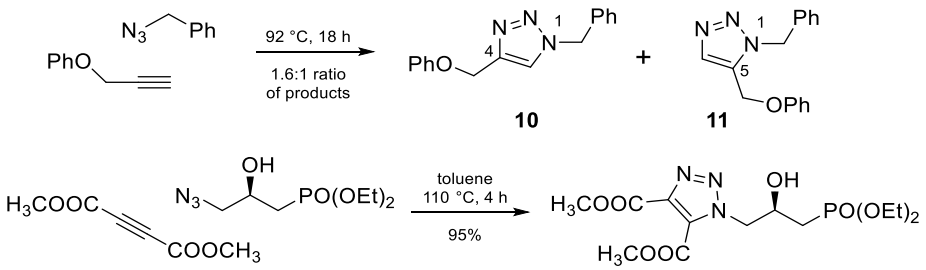
Figure 3: FMO interactions in azide-alkyne 1,3-dipolar cycloaddition.

As mentioned, azides participate in a 1,3-dipolar cycloaddition with alkynes to form 1,2,3-triazoles. A cycloaddition is a pericyclic reaction whereby two or more unsaturated molecules (or parts of the same molecule) combine to form a new cyclic molecule, in which there is a net reduction in bond multiplicity. In general, the bond-forming and bond-breaking processes happen in a synchronous, concerted fashion without intermediates or polar transition states, and thus the Huisgen reaction is not usually sensitive to solvent polarity.[148] Extremely polarised reagents may react in an asynchronous fashion however. The azide component is termed a dipole as it shares four electrons over three adjacent atoms with zwitterionic resonance states (*vida supra,* Figure 1). The alkyne is dubbed the dipolarophile, and offers two π-electrons towards the reaction. Hence a 1,3-dipolar cycloaddition to an unsaturated bond can be labelled (3+2) by counting atoms, and [4+2] by counting electrons.

A concerted pericyclic reaction can only proceed with the conservation of orbital symmetry as dictated by the Woodward and Hoffman rules[149,150] and in this regard a 1,3-dipolar cycloaddition is stereospecific [$\pi 2_s + \pi 4_s$] and allowed.[151] Frontier Molecular Orbital (FMO) theory dictates that for the reaction to take place, the HOMO and LUMO orbitals of the two species must interact constructively, which depends on the relative orbital energies and phases of the dipole and dipolarophile (Figure 3). Electron-withdrawing groups on the alkyne lower the dipolarophile LUMO energy and promote

an interaction with the HOMO of the azide.[152] Conversely, electron-donating groups on the dipolarophile favour the inverse of this interaction, bringing the alkyne HOMO closer in energy to the azide LUMO.[148,151] To interact with the π-orbitals of the alkyne, the rod-like azide must distort from linear in a bending process that requires little energy.[145] Figure 3 depicts the 1,3-dipolar cycloaddition of a bent azide to an alkyne, with curly arrows showing the flow of electrons initiating at the nucleophilic internal nitrogen. This is a mechanistic formalism, as it is meaningless to define the direction of electron flow in a concerted pericyclic process (though not in asynchronous cases).

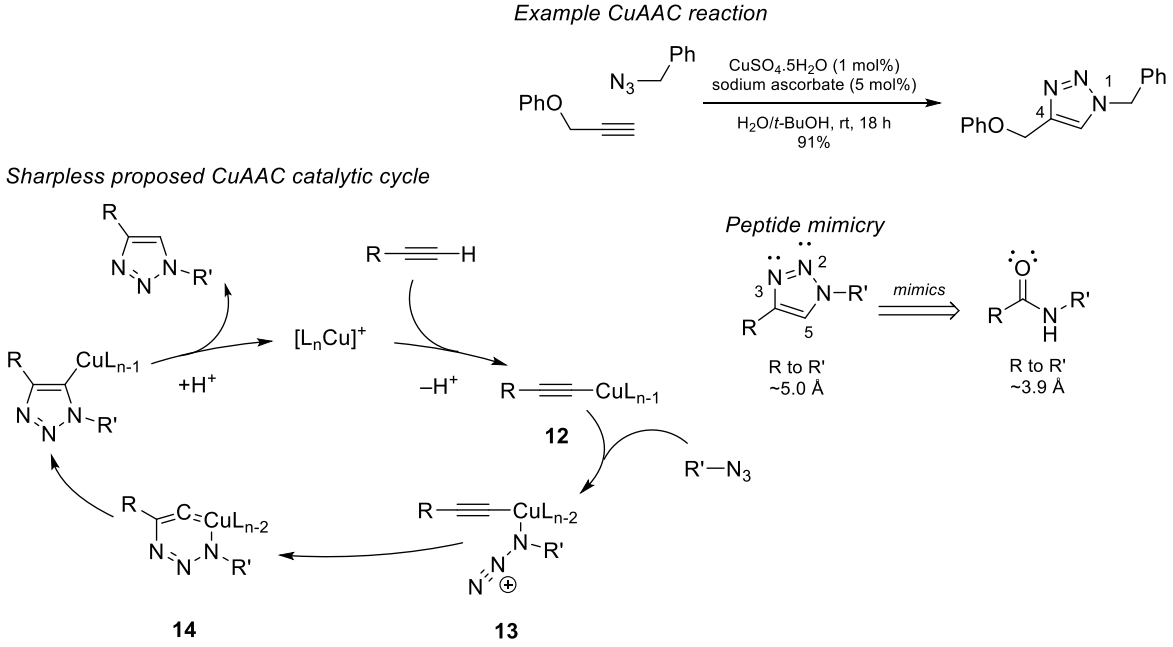
When using terminal alkynes, the 1,3-dipolar cycloaddition with azides can often produce a mixture of 1,4- **10** and 1,5-regioisomers **11** (Scheme 10),[153] though this can be biased with the use of electron withdrawing or donating groups on the acetylene component. Reactions otherwise tend to give ~1:1 mixtures of isomers and the problem of solving regioselectivity had met with little success at the turn of the millenium.[154–156] Likewise, if an internal alkyne is unsymmetrical the regioselectivity of the reaction can be poor.



Scheme 10: Example terminal[153] and symmetrical internal[157] alkyne-azide cycloadditions.

In 2002, the year following the coining of the term click chemistry, both Sharpless[153] and Meldal[158] independently reported the copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) which unites azides and terminal alkynes regiospecifically to produce 1,4-disubstituted 1,2,3-triazoles (Scheme 11). The regioselectivity comes from the copper-catalysed mechanism, which is no longer concerted.[159,160] In the presence of

a terminal alkyne, the Cu(I) coordinates to the triple bond π-orbital before metalloinsertion to form a Cu(I)-acetylide **12**. Ligand displacement *via* copper coordination of the azide may then occur forming either a monomeric Cu(I)-acetylide/azide complex **13**[159] or a dimeric Cu(I)-actetylide/Cu(I)-azide adduct.[160] Metallocyclisation **14**, followed by ring contraction to a Cu(I)-triazole, then protonolysis, regenerates the copper species and completes the catalytic cycle (Scheme 11). Thus metallocycle formation is a prerequisite for 1,4-selectivity (note the regioselectivity of the example in Scheme 11 compared to the uncatalysed version in Scheme 10).[153] However, as a terminal acetylene is key to the catalytic cycle, internal alkynes are not applicable to CuAAC conditions.[160]



Scheme 11: Plausible CuAAC mechanism,[159] illustrative reaction,[153] and peptide mimicry.[160]

The copper(I) source is often a copper(II)/reducing agent mix so as to circumvent oxygen sensitivity and lower the cost of catalyst,[153] though the reaction is so sensitive towards copper catalysis that even copper wire is sufficient to maintain the concentration of copper ions.[30] Remarkably, the CuAAC reaction increases the rate of cycloaddition by up to a factor of 10^7.[161] This eliminates the need for elevated

temperatures and allows the CuAAC reaction to be run under ambient conditions. Additionally, in compliance with "click" principles, the reaction excels in aqueous conditions, even if the reagents are insoluble in water.[153,162] This equates to a highly practical method, whose reaction protocol often involves stirring at ambient temperature and collecting product by filtration. With catalyst loadings in the range of 0.25–2%, a widely tolerated pH range (~4–12), temperature range (~0–160 °C), and unrivalled functional group tolerance that performs excellently in aqueous media, the CuAAC reaction has become synonymous with click chemistry and redefined the standard set for a "perfect" reaction.[159]

The so-formed 1,2,3-triazole unit is not found in Nature as it is difficult for biological systems to produce cyclic molecules containing three vicinal nitrogen atoms.[163] Regardless, a triazole is an aromatic nitrogen-containing heterocycle with favourable physiochemical properties. The structure is rigid, and metabolically stable. It cannot be cleaved hydrolytically under either acid or basic conditions, and is almost impossible to oxidise or reduce.[143] More than just a passive linker, 1,2,3-triazoles find use as amide surrogates in biochemistry, as their atom arrangement and electronic properties are similar to those of a peptide bond with the added bonus of superior chemical stability (Scheme 11). Despite superficial differences including an increase in R–R' distance by ~1.1 Å and a larger dipole moment, these alterations may enhance peptide mimicry by improving the hydrogen-bond capabilities of the linking unit.[160] Aside from both lone pairs on N2 and N3, the strong dipole may recruit the C5 proton to act as an H-bond donor analogous to the amide NH bond and, alongside π-stacking, allows 1,2,3-triazoles to readily interact with biological targets.

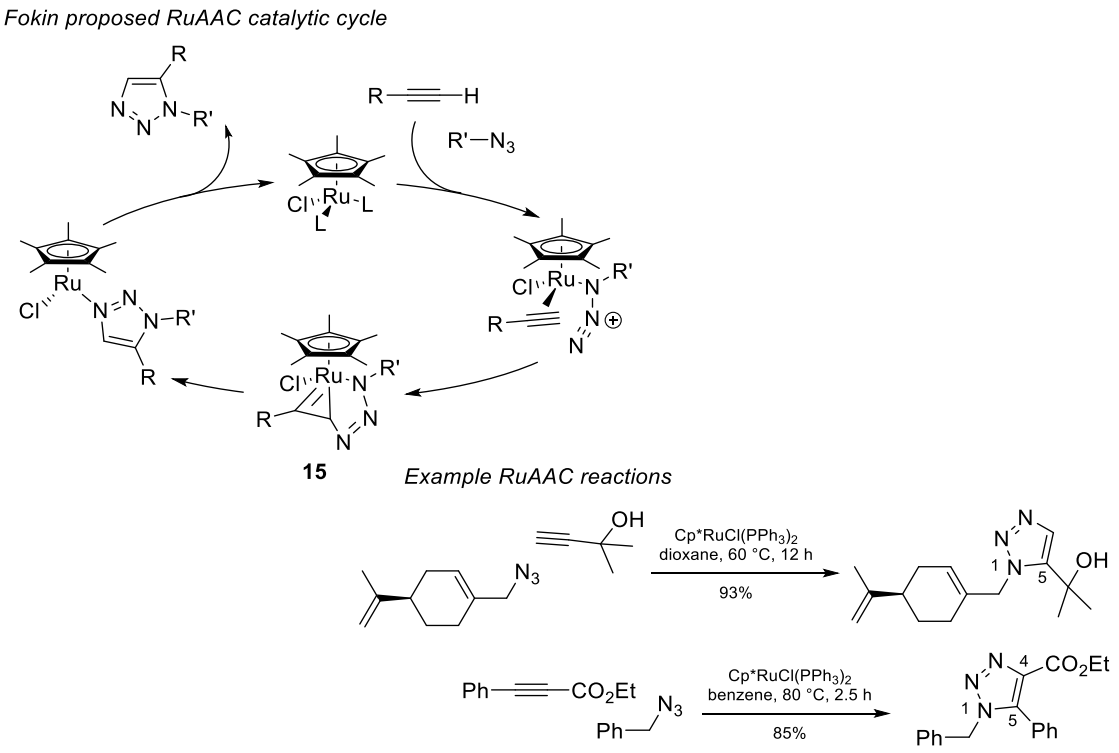
The 1,3-dipolar cycloaddition of azides and alkynes has found extensive use across fields spanning chemistry, biology, and materials science.[147,164] The CuAAC

reaction has been extensively used in drug discovery, allowing the rapid exploration of chemical space by the reliable linkage of modular units.[143,165,166] Thanks to click-based high-throughput screening and fragment-based discovery, triazole scaffolds are featured in numerous drug candidates, including antiviral, anti-HIV, antibiotic and antibacterial compounds.[165,166] The CuAAC reaction has also opened doors at the interface between chemistry and biology, in the field known as bioconjugation.[164] This powerful technique involves the covalent appendage of synthetic labels or structures to existing biomolecular frameworks both *in vitro* and *in vivo*, and is well suited to the CuAAC due to the reactions mild bioorthogonal properties.[165] As a result, key studies have been conducted on modified DNA, peptides, proteins and carbohydrates, allowing a unique insight into biological systems.[144,165,167] In addition, supramolecular chemistry,[168] polymers,[169] and nanomaterials[170] can be readily assembled, tuned, and functionalised, thanks to this most useful of reactions, allowing surface engineering and more.[164]

For 1,5-disubstituted 1,2,3-triazoles, there is a complementary catalytic method: the ruthenium(II)-catalysed azide-alkyne cycloaddition (RuAAC). In 2005, Fokin *et al.* reported that pentamethylcyclopentadienyl ruthenium chloride complexes [Cp*RuCl] catalyse the cycloaddition of azides onto terminal alkynes with 1,5-regioselectity (Scheme 12).[171,172] Unlike the CuAAC which requires terminal acetylenes, the RuAAC can be conducted on both terminal and internal alkynes, allowing the regioselective synthesis of 1,4,5-trisubstituted triazoles for the first time.[172–174] The catalytic process proceeds *via* a ruthenacycle intermediate **15** that controls the regiochemistry of the reaction (Scheme 12). Oxidative coupling of both azide and alkyne to the ruthenium centre forms a new C–N bond between the more electronegative/less sterically

demanding alkyne carbon and the terminal nitrogen of the azide. Reductive elimination regenerates the catalyst and releases the regio-enriched 1,2,3-triazole.[172,175]

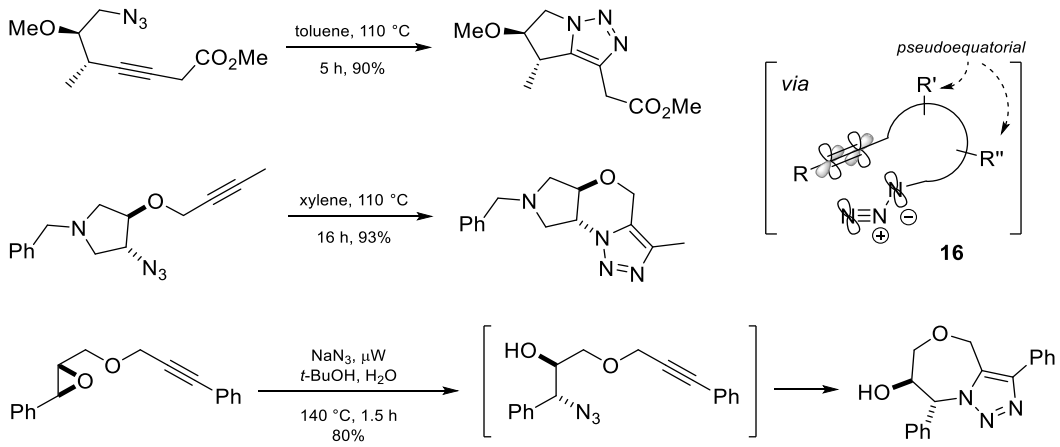
The RuAAC is not as versatile or applicable as the CuAAC and does not qualify for the moniker of click reaction. The reaction can require hours at elevated temperatures to reach completion and solvent choice is restricted to aprotic in order to attain regioselectivity and high conversion. Likewise, although the choice of alkyne substitution is broad, the steric effect of the azide has a considerable effect on reaction efficiency, with both aryl and tertiary azides being especially problematic.[171,172]



Scheme 12: Plausible RuAAC mechanism and illustrative reactions.[172,174]

Another way to direct regiochemistry in the 1,3-dipolar cycloaddition of azides to alkynes (and other dipolarophiles) is by performing the reaction intramolecularly. Intramolecular Huisgen reactions form two new rings in one sequence with a predictable substitution pattern on the triazole (Scheme 13). The azide to alkyne tether dictates how the two components will align for cycloaddition, improving regioselectivity

by virtue of the tether length. Thus there is a highly ordered bicyclic transition state, with substituents often adopting a pseudoequatorial disposition **16**. The rate-accelerating effect of intramolecularity combined with the regiospecificity eliminates the need for metal catalysis in many cases. Intramolecular Huisgen reactions are under-represented in the literature compared to their intermolecular counterparts, amounting to ~5% of the azide-alkyne publications (as of 2009).[176] This is perhaps an unfair representation, as the intramolecular variant is a powerful method for the construction of novel heterocycles.[176–184] Example intramolecular Huisgen reactions with 3, 4 and 5 atom tethers are shown in Scheme 13.[177,179,183]



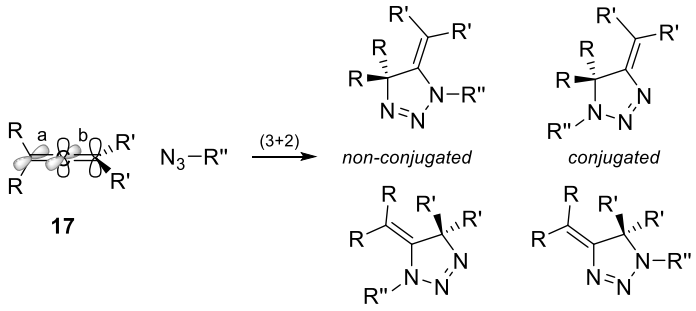
Scheme 13: Intramolecular Huisgen reactions.[177,179,183]

For the reliable formation of a stable linker, the alkyne-azide cycloaddition is a suitable reaction. For the creation of interesting structures and manifolds through cascade reactions, then there are two other azide coupling partners to consider, discussed below.

1.3.2 Allene-azide cycloadditions

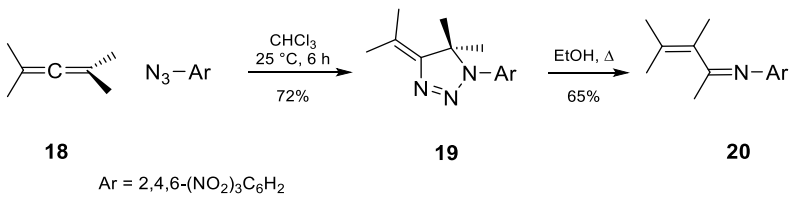
An allene is a cumulated diene that features two carbon–carbon double bonds attached to a single sp carbon centre: $R_2C{=}C{=}CR'_2$ **17** (Scheme 14). The bond angle across the three carbons is 180 °, giving a linear structure, with both R and R' substituent

planes being held at 90 ° to one another.[185] The presence of unsaturation allows allenes to act as dienophiles in (3+2) dipolar cycloadditions to form 1,2,3-triazolines.[186,187] As opposed to alkynes which offer two regioisomers, four possible regioisomers are available from the cycloaddition of allenes to azides; both conjugated and non-conjugated triazolines across the allene *a* bond or *b* bond (Scheme 14).



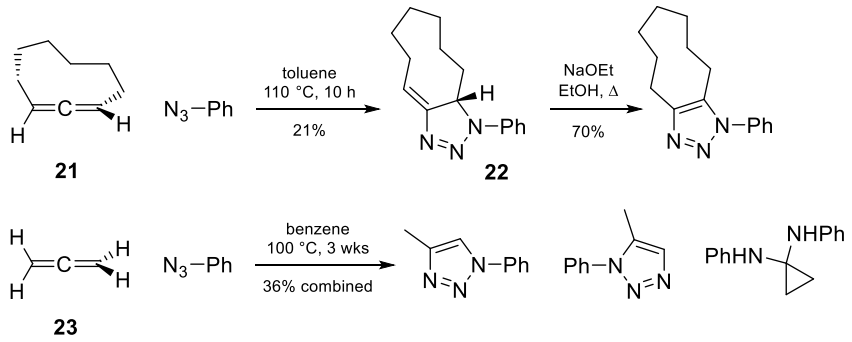
Scheme 14: Possible 1,2,3-triazoline regioisomers from allene-azide cycloaddition.

Bleiholder and Shechter reported the first allene-azide cycloaddition in 1968 through their reaction of tetramethylallene **18** with various azides (Scheme 15).[186] Stirring tetramethylallene with picryl azide at ambient temperature yielded the corresponding conjugated triazoline **19** as a red crystalline solid. Thermolysis of this compound gave 1-azadiene **20** through loss of nitrogen and methyl migration. Less electron poor aromatic azides such as *para*-nitrophenyl azide and phenyl azide required refluxing tetramethylallene (~87 °C) to yield their corresponding conjugated triazolines, which were thermally stable. The reaction of phenyl azide was particularly sluggish, requiring 4 days at elevated temperature to achieve a yield of 29%.



Scheme 15: Cycloaddition of picryl azide and tetramethylallene.[186]

In 1991, Wedegaertner *et al.* highlighted the contrasting reactivity of both a sterically hindered and sterically accessible allene in their behaviour towards phenyl azide (Scheme 16).[187] Cycloaddition was found to occur across the less hindered face of *R*-(+)-1,2-cyclononadiene **21** exclusively to give 21% of the corresponding conjugated triazoline **22** with high regioselectivity. This triazoline could be isomerised to the corresponding triazole by heating at refluxing under basic conditions. In contrast, the sterically accessible 1,2-propadiene **23** was found to give a mixture of three products in a combined yield of 36% after prolonged heating for 3 weeks (Scheme 16). Both triazole regioisomers were isolated, caused by isomerisation of their corresponding triazolines, and a cyclopropane species proposed to arise through a diradical mechanism.

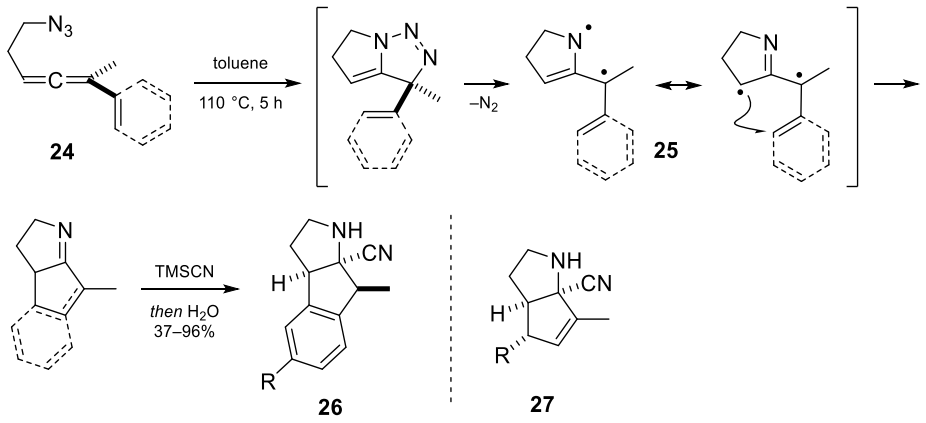


Scheme 16: Contrasting behaviour of sterically accessible allene-azide cycloadditions.[187]

Intermolecular allene-azide cycloadditions have received little attention in the literature when compared to alkyne-azide click reactions. This has been due to a combination of low yields, long reaction times, and poor selectivity, as well as products that are not generally desired and/or easier to produce by other means.

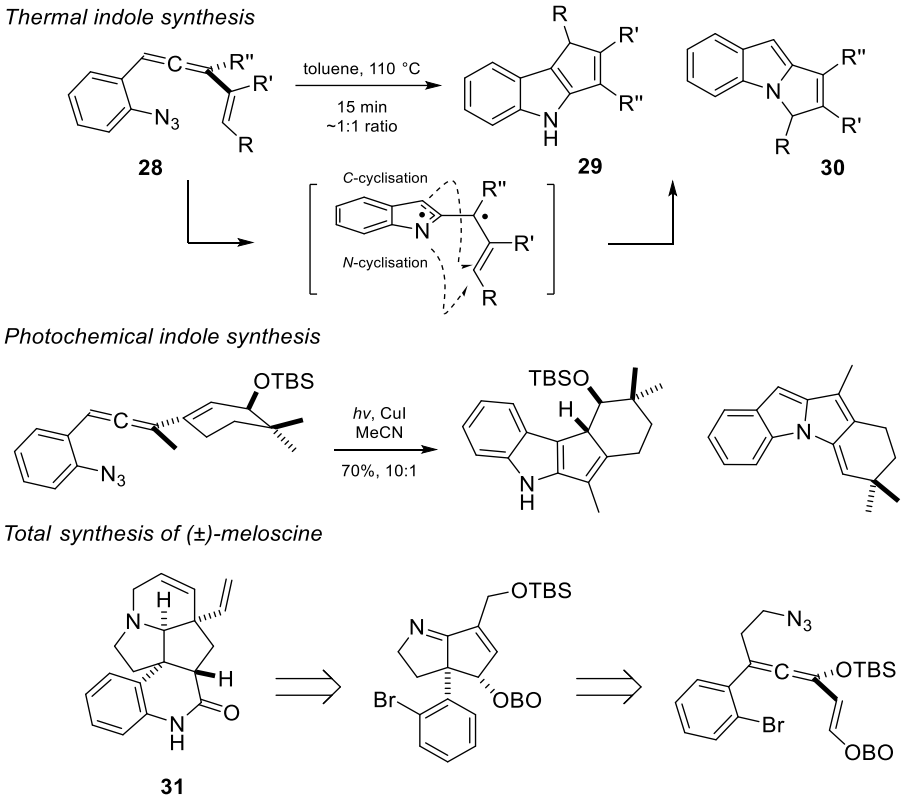
Allene-azide cycloadditions are more useful when reactions are conducted intramolecularly; tethering the allene and azide components together by an atomic bridge. Feldman has worked in this field for the past decade,[188–194] and reported that 1-aryl- and 1-vinyl-substituted 5-azidoallenes **24** undergo cycloaddition cascades to yield bicyclic **27** and tricyclic **26** pyrrolidine derivatives in yields ranging from 37–96%

(Scheme 17).[188] The regioselectity of intramolecular allene-azide cycloaddition is dictated by tether length, generating a short-lived triazoline intermediate. Expulsion of nitrogen provides an azatrimethylenemethane (ATMM) diradical **25** that cyclises onto the pendent unsaturated bond to provide the desired imine *in situ*. One pot trapping with TMSCN and hydrolysis upon work-up affords cyanopyrrolidines **26** and **27** as single diastereomers.



Scheme 17: Feldman's first reported allenyl-azide cycloaddition cascade.[188]

This methodology was later extended to 2-(allenyl)phenyl azides **28**, which upon thermolysis furnished both *C*-cyclised and *N*-cyclised cyclopentannelated indoles **29** and **30** (Scheme 18).[189] Again, this cascade proceeded *via* an initial triazoline cycloadduct, which through loss of nitrogen affords an ATMM diradical intermediate that cyclises to yield a ~1:1 mixture of indoles. The regioselectivity of this reaction class could be improved by photochemical initiation under copper conditions, providing a 10:1 ratio of indoles in favour of the *C*-cyclised product.[192] Feldman's azidoalkyl-allene chemistry was the key step in the synthesis of (±)-meloscine **31**, a *Melodinus* alkaloid (Scheme 18).[193,194]



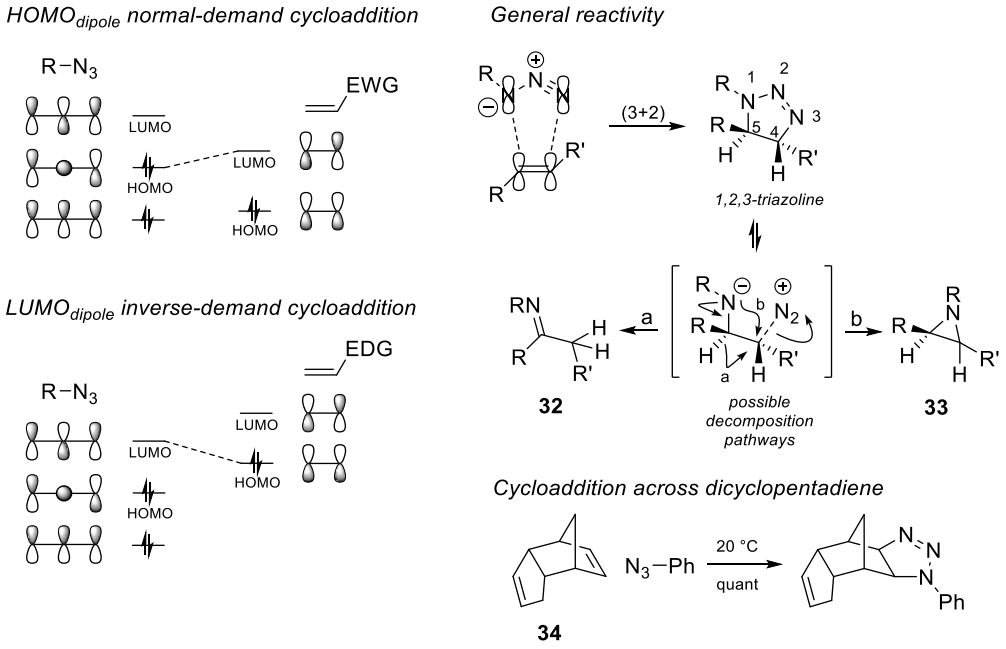
Scheme 18: Azidoalkyl allene cycloadditions – Thermal*[189] *and photochemical*[192] *approaches towards indoles, and total synthesis of meloscine.[193,194]

The Robertson group has also studied azide-allene chemistry, as discussed in Section ***1.4***.

1.3.3 Alkene-azide cycloadditions

The reaction of azides with olefins has been known since the early 20th century, starting with Wolff's seminal discovery in 1912.[195–199] Some of the early reports propose a three-membered cyclic azide structure, that was eventually revised to the familiar linear azide structure we now take for granted. The reaction of azides with olefins was categorised as a concerted 1,3-dipolar cycloaddition by Huisgen in his influential 1963 report "1,3-dipolar cycloadditions: past and future".[146]

Olefins react with azides to yield 1,2,3-triazolines, which may readily decompose to form imines **32** and aziridines **33** (Scheme 19).[186,200–203] Analogous to alkyne and allene-azide cycloadditions, the azide dipole π-orbitals must interact with the alkene π-orbital to undergo a concerted cycloaddition. This is a stereospecific process in that the alkene stereochemistry is translated directly into the product; i.e. *trans* and *cis* alkenes give *trans* and *cis* substituted 1,2,3-triazolines respectively. Electron-deficient olefins have lowered LUMOs which interact with electron-rich azide HOMOs in the normal-demand, or $HOMO_{dipole}$ controlled, 1,3-dipolar cycloaddition. Conversely, electron-rich olefins have raised HOMOs that interact with electron-poor azide LUMOs in an inverse-demand, $LUMO_{dipole}$ controlled, 1,3-dipolar cycloaddition (Scheme 19).



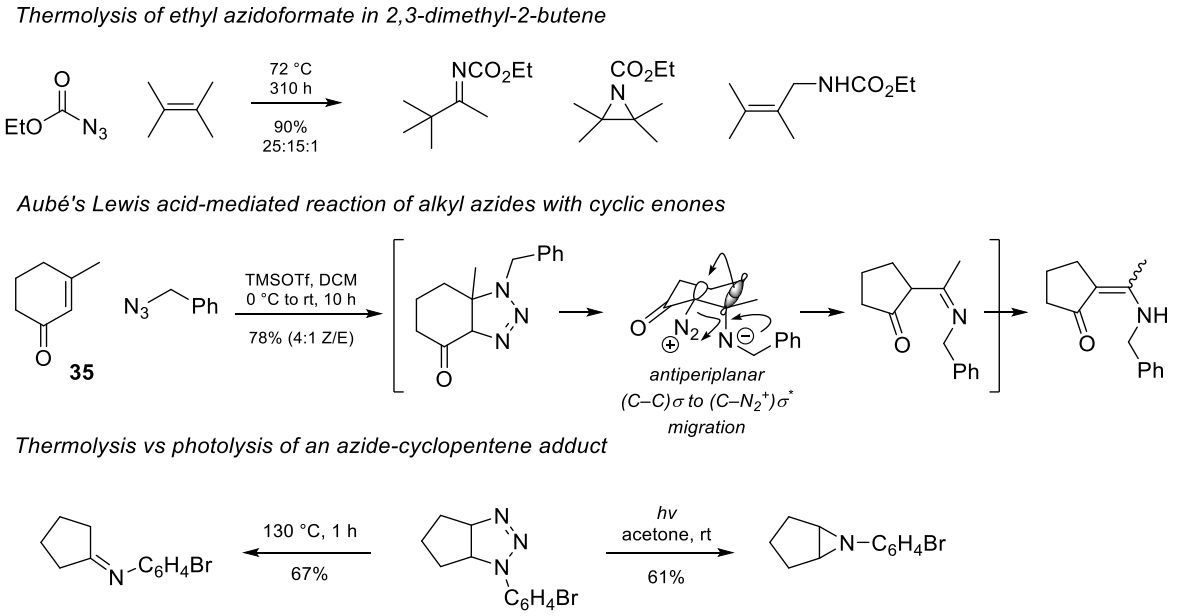
Scheme 19: FMO interactions in azide-alkene 1,3-dipolar cycloadditions, plus general reactivity, and addition across dicyclopentadiene.[145,146,196]

It was discovered early on that strained alkenes react preferentially with azides in the presence of their less strained analogues. In 1931, Alder and Stein reported the reaction of dicyclopentadiene **34** and other strained alkenes with phenyl azide at ambient temperature, giving quantitative conversion to the corresponding 1,2,3-

triazoline by relief of ring strain across the bicyclic double bond (Scheme 19).[145,146,196] So reliable was this reaction, that the capacity to add phenyl azide became a diagnostic test for angular strain in unsaturated hydrocarbons.[145,200,201]

While the isolation of stable 1,2,3-triazolines is possible, in many cases triazolines are reactive intermediates *en route* to further decomposition products. These decomposition products are most commonly imines or aziridines, which arise from loss of nitrogen followed by either 1,2-atom shift (arrow *a*, Scheme 19), or cyclisation (arrow *b*, Scheme 19) respectively. The thermal decomposition of 1,2,3-triazolines can often lead to mixtures of products, with imines taking favour over aziridines in many cases (Scheme 20).[202–204] Imine formation does not occur *via* an aziridine intermediate, as subjecting an aziridine to thermolysis simply returns starting material.[202,205]

In 2003, Aubé reported the ring contraction of cyclic enones **35** upon Lewis acid-mediated cycloaddition with alkyl azides, *via* concurrent antiperiplanar ring-carbon migration and imine formation (Scheme 20).[206] This contrasts with Aubé's azido-Schmidt chemistry in which cyclic ketones give ring-expansion products with alkyl azides. In 1965, Scheiner reported that, although thermal decomposition of 1,2,3-triazolines may favour imine formation, reactions would favour aziridines if decomposition is conducted under photolytic conditions (Scheme 20).[204,205,207,208]



Scheme 20: Thermolysis of ethyl azidoformate in 2,3-dimethyl-2-butene,[202] ***Aubé's reaction of alkyl azides with cyclic enones,***[206] ***and photolysis leading to selective aziridine formation.***[204]

Scheiner's rationale for this selectivity was that under photochemical conditions, expulsion of nitrogen from an excited 1,2,3-triazoline may proceed to leave a singlet 1,3 diradical. This 1,3 diradical may then cyclise to yield the aziridine.[207] Scheiner also theorised that the degree of rotational freedom about the triazoline C4–C5 bond determines the degree of both imine and aziridine formation (Figure 4).[207,208] When rotation is restricted, expulsion of nitrogen leaves both nitrogen and carbon orbitals in a geometry that is perfectly aligned for cyclisation **36**. When rotation *is not* restricted, bond rotation aligns both nitrogen and carbon *p* orbitals with the adjacent C–H (or C–R) sp^3 orbital **37** allowing for atom migration and imine formation. Hence, when severe rotational restraints are present, aziridine formation is preferred and *vice versa*. Though postulated for 1,3-diradical intermediates, such reasoning may be applied to ionic intermediates also, with thermal energy increasing the degree of bond rotation, orbital alignment, and imine formation.

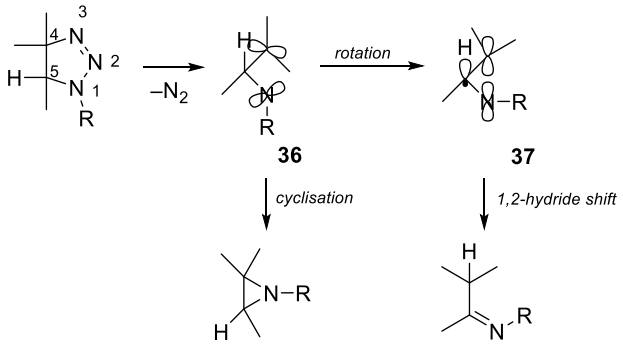
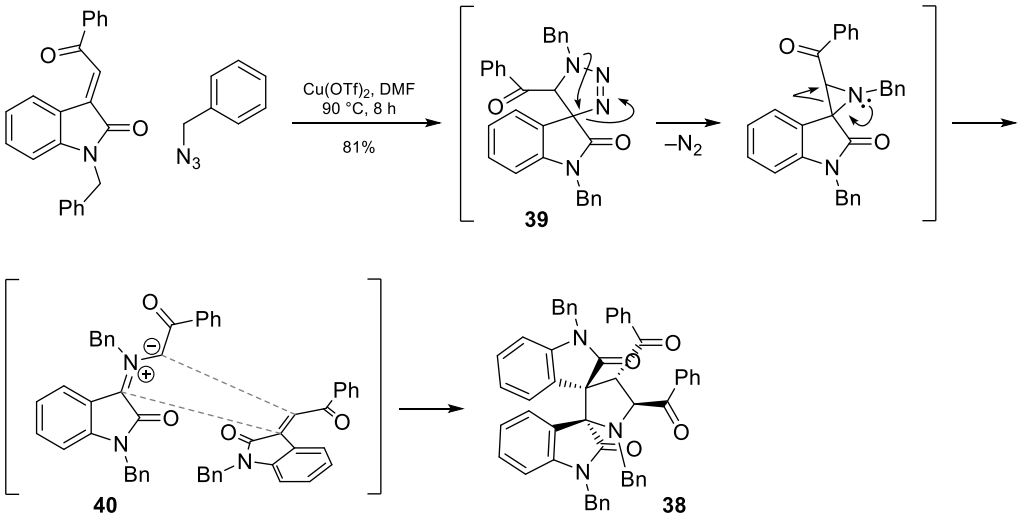


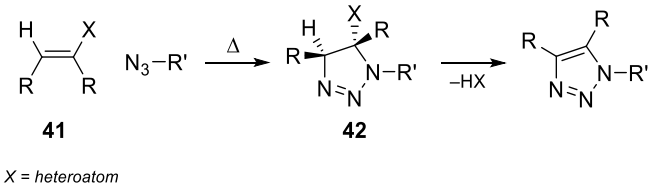
Figure 4: Scheiner rationale for aziridine and imine formation from decomposition of 1,2,3-triazolines.[207]

Owing to the reactivity of 1,2,3-triazolines and their decomposition products, azide-alkene cycloadditions can often lead to interesting cascade sequences. An intermolecular alkene-azide cascade played a key role in Thennarasu's 2014 synthesis of 3,3'-pyrrolidinyldispirooxindoles **38**.[209] It was found that in the presence of $Cu(OTf)_2$, benzyl azide underwent a thermal (3+2) dipolar cycloaddition with an α,β-unsaturated oxindole dipolarophile to yield a triazoline intermediate **39**, that decomposes *in situ* to form a strained aziridine. Rearrangement of this aziridine through C–C bond cleavage provides a reactive azomethine ylide **40** which further reacts *in situ* with a second equivalent of oxindole in a (3+2) cycloaddition to yield **38**. Overall, this tandem double dipolar cycloaddition cascade produces four contiguous stereocentres and two spiro-quaternary centres in high yield and diastereoselectivity (Scheme 21).



Scheme 21: Thennarasu's alkene-azide cascade reaction towards 3,3'-pyrrolidinyldispirooxindoles.[209]

An important class of olefin is that which contains a hetero-atom **41** (Scheme 22). Hetero-substituted alkenes may be activated towards inverse-demand dipolar cycloadditions by virtue of an electron-donating substituent, or conversely made more electron poor by a hetero-electron-withdrawing group. Hetero-substituted alkenes can partake in alkene-azide cycloadditions to yield hetero-substituted 1,2,3-triazolines **42**. These triazolines are often primed to formally eliminate a molecule of HX (X = heteroatom) to afford 1,2,3-triazoles, providing an alternative method to alkyne click chemistry (Scheme 22). The electronic bias across the olefin can increase the regioselectivity of the cycloaddition allowing the controlled synthesis of di- and trisubstituted triazoles, with electron-deficient olefins providing 1,5-disubstituted triazoles and electron-rich olefins providing 1,4-disubstituted triazoles respectively.



Scheme 22: Hetero-substituted olefins as alkyne synthons in the synthesis of 1,2,3-triazoles.

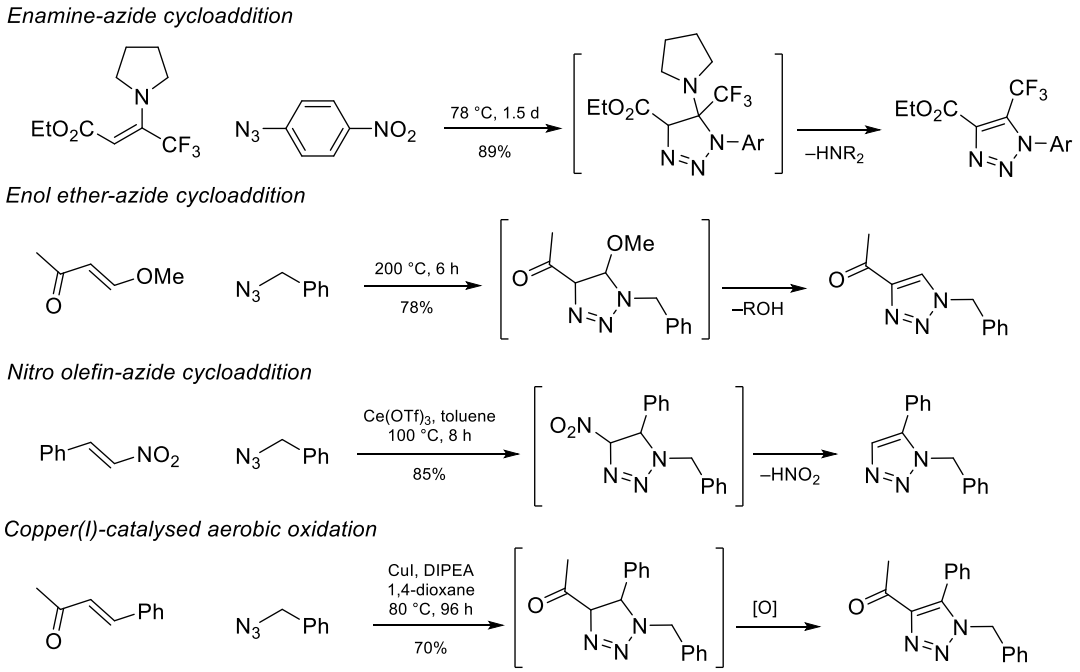
Common hetero-substituted alkenes applied in the synthesis of 1,2,3-triazoles include enamines, enol ethers, and nitro-olefins (Scheme 23). Enamines have been the most extensively studied hetero-olefin dipolarophile due to their ease of synthesis from carbonyl compounds and strong HOMO raising properties.[210–216] Of particular merit are push-pull systems that combine an enamine with an electron accepting group, providing a stabilised ylide for improved regioselectivity.[210–213]

While enamines have received the most attention as alkyne synthons in the preparation of 1,2,3-triazoles, the stability of the intermediate 5-amino-1,2,3-triazoline can be problematic. In some cases, decomposition of the triazoline ring competes with triazole formation leading to lower yields and side products.[217,218] The use of enol ethers can address these shortcomings[218–221] as the 5-alkoxy-1,2,3-triazole intermediates are more labile due to the improved leaving group ability of OR over NR_2 (Scheme 23). The trade-off however is in the rate of reaction, as enol ethers are not as electron rich as enamines and react more slowly in inverse-demand dipolar cycloadditions.[218]

Nitro-olefins, that contain an electron deficient alkene, would appear the prime substrates for normal-demand dipolar cycloadditions. However, in the absence of a suitable catalyst, cycloaddition with azides can take weeks or even months at elevated temperatures to achieve only partial conversion.[222,223] Fortunately, nitro-olefin-azide cycloadditions can be catalysed by $Ce(OTf)_3$ which increases the electrophilicity of the nitro-olefin through coordination (Scheme 23).[222] Alternatively, nitro-olefins with a second electron withdrawing group have found success in azide cycloadditions, either formed *in situ*,[224] or catalysed by TBAF.[223]

On a related note, Yao *et al.* reported the copper(I)-catalysed aerobic oxidation of enone-derived triazolines as an alternate route towards 1,2,3-triazoles (Scheme 23).[225] In this procedure, DIPEA organocatalytically activates the electron-deficient olefin

towards stepwise cycloaddition with an azide to provide a 1,2,3-triazoline. The triazoline intermediate is then oxidised in the presence of copper(I) and molecular oxygen to a triazolium ion which deprotonates to yield the 1,2,3-triazoline.

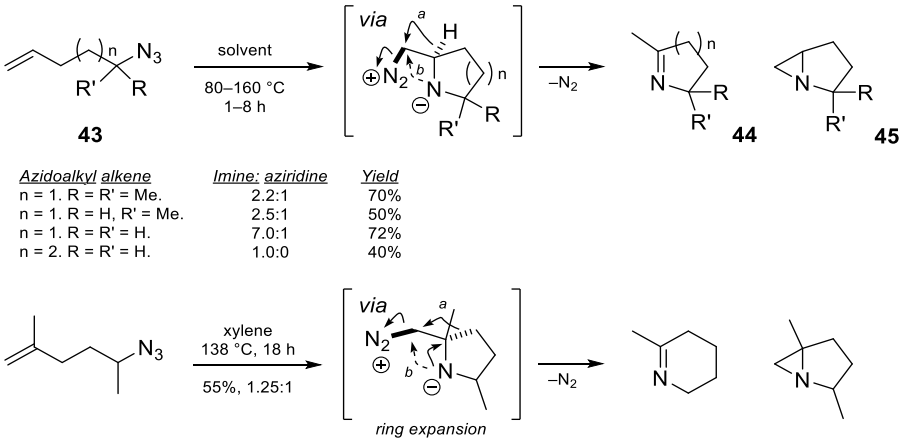


Scheme 23: Preparation of 1,2,3-triazoles from enamines, [210] ***enol ethers,*** [218] ***nitro-olefins,*** [222] ***and by copper(I) oxidation.*** [225]

On average, olefins are more reluctant partners in azide cycloaddition than alkynes, and require more forcing conditions. In addition, there has not been a comparable breakthrough in catalysis that one could compare with the CuAAC or RuAAC reactions. Unless suitably strained or electronically activated, many olefins are so unreactive towards azide cycloaddition that intramolecular reaction control is required.

Like azide-allene cycloadditions (*vide supra*), azide-alkene cycloadditions introduce complexity when conducted *intramolecularly*. Intramolecular azide-olefin cycloadditions (IAOC) are prime candidates for unique and interesting cascade sequences, both intentional and accidental.

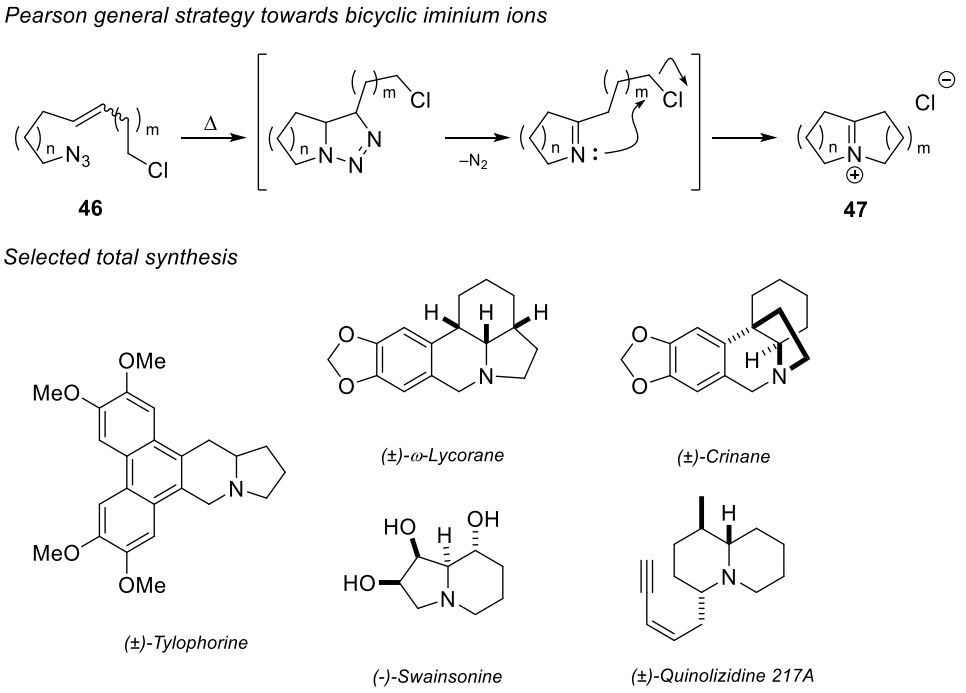
IAOC chemistry commenced in 1965, when Logothetis published his study on the thermolysis of carbon-tethered olefinic azides (Scheme 24).[226] Azidoalkyl alkenes containing a three carbon tether **43** were found to cyclise in refluxing organic solvents to yield cyclic imines as the major product **44**, with bicyclic aziridines **45** as a lesser side product. These species arise through the familiar mechanism discussed in Scheme 15; namely, (3+2) cycloaddition to provide a 1,2,3-triazoline, then fragmentation and loss of nitrogen, accompanied by either imine formation with 1,2-hydride/alkyl shift (a), or to a lesser extent by cyclisation (b) (Scheme 24). This thermal preference for imine formation is consistent with the previously discussed intermolecular cases. A four-carbon tethered azidoalkyl alkene decomposed exclusively *via* 1,2-hydride shift to provide the cyclic imine, presumably due to the increased rotational freedom granted by the tether allowing for the alignment of the requisite orbitals (*vide supra* Figure 4). Neither one, nor two carbon tethered azidoalkyl olefins could undergo intramolecular cycloaddition due to the geometric restrictions imposed by such a short linker, and were either thermally decomposed, or unreactive. Although in select cases the intermediate triazoline could be isolated and characterised, fragmentation of this labile species often precluded observation.



Scheme 24: Logothetis' seminal report on azidoalkyl alkene cycloadditions.[226]

In the 50 years since this initial discovery, many other groups have exploited the strategy of IAOC, followed by nitrogen extrusion and rearrangement to form diverse structures.[227–257]

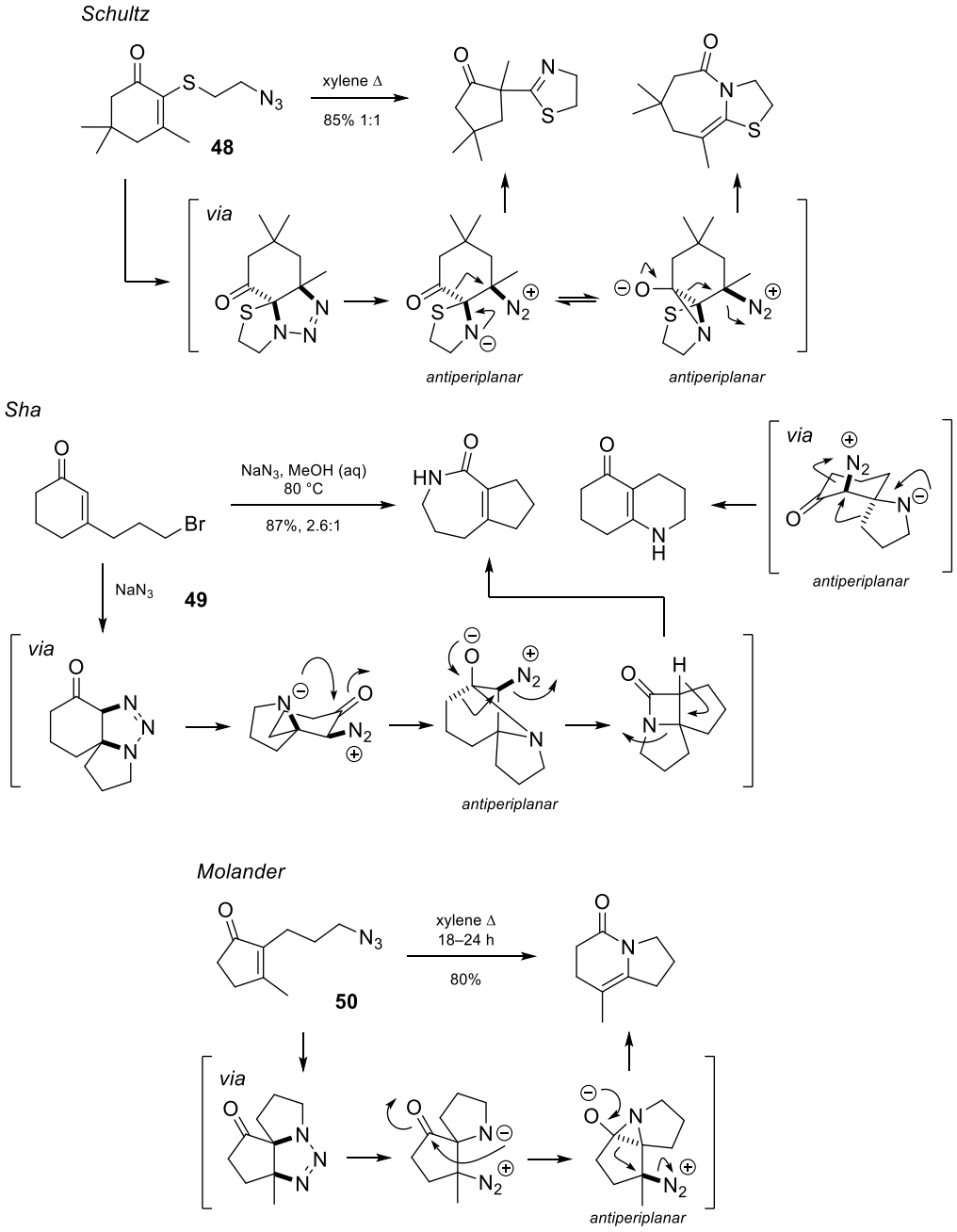
During the 1990s, Pearson was the major contributor to the field of IAOC reactions and their applications towards natural product synthesis. Pearson centred his work around the double thermal cyclisation of azidoalkyl ω-chloroalkenes **46** and their equivalents to gain access to bicyclic iminium ion intermediates **47** (Scheme 25).[238,239,242–244,256] The general strategy consisted of a familiar azido-alkene cycloaddition to give a labile 1,2,3-triazoline that decomposes through the well-documented 1,2-hydride shift to give an cyclic imine. This imine is then free to cyclise onto the pendent halide or equivalent to provide a bicyclic iminium. Such iminium ions are primed for further elaboration, often telescoping multiple steps within one reaction vessel. With this strategy in hand, Pearson synthesised a plethora of indolizidine and quinolizidine alkaloids including (–)-swainsonine,[238] (±)-γ-lycorane,[256] (±)-tylophorine,[242] (±)-crinane,[243] and (±)-quinolizidine 217A[244] (Scheme 25).



Scheme 25: Pearson's azidoalkyl ω-chloroalkene strategy and applications towards the total synthesis of (–)-swainsonine,[238] (±)-γ-lycorane,[256] (±)-tylophorine,[242] (±)-crinane,[243] and (±)-quinolizidine 217A.[244]

The groups of Schultz,[229,248] Sha,[232–234] and Molander[245,246] have all explored the chemistry of azidoalkyl-tethered enones and their rearrangement cascades (Scheme 26). In these reports the tendency towards forming product mixtures from cyclohexenones is evident, suggesting a similarity in energies between decomposition pathways. In 1980, Schultz noted that upon thermolysis, an α-(thioalkyl-azide)cyclohexenone **48** gave both ring-expansion and ring-contraction products from the same triazoline intermediate *via* competing acyl migrations.[229] In a similar vein, Sha published the thermal rearrangement of β-(azidoalkyl)cyclohexenones **49** in 1984, yielding both the product of an alkyl, and acyl migration upon fragmentation of the intermediate triazoline.[232] Longer tethered substrates were more selective however. Molander followed suit in 2002, and found α-(azidoalkyl)cyclopentenone substrates **50**

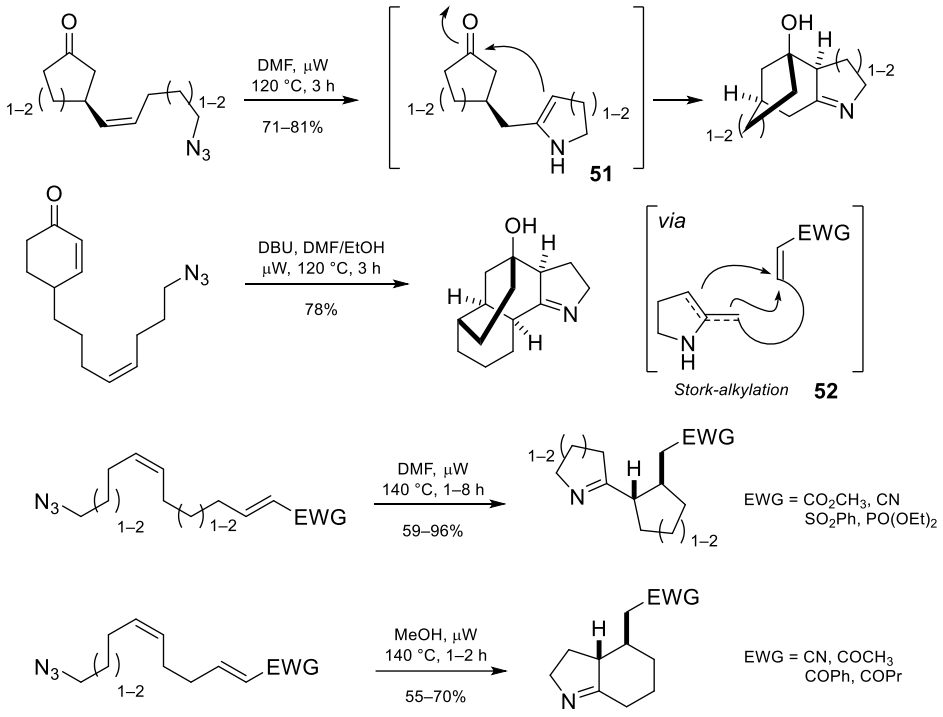
to be selective towards ring expansion,[246] in a reaction complementary to Aubé's alkyl azide Schmidt chemistry (Section **1.2**).



Scheme 26: Schultz, [229] ***Sha,***[232] ***and Molander***[246] ***group examples of azidoalkyl-enone rearrangements.***

More recently, Mann published a pair of papers focusing on the latent nucleophilicity of the enamine regioisomers **52** derived through a IAOC cascade to achieve some interesting structures (Scheme 27).[252,253] IAOC followed by triazoline

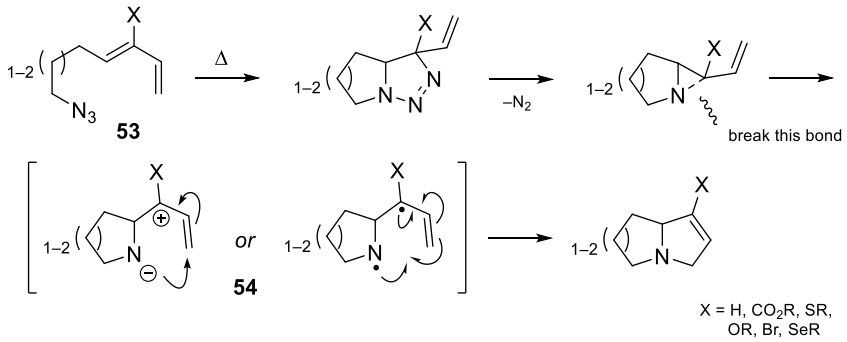
fragmentation and 1,2-hydride shift yields an intermediate cyclic imine, which is free to tautomerise to the corresponding enamine **51**. This enamine can then intercept a pendent electrophile within the starting material, giving rise to unique heterocycles (Scheme 27).



***Scheme 27: Mann IAOC/enamine addition*[252] *and IAOC/Stork alkylation cascades.*[253]**

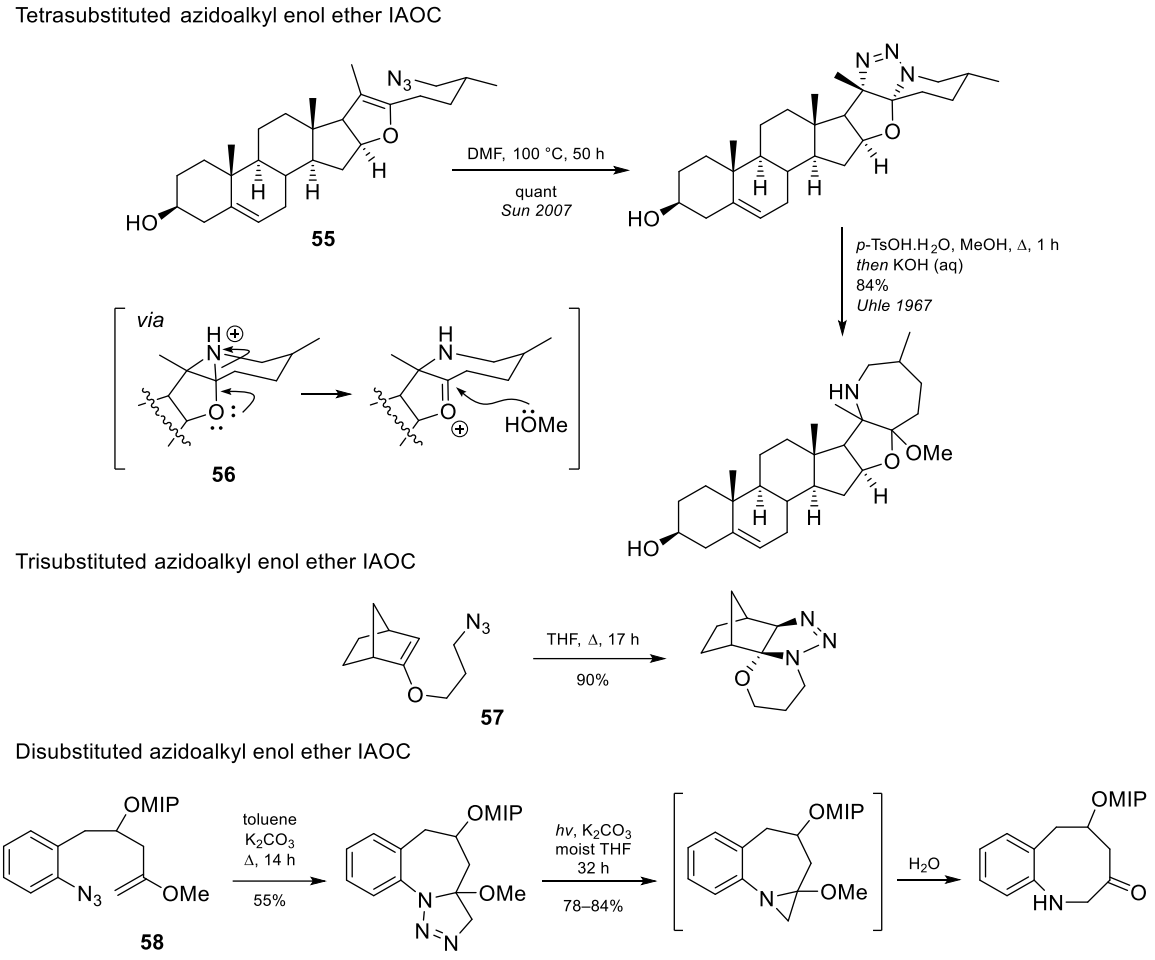
Somewhat related to the above family of IAOC reactions are the intramolecular cycloadditions of azides tethered to 1,3-dienes **53** (Scheme 28).[258–264] These cycloadditions proceed thermally *via* the aziridine intermediate, which can participate in further rearrangement with the remaining olefin of the diene to give alkaloid frameworks, essentially providing the synthetic equivalent to a nitrene-diene (4+1) cycloaddition. The inclusion of a hetero-atom into the diene component facilitates cleavage of the allylic C–N bond, through either a diradical or zwitterionic intermediate **54**, improving selectivity and promoting the clean formation of the formal (4+1) product. Without such a pre-loaded bias, mixtures of products are common.

Contributions to this field during the 1980s include studies by Hudlicky,[259,260] and more from Pearson,[261–264] Schultz,[258] and Sha.[258]



Scheme 28: Generic scheme for formal (4+1) IAOC reactions involving azidoalkyl dienes.[258–264]

As the literature currently stands, there are very few cases where IAOC reactions feature enol ethers as the olefinic component, and little has been done to elaborate the triazoline adducts in a synthetically useful manner (Scheme 29). The foremost study of a tetrasubstituted azidoalkyl enol ether cycloaddition featured in the synthesis of steroidal alkaloids, reported first by Uhle in 1964 and later repeated by Sun in 2007.[265–268] Uhle reported a ring-expansion reaction upon acidification of the 1,2,3-triazoline derived from **55**,[266] which may occur *via* the aziridine intermediate **56**. Other studies featuring di- **58** and trisubstituted **57** azidoalkyl enol ethers have also been reported,[269,270] and in all cases the resulting 5-alkoxy-1,2,3-triazolines were sufficiently stable to allow isolation. It seems in this field that the difficulty in synthesising highly substituted enol ethers precludes their detailed study.



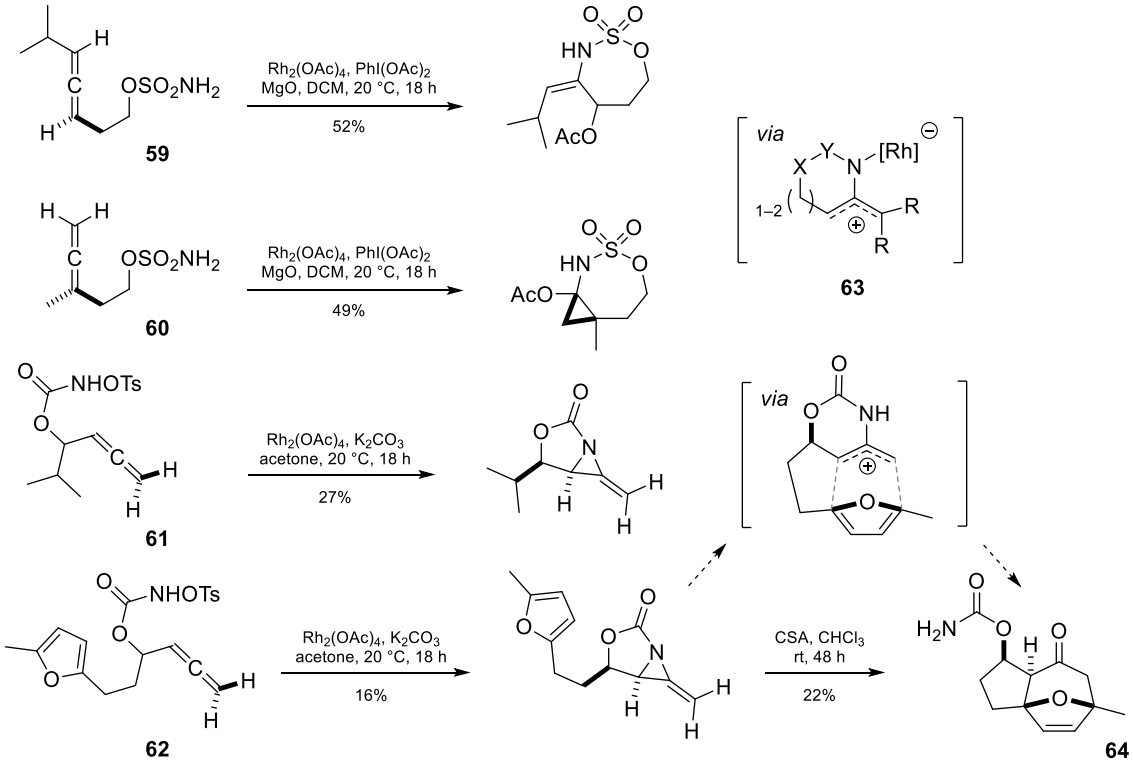
Scheme 29: Reported tetra-*[266,268] *tri-*[270] *and disubstituted*[269] *azidoalkyl enol ether IAOC reactions.

With the exception of an isolated example of an intramolecular azidoalkyl-vinylazide cycloaddition,[271] to the best of our knowledge the IAOC reaction featuring vinyl halides, enamines, thio enol ethers and other hetero-substituted olefins as the dipolarophile have yet to be reported.

1.4 Previous research in the Robertson group: Rhodium nitrenoids and azidoalkyl allene cycloadditions

A recurring theme in the Robertson group has been the application of intramolecular cascade sequences to form novel heterocyclic scaffolds. Recently, the group embarked on a programme to explore the chemistry of allenes tethered to nitrene equivalents as a means to rapidly construct complex alkaloid cores (Scheme 30).

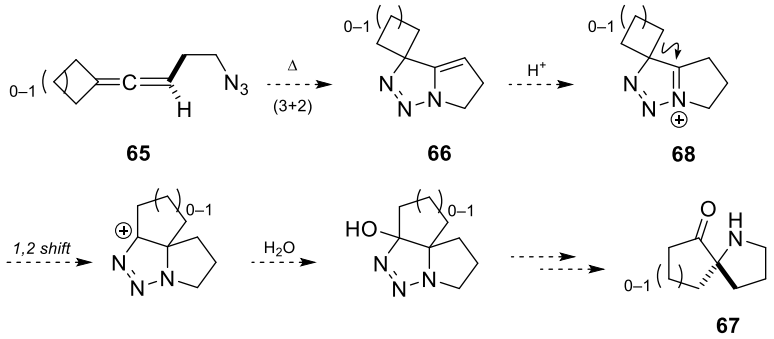
Initially, rhodium-bound nitrenoids were employed, resulting in access to small to medium-sized ring nitrogen containing heterocycles.[272] The rhodium(II)-catalysed aziridination of allene substrates **59**–**62** led to varied structures that can all be rationalised as derivatives of a 2-aminoallyl-1,3-dipolar intermediate **63**, including aminoallyl cation trapped product **64** *via* an intramolecular (4+3) cycloaddition.[273,274]



Scheme 30: George Feast Rh(II)-catalysed intramolecular amination of allenes.[273,274]

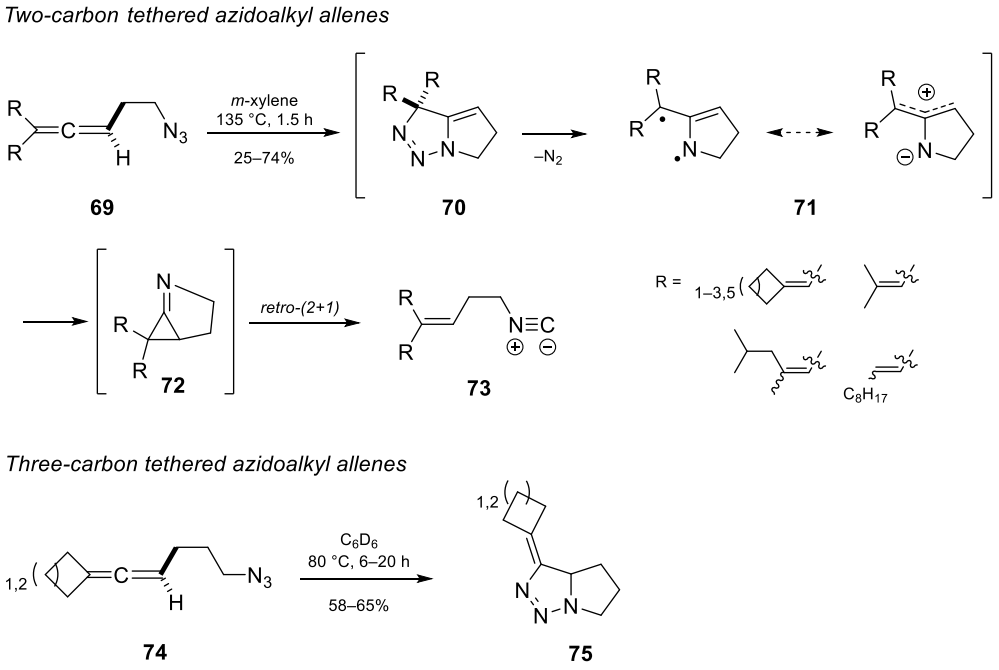
The group next sought to investigate azides as nitrene surrogates in intramolecular allene reactions.[275] Originally, it was theorised that azidoalkyl allenes **65** could give rise to 1,2,3-triazoline adducts **66** through an intramolecular (3+2) cycloaddition, which could serve as iminium ion precursors to effect ring expansion chemistry *en route* to amino-spirocycles **67** (Scheme 31). It was theorised that triazoline **66** could undergo protonation to triazolium **68**, which would promote the ring expansion of an adjacent strained carbocycle. The regioselectivity of cycloaddition

would be dictated by a constraining tether, while the 1,2-alkyl shift would release ring strain from a 3–4 membered ring.



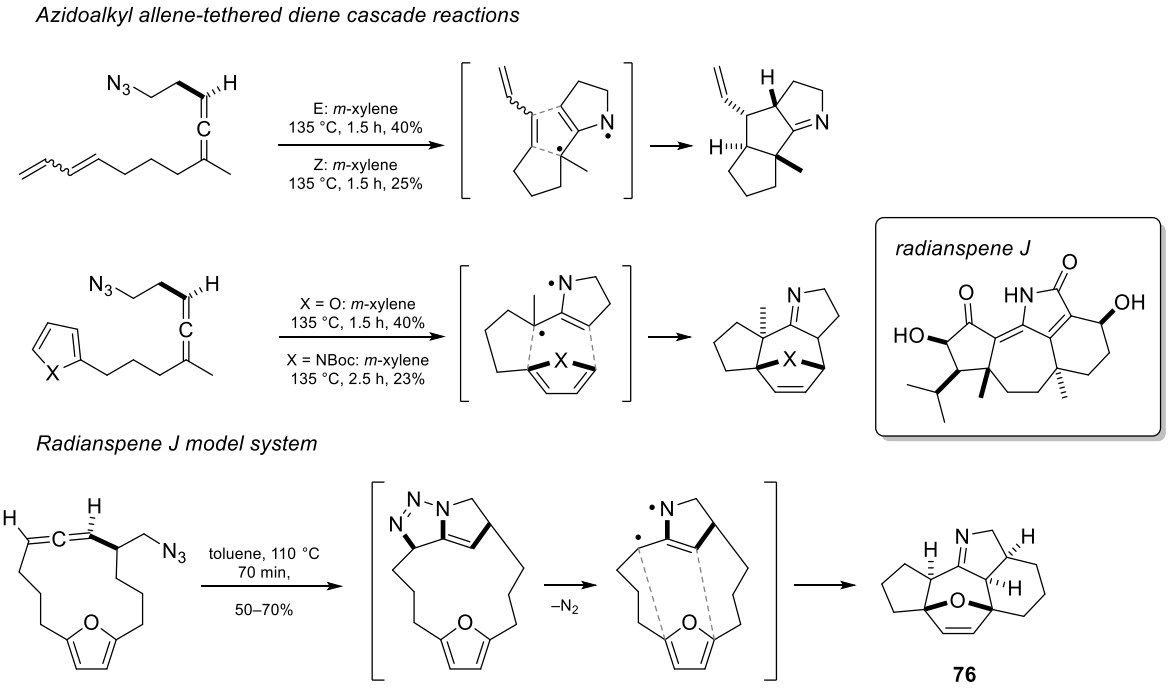
Scheme 31: Robertson group proposed synthesis of spirocycles via azidoalkyl allene cycloadditions.

When this hypothesis was put to the test however, unexpected reactivity was uncovered; thermolysis of two-carbon tethered azidoalkyl allenes **69** formed alkenyl isocyanides **73** (Scheme 32). Mechanistically, it is believed that cycloaddition occurs across the distal allenyl double bond as dictated by the restricting tether to provide the desired 1,2,3-triazoline intermediate **70**. Elimination of nitrogen from this triazoline, *via* either a radical or ionic mechanism, provides an aminoallyl dipole/diradical ATMM species **71** which can recombine to generate a strained iminocyclopropane **72**. Finally, (2+1)-cycloreversion of this species yields the final product. In contrast, three-carbon tethered azidoalkyl allenes **74** add across the proximal allenyl double bond by virtue of their longer tether, to give the more stable bicyclo[3,3,0] system, providing triazolines **75** that are inert to the intended chemistry (Scheme 32).



Scheme 32: Thermolysis of two and three-carbon tethered azidoalkyl allenes en route to isocyanides and 1,2,3-triazolines.

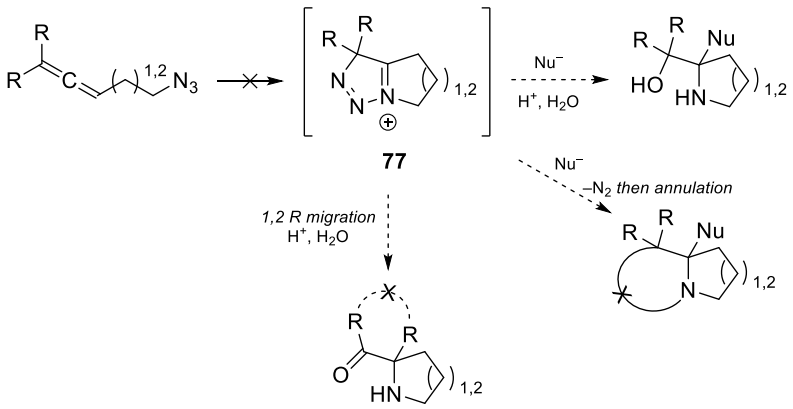
The intermediacy of dipole/diradical **71** directed Zhurakovskyi's project towards a new goal; the intramolecular trapping of this ATMM species by tethered dienes to rapidly construct polycyclic pseudoalkaloids (Scheme 33). Success in this field culminated in the total synthesis of a radianspene J model system **76** by a key transannular azidoalkyl allene (3+2) cycloaddition/(3+4) cascade.



Scheme 33: ATMM trapping cycloadditions and radianspene J model system 76.

1.5 Project proposal and aims

Triazolium ions **77** were seen as potentially privileged intermediates within the Robertson group, as a theoretical point of diversity from which various functionalised α,α-pyrrolidines and piperidine scaffolds could be accessed. Such bicyclic iminium ions would be primed for electrophilic attack with both external and internal nucleophiles, or 1,2 migration of R groups to release ring strain. The functionalised triazoline could then be cleaved under acidic conditions, as well as annulation with dipolarophiles to form diverse structures (Scheme 34). However as previously discussed, these triazolium ions could not be observed, nor exploited with the use of two or three-carbon tethered azidoalkyl allene cycloadditions (*vide supra* Scheme 32).

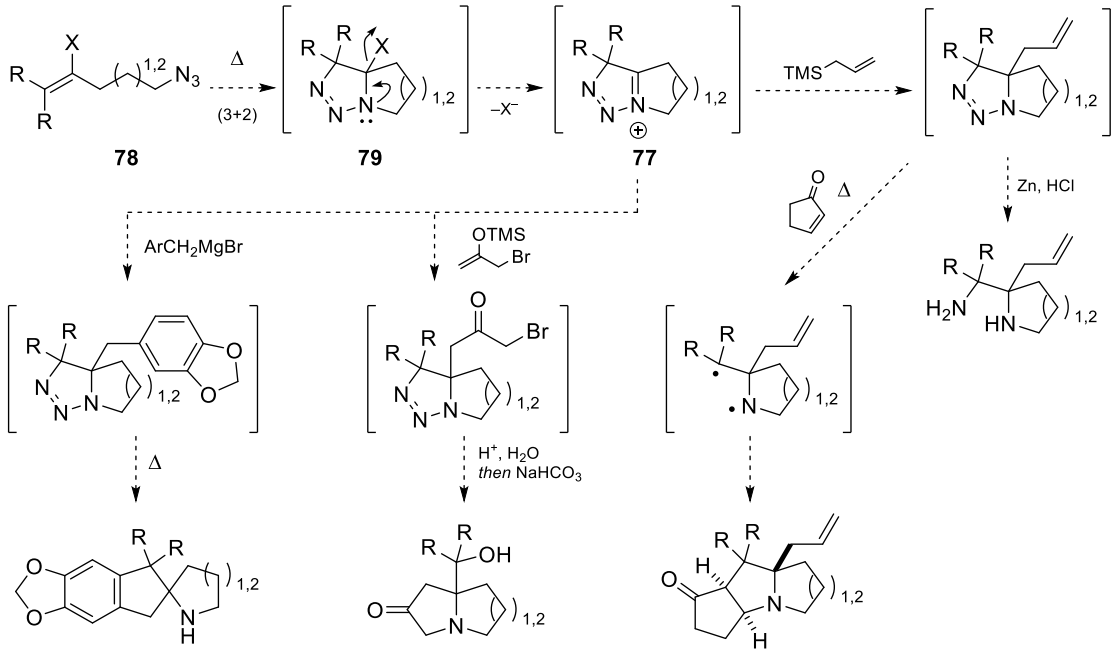


Scheme 34: Inaccessible triazolium ion diversity from one and two carbon tethered azidoalkyl allene cycloadditions.

The natural progression of these studies led to a consideration of intramolecular azide olefin cycloadditions (IAOC) bearing a heteroatom at the proximal end of the olefinic double bond **78** as allene surrogates (Scheme 35). In a forward sense, a thermally induced (3+2) cycloaddition between the azide and hetero-substituted olefin would produce a 5-hetero-substituted 1,2,3-triazoline **79** which, through careful selection of hetero atom, could provide access to triazolium ion **77**. By switching to an IAOC protocol, the regioselectivity issue inherent to azidoalkyl allene chemistry (proximal vs distal allenyl double bond reactivity in 2 vs 3 carbon tethered cases) is removed entirely, allowing more flexibility in the design of substrates. Additionally, if enol ethers are chosen as the olefinic component, there is a high likelihood that the intermediate 5-alkoxy-1,2,3-triazoline adduct will be a stable and isolatable intermediate based on existing literature precedent.[265–270] Thus the option for post-thermolysis low temperature ionisation to the triazolium by ejection of an alkoxide is available, and could be initiated under Lewis or Brønsted acid conditions.

The resulting triazolium ions could be trapped with a wide range of nucleophiles, either added as external reagents or preloaded within the substrate for intramolecular cascade purposes. The functionalised triazolines could be reduced to diamines,

hydrolysed to keto or hydroxy amines, or thermolysed with dipoles/dienes to yield annulated products, allowing the diversity-oriented synthesis of a wide range of nitrogen-containing heterocycles (Scheme 35).



Scheme 35: Proposed azidoalkyl hetero-substituted olefin cycloaddition chemistry and example structures.

With the use of hetero-substituted olefins in IAOC reactions underexploited or even untouched within the organic community, we wished to investigate their reactivity. By gaining access to the hetero-substituted triazoline adduct of the IAOC reaction, and through it, the triazolium ion **77**, the project would uncover new methodologies for the preparation of highly functionalised α,α-pyrrolidines and piperidine cores.

This thesis deals with the versatile chemistry of azidoalkyl enol ethers and their equivalents and reports their varied and often unexpected cycloaddition products.

2 Results and Discussion

2.1 Azidoalkyl enol ethers

2.1.1 Di- and trisubstituted azidoalkyl enol ethers *via* the α-metalation of vinyl ethers

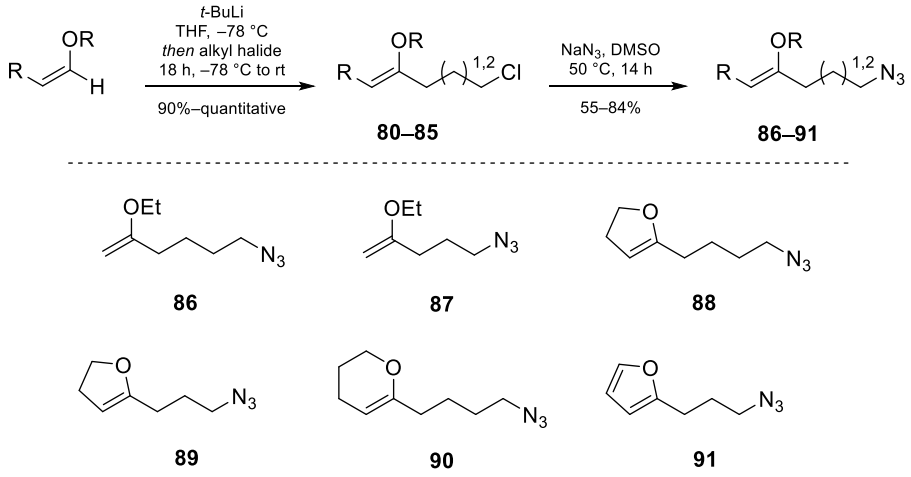
In order to test the hypothesis (Scheme 35), we first sought to prepare a series of simple di- and trisubstituted azidoalkyl enol ethers. This first campaign was intended as a "*shot across the bows*" to determine the conditions, rate, and efficiency of cycloadduct formation.

Utilising commercially available vinyl ethers (and furan), compounds **86**–**91** were synthesised *via* a short sequence of vinyl ether metalation, alkylation, and azide-halogen exchange (Scheme 36). Using methodology pioneered by Baldwin *et al.*,[276–280] the corresponding vinyl ether was deprotonated in THF by the dropwise addition of *t*-BuLi at –78 °C. Lithium-hydrogen exchange of vinyl ethers is made possible by the directing group ability of the Lewis basic ether oxygen. This oxygen can coordinate to the organolithium, in a complexation-induced proximity effect (CIPE).[281] By establishing this metal-substrate complex, the lithiating species is brought into close proximity to the acidic vinyl ether α-proton allowing deprotonation by the strongly basic *t*-BuLi.

Successful α-lithiation was indicated by the disappearance of a bright yellow colouration, known to be a 2:1 complex of *t*-BuLi and THF,[276,282] upon cycling the reaction temperature between 0 °C and –78 °C. The α-lithium enol ether reagents were then alkylated *in situ* by the low temperature addition of the corresponding alkylhalide, and then warmed to room temperature overnight. By-products from the reaction were easily removed by either aqueous extraction (lithium halide salt), or under reduced pressure (*iso*-butane) allowing chloroalkyl enol ethers **80**–**85** to be used without further

purification. Enol ethers **80** and **81**, precursors to **86** and **87**, were incredibly sensitive to acid and would rapidly hydrolyse to the corresponding methyl ketone on contact with $MgSO_4$, $CDCl_3$, or silica. This required the use of Na_2SO_4 as the drying agent and C_6D_6 for NMR analysis.

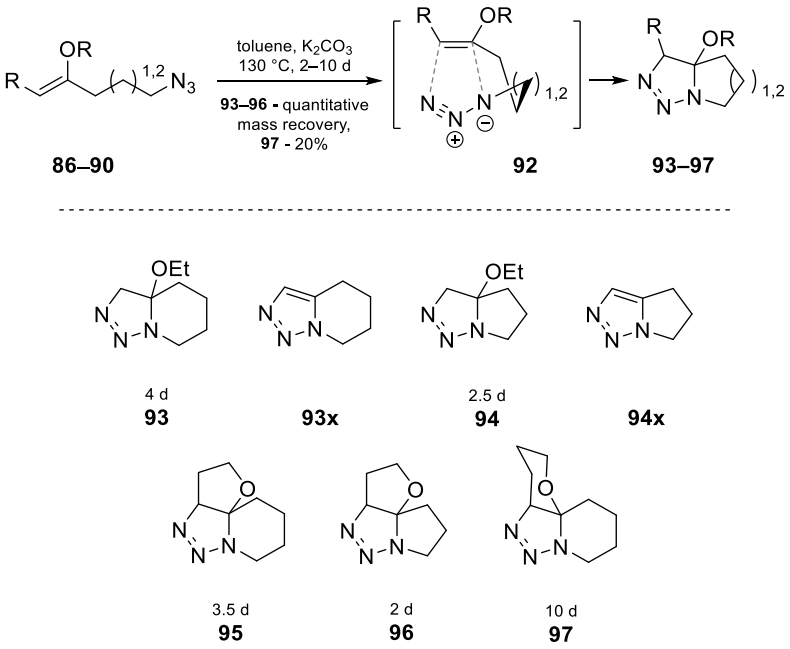
After routine azide installation by an S_N2 reaction in polar aprotic solvent,[251,283,284] the stage was set for the key thermal IAOC reaction, the centrepiece of the proposed methodology.



Scheme 36: Synthesis of di- and trisubstituted azidoalkyl enol ethers 86–91.

Initially, prolonged heating of **86** in high boiling solvents (toluene, $(MeO)_3CH$, DMF, DMSO) resulted only in decomposition, possibly in part by hydrolysis of the sensitive enol ether moiety. Gratifyingly, we found that use of super-heated toluene in the presence of K_2CO_3 was successful in generating the much sought-after 5-ethoxy-1,2,3-triazoline **93** (Scheme 37).[269] Thus, heating a toluene solution of **86** in the presence of K_2CO_3 at 130 °C for 4 days resulted in complete consumption of starting material (determined initially by ^{1}H-NMR analysis using d_8-toluene). Filtration and concentration of the reaction solution provided a near-quantitative recovery of mass, which upon ^{1}H-NMR analysis (C_6D_6) was usually a mixture of **93** and aromatic 1,2,3-triazole **93x** (ranging from 1:0–1:1 ratio of **93**:**93x**). Such 5-ethoxy-1,2,3-triazolines are sensitive

intermediates, and readily aromatise to the more stable 1,2,3-triazole by the loss of ethanol. Added K_2CO_3 was required to scavenge acid and maintain a basic reaction environment, prolonging the stability of both enol ether **86**, and triazoline **93** at high temperature. Na_2CO_3 was found to be equally effective. On the other hand, the use of triethylamine as the additive led to the exclusive formation of **93x** upon thermolysis of **86**, perhaps due to the mild acidity of Et_3NH^+. Both **93** and **93x** could be separated by careful chromatography over a basic alumina/1% Et_3N column for analytical purposes.



Scheme 37: Thermolysis of azidoalkyl enol ethers 86–90 leading to 1,2,3-triazolines 93–97, as well as 1,2,3-triazoles 93x and 94x.

By virtue of its shorter tether, **87** was found to undergo cycloaddition faster than **86**. This is due to the decrease in entropic freedom of the three-carbon azide tether in comparison to the four-carbon tether, allowing a less negative activation entropy in the transition state **92**. Thus **87** took 2.5 days at 130 °C to reach completion, yielding a near quantitative recovery of **94**, accompanied by triazoline **94x** (ranging from 4:1–2:3 ratio of **94**:**94x**). Both compounds could be separated by careful chromatography over a basic alumina/1% trimethylamine column for analysis.

Three and four-carbon tethered cyclic enol ethers **88** and **89** followed the same trend, taking 2 and 3.5 days respectively to complete cycloaddition at 130 °C (Scheme 37). This again demonstrates the benefit of a less negative activation entropy (3 vs 4 carbon tether). The dihydrofuran substrates reacted more rapidly than terminal enol ethers **86** and **87**. This is likely due to ring strain in the dihydrofuran ring. Much like cyclopentene, small cyclic alkenes are subject to ring strain resulting from distortion of the sp^2 hybridised alkene carbons from the ideal bond angle of 120 ° to ~108 ° for a flat 5-membered ring (Baeyer strain theory).[285] As the bond angle within dihydrofuran is more acute than the ideal angle, the bonds are under strain and adopt more p-orbital character to reduce the energy of the bonds. Hence these cyclic enol ethers are relatively "spring-loaded" toward cycloaddition, trading two sp^2 carbons for two sp^3 carbons and reducing the ideal bond angle from 120 ° to 109 ° upon formation of the 1,2,3-triazoline.

By having the 5-alkoxy moiety tethered to the 1,2,3-triazoline, products **95** and **96** were much more stable with respect to **93** and **94** and were not contaminated with their corresponding triazole. This is because if the alkoxy moiety is ejected by the nitrogen lone pair, it can simply re-cyclise by a 5-*exo*-*trig* ring-closure without substantial loss of entropy (Figure 5).[286] Presumably trapping of the iminium in this manner is more rapid than deprotonation by virtue of intramolecularity. Again both cycloadditions gave a near-quantitative recovery of product upon work-up, and were purified over basic-alumina for analysis.

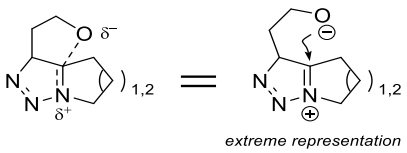


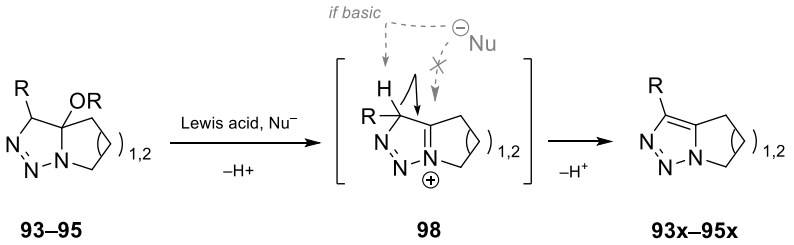
Figure 5: Rationale behind the stability of 95 and 96.

Substrate **90**, containing a dihydropyran moiety, is essentially free of angle-strain in the six-membered ring. Thus, the dihydropyran served only to increase the steric bulk around the dipolarophile, hindering alignment for the IAOC reaction. This combination of steric bulk and the longer four-carbon tether in substrate **90** necessitated 10 days at 130 °C to reach complete loss of starting material. Prolonged heating produced a crude product of poor purity and **97** was isolated in only 20% yield after chromatography. Aromatic azidoalkyl furan **91** did not react successfully at 130–170 °C, leading only to decomposition of the starting material at higher temperatures.

These results show, that the rate of the reaction depends on tether length (**86**/**88** vs **87**/**89**), strain bias (**86**/**87** vs **88**/**89**), and the steric environment around the olefinic bond (**86** vs **88** vs **90**). Thus, for relatively rapid cycloaddition, the substrate should include both a three-carbon tether and exhibit a strain bias within the dipolarophile. The reaction conditions were more severe than those reported in the literature for existing azidoalkyl enol ether cycloadditions, requiring higher temperatures and longer reaction times (compare Scheme 37 with Scheme 29). These discrepancies can be explained: both **55** and **57** benefit from varying degrees of ring strain in the starting enol ether to accelerate cycloaddition, while **55** and **58** feature substitution within the azide tether to impart an entropic rate acceleration akin to the gem-dialkyl effect[287] (to be covered in detail in Section **2.2.2**). Even with the absence of ring strain, and a 5-carbon tether, **58** features an electron-poor aryl azide as the dipole, complementing the electron-rich enol ether in terms of FMO considerations (see Scheme 19). Substrates **86**–**90** carry no organisational bias within the azide tether and feature both an electron-rich olefin* and electron-rich azide, meaning the frontier molecular orbitals likely have a poor match.

*Note: Although enol ethers are electron-rich relative to alkenes, they are not optimal for inverse-demand dipolar cycloadditions, reacting more slowly than enamines (Section **1.3.3**).

With a selection of 1,2,3-triazolines in hand, we moved onto the next phase of the proposal; low-temperature iminium formation and nucleophilic trapping (Scheme 35). Compounds **93–95** were treated with TBSOTf at –78 °C in the presence of allyltributylstannane with the aim of effecting Lewis acid-mediated ionisation and allylation (Scheme 38).[288] Rather than allylation with the nucleophilic stannane, all three reactions simply yielded the corresponding 1,2,3-triazoles **93x–95x**. The same result was found with $BF_3.Et_2O$, $Yb(OTf)_3$, $SnBr_4$ and $TiCl_4$ as Lewis acids. Treating **94** or **95** with ethylmagnesium bromide or ethynylmagnesium bromide between –78 °C and ambient temperature returned only starting material, while heating a THF solution of **95** with ethylmagnesium bromide produced conversion to triazolium **95x**, likely due to the weak Lewis acidity of magnesium halides. Finally, **95** was treated with triethylaluminium[289] but starting material was simply recovered.

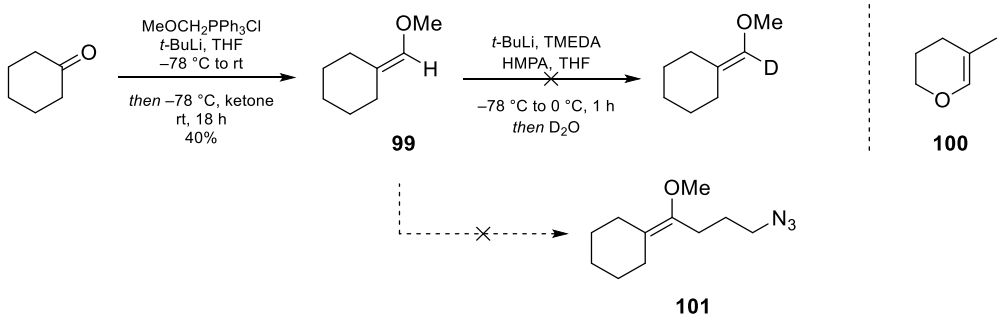


Scheme 38: Attempted ionisation and nucleophilic trapping of triazolines 93–95.

It would appear that when ionisation was successful, deprotonation and aromatisation outcompeted intermolecular nucleophilic attack. Aromatisation is a strong driving force and, once ionisation to triazolium **98** occurs, adjacent β-hydrogens become incredibly acidic and are rapidly lost. Hence, irrespective of the choice of nucleophile or Lewis acid, we reasoned that so long as aromatisation was a possibility,

this pathway would dominate, even with a relatively non-basic nucleophile such as allyltributylstannane. Regardless, we had amassed invaluable knowledge concerning the conditions required for cycloaddition, the factors affecting the rate of reaction, and validated the feasibility of low temperature iminium formation. If a tetrasubstituted azidoalkyl enol ether (**78**, X = OR) were to be heated, the corresponding triazolium ion **77** (Scheme 35) would lack the β-hydrogens required for 1,2,3-triazole formation and should favour intermolecular nucleophilic trapping.

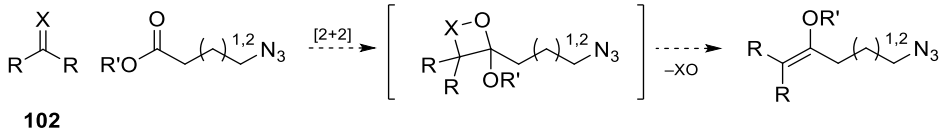
The vinyl ether metalation/alkylation approach had no precedent for the synthesis of a tetrasubstituted enol ether such as **101** (Scheme 39). Trisubstituted vinyl ether **99** was prepared by the Wittig olefination of cyclohexanone[290,291] and subjected to standard conditions for α-lithiation[276–280] but alkylation with 3-chloro iodopropane or allyl iodide failed to take place and starting material was recovered. Quenching with D_2O returned pure starting material, even in the presence of TMEDA with HMPA as co-solvent. The vinyl ether appeared completely inert to metalation. Upon combing the literature, we found a single sentence from Boeckman *et al*. wherein they had attempted to deprotonate dihydropyran derivative **100**:[292] "The presence of alkyl groups at the β-position appears to preclude metalation under these [excess t-BuLi] conditions". It could be that β-substitution within the vinyl ether provides enough hindrance such that the Lewis basic oxygen can no longer coordinate effectively to the organolithium aggregate cluster so as to initiate the CIPE deprotonation. With metalation unsuccessful, we progressed onto other routes for synthesis of tetrasubstituted azidoalkyl enol ethers.



Scheme 39: Attempted α-lithiation of 99.

2.1.2 Tetrasubstituted azidoalkyl enol ethers *via* the olefination of esters

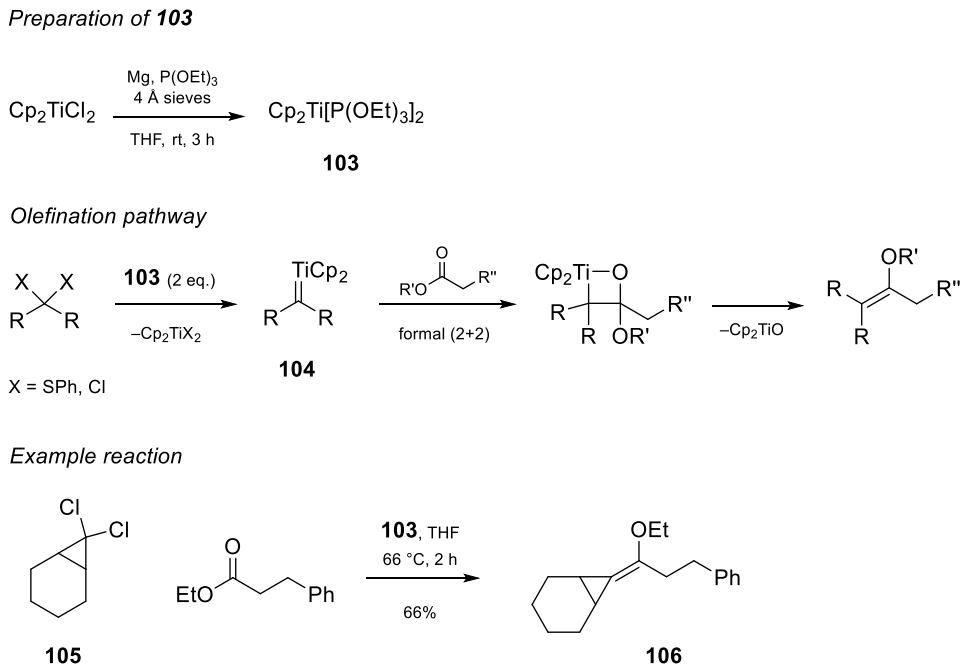
An ideal synthesis of tetrasubstituted enol ethers would arise through the direct olefination of esters, however such methodologies have yet to be developed that are both reliable and amenable to routine synthesis (Scheme 40). This is a consequence of the decreased electrophilicity of the ester carbonyl group. The alkylidenation of esters has been partially overcome by the use of titanium species such as the Tebbe,[293] Petasis,[294] and Takai[295] reagents, however these are only applicable to the preparation of simple di- and trisubstituted enol ethers.[296]



Scheme 40: Theoretical direct olefination of esters en route to tetrasubstituted azidoalkyl enol ethers.

A route into this chemistry appeared to be offered in the research of Takeda in which the use of low-valent titanium(II) species **103** for the alkylidenation of carbonyl compounds including carboxylic acid derivatives was reported.[297–306] Takeda discovered that highly reactive titanium carbene complexes **104** could be prepared by the reductive titanation of various *gem*-dichloroalkanes and thioacetals, providing

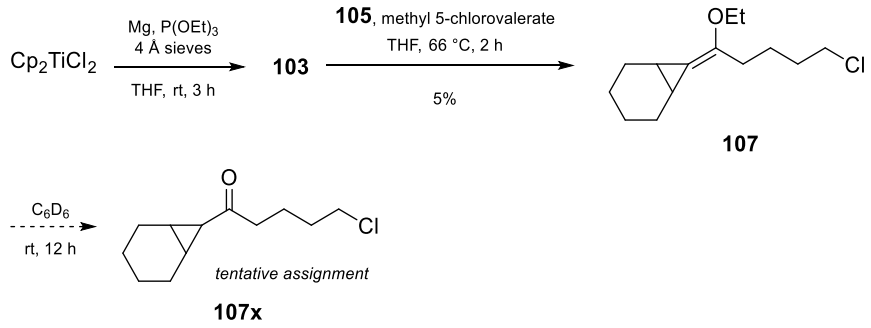
carbenes equivalent to structure **102**.[304,305] Such carbene complexes are reported to undergo metathesis with esters to produce tetrasubstituted enol ethers (Scheme 41).[299,306]



Scheme 41: Takeda's ester olefination by means of a titanocene(II) complex.[299,306]

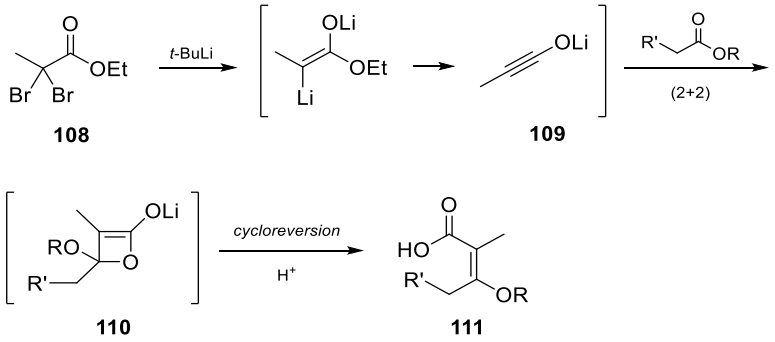
We first sought to repeat the preparation of **106**[306] from the readily synthesised *gem*-dichloro norcarane **105**.[307] Despite the potential that the chemistry held, the execution of this methodology was excessively laborious and technically demanding. The preparation of **103** had to be performed under strictly anhydrous and inert conditions, involving the heating of magnesium turnings, molecular sieves, and titanocene dichloride under vacuum, followed by the addition of two equivalents of triethyl phosphite. After 3 h at ambient temperature, 0.4 equivalents of **105**, and 0.2 equivalents of ester are added followed by heating at reflux for 2 h. What follows is a time-sensitive sequence of quenching, filtration, drying (K_2CO_3), and chromatography, performed on ≤60 mg scale in the literature (which employs preparative TLC purification over alumina). This process was made all the more complicated by the large

excess of reagents required (10 eq. triethylphosphite for each eq. of ester), making separation of product from triethylphosphite difficult. In our hands, we received a 1–5% yield of **106** after chromatography, just enough to serve as proof of concept. Conducting the procedure using methyl 5-chlorovalerate on 50 μL scale, gave enol ether **107** in ~5% yield (4 mg); but this was found to be unstable, hydrolysing overnight to **107x** in deuterated benzene presumably through traces of moisture (Scheme 42). We decided that such methodology was unsuitable for the multi-gram production of intermediates we desired. Poor reagent efficiency and reproducibility, combined with a technically-demanding procedure and lack of scale (≤60 mg) were corroborated by a stark absence of literature applications outside of Takeda's own research group.



Scheme 42: Synthesis of tetrasubstituted enol ether 107 using Takeda chemistry.

While searching for a one-step ester-to-enol ether Wittig-style transformation, we came across Shindo's synthesis of functionalised tetrasubstituted enol ethers through the alkylidination of esters with reactive ynolates (Scheme 43).[308–313] Ynolates are reactive ketene enolate equivalents that may act as multifunctional carbanions within synthesis.[314]



Scheme 43: Shindo's ester olefination by means of a reactive lithium ynolate.[308–313]

Shindo discovered that lithium ynolate **109** could be prepared *in situ* by the double lithium-halogen exchange of ethyl 2,2-dibromopropionate **108**[315–317] and then participate in a formal [2+2]/cycloreversion cascade with esters to furnish *trans*-β-alkoxy-α,β-unsaturated carboxylic acids **111**. The source of *trans* selectivity is through the torquoselective conrotatory ring-opening of β-lactone enolate intermediate **110**.[308,311,313] The electrocyclic ring opening of **110** proceeds with preferential *outward* rotation of the electron donating alkoxy substituent which forces the alkyl group (the lesser electron-donating group of the two) to rotate *inwards*, possibly stabilising the cleaving C–O bond through σ^* orbital acceptance (Figure 6). This result is in compliance with Houk's rules of torquoselectity that dictates electron-donating substituents rotate outward, so as to maximise stability in the transition state.[318–320] The alternative rotation of course would produce a destabilising electrostatic interaction between the cleaving C–O bond and the alkoxy oxygen lone pair electrons.

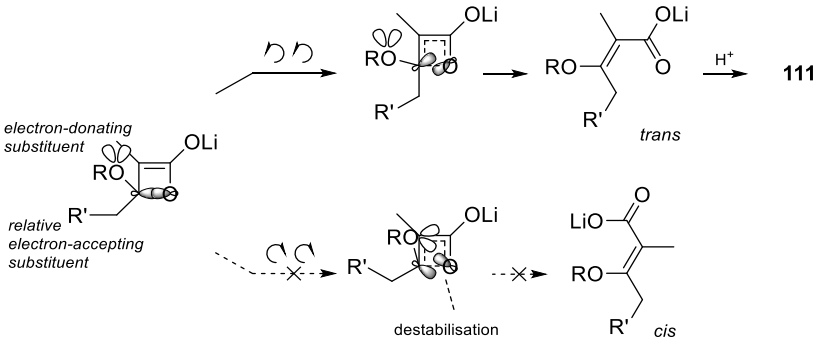
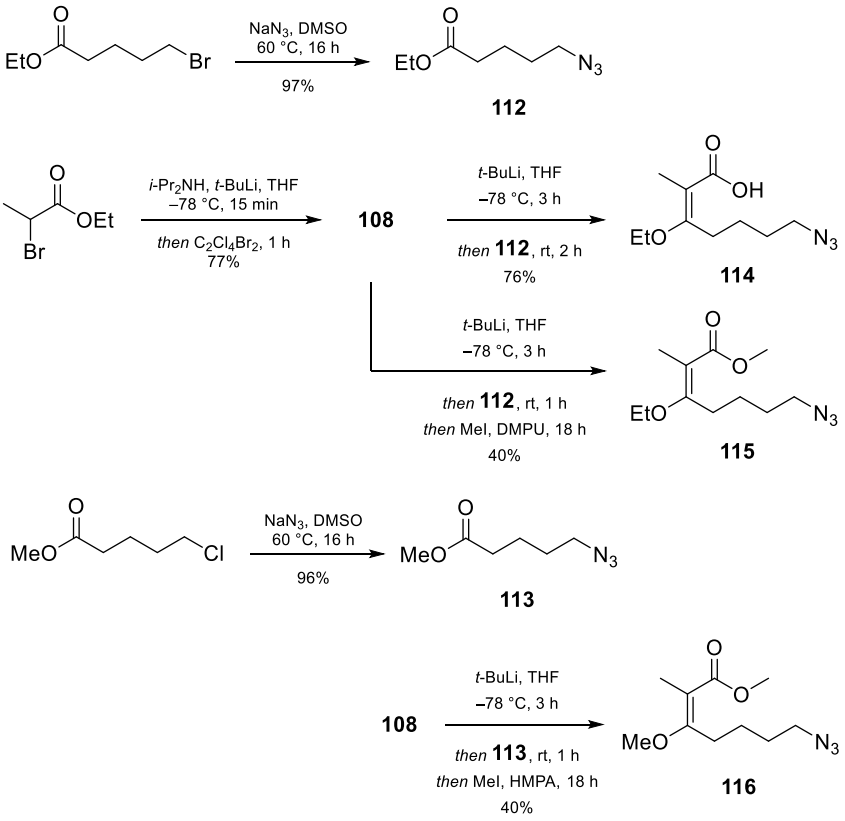


Figure 6: Torquoselectity leading to trans-enol ethers from cycloreversion of β-lactone enolates.

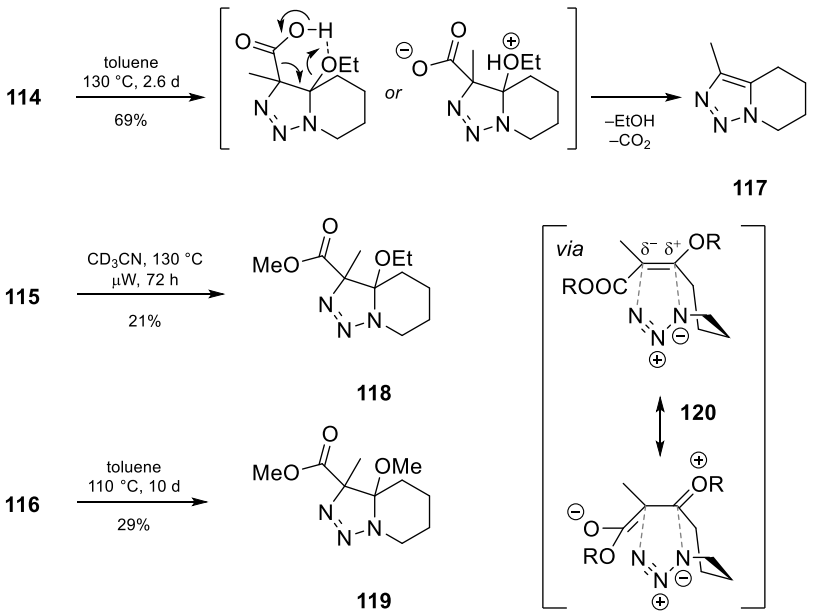
With this approach in mind, methyl and ethyl 5-azidovalerates **112** and **113** were synthesised from their corresponding halo-esters[283] and subjected to Shindo's olefination conditions, from which carboxylic acid **114** was isolated in a 76% yield (Scheme 44).[308] Alternatively, esterification could be performed *in situ* by the addition of iodomethane and a polar co-solvent to yield ethyl and methyl esters **115** and **116** each in 40% yield. While the literature choice of co-solvent was the carcinogenic HMPA, we found this could be substituted for DMPU in the interest of safety with identical effect.[321,322] Chromatography over silica/0.5% Et_3N was necessary to isolate **115** and **116** from the polar co-solvent; however, both were difficult to isolate as clean products, uniformly featuring base-line noise within their ^{1}H-NMR spectra. While a 2D-TLC analysis indicated stability on silica, the cause and solution to these impurities could not be established. Similar results were achieved when utilising the corresponding halo-esters, removing the likelihood of decomposition pathways made possible by the pendent azide. The low yield of product was attributed in part to the practicalities of separation, as often 200 mg of product would need to be isolated from ~3 g of crude oil (containing both product and involatile co-solvent).



Scheme 44: Preparation of functionalised tetrasubstituted azidoalkyl enol ethers using Shindo chemistry.

Azidoalkyl enol ether **114** was found to undergo cycloaddition in super-heated toluene at a rate comparable to the previously described di- and trisubstituted enol ethers (Scheme 45). Despite the longer four-carbon tether and more substituted/sterically hindered olefin, **114** took 2.6 d at 130 °C to reach completion, a higher rate than for four-carbon tethered enol ethers **86**, **88**, and **90** (4, 3.5 and 10 d respectively). This is likely due to the existence of a *push-pull system* across the olefinic bond, with both electron-donating ethoxy and electron-withdrawing carboxyl group creating an electronically polarised double bond. Hence, during the transition state **120**, electron delocalisaton towards the zwitterionic representation may facilitate a distorted, step-wise cycloaddition. Compound **114** yielded 1,2,3-triazole **117** in a 69% yield, through *in situ* decarboxylation of the intermediate 1,2,3-triazoline at elevated

temperatures (Scheme 45). This is unsurprising, as the carboxylic acid is free to activate the adjacent ethoxy leaving group, forming either a zwitterionic triazoline that is primed for fragmentation, or by a concerted cyclo-fragmentation.



Scheme 45: Thermolysis of functionalised tetrasubstituted azidoalkyl enol ethers 114–116.

Ester **115** was subjected to microwave irradiation in d_3-MeCN at 130 °C. After 72 h, ^{1}H-NMR analysis of the reaction mixture revealed an 80% conversion to product, upon which chromatography yielded triazoline **118** as a brown oil of low analytical purity (~21% yield). Likewise, **116** yielded **119** after heating in refluxing toluene for 10 d in ~29% yield with low analytical purity. The lower reaction temperature was chosen in an effort to achieve a cleaner reaction, and would extrapolate to a reaction rate of 2.5 d at 130 °C (in scale with **114**). Again, both cycloadditions could proceed through an ordered transition state **120**, accelerated by the highly polarised olefin.

Disappointingly, the quantity and quality of material produced precluded a detailed study of ionisation and nucleophilic trapping, though a single attempt with **118** using $BF_3.Et_2O$ and trapping with allyltributylstannane was unsuccessful.

Both **118** and **119** were seen as contrived substrates, whose difficulties in synthesis and requisite ester functionalities were not ideal. With projects running in parallel to this study starting to bear fruit, attention shifted to more lucrative endeavours, with the intention of returning to these substrates at a later date.

2.1.3 Tetrasubstituted azidoalkyl silyl enol ethers

We required the synthesis of a tetrasubstituted azidoalkyl enol ether in order to examine the methodology proposed in Scheme 35, preferably a simple, naked test-substrate free of undue functionality. However, reliable methods for the synthesis of simple fully-substituted enol ethers have yet to be described in the literature. Closer examination of Scheme 35 revealed that the heteroatom on olefin **78**, and ergo 1,2,3-triazoline **79** need not necessarily be an alkoxy group; the group is sacrificial and therefore inconsequential *en route* to triazolium **77**.

Fully-substituted enol ethers cannot reliably be synthesised by the enolisation and *O*-alkylation of ketones with alkyl halides. An enolate is a delocalised system wherein the anionic charge is carried on both oxygen and carbon **121**, hence enolates are nucleophilic at both of these sites (Figure 7). Because oxygen is more electronegative than carbon, the orbital coefficients on the enolate are distorted, with the lower-energy occupied molecular orbital (Ψ_1) featuring a greater contribution from this oxygen.[323] The reactive HOMO orbital (Ψ_2), features larger orbital coefficients at the terminal atoms, with the largest coefficient residing on the carbon. Hence the oxygen of the enolate has the larger negative charge, but the carbon has the larger HOMO coefficient. A consequence of this is that reactions dominated by electrostatic interactions occur at the enolate oxygen (hard nucleophilic site), while reactions dominated by orbital interactions occur at the enolate carbon (soft nucleophilic site).

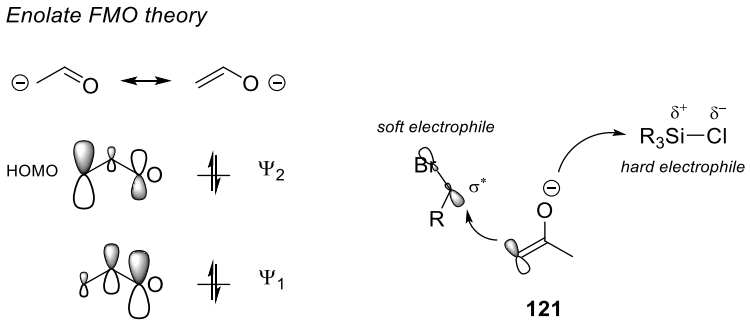
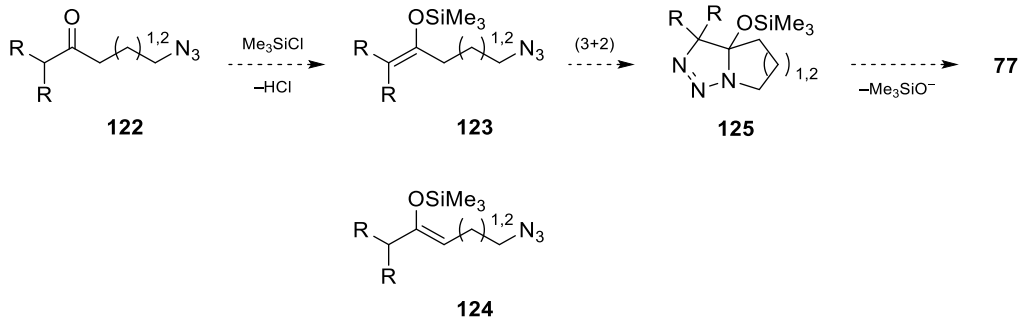


Figure 7: FMO theory of enolates regarding C-alkylation and O-silylation.

Alkyl halides are soft electrophiles, with low polarisation within the C–X bond. The reactivity of alkyl halides are therefore dictated by orbital overlap, rather than electrostatic interactions. There is a greater overlap between the (higher energy) enolate carbon HOMO coefficient and the alkyl halide σ* orbital, than with the (lower energy) oxygen coefficient.[323] Thus enolates alkylate on carbon with alkyl halides. Silicon halides on the other hand are hard electrophiles, with greater polarisation between the electropositive silicon and electronegative halide. Therefore silicon electrophiles tend to react with hard oxygen nucleophiles and O-silylate with enolates, forming a strong Si–O bond.

Note: Such dogma has been challenged recently with the release of Mayr *et al.*'s *Farewell to HSAB Treament of Ambident Reactivity*,[324] and is perhaps related to solvent and counterion effects. *O*-alkylation would represent the product of an early transition state governed by electrostatics, while *C*-alkylation the product of a late transition state governed by product stability (Hammond's postulate).[325]

Tetrasubstituted azidoalkyl silyl enol ethers **123** were seen as an attractive substitute for azidoalkyl enol ethers, and could conceivably be prepared from the enolisation and silylation of a parent azidoalkyl ketone **122** (Scheme 46). Following cycloaddition, 5-silyloxy-1,2,3-triazoline **125** could act as an intermediate *en route* to triazolium **77**.



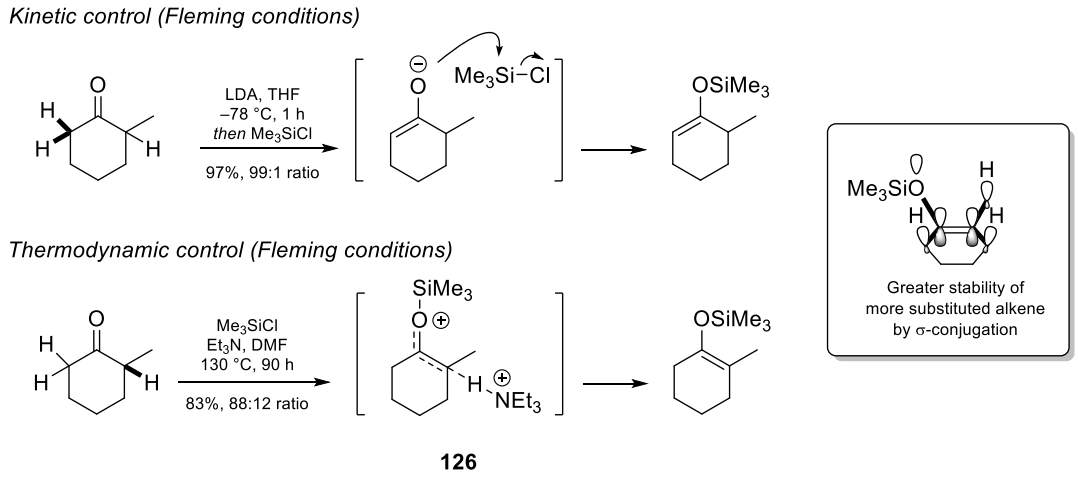
Scheme 46: Preparation of tetrasubstituted azidoalkyl silyl enol ethers from ketones.

Silylation of **122** could occur to give either a tetra- or trisubstituted azidoalkyl silyl enol ether, **123** vs **124**. The regiochemistry of enolisation is dictated by a combination of kinetic and thermodynamic factors.[326–330] Under kinetic control, the more accessible/ least-hindered protons are removed preferentially, leading to the less stable, less-substituted enol regioisomer **124**. Conditions that favour the kinetic product include a combination of strong base (LDA), low temperature (–78 °C), and a mild dipolar aprotic solvent (THF) (Scheme 47).[328]

Thermodynamic control, on the other hand favours the more stable, more substituted enol regioisomer **123**. The initial kinetic product must be able to able to equilibrate to a mixture of the two enol ethers (by a transition state such as **126**), made possible by the presence of a proton source (e.g. Et_3NH^+). The distribution of enol ethers will represent the difference in free energy between the two transition states (Curtin–Hammett principle). Conditions that favour the thermodynamic product include a combination of weak base (Et_3N), high temperature (130 °C), and long reaction times to reach equilibration (Scheme 47).[328]

Another way of rationalising the formation of either the kinetic or thermodynamic product is that under kinetic control, regioselective deprotonation of the more acidic/less hindered protons by the strong base occurs first, and is followed by silylation of the enolate (Scheme 47).[331] Under thermodynamic control however, the

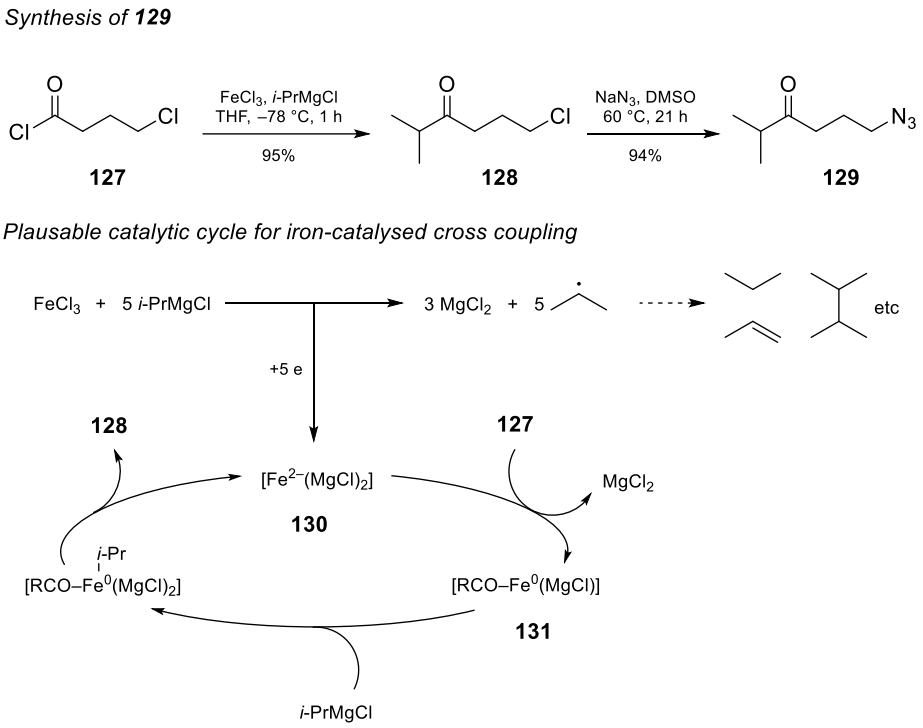
base is too weak to effect deprotonation first, and instead occurs second *via* a cationic transition state **126** following an oxygen-silicon interaction. Under thermodynamic control the rate of deprotonation is inconsequential (accessible vs hindered), the products can interconvert through re-protonation, and equilibrate to the more stable isomer. This will be the more substituted olefin due to greater σ-conjugation from the appended groups.



Scheme 47: Kinetic vs thermodynamic control in silylation of 2-methyl cyclohexanone.[328,331]

Azidoalkyl ketone **129** was prepared in two steps from 4-chlorobutanoyl chloride **127** (Scheme 47). To ensure mono-addition to the acid chloride, a modified literature procedure was used, converting **127** to isopropyl ketone **128** utilising a selective "iron-catalysed cross coupling reaction".[332] A plausible catalytic cycle for the cross coupling is given in Scheme 48, constructed from references within the original paper.[332–335] The active species, **130** is an "inorganic Grignard" with the formal composition of $[Fe^{2-}(MgX)_2]$. This highly nucleophilic species is able to oxidatively add the acid chloride to form formal Fe^0 species **131**. This species can be alkylated by the excess Grignard, before reductive elimination liberates **128** and regenerates the active species **130**. It should be noted that simple sterics may be a contributor for the effective

single addition of Grignard to **127**, but the reaction in the absence of $FeCl_3$ was not attempted.

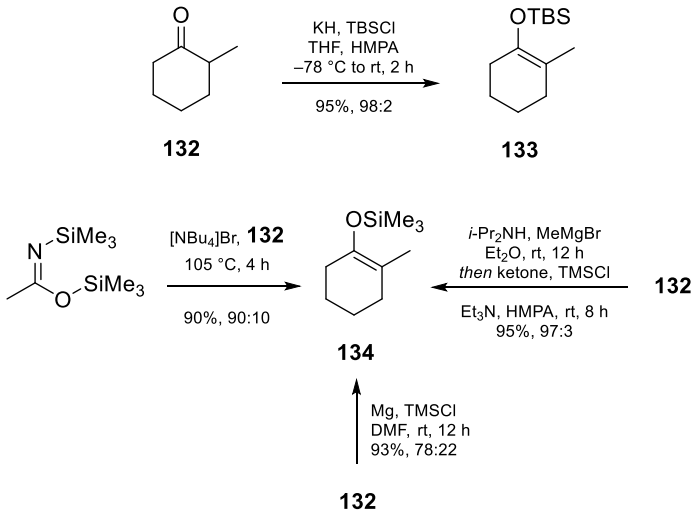


Scheme 48: Preparation of azidoalkyl ketone 129 and plausible catalytic cycle.[332–335]

We first sought to repeat the classical Fleming conditions for thermodynamic silyl enol ether formation on 2-methyl cyclohexanone (Scheme 47) before attempting reactions with **129**.[327,328] On a 300 mg scale, this route was ineffective, and simply returned starting material (note that Fleming conducted the reaction on a 14 g scale). As the Fleming conditions require prolonged heating at high temperatures, we felt this protocol, if successful, would allow the cycloaddition of **123** in one pot. This would be undesirable as it would complicate characterisation, and require extraction of a polar triazoline species from an equally polar solvent. Because of this, we sought milder conditions for the preparation of more substituted silyl enol ethers, so as to conduct controlled cycloaddition in a separate step.

A selection of "mild" thermodynamic conditions were screened on 2-methyl cyclohexanone **132** and found to provide reproducible selectivities (Scheme 49). KH is

a strong, but small base, removing hindered protons with ease. In methodology developed by Turner, equilibrium between the potassium-enolate isomers in HMPA occurs quicker than trapping with TBSCl, allowing the more hindered TBS enol ether **133** to be formed almost exclusively.[336] Mioskowski reported the preparation of **134** using (bistrimethylsilyl)acetamide (BSA) in molten $[NBu_4]Br$,[337] BSA being a mild, neutral silylating agent that does not require the addition of an added base. Gentle heating in the ionic liquid promotes equilibration to the more stable enol ether, and the product is isolated by simple distillation from the involatile reaction mixture. Compound **134** could also be prepared by the Mg-promoted coupling of **132** with Me_3SiCl.[338] This likely occurs through silylation of the enol tautomer of **132**, *via* a cationic intermediate stabilised by the polar solvent, then electron transfer from magnesium ($Mg + 2\ H^+ \rightarrow Mg^{2+} + H_2$). Finally, Krafft and Holton reported the regiospecific preparation of thermodynamic silyl enol ethers using bromomagnesium diisopropylamine (BMDA) as base.[339] Prepared *in situ* from MeMgBr and *i*-Pr_2NH, BMDA can deprotonate **132**, and the resulting magnesium enolate can then be trapped with TMSCl in the presence of Et_3N and HMPA (equilibrating conditions) with remarkable selectivity.

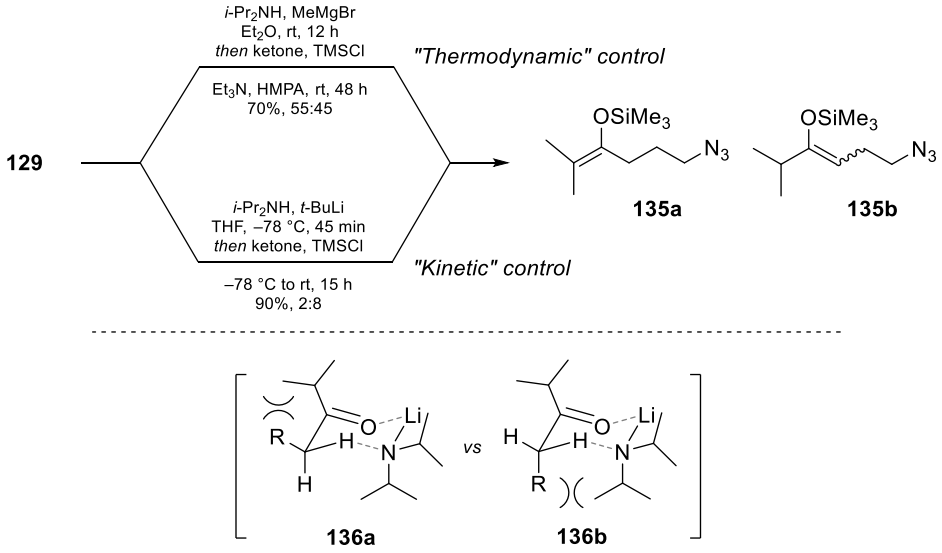


Scheme 49: Literature results for mild thermodynamic formation of silyl enol ethers from 132.[336–339]

Despite the literature procedure being highly reproducible with cyclic ketone **132**,[336] silylation of substrate **129** using KH and TBSCl was ineffective in our hands, instead providing full recovery of starting material. The Mg-mediated coupling[338] of **129** with TMSCl led to decomposition of starting material, possibly through complications involving the pendent azide functionality. Though the conversion was poor, the silylation of **129** using BSA in molten [NBu_4]Br[337] was effective qualitatively, but distillation of product from the reaction mixture on our scale (300 mg) was impractical. Additionally, the trace of product isolated was consistent with the "kinetic" isomer **135b**.

Finally, we found a successful route towards "thermodynamic" silyl enol ether **135a** by implementing BMDA with TMSCl, affording a 70% yield of both **135a** and **135b**, in a 55:45 ratio in favour of **135a**. (Scheme 50).[339–341] We found both isomers inseparable due to instability during chromatography (silica and alumina), but together were pure enough to be used crude in the next reaction. The 48 h reaction time was chosen to provide ample time for equilibration, though the reaction could be conducted at reflux over 24 h, with no improvement in regioselectivity.

In comparison, silylation of **129** under purely kinetic conditions[328] yielded an 2:8 ratio of enol ethers in favour of **135b**, and was identical in appearance to **135b** produced previously (Scheme 50). The configuration of **135b** was left unassigned, based on steric hindrance in both transition states **136a** and **136b**.

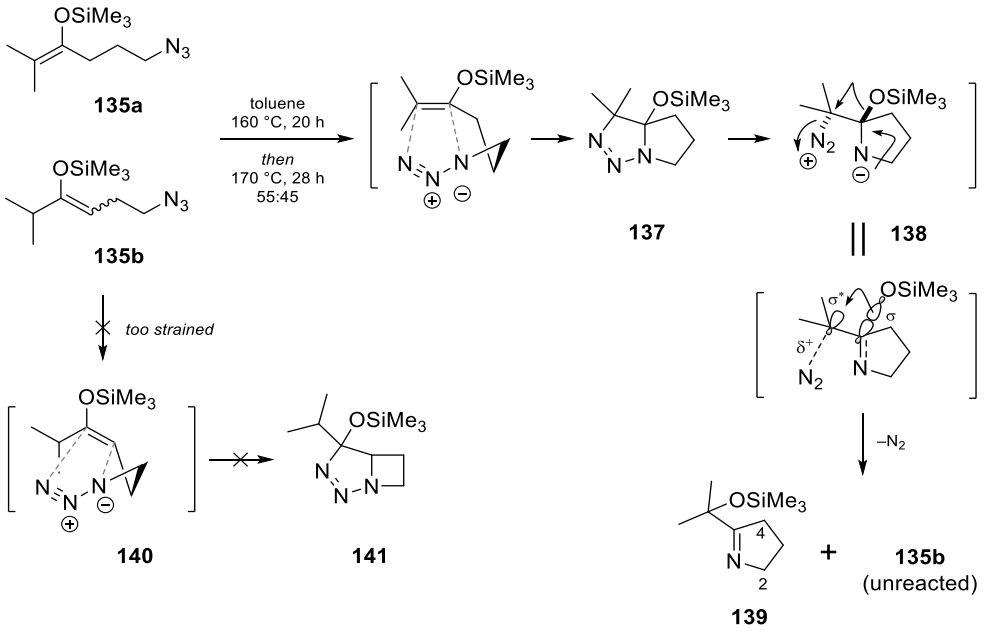


Scheme 50: Preparation of 135a and 135b by silylation under "thermodynamic" or "kinetic conditions".

The lower selectivities observed with **129** when compared to **132** may be a consequence of the acyclic ketone's more flexible open chain structure.

With **135a** in hand, albeit as part of an inseparable mixture, we were ready to test its cycloaddition, with the hope of achieving either an isolable triazoline, or evidence of triazolium **77**. When the **135a**/**135b** mixture was heated in toluene in a sealed tube (160 °C, 20 h, then 170 °C, 28 h), the selective reaction of **135a** was observed to take place, leading to a qualitative 55:45 mixture of α-silyloxy imine **139** and the recovered thermally stable **135b** (Scheme 51). Presumably, **135a** undergoes cycloaddition to provide the 5-silyloxy-1,2,3-triazoline intermediate **137**. Under the reaction temperature used for cycloaddition, **137** cleaves to form zwitterion **138** and fragments with imine formation, concurrent antiperiplanar 1,2-$OSiMe_3$ migration and nitrogen expulsion to form the α-silyloxy imine **139**. Analogous to the semipinicol rearrangement of a diazo salt (Tiffeneau–Demjanov rearrangement),[342] as imine formation cleaves the adjacent C–O bond, the filled (C–O)σ orbital migrates smoothly in a concerted 1,2-fashion to the cleaving antiperiplanar C–N_2 σ* **138**. Alternatively, if N_2 expulsion occurs

first, then $OSiMe_3$ simply migrates 1,2 into the empty p orbital. This 1,2-migration is consistent with IAOC reactivity discussed in Section **1.3.3**, though the migration of a hetero-atom is not known to our knowledge.



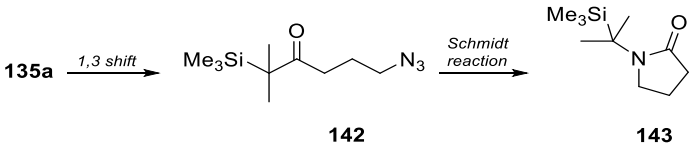
Scheme 51: Thermolysis of the 135a/135b mixture.

Regioisomer **135b** on the other hand has a restricting two-carbon tether, and therefore does not undergo cycloaddition.[226] This is due to the unfavourable strain present in both transition state **140** and azetidine **141**. The crude reaction solution was concentrated under reduced pressure to yield a brown oil, and characterised fully by NMR, m/z, and IR. The presence of an imine bond was indicated by both a weak IR absorption at 1660 cm^{-1}, and an imino carbon at 183 ppm. We have found pyrrolines such as **139** to have characteristic triple triplets in their ^{1}H-NMR spectra, corresponding to the CH_2 protons at both C2 (3.84 ppm) and C4 (2.64 ppm) coupling through the imine bond (Scheme 51).

When the crude mixture of **139/135b** was subjected to chromatography, the material could not be recovered from the silica column, and therefore a yield was not recorded. Frustratingly, we found this reaction to be irreproducible with subsequent

repeats (between 130–170 °C), and instead we simply observed a selective loss of **135a** and recovery of **135b**. This is consistent with the cycloaddition of **135a** and ensuing unknown decomposition pathways.

Compound **139** would be comparable in mass, IR, and NMR data to pyrrolidinone **143**, and thus we cannot rule out the possibility of this being the correct structure (Scheme 52). Such a product could arise through a 1,3-O to C migration of silicon during heating, giving **142**, followed by an intramolecular Schmidt reaction catalysed by trace acid. Because of the weight of corroborating IAOC literature (Section **1.3.3**), and subsequent results (discussed *vide infra*), we find **139** to be more plausible.



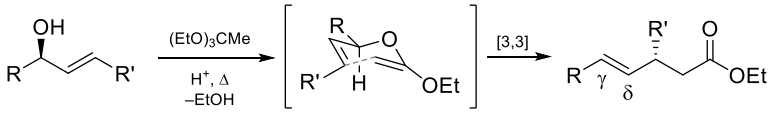
Scheme 52: Possible intramolecular Schmidt reaction en route to 143.

2.1.4 Johnson–Claisen rearrangement *en route* to tetrasubstituted azidoalkyl enol ethers.

In a project running parallel to the preparation of azidoalkyl enol ethers, we had utilised the Johnson–Claisen rearrangement (hereafter "JC rearrangement") of allylic alcohols *en route* to tetrasubstituted azidoalkyl vinyl bromides (Section **2.2**). Though unprecedented, we sought to extend this methodology to the preparation of tetrasubstituted azidoalkyl enol ethers.

In the classical JC rearrangement, allylic alcohols are transformed thermally into γ,δ-unsaturated esters **145** (Scheme 53).[343] By heating an allylic alcohol in the presence of $(EtO)_3CMe$ and a weak acid, the alcohol is converted into ketene-acetal **144** which undergoes [3,3]-sigmatropic rearrangement *via* an organised chair-like transition state. The driving force of the reaction is the generation of a stable carbonyl group, making the

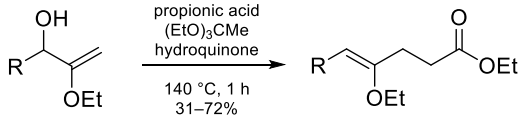
process irreversible. The JC rearrangement is usually conducted in glassware that allows the removal of volatile intermediates, as ethanol, the by-product *en route* to **145**, must be removed to drive the equilibrium towards the product. By virtue of the chair-like transition state, the rearrangement occurs with a high degree of stereospecificity.



144 **145**

Scheme 53: The Johnson–Claisen rearrangement of allylic alcohols to γ,δ-unsaturated esters.

While the JC rearrangement of aliphatic allylic alcohols is common, the analogous rearrangement of 2-alkoxy-allylic alcohols has received considerably less attention (Scheme 54). In 1992, Herradón's group reported the JC rearrangement of **146** to trisubstituted enol ethers **147** in low to good yields (31–72%).[344] Based on this precedent, we set out to extend this methodology towards the synthesis of tetrasubstituted azidoalkyl enol ethers.

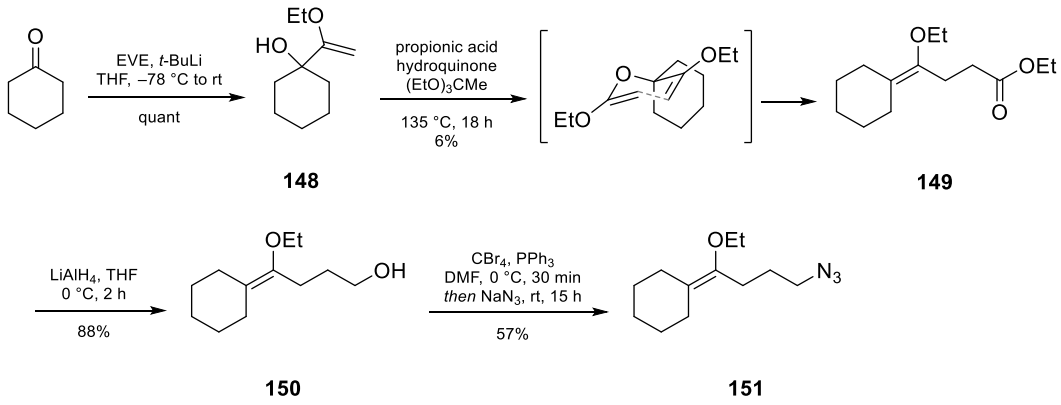


146 **147**

Scheme 54: Herradón's Johnson–Claisen rearrangement of 2-ethoxy-allylic alcohols to trisubstituted enol ethers.[344]

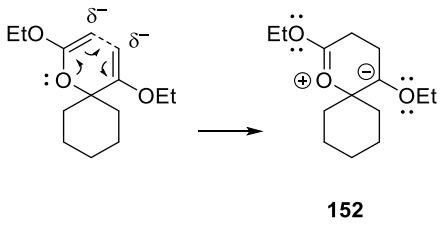
JC precursor **148** was prepared in quantitative yield from cyclohexanone using the α-metalation of ethyl vinyl ether (EVE),[276,345] as discussed in Section **2.1.1** (Scheme 55). **148** was first subjected to the JC conditions utilised for compound **187** (Section **2.2.3**).[343,346–348] Using a standard Claisen set-up for distillation, **148** (340 mg) was heated to 135 °C in $(EtO)_3CMe$ with hydroquinone as a radical scavenger.[344] Two drops of propionic acid were added every hour for 5 h, before leaving to heat overnight. Upon

work-up, the crude reaction profile suggested the consumption of starting material, however following chromatography, enol ether **149** was isolated in just ~6% yield (30 mg) and in low purity (Scheme 55). Modifying the concentration of acid resulted in either no conversion, or decomposition of the starting material, while substitution of propionic acid for either pivalic acid or PPTS offered no improvement.



Scheme 55: Preparation of enol ether 151 using a Johnson–Claisen rearrangement as the key step.

The unsuitability of **148** to undergo the JC rearrangement can be justified by considering several factors. Herradón speculated that the electron donating ethoxy group at the C2 position of **146** will retard the Claisen rearrangement,[344] which explains the absence of this class of rearrangement from the literature. The destabilising effect of the C2 ethoxy group can be explained by considering a theoretical transition state component **152** (Figure 8). While electron-withdrawing groups would expect to stabilise this transition state, electron-donating groups such as an ethoxy will have the opposite effect.[349] Alternatively, the effect could be due to a poor electrostatic match between the two δ^- methylidene terminals that must interact during the rearrangement.



152

Figure 8: Destabilising effect of C2 ethoxy group in the Johnson–Claisen rearrangement.

While Herradón achieved poor-to-good yields with secondary allylic alcohols **146** (31–71%), substrate **148** may impose additional reaction-retarding effects into the rearrangement. JC precursor **148** features both an acid labile enol ether, and an acid labile tertiary allylic alcohol. The addition of acid could promote both the dehydration, and hydrolysis of **148** under the thermolysis conditions, leading to several decomposition pathways (Figure 9) (Section **2.2.3**).

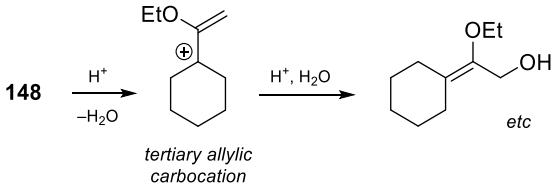
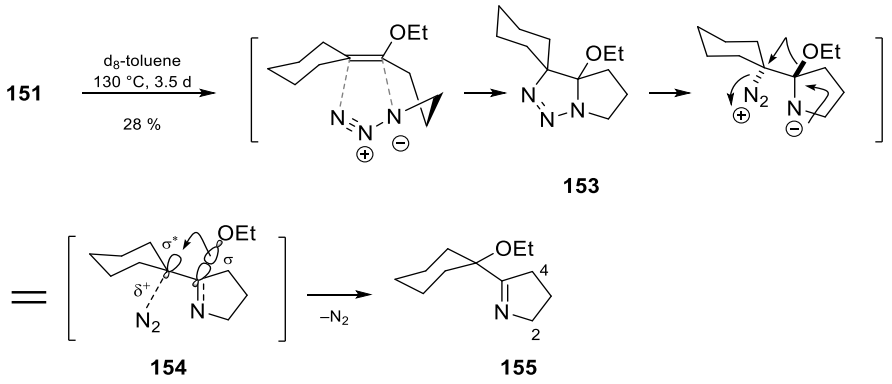


Figure 9: Theoretical acid-promoted decomposition of 148.

Despite the low yield of **149**, sufficient material was available to move forward with the intended synthesis (Scheme 55). Following routine $LiAlH_4$ reduction (**150**) and azide installation, a simple tetrasubstituted enol ether **151** was isolated in 50% yield over 2-steps (13 mg).

Substrate **151** (6 mg) was found to undergo complete cycloaddition in 3.5 d at 130 °C in deuterated toluene (Scheme 56). This rate is lower than fellow three-carbon tethered enol ethers **88** and **90**, likely due to an increase in steric hindrance around the fully-substituted dipolarophile. Additionally, the rate is lower than for four-carbon tethered **114**–**116** despite all being fully substituted, but this is due to the highly polarised olefin accelerating the reaction in those cases. The rate was comparable with

that of **89**, suggesting that a longer tether is offset by the existence of ring strain and *vice versa*.



Scheme 56: Thermolysis of 151 and proposed mechanism towards 155

α-Ethoxy imine **155** (1.5 mg) was isolated as the major product from chromatography of the crude reaction mixture, and characterised by ^{1}H-NMR and MS (Scheme 56). Mechanistically, cycloaddition of **151** provides the short-lived triazoline intermediate **153**. In the key step, 1,2-migration of the ethoxy group likely occurs with simultaneous imine formation and evolution of nitrogen **154**. The existence of **153** must be fleeting, as it could not be observed by ^{1}H-NMR analysis of the reaction mixture. This result is in line with that of **139** (**2.1.3**) and the wealth of 1,2-H/C migrations reported for IAOC reactions (**1.3.3**), but is a first for featuring a migrating heteroatom.

The troublesome JC rearrangement that was key to the synthesis of **151** precluded further study of this reaction class, and the sequence of reactions **150** to **155** was only conducted once. However, from this short study, it appears that tetrasubstituted azidoalkyl enol ethers do not lead to isolable triazolines upon cycloaddition, preventing the exploitation of triazolium **77**. The formation of α-hetero imines **139** and **155** was in agreement with work run parallel to this project (Section **2.2**), and so the study of azidoalkyl enol ethers was postponed in favour of more readily accessible equivalents: azidoalkyl vinyl bromides, discussed below. An additional

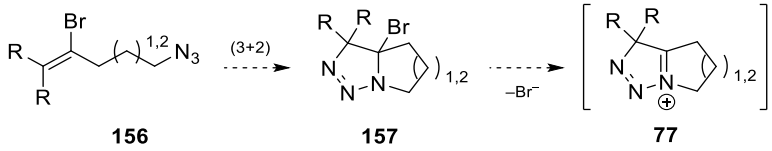
unsuccessful route *en route* to a tetrasubstituted azidoalkyl enol ether is featured in Section **4.2**.

Note: Compounds **150**, **151** and **155** were only prepared once and on small scale (30, 20 and 2 mg respectively) and, as such were not fully characterised. Compound **155** was characterised by ^{1}H-NMR and MS and featured the characteristic pyrroline splitting pattern observed for compounds of this type within this thesis; triple triplets for protons at both C2 (3.89) and C4 (2.59) due to long range coupling through the imine bond.

2.2 Azidoalkyl vinyl bromides

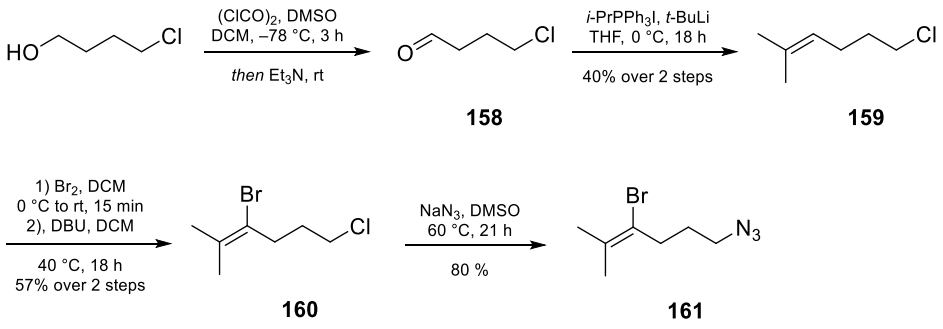
2.2.1 Azidoalkyl vinyl bromide test substrate

With the synthesis of fully-substituted enol ethers proving problematic (Section **2.1**), we decided to re-evaluate our design of precursors towards triazolium **77**. Scheme 35 reveals that the heteroatom in 1,2,3-triazoline **79** is sacrificial, and therefore inconsequential *en route* to triazolium **77**. We decided to investigate IAOC reactions of azidoalkyl vinyl bromides **156**, which theoretically would cyclise to 5-bromo-1,2,3-triazolines **157** before ionisation to triazolium **77** (Scheme 57). Intermolecular azide-vinyl bromide cycloadditions are scarce in the literature,[350] and to the best of our knowledge there have been no prior reports of an intramolecular azide-vinyl bromide cycloaddition (IAVBC).



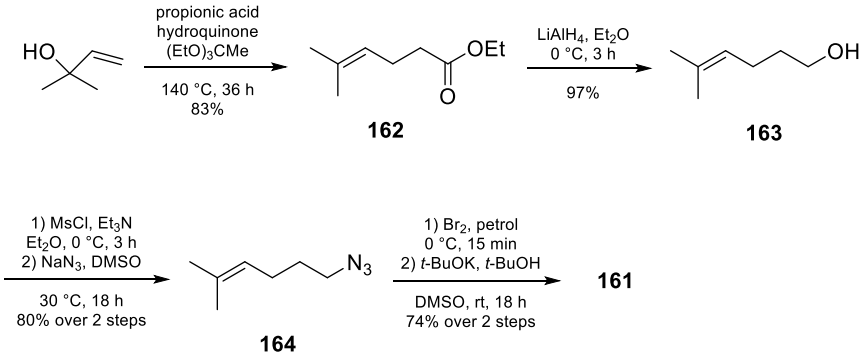
Scheme 57: Proposed IAVBC en route to 77.

The synthesis of test substrate **161** had two iterations. The first featured a Wittig reaction as the key carbon–carbon bond forming step, providing substrate **161** in 18% over 5 steps (Scheme 58).[351,352] The atom-inefficient nature of the Wittig reaction, in combination with a low yield and difficulties in separating the product from Ph_3PO, led us to seek an alternative route.



Scheme 58: First generation synthesis of 161 via a key Wittig reaction.

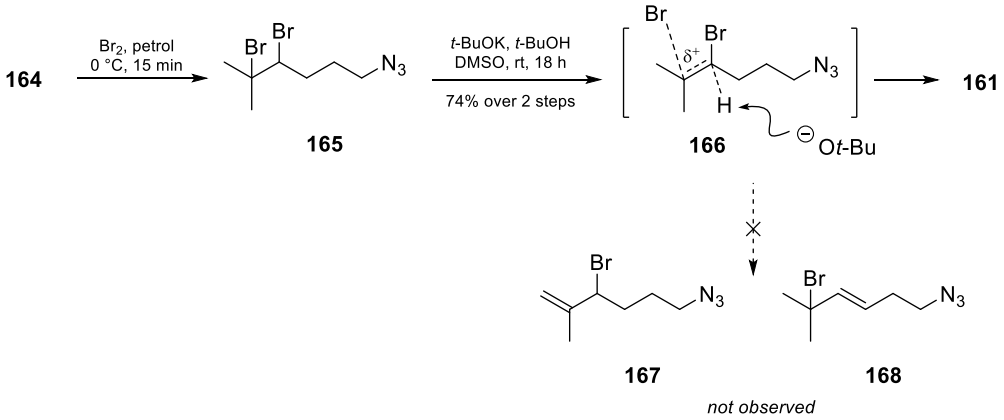
The second generation route featured a Johnson–Claisen (JC) rearrangement (*vide supra* **2.1.4**) as the key carbon–carbon bond forming step, and resulted in an improved yield (47% over 6 steps, Scheme 59). Starting from the commercially available 2-methyl-3-buten-2-ol, a JC rearrangement set in place the required carbon skeleton in γ,δ-unsaturated ester **162**.[343,346–348] Hydride reduction, *O*-mesylation, and azide installation yielded azidoalkyl olefin **164**.



Scheme 59: Second generation synthesis of 161 via a key JC rearrangement.

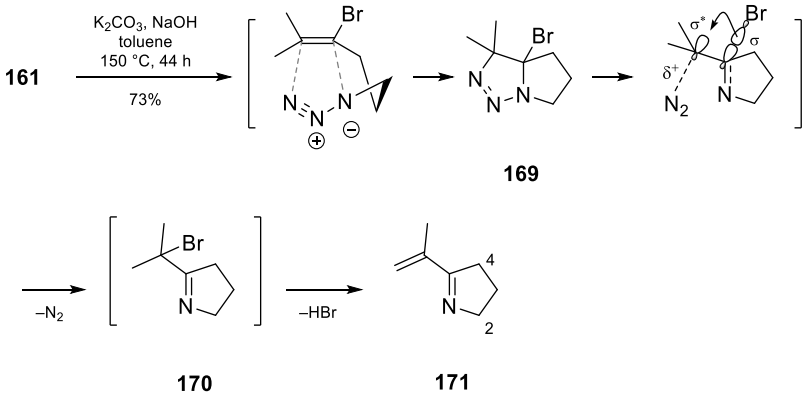
Unlike tetrasubstituted enol ethers, tetrasubstituted vinyl bromides are readily available from their corresponding trisubstituted olefins.[353–355] Alkylidene **164** was subjected to a bromination/dehydrobromination protocol in order to yield the fully substituted azidoalkyl vinyl bromide test substrate **161** (Scheme 59). Pleasingly, deprotonation of dibromide **165** with *t*-BuOK in DMSO at ambient temperature (or with DBU in DCM at 40 °C) provided the desired regioisomer **161** selectively (Scheme 60). There was no detectable trace of either of the undesired dehydrobromination regioisomers **167** or **168**, which would arise through removal of the more accessible, protons in **165**. This suggests a late transition state (Hammond's postulate)[325] with regioselective deprotonation driven by forming the more substituted double bond, with the cationic transition state **166** being stabilised by σ-conjugation from the appended

alkyl groups. DMSO was the solvent of choice, both for increasing the basicity of *t*-BuO⁻ through K-ligation, and presumably for stabilising the transition state **166**.



Scheme 60: Dehydrobromination of 165.

With test substrate **161** in hand, its cycloaddition was investigated. Heating **161** at 130 °C under either microwave conditions in MeCN, or in a pressure tube with toluene, resulted only in the slow decomposition of starting material to an intractable brown tar. Taking inspiration from **2.1.1**, K_2CO_3 was added to the reaction and the product of the reaction could then be determined; alkenylpyrroline **171** (Scheme 61).

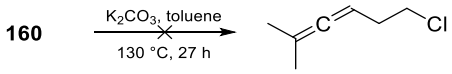


Scheme 61: Conversion of 161 to 1-azadiene 171 and proposed IAVBC mechanism.

Upon heating, **161** undergoes an IAVBC to yield the triazoline **169** *in situ*, which spontaneously fragments with concerted 1,2-migration of bromine, imine formation, and nitrogen evolution to afford α-bromo imine **170** (see **2.1.3**–**2.1.4** for similar

reactivity). Driven by the stability of conjugation, the labile tertiary bromide dehydrobrominates *in situ*, likely *via* an E1 mechanism, to yield alkenylpyrroline **171**, a 1-azadiene (Scheme 61). Thus, K_2CO_3 was required to neutralise the liberated HBr and prevent acid-catalysed decomposition. The alkenylpyrroline contained the characteristic pyrroline triple triplet splitting pattern for protons at C2 (3.85 ppm) and C4 (2.26 ppm), as observed for pyrrolines **139** and **155** (*vide supra*).

In support of the proposed IAVBC mechanism, elimination of HBr from **161**, followed by an analogous allene-azide cycloaddition appears unlikely, as subjecting **160** to identical reaction conditions produced no reaction (Scheme 62).



Scheme 62: Attempted dehydrobromination of 160.

A brief optimisation study was performed in order to improve the efficiency of 1-azadiene formation. The standard reaction set-up is shown in Figure 10. Using an appropriately sized Ace pressure tube (often 14 mL); starting material, stir-bar, solvent, and additives were degassed with argon, and the vessel thread-sealed with PTFE tape and sealed using a screw-cap with O-ring. The outer vessel was insulated using cotton wool/ aluminium foil, and the pressure tube heated for the appropriate time with vigorous magnetic stirring.

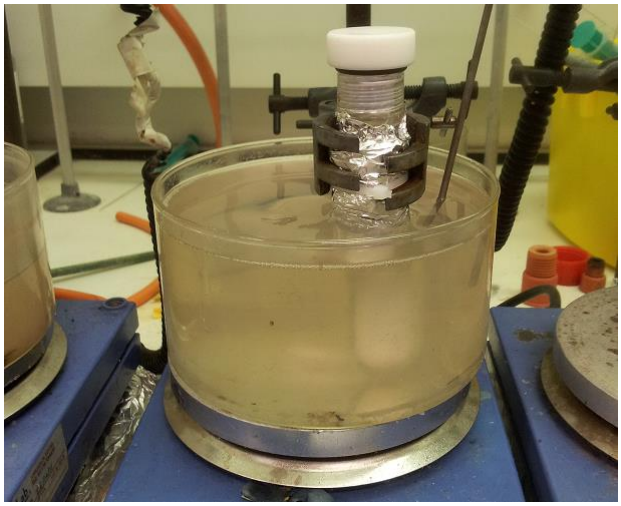


Figure 10: Standard set-up for cycloaddition reactions using Ace pressure tubes.

Using high-boiling deuterated solvents of varying polarity, **161** was heated at 100 °C for 3 d 17 h (Table 1). This temperature and time were chosen so as to be below the boiling point of the solvents used and to provide an appreciable observed conversion. By comparing the relative integration of starting material to product peaks by ^{1}H-NMR spectroscopy, the percentage conversion of the crude reaction was estimated. The conversion was found to follow the dipole moment of the solvent, perhaps by stabilising the build-up of charge during the reaction transition state (Scheme 61). The conversion appeared marginally greater in DMSO (~11%) > pyridine (~10%) > toluene (~7%). Due to its inert nature and ease of removal, toluene was progressed further in trade off of cycloaddition rate.

Solvent	Dipole moment[a] (D)	Estimated conversion[b] (%)
d_6-DMSO	3.960	11
d_5-pyridine	2.200	10
d_8-toluene	0.375	7
[a] Source: Sigma Aldrich. [b] by ^{1}H-NMR		
Set up: **161** (10 mg), K_2CO_3 (10 eq.), solvent (0.75 mL), 100 °C, 3 d 17 h		

Table 1: Solvent study on cycloaddition of substrate 161.

We next sought to determine which additive(s) would most effectively quench the liberated HBr from the reaction and preserve **171** at high temperature (Table 2). K_2CO_3 is both a base and a desiccant, so additives were chosen to replicate these properties. Propylene oxide was included as a non-basic scavenger of HBr, in the event that any future prepared substrates prove to be base sensitive. As shown in Table 2, a combination of K_2CO_3 and NaOH was taken forward as optimal for preserving **171** in solution. The equivalents of K_2CO_3 were maintained at 10 to ease with weighing operations on small scale, while the equivalents of NaOH were reduced to 2 to minimise etching of the glassware at high temperatures.

Additive(s)	Estimated conversion[a] (%)
K_2CO_3 + NaOH	17
NaOH + $MgSO_4$	16
K_2CO_3	14
NaOH	14
propylene oxide	10
Ag_2O + $MgSO_4$	3
[a] by ^{1}H-NMR	
Set up: **161** (10 mg), additive(s) (10 eq.), d_8-toluene (0.75 mL), 130 °C, 20 h	

Table 2: Additive study on cycloaddition of substrate 161.

The reaction was remarkably slow, taking 7 d at 130 °C in toluene to reach completion (Table 3). This is understandable, as the olefin electron density, and reactivity towards *inverse-demand* $HOMO_{dipolarophile}$ cycloaddition, decreases in the order enamine > enol ether > vinyl bromide, so **161** would expect to take longer than enol ether substrates (Section **2.1**). The rate of reaction doubled for each 10 °C rise in temperature and, consequently, 44 h at 150 °C was found to be a suitable compromise between rate and temperature.

Temperature (°C)	Time
130	7 d
140	3 d 20 h
150	1 d 20 h
Set up: **161** (10 mg), K_2CO_3 (10 eq.), d_8-toluene (0.75 mL)	

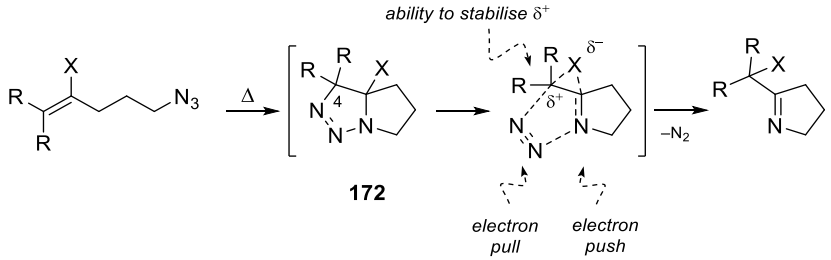
Table 3: Temperature study on cycloaddition of substrate 161.

Finally, the concentration of the reaction was varied so as to identify the cleanest reaction profile. A concentration of 0.05 M resulted in a clean crude profile by ^{1}H-NMR analysis, presumably by supressing dimerisation of product **171** at high temperature (unconfirmed). Under identical conditions, a 0.41 M reaction provided an unclean crude ^{1}H (d_8-toluene) baseline, while 0.1 M was acceptable.

Using the optimised conditions, a 0.05 M solution of substrate **161** (60 mg) in toluene (5.5 mL) with 10 eq. K_2CO_3 and 2 eq. NaOH was heated for 44 h at 150 °C (Scheme 61). Careful chromatography over silica/0.1% Et_3N yielded product **171** in a 73% yield (as a 63% w/w mixure with Et_3N). A solvent-free analytical sample could be obtained by further concentration, but at the expense of some loss of the volatile, low molecular weight product.

At this point, sufficient evidence had been gained to allow an evaluation of triazolium **77** and its proposed elaboration (Scheme 35). Di- and trisubstituted enol ethers **87**–**90** provided stable triazolines on heating, but the results of Section **2.1.1** indicated the need for a fully substituted enol ether in order to prevent aromatisation to the corresponding triazole (Scheme 38). However, based on the results obtained for substrates **135a**, **152**, and **161**, it would appear that the more substituted the olefin, the greater the ability to stabilise a positive charge at the 4-position of the subsequent substituted-triazoline **172** (Scheme 63). Experimental evidence suggests that triazolines with such substitution are biased towards spontaneous 1,2-heteroatom

migration at the high temperatures of cycloaddition, initiated by a concerted electron *push* from the forming imine nitrogen and *pull* from the forming carbocation at the 4-position.



Scheme 63: Rationale behind fragmentation of 4-disubstituted hetero-triazolines.

Triazolines that could not readily stabilise a positive charge at this position (**94**–**98**, **118**, and **119**) were isolable following cycloaddition.

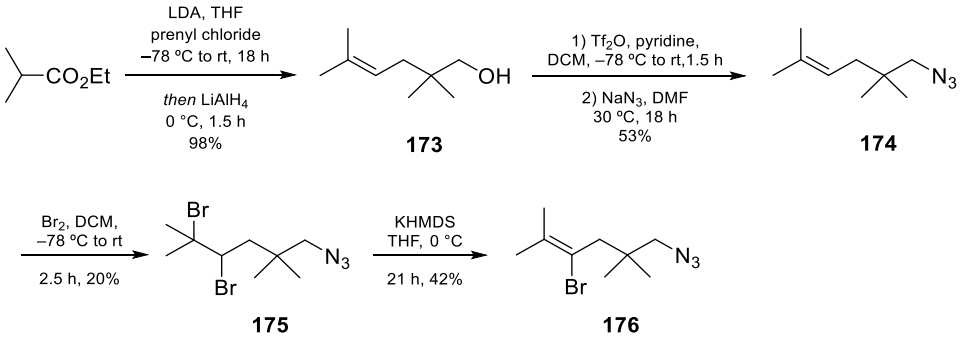
2.2.2 Effect of tether substitution and length upon IAVBC reactions

With vinyl bromide substrate **161** yielding 1-azadiene **171** at the end of a novel cascade sequence, we were curious to test the generality of this reaction. Under the temperature required for cycloaddition, the intermediate triazoline **169** spontaneously fragments to form an α-bromo imine **170** before dehydrobrominating to **171** (Scheme 61). We expected that lowering the reaction temperature by increasing the cycloaddition bias within the system would enable the intermediate triazoline to be isolated and exploited.

The rate-acceleration arising from the gem-dialkyl effect has been classically explained as an angle compression relative to unsubstituted cases, whereby increasing the size of two substituents on an sp^3-carbon centre leads to enhanced reactivity between the other two appended functionalities (Thorpe–Ingold effect).[287] The rate acceleration is likely entropic in origin, increasing the proportion of conformers

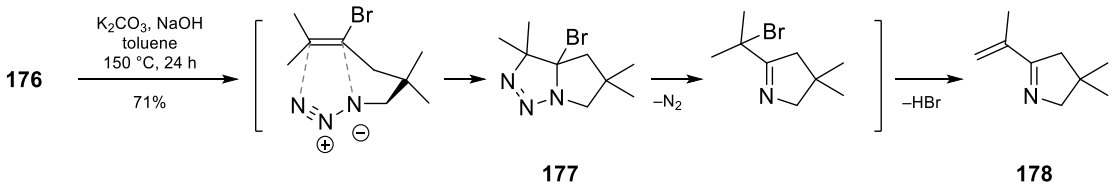
appropriate for reaction. The gem-dialkyl effect is frequently exploited to increase the rate of ring closures by cyclisation and cycloadditions.

Gem-dimethyl substrate **176** was prepared in a 4% yield over 5 steps (Scheme 64). The low-yield was attributed partially to a problematic bromination, whereby the gem-dialkyl substituents may bring the pendent azide functionality into close proximity with the intermediate bromonium ion, causing undesired decomposition pathways. When bromination was conducted on alcohol **173**, bromoetherification took preference. The dehydrobromination of dibromide **175** was entirely selective, although only moderate yielding, with no observable trace of undesired regioisomers (see **2.2.1**).



Scheme 64: Synthesis of gem-dimethyl substrate 176.

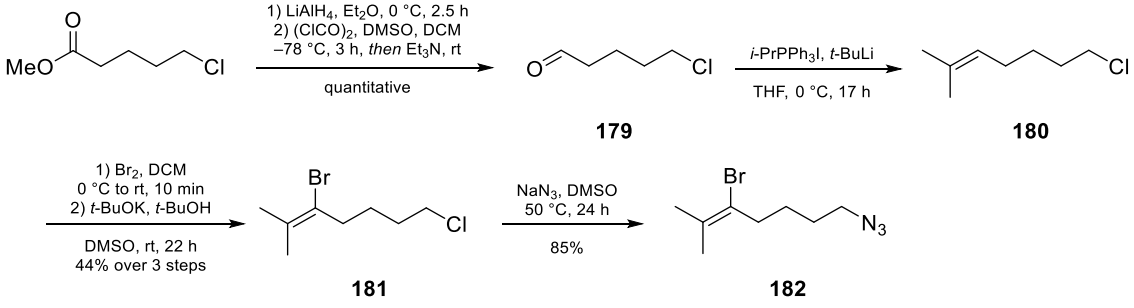
Gem-dimethyl vinyl bromide **176** required 4 days at 130 °C, or 24 h at 150 °C to undergo complete cycloaddition (Scheme 65). The gem-dialkyl effect roughly halved the reaction time in comparison to the naked system **161**, indicating a small increase in cycloaddition bias within the system. The reaction pathway was analogous to the previous substrate **161**, with fragmentation and dehydrobromination following cycloaddition *in situ*, yielding alkenylpyrroline **178** in a 71% yield after chromatography.



Scheme 65: Cycloaddition of 176 to 1-azadiene 178.

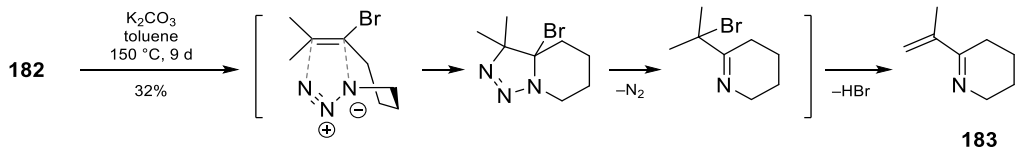
Despite the rate acceleration, the intermediate triazoline **177** could not be observed by ^{1}H-NMR (d_8-toluene) analysis during cycloaddition at 130 °C. Lowering the reaction temperature to 75 °C gave only a 3% conversion to alkenylpyrroline **178** after 3 days, with no sign of intermediate triazoline in the ^{1}H-NMR spectra. It appears that even at the lower limit of temperature/ reactivity, the triazoline is still too unstable to survive fragmentation. The fragmentation temperature of intermediate **177** must be well below 75 °C, making isolation and exploitation unlikely.

Decreasing the entropic freedom of the azide tether, as demonstrated by the gem-dialkyl effect, had a rate accelerating influence on the reaction (**161** vs **176**). Therefore increasing the entropic freedom of the azide tether should have the opposite effect. We wished to investigate the rate of reaction using a four-carbon tethered azidoalkyl vinyl bromide, and determine the extent of hindrance the longer tether imparted. Four-carbon tethered azidoalkyl vinyl bromide **182** was prepared in 37% yield over 6 steps using a Wittig olefination as the key carbon–carbon bond forming procedure (Scheme 66).



Scheme 65: Synthesis of four-carbon tethered substrate 182.

When compared to the three-carbon tethered analogue **161**, the extra methylene had a remarkable rate-retarding effect on the cycloaddition. Vinyl bromide **182** took 9 days at 150 °C to complete cycloaddition, a decrease in rate by a factor of ~5 (**182** vs **161**). This is a far greater effect than observed for the three and four-carbon tethered enol ethers (**87**–**90**) in Section **2.1.1**. Due to the prolonged heating, the reaction was performed at a higher dilution (0.036 M) and in the absence of NaOH to prevent dimerisation of the product and damage to the pyrex pressure tube. 1-Azadiene **183** was isolated in a low 32% yield following chromatography, presumably due to the prolonged reaction time (Scheme 66).

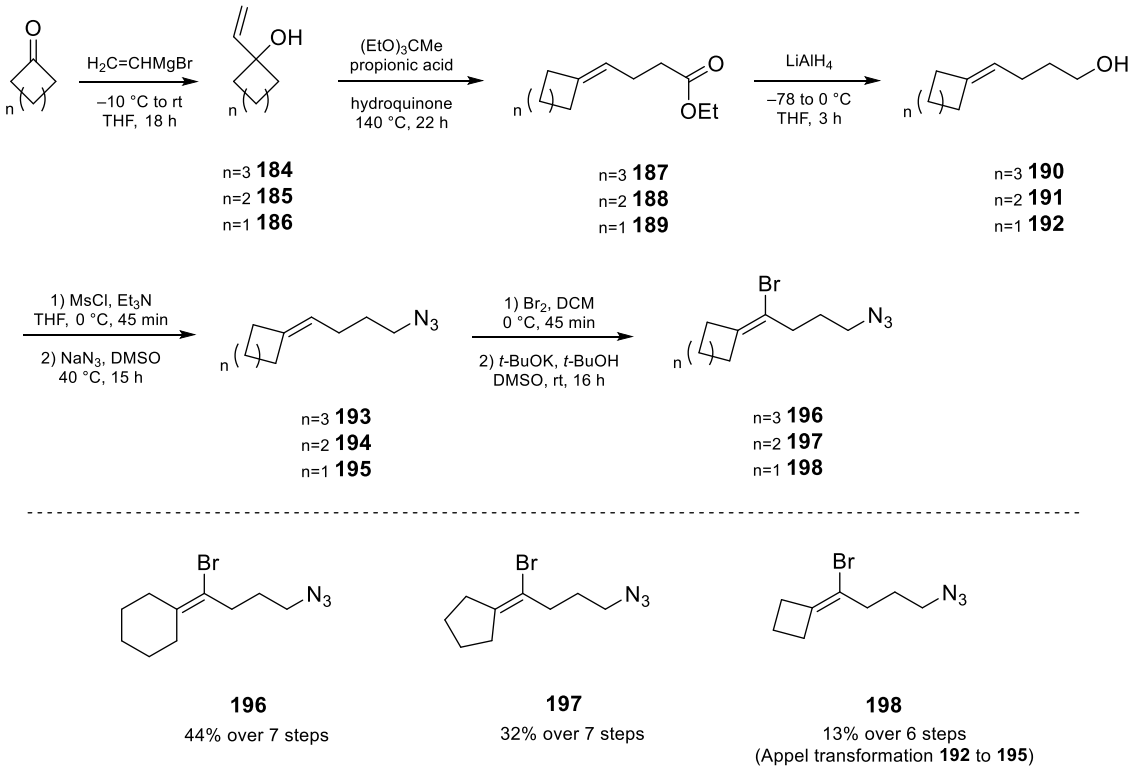


Scheme 66: Cycloaddition of 182 to give 1-azadiene 183.

The above result shows that to be synthetically useful, a four-carbon tethered azidoalkyl vinyl bromide would need additional conformational or electronic bias within the system, either in the form of ring-strain across the olefin, or a dialkyl-substituted azide tether.

2.2.3 Effect of ring-strain on IAVBC reactions

It was theorised that ring-strain across the olefinic bond would have a rate-accelerating effect on the IAVBC reaction when compared to substrate **161**. Starting from the corresponding cyclic ketone, cyclohexyl, cyclopentyl, and cyclobutyl vinyl bromides **196**–**198** were prepared using a key JC rearrangement to construct the carbon skeleton (Scheme 67).[343,346–348] Over 11 g of substrate **196** was prepared starting from 10 g of cyclohexanone, in 44% yield over 7 steps with just one final chromatographic separation.



Scheme 67: Synthesis of cyclic vinyl bromides 196–198.

Initially, the JC rearrangement on cyclic tertiary alcohols **184**–**186** was troublesome and low yielding using propionic acid. The JC rearrangement of acyclic tertiary allylic alcohols is rare in the literature, and the reaction of cyclic tertiary alcohols have no precedent. The tertiary alcohol is acid labile and able to stabilise an allylic carbocation. Thus, in high concentrations, the acid catalyst causes decomposition of the starting material with NMR data suggesting structures shown in Figure 11. It was found that the minimal addition of propionic acid (~5 mol%) at hourly intervals for 5–6 h was effective at promoting the clean JC rearrangement of tertiary allylic alcohols. The reaction was optimised to yields of >84%, >61%, and 79% for **187**–**189** respectively.

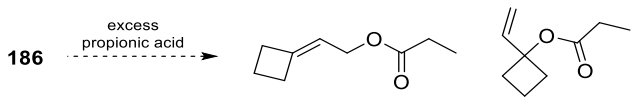
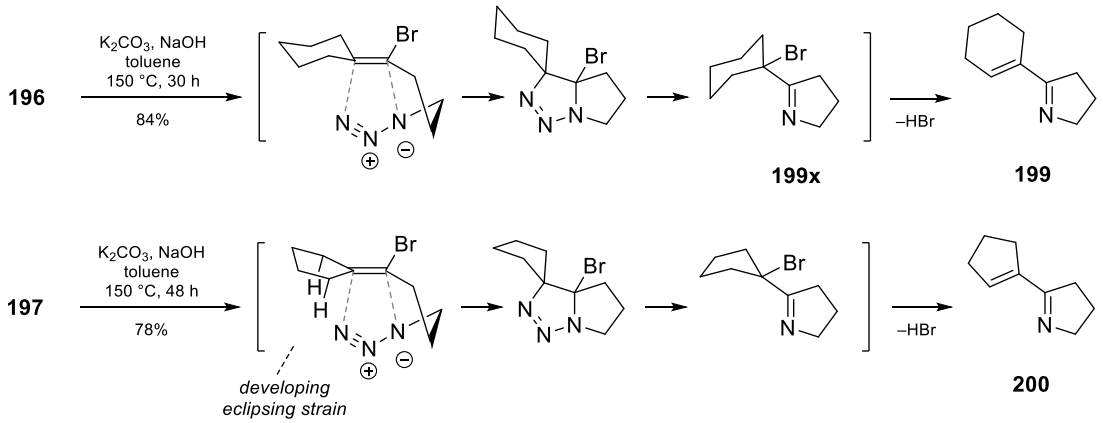


Figure 11: Proposed acid-mediated decomposition structures during the JC rearrangement of 186.

Both cyclohexyl, and cyclopentyl vinyl bromides **196** and **197** provided clean conversion to their corresponding alkenylpyrrolines **199** and **200** upon heating, which were isolated in yields of 84% and 78% respectively (Scheme 68). In a test-cycloaddition using substrate **196**, the proposed α-bromo imine intermediate **199x** was isolated in low yield (12%) and fully characterised, supporting the proposal of this type of intermediate *en route* to 1-azadienes.

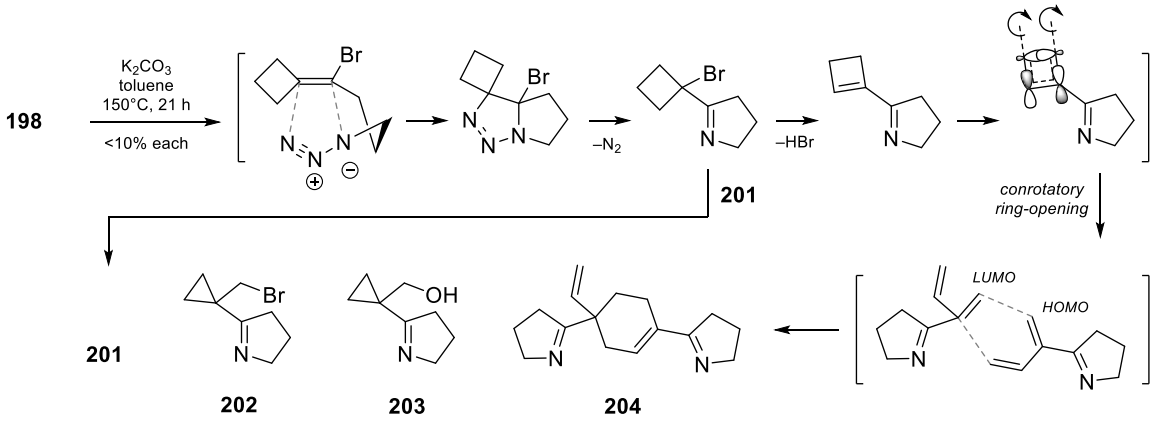


Scheme 68: Conversion of cyclic substrates 196 and 197 to 1-azadienes 199 and 200.

The presence of an exo-cyclopentyl group across the olefinic bond did not have a rate-accelerating effect on the cycloaddition as compared to the naked system. Substrate **197** took 48 h at 150 °C to undergo cycloaddition, compared to 44 h for substrate **161**. On the contrary, the cyclohexyl substrate **196** proved much more reactive towards cycloaddition, taking just 30 h at 150 °C. This result at first seems counterintuitive; that a larger, more flexible six-membered ring with its chair-conformation, would have a greater relative influence on cycloaddition than a smaller five-membered ring. This reactivity trend parallels that observed for the rate of $NaBH_4$ reduction of cyclic ketones.[356] The transformation of an sp^2 to an sp^3 centre upon cycloaddition is unfavoured in the cyclopentyl case due to eclipsing strain in the transition state between the forming sp^3 centre and the adjacent ring hydrogens (Scheme 68). Thus, any rate-

accelerating Baeyer strain within the cyclopentyl system is offset by this effect. The larger, more flexible cyclohexyl ring does not develop this form of strain during the cycloaddition, and thus is not hindered.

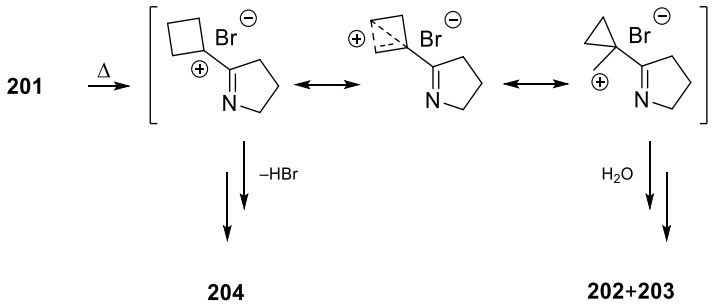
The strained cyclobutyl vinyl bromide **198** gave the largest increase in reaction rate, with the cycloaddition taking <21 h at 150 °C. This added strain would lead to further complications, discussed below (Scheme 69).



Scheme 69: IAVBC reaction of cyclobutyl substrate 198 leading to 201–204.

Under the temperature of reaction, the cyclobutyl vinyl bromide **198** undergoes IAVBC and fragmentation *in situ* to yield α-bromo imine **201**. The α-bromo imine was isolable, as well as two ring-contraction derivatives **202** and **203**. The alcohol **203** may result from hydrolysis during chromatography. The α-bromo imine **201** can also dehydrobrominate to provide a strained 1-azadiene that after conrotatory[149,150] electrocyclic ring-opening, affords an 1-azatriene. This 1-azatriene apparently undergoes an intermolecular Diels–Alder dimerisation to yield **204**. Compounds **201**–**204** were isolated in <10% yield each. Lowering the temperature (7 d at 115 °C, 2 d at 130 °C) did little to tame this reaction, serving only to decrease the formation of Diels–Alder product **204**.

Cyclobutyl cations are equivalent to methyl-cyclopropyl cations,[357,358] which explains the formation of products **202** and **203** (Scheme 70). Thus, as α-bromo imine **201** undergoes E1 bromide elimination to form an tight ion pair, the resulting cation may proceed down either reaction pathway towards ring-contraction products **202** and **203**, or dimer **204**.

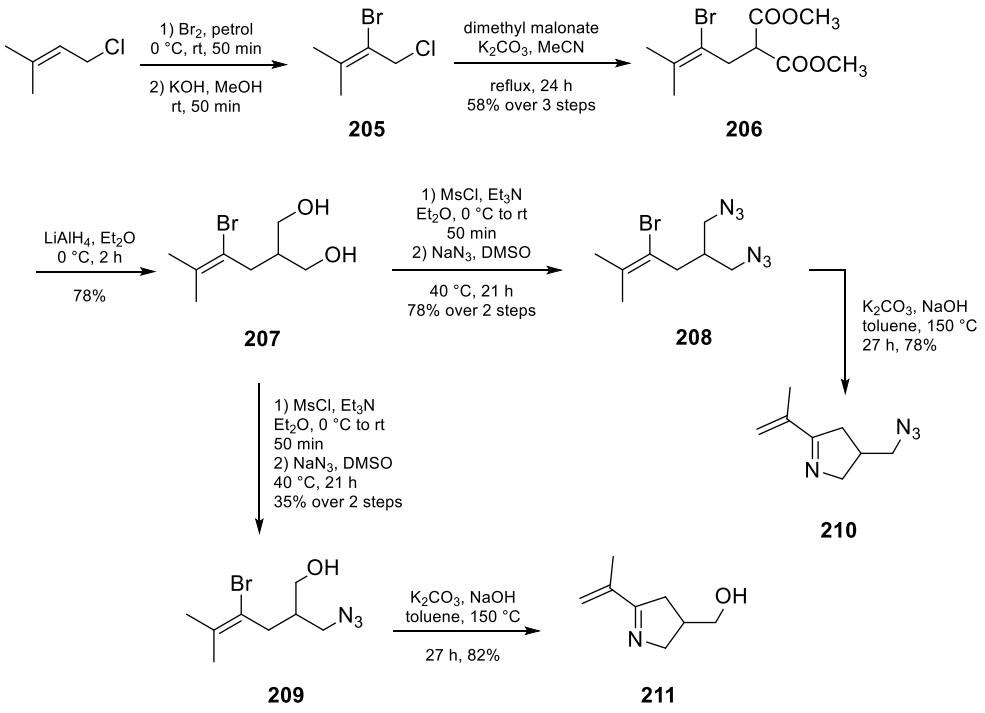


Scheme 70: Conversion of 201 into 202–204.

This study demonstrated that there is a delicate balance between the strain-induced rate-acceleration towards IAVBC and the high reactivity of the resulting intermediates. Among four to six membered alkylidene ring-systems, cyclohexyl systems provide a good balance of cycloaddition reactivity and clean conversion to the corresponding 1-azadiene.

2.2.4 Functionalised azidoalkyl vinyl bromides

To access more complex 1-azadienes and test functional group tolerance, we set out to prepare azidoalkyl vinyl bromide substrates that contain functionalised tethers. Prenyl chloride derivative **205** was used to alkylate dimethyl malonate which, upon reduction with $LiAlH_4$, yielded the parent diol **207** in 45% over 4 steps (Scheme 71).



Scheme 71: Synthesis of substrates 208 and 209 and IAVBC to 1-azadienes 210 and 211.

Diol **207** was a common precursor to access both azide and alcohol functionalised azidoalkyl vinyl bromides **208** and **209**. Diol mesylation followed by azide displacement yielded diazide compound **208** in good yield (78%). Mono-mesylation was more difficult, with dimesylation competing heavily, even with a single equivalent of MsCl. Due to this poor selectivity, alcohol-functionalised substrate **209** was isolated in a lower yield (35%), with diazide **208** as a side-product (18%). The use of a bulkier activating group (TsCl) offered no improvement.

Despite diazide substrate **208** possessing an alarming carbon/nitrogen ratio of 1:0.75 ($C_8H_{13}BrN_6$), we experienced no detonation of substrate during handling, both at room temperature with glass pipettes, or under high temperatures during cycloaddition. The compound could be concentrated to a neat oil without issue. Academics have offered varying safety guidelines for the handling of highly nitrogenous compounds, including Smith, who suggested that the number of nitrogens must not exceed those of carbon and

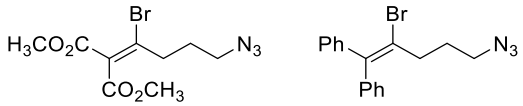
that $(N_n+C_m)/N_n \geq 3$ for compounds to be safe (**208** = 2.33).[30] Sharpless suggested a "rule of six" (six carbons per energetic azide functional group) in order to effectively dilute the reactivity within the molecule (**208** is short by 4 carbons).[142]

Both substrates **208** and **209** were cleanly converted upon heating to their corresponding 1-azadienes **210** and **211** in good yields (Scheme 71). The tertiary centre within the three-carbon tether increased the bias towards cycloaddition in a manner akin to the gem-dialkyl effect (Section **2.2.2**). Thus, both mono-substituted substrates required 27 h at 150 °C to undergo complete cycloaddition. Gratifyingly, this rate is in scale with dimethyl substituted substrate **176** (24 h), and far higher than the un-substituted, un-functionalised system **161**, (44 h).

While substrate **209** reacted successfully at a 0.05 M concentration as according to the optimised conditions, **210** required greater dilution to obtain comparable yields (0.02 M). This presumably supresses unconstructive interactions between the azide and the olefin moieties between molecules at high temperatures.

2.2.5 Azidoalkyl vinyl bromides lacking β-hydrogens

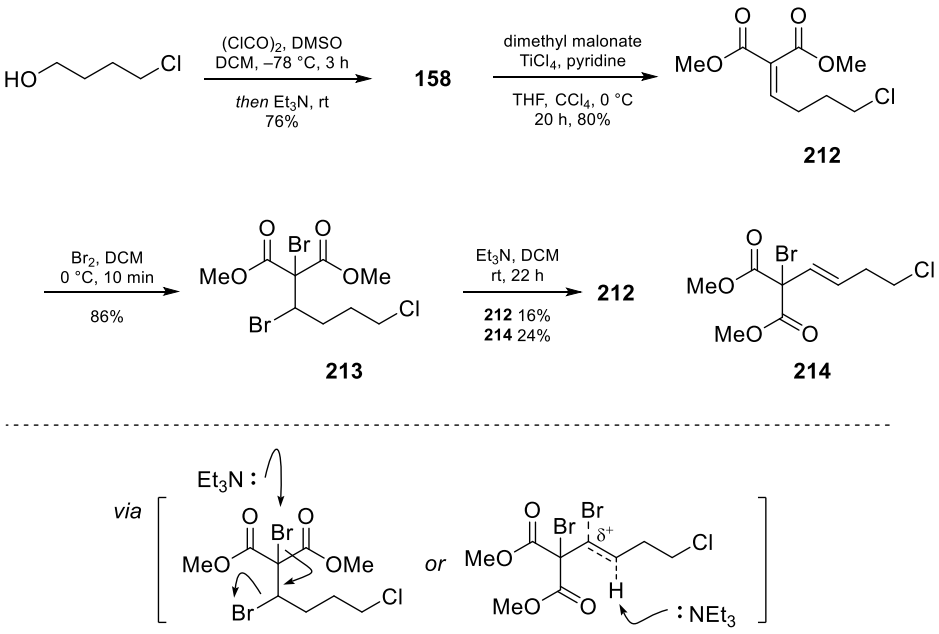
It has already been explained that the intermediate IAVBC triazolines fragment to provide α-bromo imines. When β-hydrogens are present, the α-bromo imine dehydrobrominates *in situ* to give a 1-azadiene (Scheme 61, **170** → **171**). To determine the fate of the α-bromo imine under different circumstances, azidoalkyl vinyl bromides were chosen that lack the requisite β-hydrogens: a diester azidoalkyl vinyl bromide **224**, and a diphenyl azidoalkyl vinyl bromide **231** (Figure 12). In such an environment, the cascade will either terminate at the α-bromo imine, or proceed further through unforeseen rearrangement pathways.



224 **231**

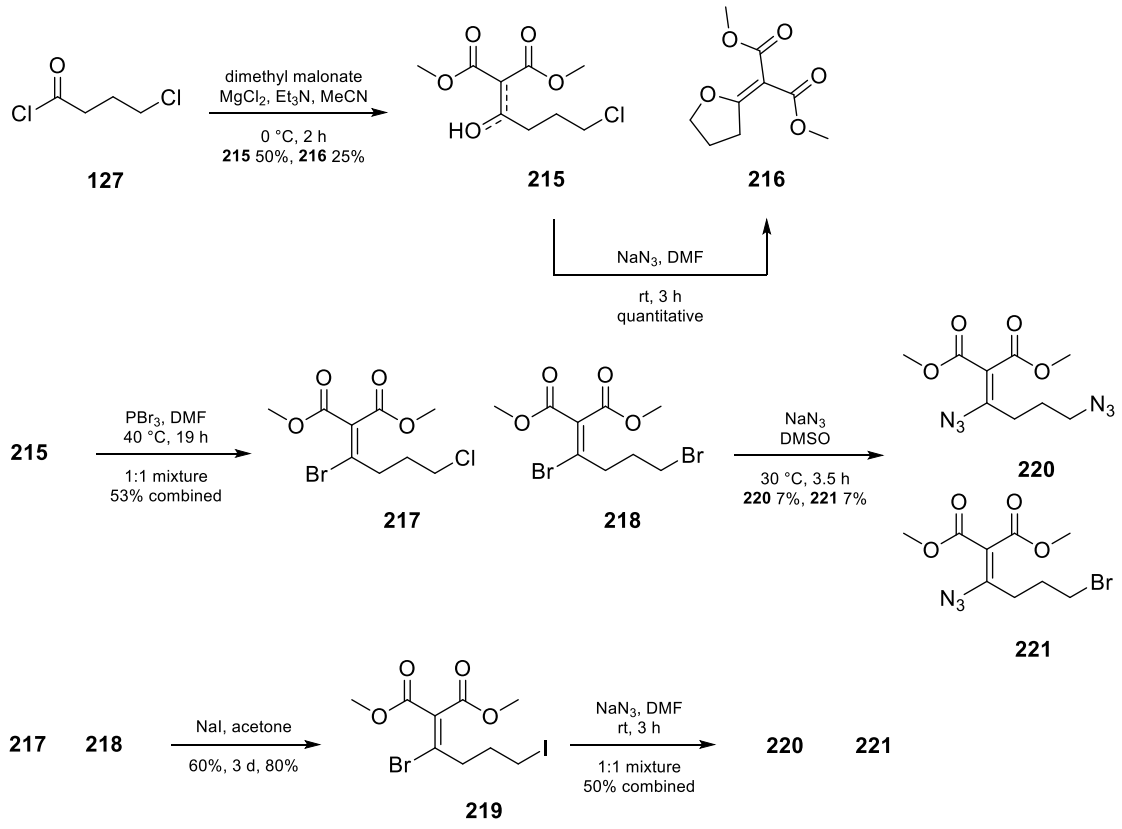
Figure 12: Azidoalkyl vinyl bromides lacking β-hydrogens.

Towards the synthesis of malonate derived **224**, a Knoevenagel condensation[359] between dimethyl malonate and 4-chlorobutanal **158** provided the alkylidene **212**, which was cleanly brominated to dibromide **213** (Scheme 72). Treatment of **213** with base (Et_3N, NaH, or *t*-BuOK) either returned the starting alkene **212** through debromination, or the wrong dehydrobromination regioisomer **214**. This can be rationalised by the destabilising effect of two esters on any build-up of positive charge at the gem-diester carbon. LUMO combination between the (C–Br)σ* and the gem-diester (C=O)π* facilitates debromination by increasing the electrophilicity of the tertiary bromide centre (Scheme 72).



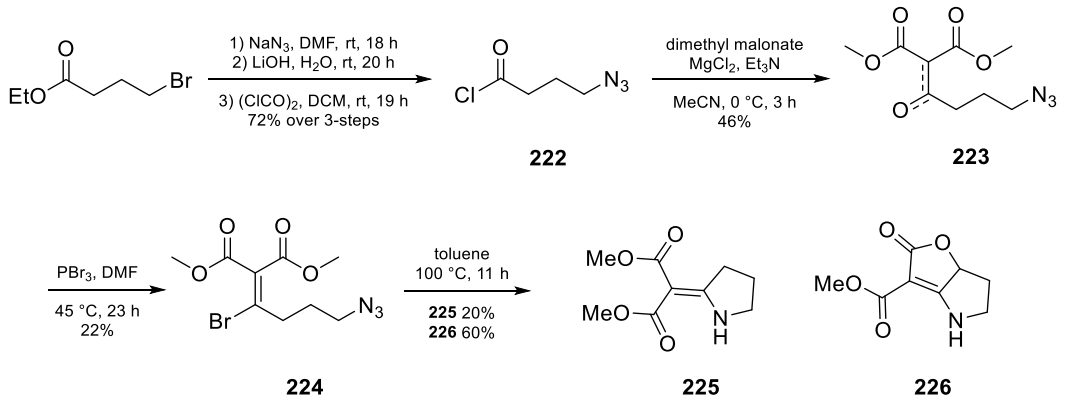
Scheme 72: First attempted route towards vinyl bromide 224 featuring a Knoevenagel condensation.

In a second route, acylation of the magnesium enolate of dimethyl malonate[360] using 4-chlorobutyryl chloride **127** gave 50% of the desired enone **215** and 25% of an enol ether by-product **216** (Scheme 73). The enone **215** existed as a 53:47 mixture of keto-enol tautomers, in favour of the ketone. Rather than a bromination/dehydrobromination protocol, vinyl bromide formation was achieved under Vilsmeier conditions using PBr_3 in DMF.[361,362] As a side-effect of the reaction, the product was isolated as an inconsequential 1:1 mixture of alkyl halides **217** and **218**. This mixture was converted to the iodide **219** under Finkelstein conditions.[363] Neither chloride **217**, bromide **218**, nor iodide **219** could yield the desired product **224** upon treatment with NaN_3, with 1,4 addition to the activated vinyl bromide leading to undesired vinyl azide formation **220**/**221** (Scheme 73). The azide could not be installed prior to the Vilsmeier reaction, as NaN_3 promoted the intramolecular Williamson etherification of **215** to **216** (Scheme 73).



Scheme 73: Second attempted route towards vinyl bromide 224 featuring a Vilsmeier bromination.

The solution was to install the azide prior to the acylation procedure. Thus, dimethyl ester azidoalkyl vinyl bromide **224** was prepared from ethyl 4-bromobutyrate in a 7% yield over 5 steps (Scheme 74). The low yield can be attributed to the Vilsmeier bromination, where a competing Staudinger reaction (see Section **1.2**) may take place between the pendent azide functionality and PBr_3.

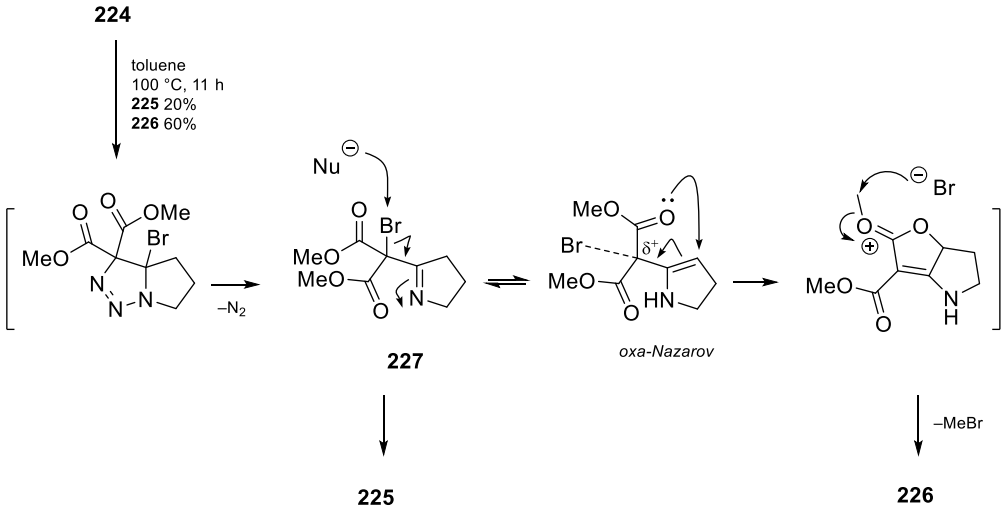


Scheme 74: Synthesis of vinyl bromide 224 and IAVBC towards products 225 and 226.

The two electron-withdrawing groups on vinyl bromide **224** had a vast rate accelerating effect on the IAVBC, taking just 11 h at 100 °C in toluene (Scheme 74). This is in contrast to the ~24–48 h at 150 °C required for the previous electronically unbiased vinyl bromide substrates (Sections **2.2.1**–**2.2.4**). When running the cycloaddition in the presence of K_2CO_3, filtration followed by chromatography yielded solely the enamine **225** in a low yield (<20%). However, without base, it was observed that a white precipitate formed that had been previously masked by the heterogeneous carbonate. Isolation of this precipitate yielded bicycle **226** in a 60% yield, while enamine **225** was isolated in 20% yield from the filtrate. The bicycle **226** was soluble in CD_3OD and DMSO-d_6, and had poor solubility in $CDCl_3$.

Both products can be rationalised as derivatives of the α-bromo imine intermediate **227** (Scheme 75). Cycloaddition of **224** occurs under heating to give a triazoline intermediate that fragments with loss of nitrogen to provide α-bromo imine

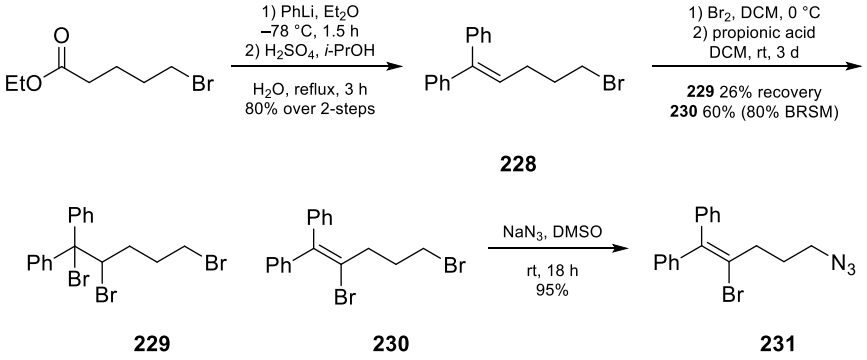
227 *in situ*. Due to conjugation with 3 flanking π-systems, one can imagine **227** acting as an electrophilic source of bromine that could stabilise an anion at the α-position. Attack of an adventitious nucleophile at this α-position would lead to product **225**. Tautomerisation of **227** to an α-bromo enamine would provide an intermediate that is able to undergo a cationic oxa-Nazarov cyclisation,[364] that upon demethylation would yield the bicyclic product **226** (Scheme 75).



Scheme 75: Plausible mechanism for IABVC towards products 225 and 226.

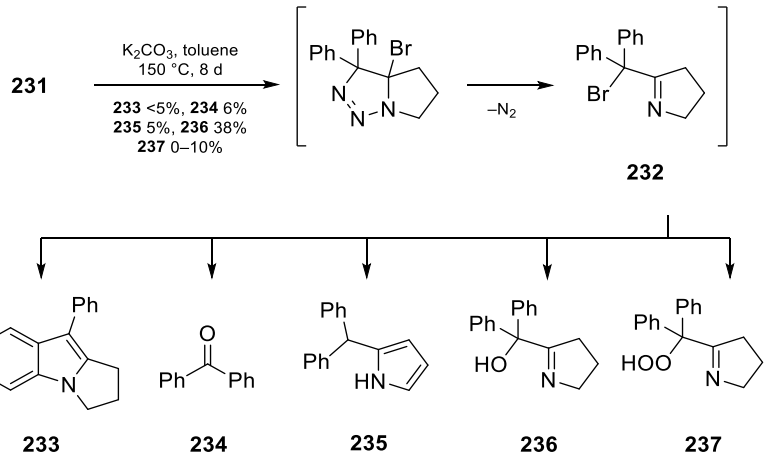
En route to diphenyl substrate **231** (Scheme 76), two equivalents of phenyl lithium were added to ethyl 5-bromovalerate, followed by acid mediated dehydration to alkene **228**. Dibromination of this alkene afforded the 1,2,5 tribromide **229**, but the dehydrobromination of this species was found to be non-trivial. Treatment under basic conditions yielded only the starting alkene through a base-mediated debromination. Gratifyingly, it was discovered that treatment of the crude tribromide with propionic acid yielded the desired vinyl bromide **230** *via* a sluggish E1 elimination reaction. The un-optimised reaction provided 60% of the desired vinyl bromide after 3 days at room temperature along with 26% of the unreacted tribromide (80% BRSM). Curiously, this acid catalysed elimination was only successful when the crude tribromide was used, as

the chromatographically pure tribromide was completely unreactive under these conditions. Simple azide installation with NaN_3 furnished the diphenyl azidoalkyl vinyl bromide **231** in 45% yield over 5 steps (Scheme 76).



Scheme 76: Synthesis of diphenyl vinyl bromide 231.

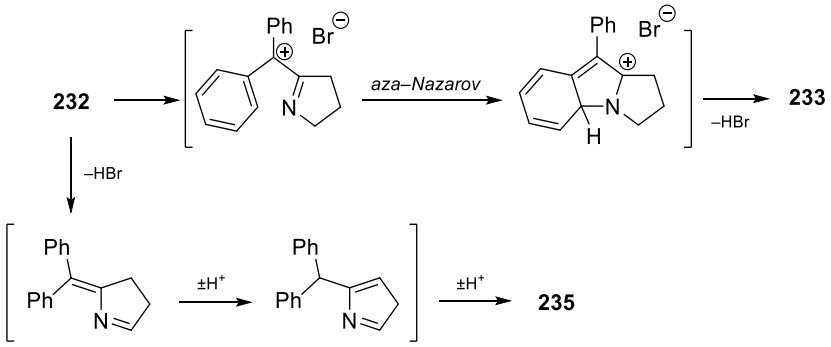
The sterically demanding aromatic rings imparted a severely rate-retarding effect onto the cycloaddition, with compound **231** requiring 8 days at 150 °C to reach completion. The reaction produced a plethora of products, which can be rationalised as derivatives of the α-bromo imine intermediate **232** (Scheme 77).



Scheme 77: IAVBC of substrate 231.

The dominant reaction product at 38% was α-hydroxy imine **236**. The α-bromo imine is a labile electrophile, which would yield **236** from trace water in the reaction or hydrolysis during chromatography. Following this is a series of minor products that

constitute ~5–6% isolated yield each. Benzophenone **234** may derive from decomposition of the α-hydroxy imine. The substituted pyrrole **235** may derive from elimination of HBr from the α-bromo imine followed by a series of proton shifts (Scheme 78). Finally, an interesting indole product **233** (<5% yield) could arise from a cationic aza–Nazarov cyclisation (Scheme 78). An α-perhydroxy imine **237** was also isolated inconsistently from occasional experimental runs, possibly due to trace oxygen in those reactions.



Scheme 78: Plausible pathway for the production of 233 and 235 from α-bromo imine 232.

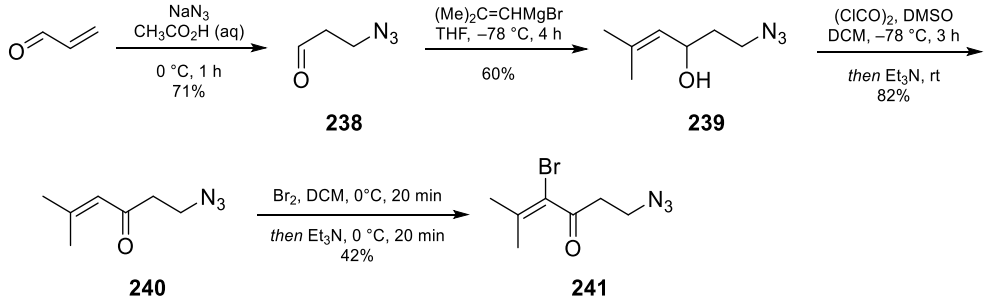
Without β-hydrogens in the α-bromo imine to facilitate 1-azadiene formation, this reactive tertiary bromide may participate in diverse (and sometimes unruly) cascade sequences with pre-loaded functionality within the system. Thus, novel reactivity could be built around the interception of this reactive intermediate through the careful design of functionalised substrates.

2.2.6 Effect of carbonyl position within azidoalkyl vinyl bromide tether

The presence of two electron-withdrawing esters in substrate **224** brought the conditions for IAVBC down to a respectable temperature and timeframe. This is due to the initially electron-rich vinyl bromide being rendered electron-deficient and entering into a *normal-demand* $LUMO_{dipolarophile}$ cycloaddition. It was theorised that by using an

α,β-unsaturated ketone substrate, the carbonyl group would bias the substrate electronically towards *normal-demand* $LUMO_{dipolarophile}$ cycloaddition, while retaining the possibility for 1-azadiene formation.

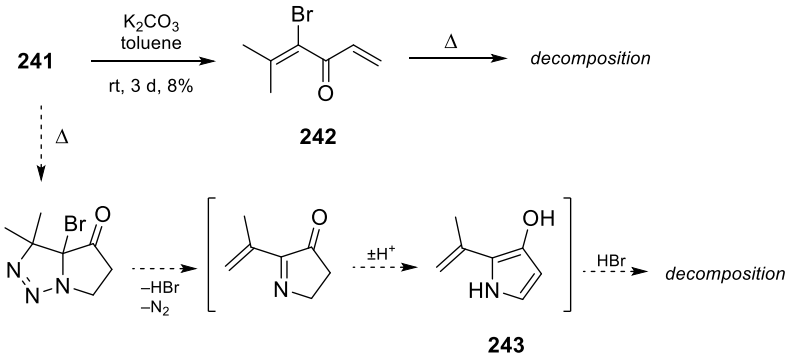
Three-carbon tethered α,β-unsaturated ketone **241** was prepared in 14% yield over 4 steps from acrolein (Scheme 79). Selective dehydrobromination was facile using Et_3N, but necessitated a short reaction time to prevent E1cb elimination of the azide group beta to the carbonyl, foreshadowing the results to come.



Scheme 79: Synthesis of three-carbon tethered α,β-unsaturated ketone 241.

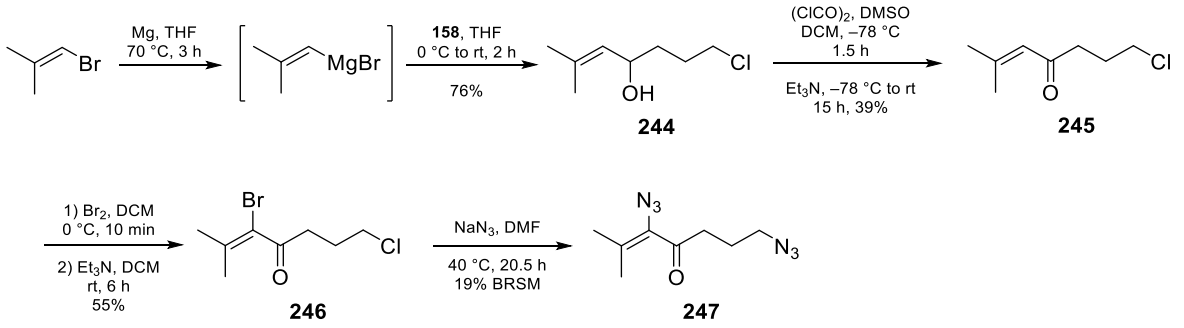
So labile was the β-keto azide that stirring a toluene solution of **241** in the presence of K_2CO_3 caused E1cb elimination of the azide group to yield 1,4-diene **242** (Scheme 80). Heating a toluene solution of substrate **241** in the absence of base at 90 °C or above caused decomposition of starting material to an intractable tar. Thus, a non-basic scavenger of HBr was required. When propylene oxide was included in the reaction, heating between 100–140 °C resulted only in decomposition of starting material. Trace quantities of 2-bromopropanol were detected by ^{1}H-NMR spectroscopy, indicative of HBr release. With decomposition of starting material occurring at relatively low temperatures, it was theorised that substrate **241** may undergo IAVBC, but that the 1-azadiene product may tautomerise to a 3-hydroxy pyrrole **243**, which then polymerises, precluding observation (Scheme 80). E1cb elimination of the azide group may occur spontaneously upon heating, and at elevated temperatures 1,4-diene **242**

decomposes. The instability of **242** is corroborated by a low isolated yield following silica chromatography.



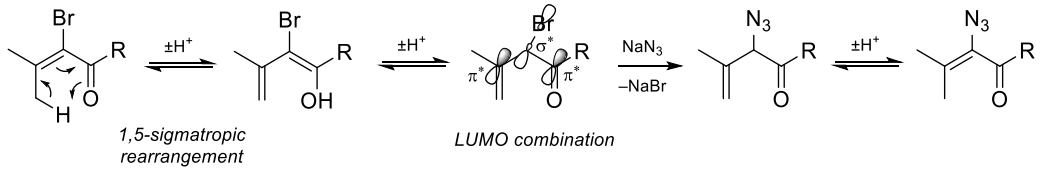
Scheme 80: Reactivity of three-carbon tethered α,β-unsaturated vinyl bromide 241.

In order to avoid this β-elimination, the homologous substrate **247** was prepared. Following the procedure outlined in Scheme 81, treatment of chloroalkyl vinyl bromide **246** with NaN_3 afforded an azidoalkyl product **247**. At the time it was not realised that vinyl bromide functionality had not survived this transformation, instead yielding an azidoalkyl vinyl azide **247** whose structure was assigned subsequently.



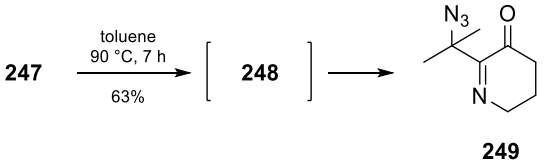
Scheme 81: Unexpected synthesis of four-carbon tethered α,β-unsaturated vinyl azide 247.

This formal S_NV substitution could occur *via* prior deconjugation of the α,β-unsaturated ketone, followed by a rapid S_N2 substitution at the reactive α-bromo ketone (Scheme 82).



Scheme 82: Plausible explanation for formal S_NV substitution towards 247.

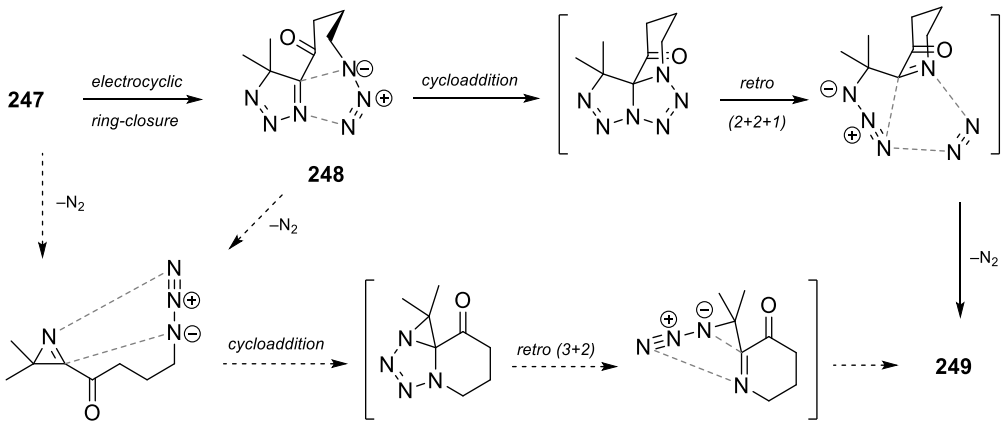
Believing that we had obtained the desired vinyl bromide, we subjected substrate **247** to a test cycloaddition at 90 °C in d_8-toluene and found it to convert fully to an α-azido imine **249** within 7 h (Scheme 83). Thus, the yield of **247** in the previous reaction was low due to further reaction *in situ* at 40 °C. Interestingly, while running the reaction at 50 °C, an intermediate species, **248**, built up to an appreciable concentration (1:2:2 **247**/**248**/**249**) over 29 h.



Scheme 83: Unexpected reaction of vinyl azide 247 to α-azido imine 249.

Compound **248** contained no stereocentres, and appeared to retain the azide tether intact, eliminating its structure as an IAOC intermediate. We proposed the identity of intermediate **248** to be either a 4*H*-triazole, or 2*H*-azirine, formed by rearrangement of the vinyl azide moiety, which could take part in a further cycloaddition/cycloreversion sequence to yield the final product **249** (Scheme 80). Vinyl azides are known to rearrange thermally to 2*H*-azirines under mild conditions.[30] Though this may proceed through a 4*H*-triazole intermediate, it is generally believed to be either a concerted transformation, or *via* a nitrene.[125,365–368] To paraphrase Hassner,[125] if the α-substituent is a keto carbonyl or able to destabilise a positive charge (as in substrate **247**), the azirine is rarely isolated and instead further rearranges.

The intermediate could not be separated from the reaction mixture by chromatography, instead decomposing to the finished product, nor could it be distinguished from **247**/**249** by MS. The $^{1}H/^{13}C$-NMR data for **248** was consistent with both the azirine or triazole structure, with no literature data available to corroborate the imine bond carbon shift (179 ppm).



Scheme 84: Proposed identity of 248 and plausible mechanism towards 249.

Taking the 2:2:1 reaction mixture, $^{15}N–^{1}H$-NMR correlation studies revealed the most likely identity of **248** to be the 4*H*-triazole (**Appendix 6.1**). An HMBC study revealed a three bond coupling between the methyl protons at 1.39 ppm, and the triazoline nitrogen at the 3-position (Figure 13). The ^{15}N chemical shift of the triazole 3-nitrogen (342 ppm) is consistent with ACD/I-lab predictions for this structure, as opposed to that predicted for an analogous azirine nitrogen (269 ppm).

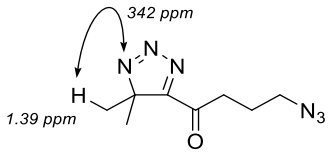
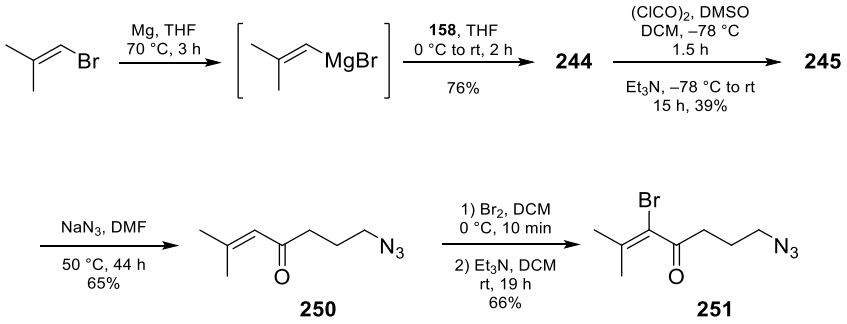


Figure 13: $^{15}N–^{1}H$-NMR correlation suggesting the triazole structure of 248.

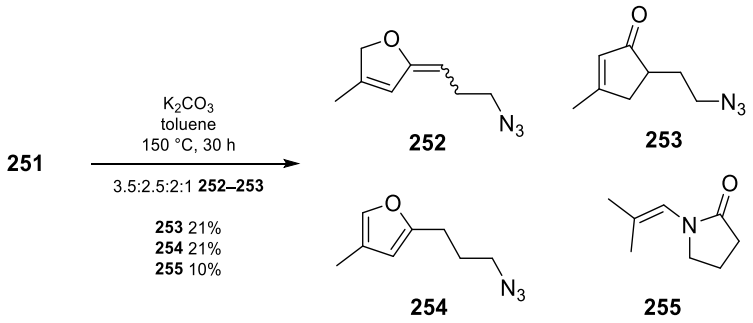
With this avenue explored to its conclusion, we returned to the synthesis of the four-carbon tethered α,β-unsaturated vinyl bromide. Installation of the alkyl azide prior

to the dehydrobromination allowed access to product **251** in 9% yield over 6 steps (Scheme 85).



Scheme 85: Synthesis of four-carbon tethered α,β-unsaturated ketone 251.

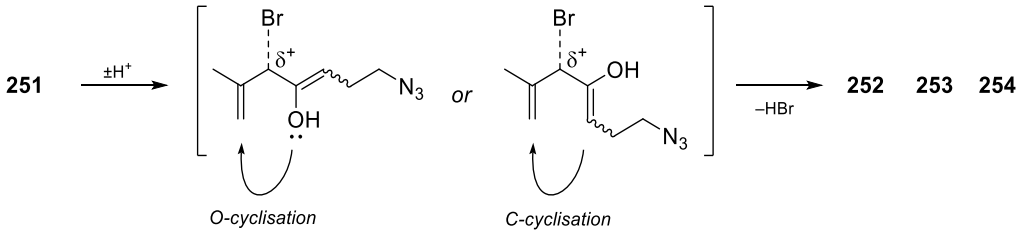
Disappointingly, substrate **251** did not undergo IAVBC, and therefore it is not possible to comment on the rate-acceleration of the α,β-unsaturated system. Under the standard conditions for cycloaddition, a toluene solution of **251** in the presence of K_2CO_3 was consumed fully within 30 h, but was found to give a series of oxa- and carbo-Nazarov cyclisation products (Scheme 86).



Scheme 86: Reactivity of four-carbon tethered α,β-unsaturated vinyl bromide 251.

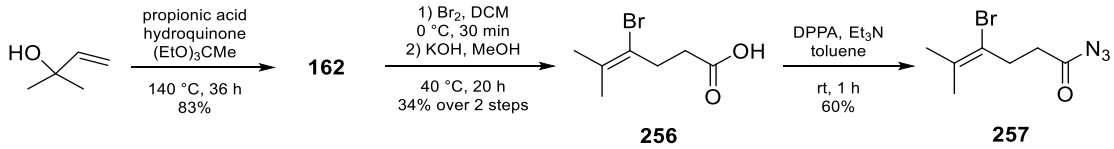
By analysis of the ^{1}H-NMR spectrum of crude product, the reaction produced a 3.5:2.5:2:1 mixture of products **252**–**255**. Compound **252** was unstable towards chromatography, presumably isomerising to furan **254**. Deconjugation of starting material **251**, would produce an intermediate that is able to cyclise by a Nazarov-style conjugate elimination (Scheme 87). *O*-cyclisation would lead to products **252** and **254**,

while *C*-cyclisation would lead to **253**. As a formal 5-*endo-trig* process, the bromine is likely in the process of leaving to create a cationic transition state. γ-Lactam **255** could arise through a Schmidt rearrangement (see Section **1.2**) and with a reductive loss of bromine *in situ*.



Scheme 87: Plausible rationale for products 252–254.

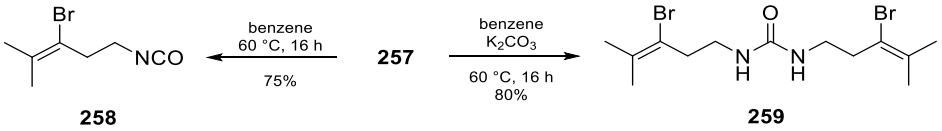
With α,β-unsaturated ketones **241** and **251** unable to undergo IAVBC, we decided to move the carbonyl group along the azide tether to the azide α-carbon. By taking advantage of the electron rich vinyl bromide olefin, and increasing the electron deficiently of the alkyl azide, we hoped to lower the azide LUMO so as to adopt a faster inverse demand $HOMO_{dipolarophile}$ cycloaddition. The acylazidoalkyl vinyl bromide **257** was prepared in 16% yield over 4 steps, featuring a tandem dehydrobromination/ saponification, and with DPPA as the azide transfer reagent (Scheme 88).[369,370]



Scheme 88: Synthesis of acylazidoalkyl vinyl bromide 257.

In practice, a Curtius rearrangement (see Section **1.2**) occurred more rapidly than IAVBC reaction, occurring spontaneously in $CDCl_3$ or over several days at room temperature in C_6D_6 (Scheme 89). Heating a benzene solution of acyl azide **257** in base-washed glassware gave a 75% isolated yield of isocyanate **258**, while the same reaction

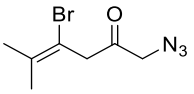
in the presence of K_2CO_3 yielded urea derivative **259** by hydrolysis reaction with **258** *in situ*.



258 **259**

Scheme 89: Curtius rearrangement of substrate 257.

This study had not been able to reveal any IAVBC rate acceleration by the positioning of a carbonyl group within the azidoalkyl tether due to preferential decomposition pathways made possible by this added functionality. Thus, while entropic bias within the azide tether is favourable (**176**, **208**, **209**), electronic bias is most effective when present at the alkene terminals (**224**). To complete this study on carbonyl placement within a three-carbon tether, a third possible regioisomer **260** would be required, but this was not pursued (Figure 14).



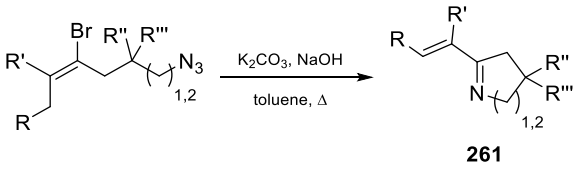
260

Figure 14: Theoretical azidoalkyl ketone substrate 260.

2.3 1-Azadienes: Diversity-oriented synthesis

2.3.1 Introduction to 1-azadienes

During the IAOC study of azidoalkyl enol ethers (Section **2.1**) and azidoalkyl vinyl bromides (Section **2.2**) we were unable to observe, nor therefore exploit, the existence of triazolium ion **77** (Scheme 35). However, we discovered a novel, general, IAVBC method towards the synthesis of α-substituted cyclic 1-azadienes **261** (Scheme 90).



261

Scheme 90: IAVBC towards α-substituted cyclic 1-azadienes.

1-Azadienes **262** are densely functionalised systems that contain a plethora of reactive sites (Figure 15).[371–373] The vast majority of studies have featured activated 1-azadiene systems as the diene component in hetero-Diels–Alder reactions.[373–384] In addition, the imino nitrogen may act as a nucleophile, and the α,β-unsaturated system as an electrophilic 1,2-[385–389] or 1,4-acceptor,[387,390–393] while both the imine or alkenyl unit may in principle participate as a dienophile in cycloaddition reactions.[394–398] With such versatile functionality, 1-azadienes have the potential to act as a branching-point from which a large number of diverse nitrogen-containing heterocycles can be accessed.[371]

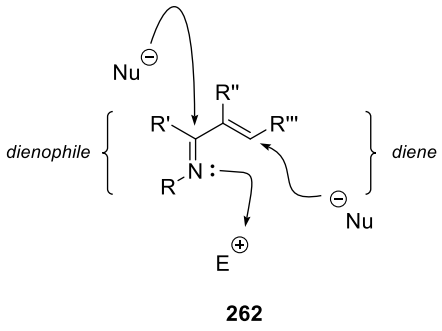


Figure 15: Potential 1-azadiene reactivity.

Acyclic 1-azadienes are commonly prepared by the condensation of an α,β-unsaturated carbonyl compound with an amine (Figure 16).[378,383,392,393,399–402] If this is complicated by undesired 1,4-addition reactions, both the aza-Wittig reaction,[387,403] as well as the olefination of α-phosphonated imines with aldehydes,[388,389,404,405] can be useful alternatives. There are many individual variations towards this simple structure and additional methods are summarised in a recent review.[371]

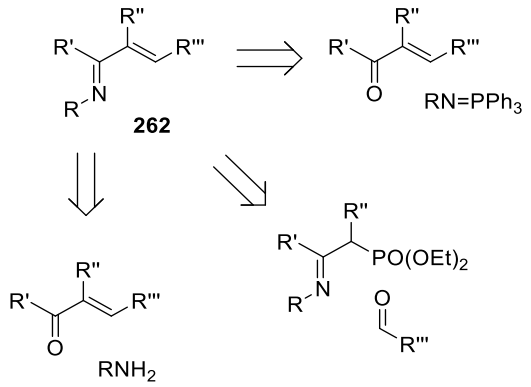
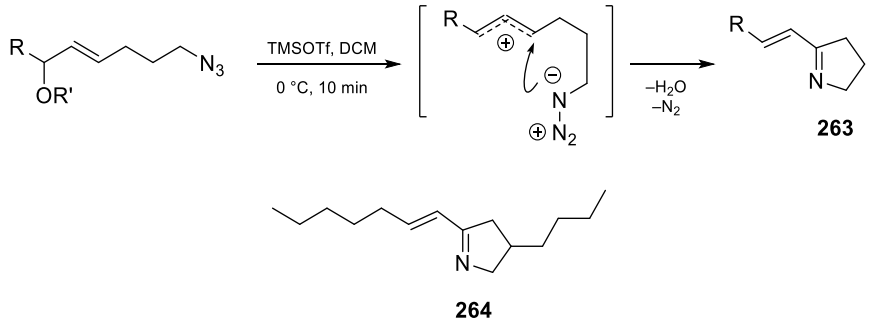


Figure 16: Selected retrosynthetic disconnections towards 1-azadienes.

Related to the IAVBC methodology discussed in Section **2.2** is a recent report by Kakiuchi *et al.* of the synthesis of alkenylpyrrolines **263** through the ionisation and trapping of allylic alcohols with azides under mild acid conditions (Scheme 91).[406] As an application of this methodology, Costa Rica ant venom alkaloid **264** was synthesised. 1-

Azadiene products with α-substitution (such as **261**) were only demonstrated twice, with low to medium yield.



Scheme 91: Synthesis of alkenylpyrrolines by ionisation of allylic alcohols.[406]

The electronic character of 1-azadienes is important for controlling their properties and selectivities as reaction partners. Reactive 1-azadienes are often electronically biased, with electron-deficient azadienes (typically *N*-sulfonyl derivatives[381,383,390,392,393,401]) reacting as dienes in inverse-demand Diels–Alder reactions as well as 1,4-acceptors, while electron-rich azadienes (typically *N*-alkoxy or *N*-dialkylamino derivatives[377,378,384,398,399]) participate in regular-demand Diels–Alder reactions as well as nitrogen nucleophiles. The overwhelming majority of studies have been on acyclic 1-azadienes, with one or more electron-attenuating groups featured within the system. The reactivity and selectivity of 1-azadienes is therefore usually substrate specific, and tailored on a case-by-case basis for a particular reaction.

Diversity-oriented synthesis (DOS) aims to produce structurally diverse compounds that are representative of a large portion of chemical space. By applying a variety of reaction conditions to starting materials with multiple functional groups, multiple iterations result in rapid access to structurally diverse products suitable for screening.[407] Densely functionalised 1-azadienes appear to be under-utilised in DOS studies. Alkenylpyrrolines (and alkenyltetrahydropyridines) of the structure **261** are electronically unactivated and have rarely been reported, let alone subjected to a study

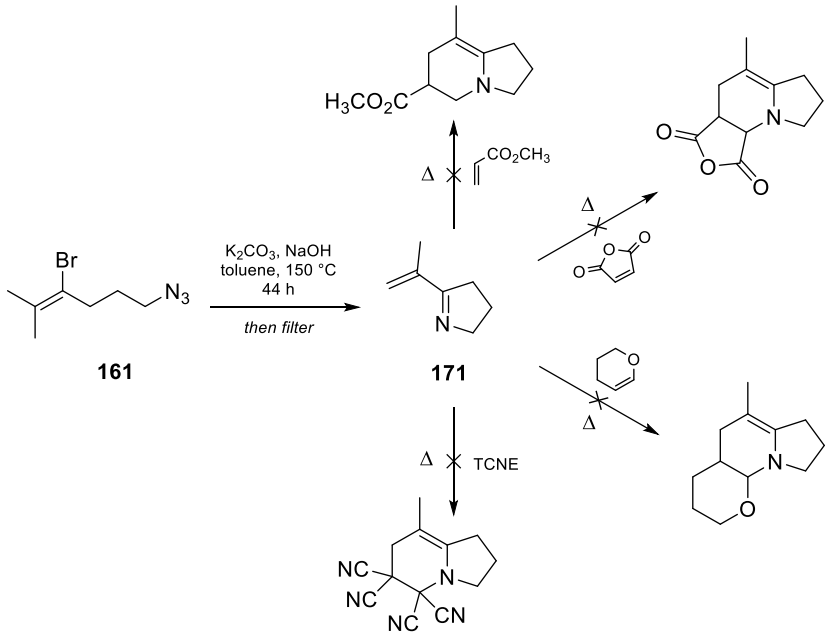
of reactivity in the existing literature. In order to map the potential reactivity of 1-azadienes **261** we set out to study DOS from these systems.

2.3.2 Formal cycloadditions between 1-azadienes and diphenylketene

The introduction of a nitrogen at the 1-position of a diene creates a π-deficient system that lowers the reactivity of 1-azadienes in the normal-demand $HOMO_{diene}$ Diels–Alder reaction with electron poor dienophiles.[374,408] Furthermore, the aza-Diels–Alder is thermodynamically less favourable than for the all-carbon analogue, due to the increased strength of the C=N π-bond, which must be broken during the process.[409] Because of this, Diels–Alder reactions of unactivated 1-azadienes are incredibly sluggish and often of no synthetic significance.[374,408]

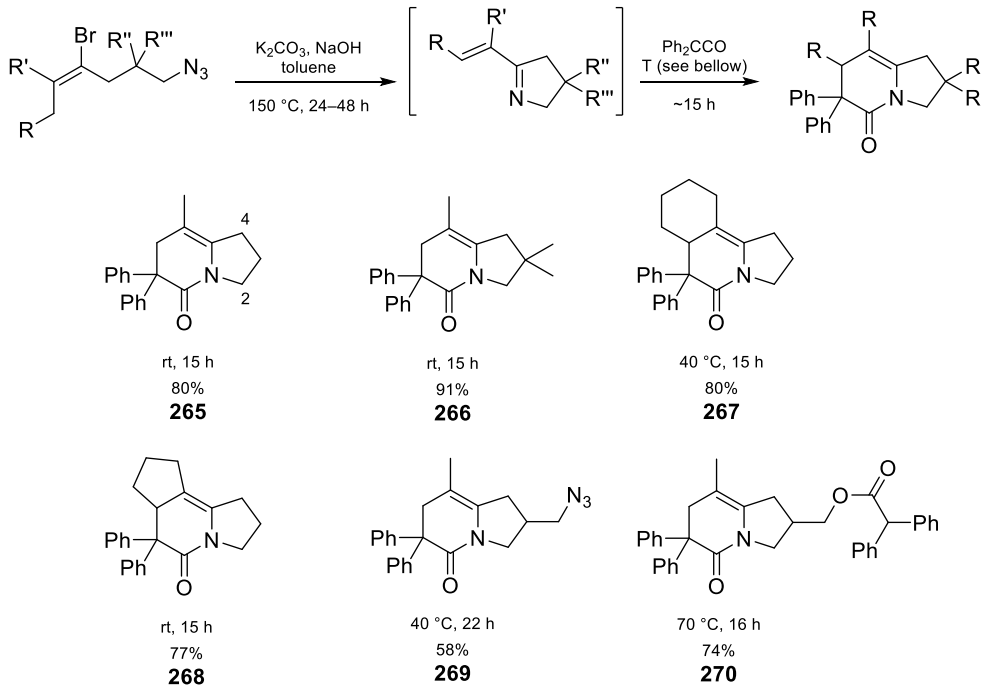
1-Azadiene **171**, prepared *in situ* from vinyl bromide **161**, failed to react with electron poor alkenes such as methyl acrylate and maleic anhydride under purely thermal conditions (130 °C), while the addition of a Lewis acid ($Nd(OTf)_3$) served only to decompose the starting material (Scheme 92). 1-Azadiene **171** was unreactive towards tetracyanoethylene (TCNE) at –78 °C but at ambient temperature decomposed spontaneously to a polymeric tar, likely initiated by electron transfer processes.

Because of their intrinsic electron-deficiency, 1-azadienes tend to participate in inverse-demand $LUMO_{diene}$-controlled Diels–Alder reactions with electron-rich alkenes.[408] However, substrate **171** was unreactive towards dihydropyran at temperatures up to 170 °C, even in the presence of $Cu(OTf)_2$ as Lewis acid.[410]



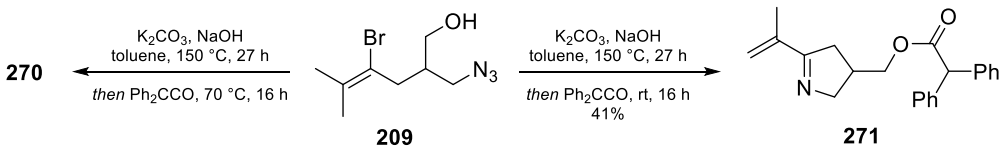
Scheme 92: Attempted Diels–Alder reactions with 1-azadiene 171.

Gratifyingly, alkenylpyrrolines **171**, **178**, **199**, **200**, **210**, and **211** were trapped with diphenylketene[411] in a formal (4+2) process to yield δ-lactam products **265**–**270** in good to excellent yields (Scheme 93).[412–414] The reactions were performed in one pot; following cycloaddition at 150 °C, the reaction was cooled to the appropriate temperature and diphenylketene added to the crude mixture and stirred over night. The presence of K_2CO_3 and NaOH did not interfere with the cyclisation. The one pot yields of **267** and **268** (80% and 77% respectively) were comparable to the corresponding two pot yields (77% and 65% respectively), considering losses due to transfer operations.



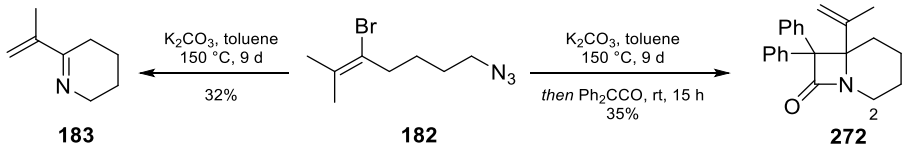
Scheme 93: One pot (4+2) trapping of alkenylpyrroline 1-azadienes with diphenylketene.

Unhindered azadienes **171** and **178**, and strained cyclopentyl substrate **200** were trapped by diphenylketene at room temperature to yield **265**, **266** and **268** respectively. The most structurally simple δ-lactam, **265**, featured a triplet splitting pattern at C2 and C4, suggesting a flat structure without significant pyramidal character in the nitrogen (at least on the NMR timescale). The cyclohexyl compound **199**, comparatively free of strain, required gentle heating (40 °C) to undergo cycloaddition. The alcohol functionalised substrate **211** was found to *O*-acylate with diphenylketene at room temperature to provide acylated product **271** first, which then became sterically encumbered towards the formal (4+2) process across the 1-azadiene at that temperature (Scheme 94). For this reason, elevated temperatures were required (70 °C) so as to attain the 2:1 adduct **270**. Azide compound **269** was not optimised further, and likely did not require gentle heating to undergo cycloaddition.



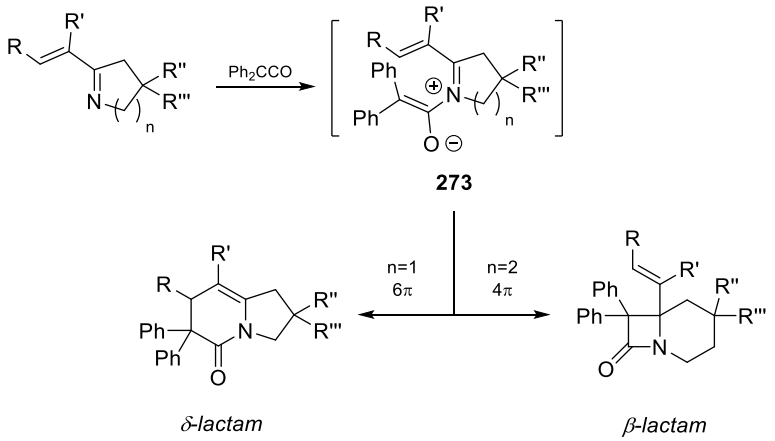
Scheme 94: Temperature dependence of the (4+2) cycloaddition of alcohol tethered 1-azadiene 211 (IAVBC product of 209) with diphenyl ketene.

Curiously, tetrahydropyridine derivative **183** was trapped with diphenylketene to give the formal (2+2) adduct **272** solely (an example of a Staudinger synthesis,[415] Scheme 95). The formation of this β-lactam contrasts with the δ-lactams derived from the pyrroline substrates (*vide supra*). The C2 protons in **272** were separated by ~1.5 ppm, indicating a cupped structure with significant pyramidal character in the nitrogen.



Scheme 95: One pot (2+2) trapping of tetrahydropyridine 1-azadiene 183 with diphenylketene.

This difference in selectivity, based on an increase in the cyclic imine ring by one methylene (pyrroline vs tetrahydropyridine) deserves comment. Mechanistically, these formal cycloadditions are likely step-wise processes that occur *via* a dipolar intermediate (**273**, Scheme 96), taking advantage of the nucleophilic 1-azadiene nitrogen.[372,414]



Scheme 96: Stepwise mechanism for formal cycloadditions between 1-azadienes and diphenylketene.

This dipole may then partake in either a disrotatory $\pi 6_s$, or a conrotatory $\pi 4_a$ pseudo-electrocyclisation to yield the δ-lactam or β-lactam product respectively (Figure 17). When the system contains a tetrahydropyridine unit, the 6-membered ring is likely in a predominant half-chair conformation. The (2+2) preference when the system contains a tetrahydropyridine unit may be because the flexible 6-membered imine is better able to accommodate the forming sp^3 centre as the imine carbon π-bond rotates during the 4π pseudo-electrocyclisation transition state. This may produce additional strain in the more rigid 5-membered pyrroline cases, favouring the available 6π electrocyclisation mode. Torquoselectivity is inconsequential in both cases. Because the cyclisation may not be a true pericyclic reaction, with the electron-flow terminating at the nitrogen, the process likely contains both electrocyclic and nucleophilic addition character.

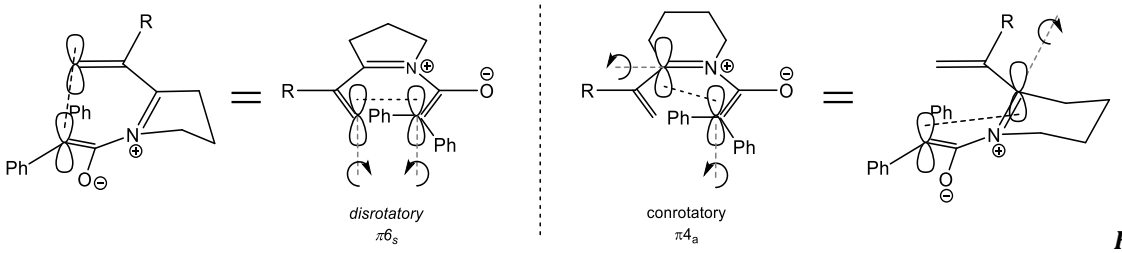


Figure 17: Disrotatory 6π vs conrotatory 4π electrocyclisations.

Note: When represented in 3D, the alkenyl π-systems would be tipped out of plane to one another, due to the steric hindrance caused by the cis-phenyl ring.

Energy calculations based on 6π vs 4π products for both pyrroline and tetrahydropyridine 1-azadiene structures are shown in Figure 18. The calculations, which are purely enthalpic, show that in both cases the δ-lactam product is significantly more thermodynamically stable than the corresponding β-lactam (Δ132.48 kJ mol^{-1} and Δ101.51 kJ mol^{-1} for the pyrrolidine and piperidine respectively). Secondly, the δ-lactam stability (6π vs 4π) is ~30% greater for the pyrrolidine system than the analogous piperidine system (Δ132.48 kJ mol^{-1} vs Δ101.51 kJ mol^{-1}). Thus, the observed experimental results indicate a kinetically controlled reaction, which would allow for the formation of the formal (2+2) product **272** over the analogous (4+2) product in the tetrahydropyridine case. This suggests an early transition state that is not influenced by the greater product stability of the 6π product. This reasoning leads back to the transition state strain argument discussed above (Figure 17): the forming sp^3 centre is more readily accommodated in the tetrahydropyridine case, than in the pyrroline case, which leads to 4π product **272**. In the pyrroline case, developing strain is avoided by undergoing the available 6π electrocyclisation, yielding products **265**–**270**.

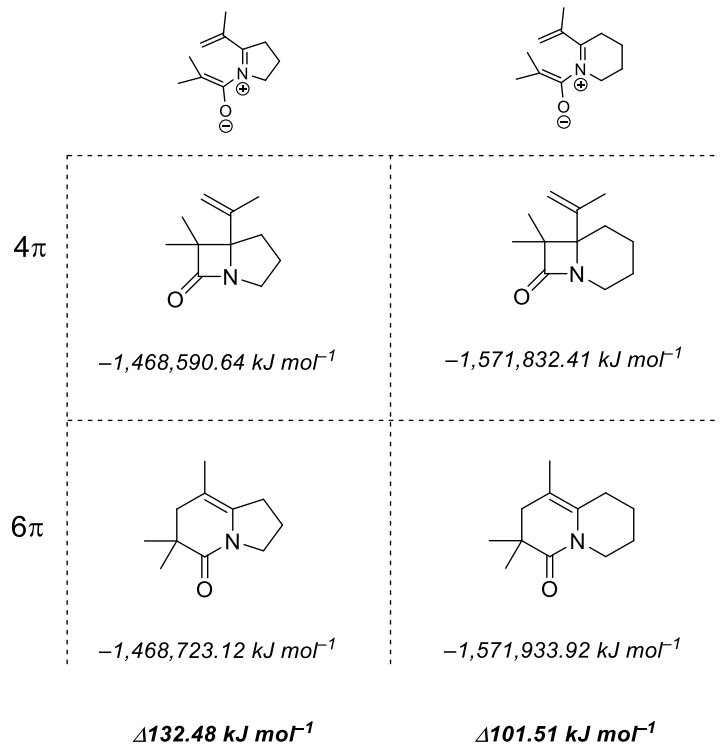


Figure: 18 Enthalpic energy calculations for 6π vs 4π electrocyclisation products. (Based on a Monte Carlo conformation search/ DFT (B3LYP/6-31G*) equilibrium geometry calculation/Boltzmann-weighted energy calculation).

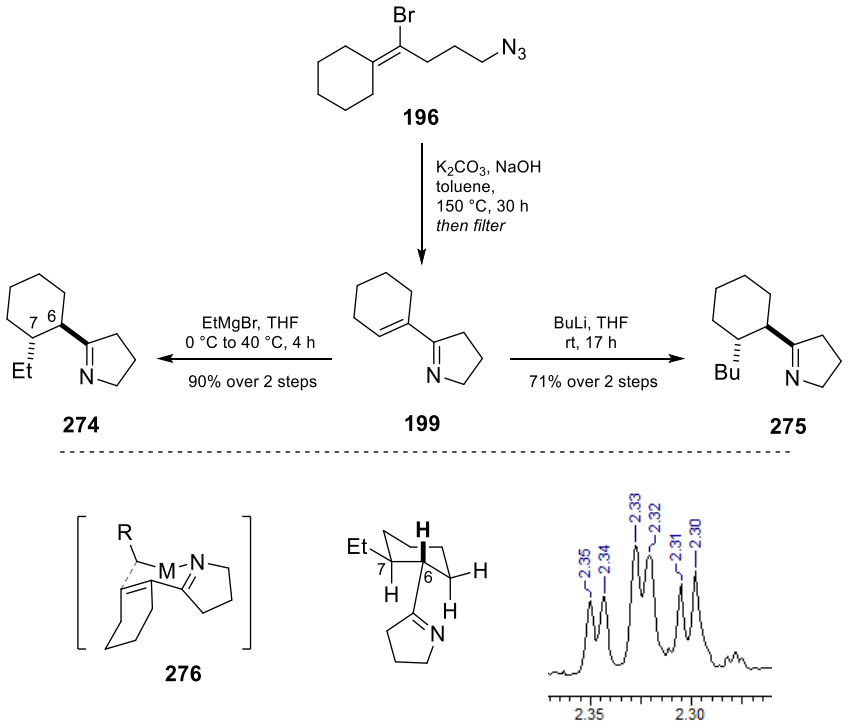
Analagous (4+2) selectivity has been observed for reactions between alkenyl-oxazolines and thiazolines (heterocyclic analogues of the alkenylpyrroline frame) with ketenes and isocyanates, in accordance with these results.[412,413,416,417]

2.3.3 Diversity-oriented synthesis from crude cyclohexylenylpyrroline

Having demonstrated the formal cycloaddition of 1-azadienes to δ- and β-lactams, a short diversity-oriented synthesis study was carried out on cyclohexenylpyrroline **199** to expose the remaining reactivity indicated in Figure 15. All DOS reactions **196** were conducted on 100–150 mg scale using the standard set up shown in Figure 10, or in crimped Biotage microwave vials using a heating block. After cycloaddition (**196 → 199**), the reaction mixture was filtered into a round-bottom flask,

the head space flushed with inert gas (N_2 or Ar), and the reagents added directly to this crude solution.

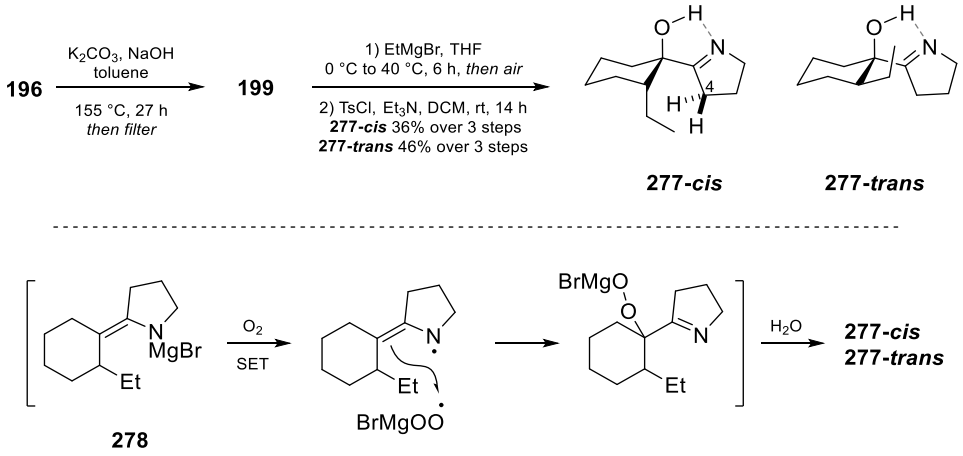
Cyclohexenylpyrroline **199** reacted with both MeMgBr and BuLi to provide 1,4-addition products **274** and **275** respectively (Scheme 97). The *trans*-selectivity was indicated by ^{1}H-NMR analysis: The C6 and C7 protons appear as triple doublets, with two large coupling constants to the neighbouring axial protons, and a smaller coupling to their single neighbouring equatorial proton. A NOESY experiment was supportive of this assignment. The 1,4-selectivity could be due to the formation of a relatively stable 6-membered transition state, whereby the nitrogen-coordinated organometallic directs the alkyl group to the 4-position **276**.



Scheme 97: 1,4-Addition of MeMgBr and BuLi to cyclohexenylpyrroline 199.

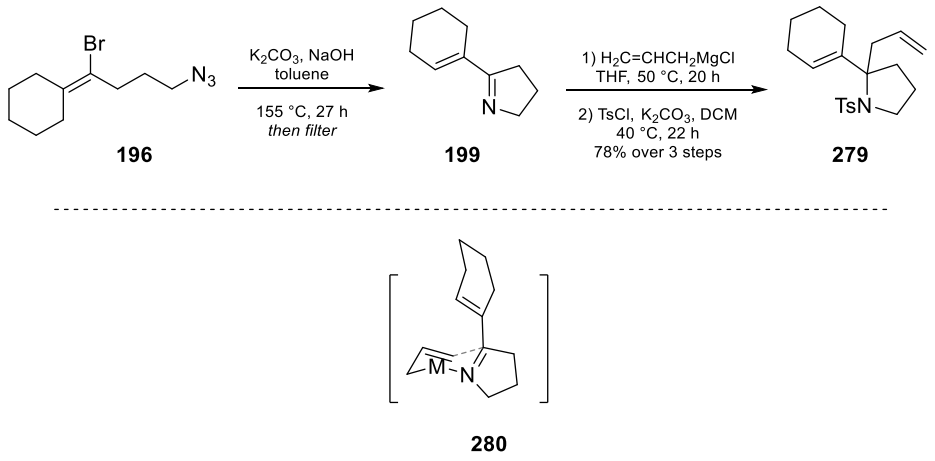
Serendipitously, it was discovered that compound **274** could undergo oxidation at the α-position by bubbling air through the reaction mixture prior to workup (Scheme 98). The resulting α-hydroxy imine was isolated as a separable ~1:1 mixture of

diastereomers, **277-*cis*** and **277-*trans***. The relative stereochemistry was assigned based on the diastereotopic splitting of the C4 protons in the **277-*cis*** isomer: intramolecular hydrogen bonding will form a conformation in which the C4 protons are close to the axial ethyl group, providing two distinct chemical environments. **277-*trans*** did not feature this diastereotopic splitting, as the equatorial ethyl group has a reduced influence. The pyrroline nitrogen in both isomers of **277** was non-nucleophilic towards TsCl which allowed the unoxidised **274** to be conveniently separated from the reaction mixture by tosylation and chromatography. Mechanistically, it is plausible that the intermediate metallo-enamine **278** undergoes aerial oxidation *via* a single electron transfer (SET) mechanism, shown in Scheme 98. This avenue was not pursued with BuLi (**199 → 275**).



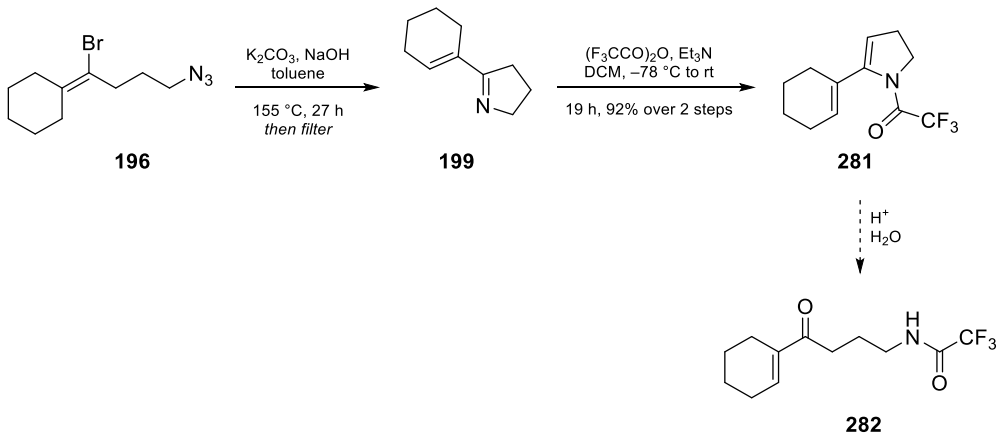
Scheme 98: 1,4-Addition of MeMgBr and aerial oxidation of cyclohexenylpyrroline 199.

Cyclohexenylpyrroline **199** was alkylated with allylmagnesium chloride with 1,2-selectivity, providing a secondary amine that was protected by tosylation before chromatography **279** (Scheme 99). The 1,2-selectivity may be attributed to a 6-membered transition state **280**, whereby the nitrogen-coordinated organomagnesium directs the allyl group to the 2-position *via* an allylic rearrangement.



Scheme 99: 1,2-Addition of allylmagnesium bromide to cyclohexenylpyrroline 199.

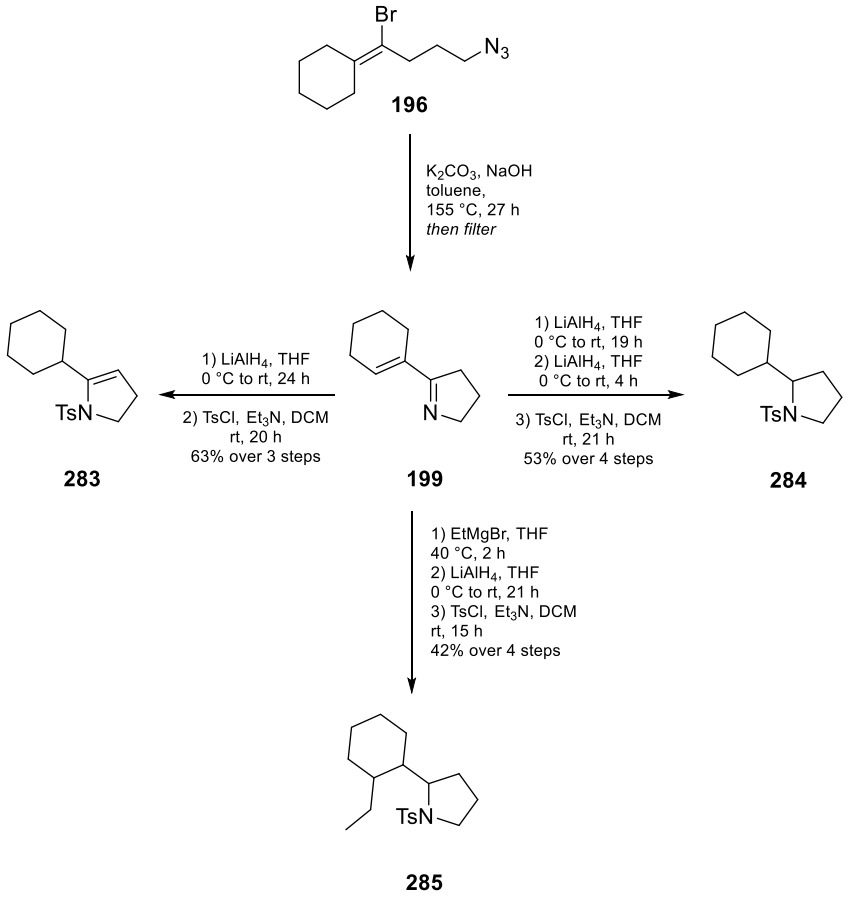
With 1,4- and 1,2-selectivity determined, we next sought to exploit the nucleophilic character of the imine nitrogen. The cyclohexenylpyrroline **199** was acylated with trifluoroacetic anhydride at –78 °C, providing enamide **281** in excellent yield (Scheme 100). Acyl enamine **281** was highly sensitive to acid and required rapid chromatography so as to avoid hydrolysis to the corresponding open chain amide **282** (see also Section **2.3.5**).



Scheme 100: Trifluoroacetylation of cyclohexenylpyrroline 199.

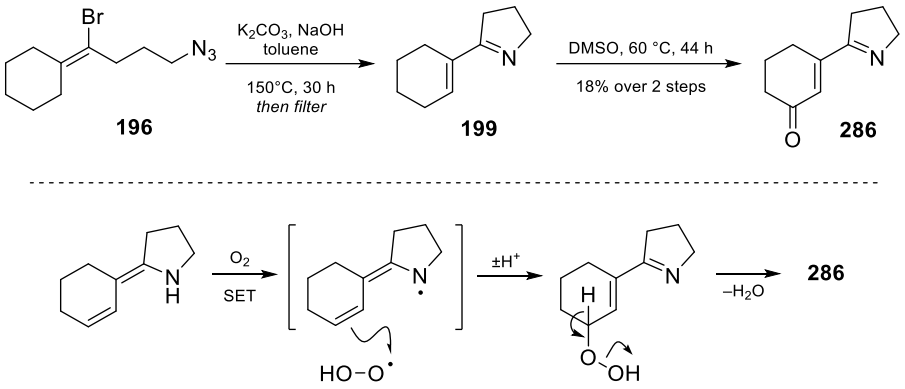
The 1-azadiene system could also be reduced sequentially using $LiAlH_4$ to provide either the 1,4- or fully-reduced products **283** and **284** respectively (Scheme 101). Grignard addition and reduction were combined to afford pyrrolidine derivative

285 as an inseparable 4:3:1 mixture of three (observed) diastereomers, whose relative configurations were not determined.



Scheme 101: Sequential reduction of cyclohexenylpyrroline 199.

When attempting a Heck arylation on cyclohexenylpyrroline **199**, a propensity towards allylic oxidation in polar solvents was demonstrated. A solvent swap of toluene for a polar aprotic solvent (DMSO or DMF) and stirring under argon with mild heating would reproducibly provide 1-azadienone **286** in a low yield as the sole product (Scheme 102). This was thought to arise through a SET process with adventitious oxygen, despite the reaction being conducted under an inert atmosphere. Such allylic oxidation was not observed during cycloaddition in toluene to produce **199**, suggesting a polar reaction medium is necessary.

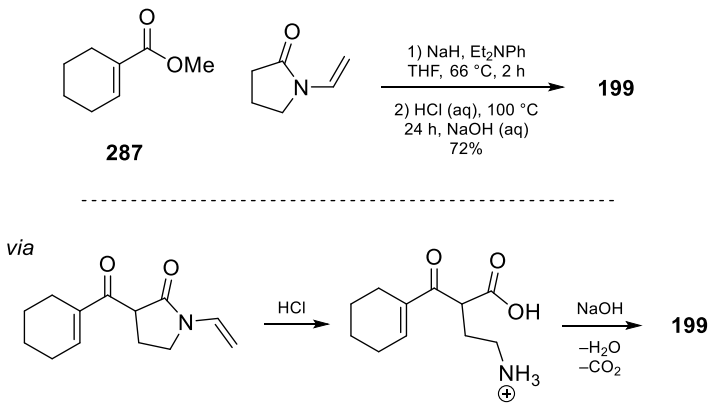


Scheme 102: Allylic oxidation of cyclohexenylpyrroline 199 in DMSO.

Finally, an attempt was made to demonstrate the ability of the 1-azadiene to act as a dienophile in a (4+2) reaction. Substrate **199** prepared in situ from **196** did not react with excess Danishefsky's diene or cyclopentadiene, thermally up to 180 °C, or with either $Yb(OTf)_3$ or $BF_3.Et_2O$ added.

2.3.4 Alternative preparation of cyclohexenylpyrroline

To prepare more material for a downstream study and provide an informed critique of the analogous IAVBC methodology (Scheme 68), we sought an alternative method for the production of cyclohexenylpyrroline **199**. Using a modified literature procedure,[418–420] 1-vinyl-2-pyrrolidinone and methyl cyclohex-1-enecarboxylate[421] **287** were united in a double condensation procedure to yield **199** in a 72% yield on gram scale (Scheme 103). The isolated yield was higher when diethylaniline was included in the reaction, likely by providing a buffered environment during the hydrolysis, and by neutralising the silica during chromatography.

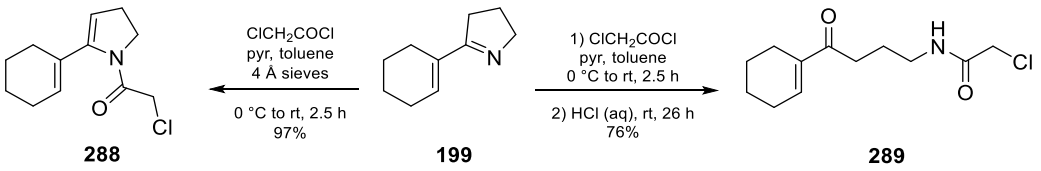


Scheme 103: Alternative preparation of cyclohexenylpyrroline 199.

Pragmatically, this route features lower temperatures and shorter reaction times than the corresponding IAVBC method, and can be performed on gram scale. IAVBC towards **199** was not conducted on scales >200 mg, due to the risk of pressure build up in the reaction vessel (N_2). However, due to the extremes in pH levels required during the hydrolysis and cyclisation, the above condensation route may not be suitable for delicate structural motifs. The IAVBC route, on the other hand, requires only a heterogeneous base to scrub the liberated acid by-product. In addition, this method (**287 → 199**) does not proceed *via* the reactive α-bromo imine, which may lend itself to the design of intricate reaction cascades in the near future.

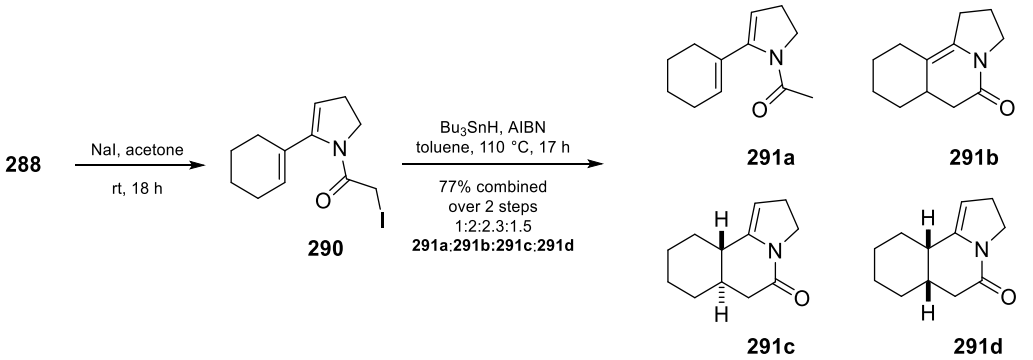
2.3.5 1-Azadiene derivatives as radical cyclisation precursors

Due to the presence of a α,β-unsaturated imine, it was theorised that 1-azadienes could be converted into precursors for intramolecular radical cyclisation reactions. Cyclohexenylpyrroline **199** was acylated with chloro acetylchloride, and purified quickly over silica to yield the α-chloro enamide **288** in high yield (Scheme 104). Much like **281**, the enamide would readily hydrolyse to an open-chain amide **289** in contact with silica, $CDCl_3$, or even standing in a C_6D_6 solution overnight, requiring rapid silica chromatography in the presence of Et_3N.



Scheme 104: Preparation of α-chloro enamine 288.

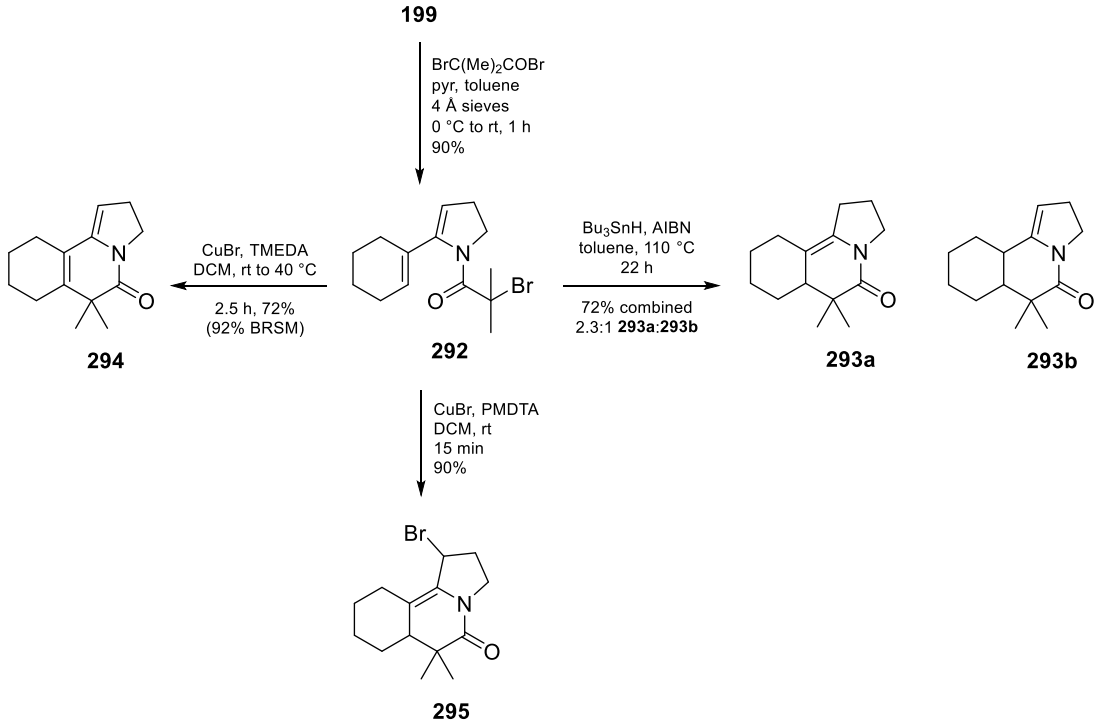
α-Iodo enamide **290**, arising from a Finkelstein reaction applied to chloride **288**,[363] was subjected to a reductive radical cyclisation under classical tin conditions (Scheme 105).[422–426] Products **291a**–**291d** were isolated in a 1:2:2.3:1.5 ratio and in 77% combined yield over two steps. δ-Lactam isomers **291b**–**291d** are the product of a regioselective *6-endo-trig* cyclisation and were complementary in structure to the previous ketene derived δ-lactams (Section **2.3.1**). The relative configurations of **291c** and **291d** were assigned tentatively based on energy calculations for the most stable isomer. The formation of acyl compound **291a**, originating from a premature radical reduction, was suppressed by the dropwise addition of a dilute Bu_3SnH/AIBN solution (0.022 M) to a dilute solution of **290** (0.025 M). The radical cyclisation appeared to be entirely site selective, with no detectable trace of either *5-exo-trig* or *4-exo-trig* products.



Scheme 105: Reductive radical cyclisation of α-chloro enamide 290.

Next, cyclohexenylpyrroline **199** was acylated with α-bromoisobutyryl bromide to provide a more labile radical precursor incorporating a quaternary centre. α-Bromo enamide **292** was an effective substrate in three complementary radical cyclisation

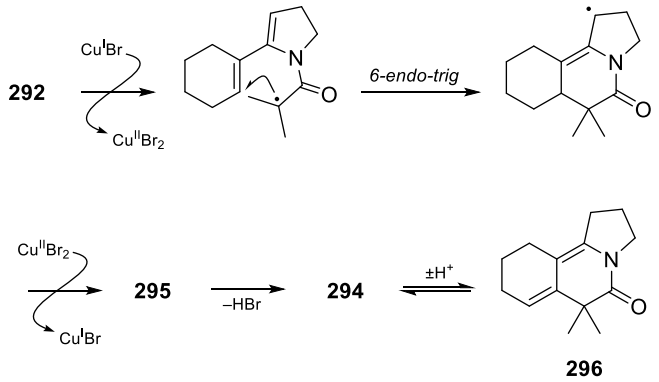
procedures (Scheme 106). Treatment of **292** under reductive radical cyclisation conditions afforded a 72% combined yield of δ-lactam alkene regioisomers **293a**–**293b**.[422–426]



Scheme 106: Reductive and atom transfer radical cyclisations of α-bromo enamide 292.

Using a modified literature procedure,[427,428] the atom-transfer radical cyclisation of α-bromo enamide **292** was undertaken, and revealed a unique quirk of ligand-directed product selection (Scheme 106). When a DCM solution of **292** was heated at reflux in the presence of stoichiometric CuBr with TMEDA as ligand, the α-bromo enamide was found to yield a tricyclic δ-lactam **294** that retains the oxidation level of the starting material. Mechanistically, the atom transfer radical *6-endo-trig* cyclisation occurs to give the allylic secondary bromide **295**, followed *in situ* by a dehydrobromination to **294** (Scheme 107). The reaction required a strictly air-free environment using degassed solvents, so as to prolong the lifespan of the copper catalyst. Product isolation required chromatography over basic alumina treated with

Et_3N, in order to prevent acid catalysed isomerisation. When purified over silica, the product was found to equilibrate into a ~1:1 mixture of double bond isomers **294/296** (Scheme 107).



Scheme 107: Plausible atom transfer radical cyclisations mechanism.

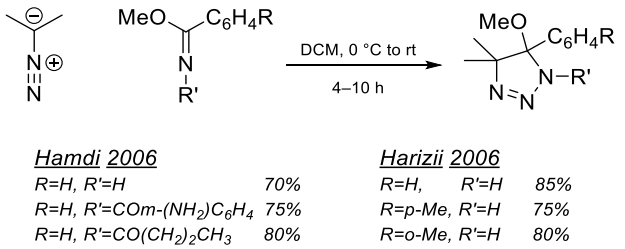
When bidentate TMEDA was swapped for the tridentate PMDTA, the reaction could be conducted with catalytic copper(I) bromide (30 mol%), and under milder reaction conditions (ambient temperature, 15 min). Thus, the highly chelating ligand appears to envelop the copper and provide a more reactive catalyst. Curiously, the product isolated from the reaction was the tricyclic allylic bromide **295**, suggesting PMDTA supresses *in situ* dehydrobromination, when compared to TMEDA. This may simply be a result of the mild conditions required for the radical cyclisation in this case. The product required purification by filtration through a plug of silica in order to retain the allylic bromide, which was unstable to full chromatographic purification due to the lability of the allylic bromide, leading to on-column dehydrobromination to **294**.

The three modes of radical cyclisation shown in Scheme 106 are highly complementary; simply by altering the conditions one can dictate the oxidation level or functionality of the resulting δ-lactam. Of particular merit is the synthesis of bromide **295**, which includes a functional bromide handle for further chemistry.

2.4 Miscellaneous routes towards 5-alkoxy-1,2,3-triazolines and tetrasubstituted enol ethers

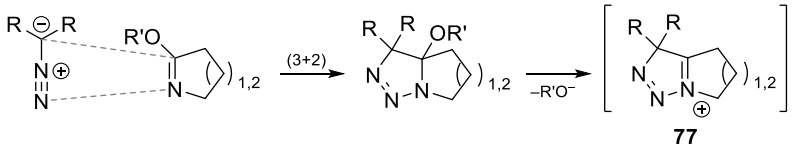
2.4.1 Attempted diazo-imine (3+2) cycloadditions towards 5-alkoxy-1,2,3-triazolines

In 2006, both Hamdi[429] and Harizi[430] independently claimed to report the first synthesis of 1,2,3-triazolines by an intermolecular (3+2) cycloaddition of 2-diazopropane with iminoethers (Scheme 108).



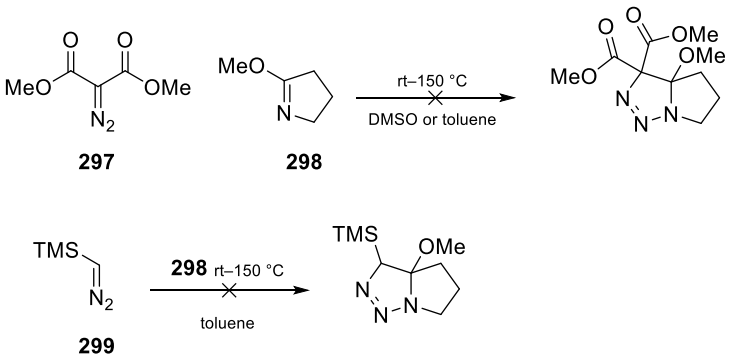
Scheme 108: Intermolecular (3+2) cycloaddition of 2-diazopropane with iminoethers.[429,430]

Inspired by this precedent, it was theorised that 1,2,3-triazolines and ergo triazolium **77** could be accessed *via* this strategy (Scheme 109).



Scheme 109: Proposed intermolecular (3+2) cycloaddition of diazoalkanes with iminoethers.

Both diazomalonate **297**,[431] and (trimethylsilyl)diazomethane **299**, failed to interact with 2-methoxy pyrroline **298**[432] at temperatures up to 150 °C (Scheme 110). As stable diazo compounds, it was presumed that neither **297** nor **299** were as reactive/nucleophilic as the literature-cited 2-diazopropane.

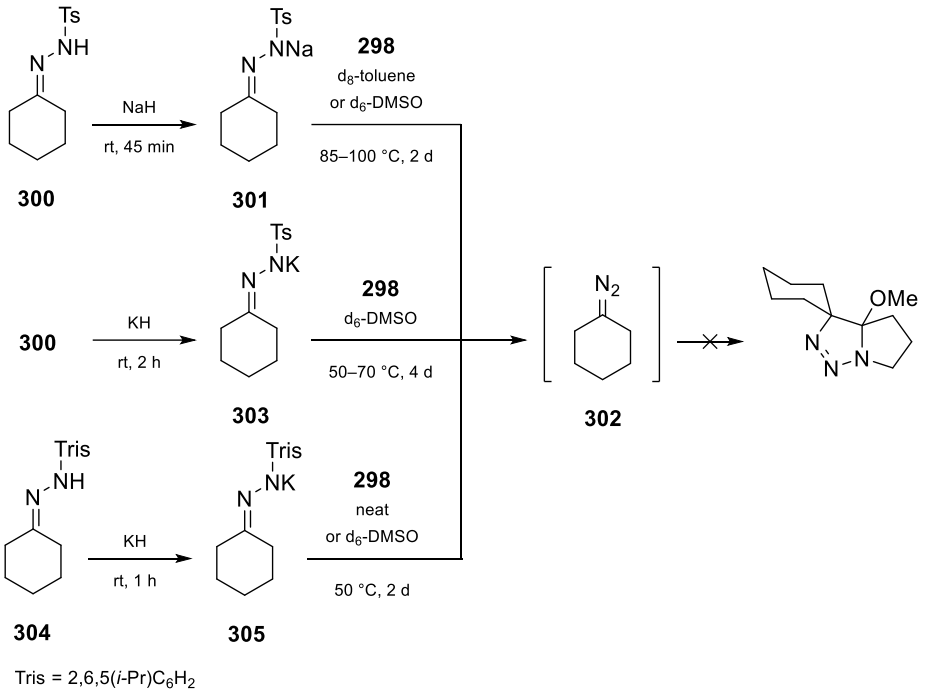


Scheme 110: Failed reaction between diazoalkanes 297 and 299 with 2-methoxy pyrroline 298.

We next sought to prepare a more reactive diazoalkane so as to emulate the literature success of 2-diazopropane.[429,430] Tosylhydrazone salts are a well-known safe alternative for generating unstable diazo compounds *in situ*,[433] and this method has been applied to diazo-alkyne (3+2) cycloadditions in the past.[434,435]

The tosylhydrazone of cyclohexanone **300** was converted to sodium salt **301** using NaH in THF, which was concentrated to a crude solid (Scheme 111).[436] Warming **301** in d_6-DMSO, or d_8-toluene solution in the presence of **298** did not lead to any detectable trace of cycloaddition, though cyclohexene was observed, indicative of a Bamford–Stevens reaction.[437] It was thought that if the diazo compound **302** could be formed at a lower temperature, the species would have a longer half-life in solution and a greater chance of undergoing cycloaddition with **298**. Potassium salt **303**, prepared from **300** using KH, could decompose to **302** at 60 °C, but did not react with **298**. Again cyclohexene was detected, indicative of diazo formation.

Trisylhydrazones decompose more readily to the corresponding diazo compound compared to tosylhydrazones, due to the steric destabilising effect of the bulky ortho substituents.[438] The potassium salt **305** of trisylhydrazone **304** showed no sign of cycloaddition with **298**, both in DMSO, or using **298** as solvent (Scheme 11).



Scheme 111: Failed reaction between in situ diazocyclohexane 302 with 2-methoxy pyrroline 298.

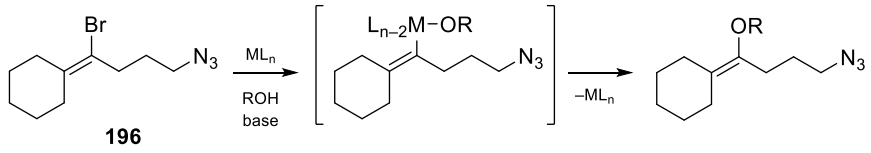
As a definitive test, 2-methoxy pyrroline **298** was added to an ether solution of freshly prepared diazomethane[439] and left at room-temperature overnight. Extremely reactive and unhindered, it was assumed that diazomethane would either confirm, or disprove, the feasibility of cycloaddition using **298**. The crude reaction mixture showed no sign of triazoline, or triazole formation.

It would appear that 2-methoxy pyrroline is too unactivated when compared to the aryl imines shown in Scheme 108, possibly due to alkyl substitution on nitrogen.

2.4.2 Attempted synthesis of tetrasubstituted enol ethers from vinyl bromides

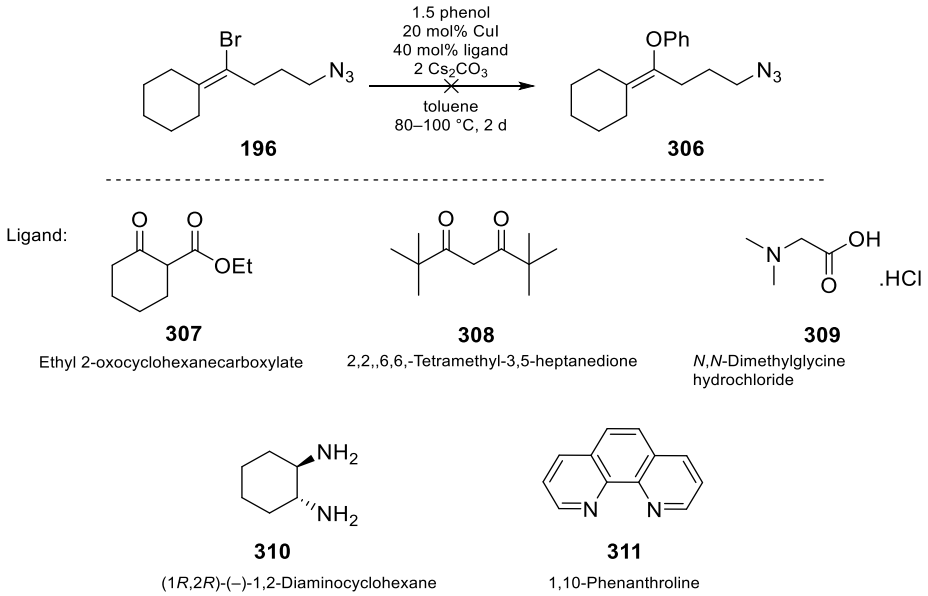
While there is not a reliable method for the synthesis of tetrasubstituted enol ethers (Section **2.1**), tetrasubstituted vinyl bromides can be readily prepared from their corresponding alkene precursor (Section **2.2**). With an abundance of cyclohexyl substrate **196** in hand, we wished to explore methodology to cross-couple this vinyl

bromide with an alcohol to prepare a fully-substituted azidoalkyl enol ether (Scheme 112).



Scheme 112: Proposed cross-coupling methodology towards tetrasubstituted enol ethers.

The Ullmann coupling has often been used for the formation of enol ethers from vinyl halides and alcohols.[440–444] Using the conditions shown in Scheme 113, we attempted the CuI mediated coupling of **196** with phenol using ligands **307**–**311**, plus an extra control experiment in the absence of ligand. In our hands there was no evidence of coupling nor oxidative addition by NMR or MS, instead starting material was returned intact.

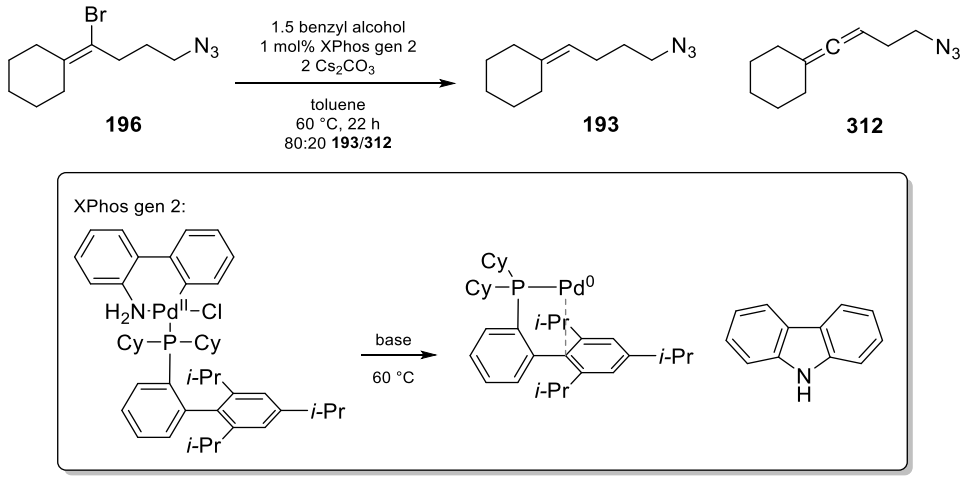


Scheme 113: Attempted Ullmann coupling towards enol ether 306.

Recently, Buchwald and co-workers have reported the preparation and use of palladium-ligand pre-catalyst complexes.[445,446] While the Buchwald etherification is commonly used for the coupling of aryl halides with alcohols,[447–449] we subjected vinyl

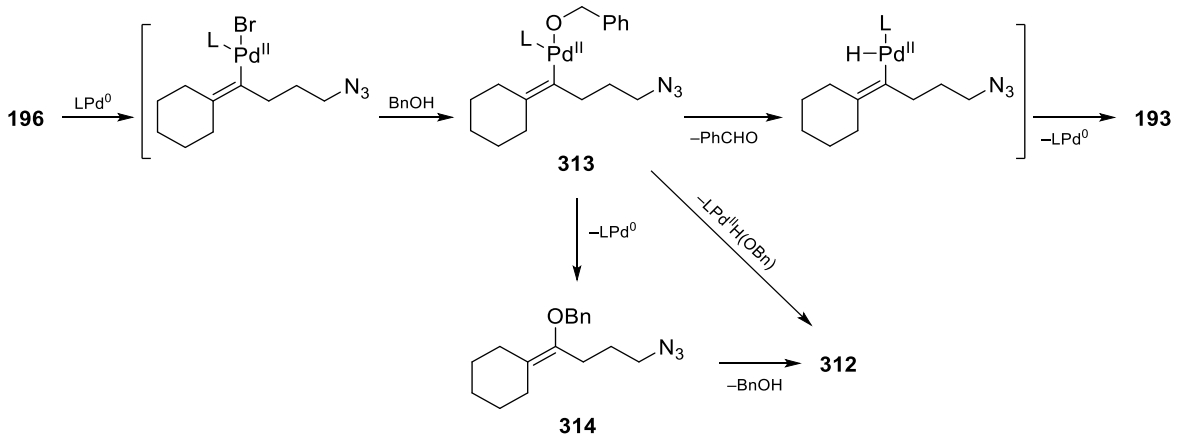
bromide **196** to a screen of bases, solvents, alcohols, and Buchwald pre-catalysts. Results worthy of comment are discussed below.

When vinyl bromide **196** was treated with XPhos in the presence of benzyl alcohol, the desired coupling product was not observed, but rather an 80:20 mixture of alkene **193** and allene **312** by ^{1}H-NMR analysis of the crude product (Scheme 114).



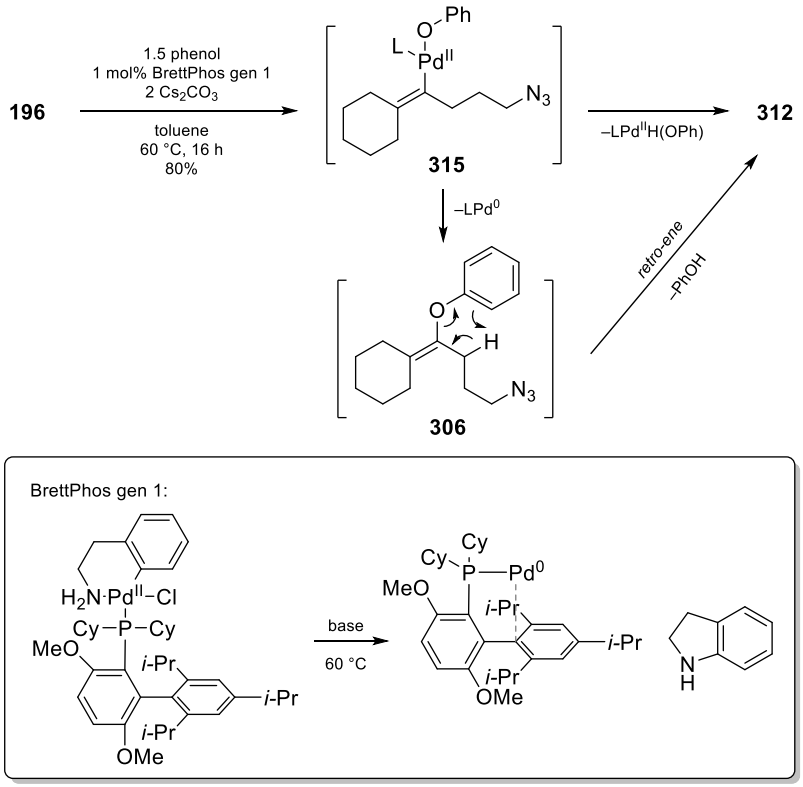
Scheme 114: Coupling reaction leading to 193 and 312 under Pd catalysis with benzyl alcohol.

Mechanistically, it is believed that oxidative addition occurs to give a Pd^{II} intermediate which can undergo ligand exchange with benzyl alcohol to give **313** (Scheme 115). β-Hydride elimination from the primary alcohol[447] may generate a palladium-hydride species that can reductively eliminate to yield the alkene **193**. Competing β-hydride elimination from **313** would provide allene **312**. Alternatively, any reductive elimination to the desired product **314** may be followed by *in situ* elimination to yield the allene **312**.



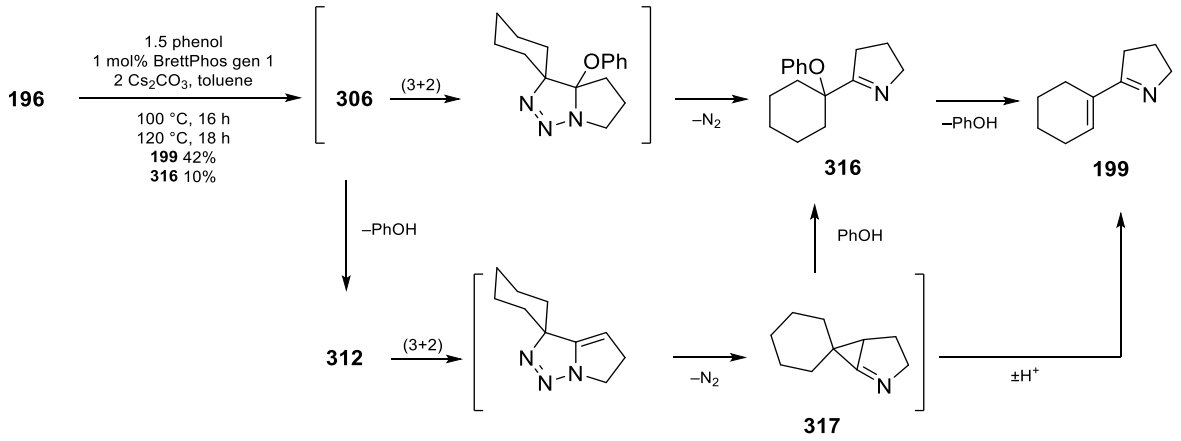
Scheme 115: Plausible mechanisms leading to 193 and 312 under Pd catalysis with benzyl alcohol.

In contrast, using phenol as the coupling partner (with either XPhos or BrettPhos) gave solely the allene **312**, this time in an 80% isolated yield (Scheme 116). Mechanistically, this may suggest direct β-hydride elimination from the Pd^{II} species **315** to allene **312**, or alternatively successful reductive elimination to compound **306**, followed by elimination to **312** (analogous to Scheme 115), or alternatively, a retro-ene reaction from **306** leading to **312** (Scheme 116).



Scheme 116: Coupling reactions leading to 312 under Pd catalysis with phenol.

When conducted at higher temperatures, the BrettPhos-mediated coupling between **196** and phenol afforded 1-azadiene **199** in a 42% isolated yield, along with a novel α-phenoxy imine **316** in a 10% yield (Scheme 117). Several plausible explanations can be provided to deliver these two products, including the IAOC reaction of an intermediate enol ether **306** (analogous to the IAVBC of **196** discussed in Section **2.2.3**), an intramolecular allene-azide cycloaddition *via* methyleneaziridine **317** (analogous to previous work in the Robertson group[275]), or a combination of both. Support of the IAOC manifold is that allene-azide cycloadditions *via* **317** yielded isocyanides in previous group work (Scheme 32).[275]



Scheme 117: Coupling reactions leading to 199 and 316 under Pd catalysis with phenol and proposed mechanistic pathways.

Control experiments were conducted to clarify these observations; in the individual absence of alcohol, catalyst, or base, no reaction would occur, indicating the necessity of each of these components. This may support the intermediacy of the enol ether product, or that β-hydride elimination to form allene **312** occurs rapidly once the Pd^{II} species **313** or **315** is formed.

SPhos and RuPhos were also effective as pre-catalysts, while dioxane and *t*-BuOH were unsuccessful as the solvent and alcohol component respectively.

3 Conclusion

In the original research proposal, we wished to use the IAOC reaction of heteroatom-substituted olefins in order to access and exploit triazolium ion **77** (Scheme 35). Preliminary studies on di- and trisubstituted azidoalkyl enol ethers indicated the necessity for a fully-substituted enol ether so as to prevent the initial 5-alkoxy-1,2,3-triazoline from aromatising to the corresponding triazole upon ionisation (Section **2.1**, Schemes 37 and 38). Difficulties in synthesising fully-substituted azidoalkyl enol ethers have precluded their detailed study in this project (Sections **2.1** and **2.4.2**).

From the evidence gathered it appears that, at the temperatures required for cycloaddition, 4,4-disubstituted-5-hetero-1,2,3-triazolines **172** are biased to undergo concerted imine formation, 1,2-heteroatom migration, and nitrogen release to give α-hetero-substituted imines (see Scheme 63). This is due to the ability to stabilise a positive charge at the 4-position of the intermediate 4,4-disubstituted triazoline, promoting fragmentation at this point. Thus, it would appear the theoretical iminium ion **77** cannot be accessed or exploited in these cases. Characterised structures that support this atom-migratory reactivity are shown in Figure 19, for enol ether, TMS-enol ether, and vinyl bromide IAOC reactions.

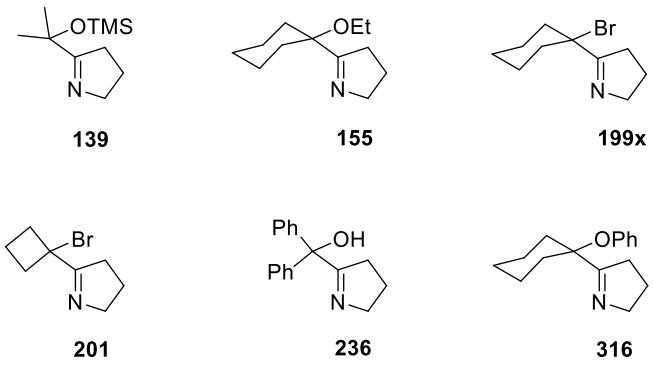


Figure 19: Isolated and characterised α-hetero-substituted imines.

1,2,3-Triazolines that could not stabilise a positive charge at the 4-position were isolable and did not fragment under the cycloaddition conditions (Figure 20). The only anomalous result is that for dimethyl ester-derived vinyl bromide **224** which fragmented under relatively mild reaction conditions (see Scheme 75). This result may be driven by the leaving group ability of bromine adjacent to a nitrogen, as compared to 5-alkoxy-1,2,3-triazolines in which RO^- is a relatively poorer leaving group (than Br^-).

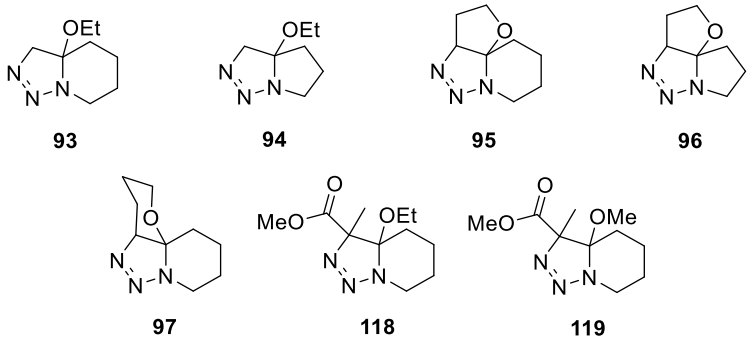


Figure 20: Isolable 5-alkoxy-1,2,3-triazolines.

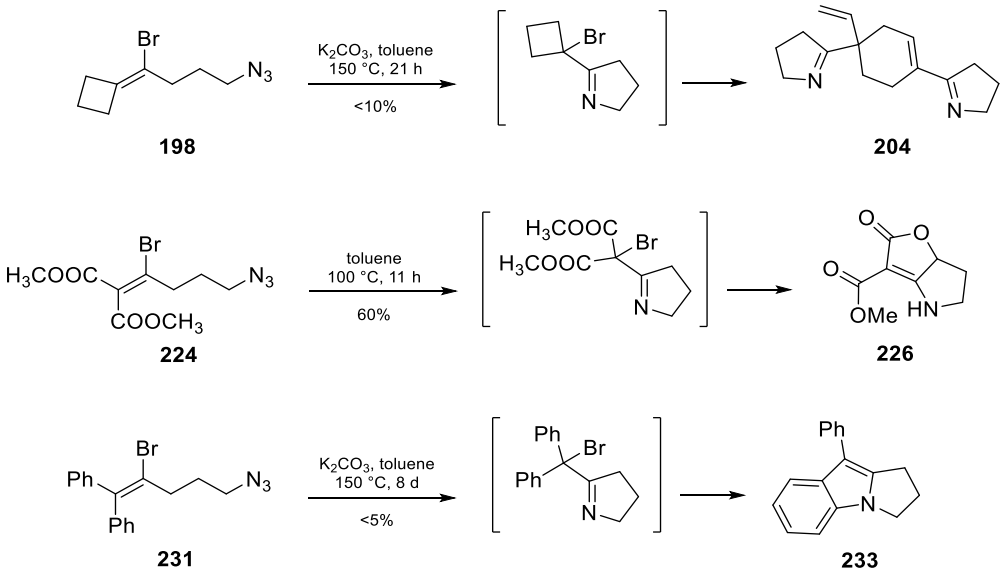
As a consequence of the formation of an α-bromo imine intermediate, we discovered a novel IAVBC route towards 1-azadienes and explored the scope and limitations of this reaction (Section **2.2**). With the exception of electronically-activated substrate **224**, the vinyl bromide substrates studied required high temperatures and long reaction times to complete IAVBC (150 °C, ~1–2 d). However, it was demonstrated that the cycloaddition rate could be increased through strain and/ or entropic bias within the starting material.

1-Azadienes were shown to be versatile molecules for the generation of a small DOS library. The ability of **199** to undergo selective 1,4 or 1,2-addition, and the nucleophilic potential of the pyrroline nitrogen was demonstrated, (Section **2.3.3**). Of particular merit was the ability of alkenylpyrrolines to undergo a selective formal (4+2) cycloaddition with diphenylketene to provide δ-lactams (Section **2.3.2**). Complimentary

to this methodology was the ability of 1-azadiene **199** to act as radical-cyclisation precursor, providing an alternate route into 6,6,5 tricyclic systems (Section **2.3.5**). Both of these reaction modes were perhaps underexploited during this methodological campaign, and deserve further attention. Future work should focus on varying the ketene used, the diastereoselectivity of the reaction, and eventually the synthesis of polycyclic cores for incorporation into natural product synthesis.

The IAVBC systems studied were simple test substrates, lacking extensive structural bias. If built into an existing conformationally rigid skeleton, such as a steroidal core, we may expect milder reaction conditions than those exhibited here. An IAVBC strategy towards a 1-azadiene motif embedded within such a drug-like structure would provide a convenient handle from which a diverse DOS library could be assembled.

A potentially powerful application of the IAVBC reaction would be to pre-functionalise substrates so as to intercept the reactive α-bromo imine *in situ*, such as was observed for substrates **198**, **224**, and **231** (Scheme 118). With this end in mind, careful substrate design may provide improved selectivity towards a single outcome.



Scheme 118: IAVBC reactions with the interception of the α-bromo imine intermediate.

4 Experimental

General information

Atom numbering. Atom numbering in compounds reflects NMR signal assignment and does not necessarily correspond to IUPAC nomenclature.

Solvents and reagents. All reactions were performed using oven-dried glassware under an atmosphere of argon unless otherwise stated. When base washed, glassware was treated with saturated aqueous NaOH solution and washed with water, acetone, and then oven dried. Magnetic stirrer bars were stirred vigorously using stirrer hot plates. Heating was conducted using oil baths. Rubber septa were wrapped in Parafilm. "Petrol" refers to the fraction of petroleum ether boiling in the range 30—40 °C. "Ether" refers to diethyl ether. Dry ether, dichloromethane and toluene were obtained from Grubbs canisters. Tetrahydrofuran was freshly distilled from sodium and benzophenone under a nitrogen atmosphere. Pyridine and triethylamine were distilled prior to use and stored over KOH. Unless otherwise stated, all other reagents and solvents were used as supplied.

Chromatography. Thin layer chromatography (TLC) was carried out using Merck aluminium-backed DC60 F_{254} precoated plates (particle size 0.2 mm). Spots were visualised by ultraviolet (UV) light (λ_{max} = 254 nm) and then stained with anisaldehyde or potassium permanganate as appropriate. Flash column chromatography was performed using Merck 60 silica gel (particle size 40—63 μm) or Sigma-Aldrich aluminium oxide, activated, basic, Brockmann I (particle size ~150 mesh) as appropriate.

Microwave reactions. Microwave reactions were conducted using a CEM Discover S-class manual single-node reactor (150 μW) in thick-walled 8 mL glass microwave tubes.

Pressure tube reactions. Pressure tube reactions were carried out in ~4 inch "ACE glassware #15" thick-walled vessels with an approximate volume of 14 mL. Tube threads were wrapped with PTFE tape and capped with PTFE screw tops complete with FETFE® O-ring seal (from Sigma-Aldrich).

Nuclear magnetic resonance (NMR) spectroscopy. Proton (^{1}H) and carbon (^{13}C) spectra were recorded on Bruker AVC-500 (500/125 MHz), Bruker DQX-400, AVF-400, or AVG-400 (400/100 MHz), or Bruker DPX-200 (200/50 MHz) spectrometers in deuterated solvents. Peak assignments were made on the basis of chemical shifts, integrations, coupling constants, using COSY, DEPT, HSQC, and HMBC were appropriate. Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent), sextet (sext), septet (sept), multiplet (m), apparent (app.) and broad (br). Coupling constants (*J*) are quoted to the nearest 0.5 Hz.

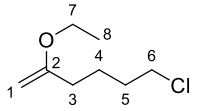
Infrared (IR) spectroscopy. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR spectrometer on NMR samples evaporated from the appropriate deuterated solvent. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) and broad (br).

Mass spectrometry (MS). Low-resolution mass spectra were recorded on a Micromass LCT Premier spectrometer (ESI). High-resolution mass spectra (HRMS) were recorded by the staff of the Chemistry Research Laboratory on a Bruker Daltonics MicroTOF spectrometer. Mass to charge ratios (*m/z*) are reported in Daltons.

Melting points (M.p). Melting points were determined using a Griffin MFB-700-010U melting point apparatus and are uncorrected.

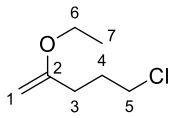
Compounds

6-Chloro-2-ethoxyhex-1-ene (80)



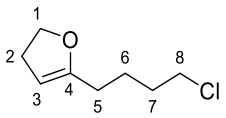
A modified literature procedure[276–280] was used. To an oven-dried 50 mL RBF under an atmosphere of argon was added ethyl vinyl ether (1.8 mL, 19 mmol) and freshly distilled THF (14 mL). The flask was cooled to –78 °C and *t*-BuLi (12.5 mL, 1.6 M in pentane, 20.0 mmol) added dropwise via syringe over 10 min causing an intense yellow colouration. After stirring at –78 °C for 1 h, the reaction mixture was warmed to 0 °C and stirred for 2 h, during which time the solution changed from yellow to brown, and was then cooled to –78 °C and stirred for 1 h. Neat 1-chloro-4-iodobutane (1.0 mL, 8.2 mmol) was added dropwise, causing a light purple colour that faded to colourless within seconds. The reaction mixture was stirred overnight while the acetone bath was allowed to thaw from –78 °C to ~15 °C. The resulting white slurry was cooled to 0 °C, quenched with brine (6 mL) and extracted with ether (3 x 30 mL). The combined organic layers were washed successively with water (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to yield a colourless oil (1.36 g, 100%) that was sufficiently pure to be used in the next reaction. An analytical sample was obtained by chromatography using basic alumina and eluting with 1% triethylamine/petrol. R_f 0.25 (petrol); ν_{max} 2934w, 2972w, 1653m, 1277m, 1081m, 796s, 652m; δ_H (400 MHz, C_6D_6) 1.06 (3 H, t, *J* = 7.0 Hz, H8), 1.42–1.55 (4 H, m, H4 and H5), 1.99 (2 H, t, *J* = 7.0 Hz, H3), 3.08 (2 H, t, *J* = 6.5 Hz, H6), 3.44 (2 H, q, *J* = 7.0 Hz, H7), 3.82 and 3.86 (2 x 1 H, 2 x d, *J* = 1.5 Hz, H1); δ_C (100 MHz, C_6D_6) 14.5 (C8), 24.8 (C4), 32.1 (C5), 34.6 (C3), 44.6 (C6), 62.6 (C7), 81.1 (C1), 162.9 (C2); HRMS (FI^+) found 162.0813, $C_8H_{15}{}^{35}ClO$ (M^+) requires 162.0806.

5-Chloro-2-ethoxypent-1-ene (81)



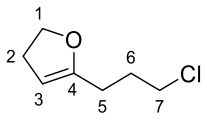
A modified literature procedure[276–280] was used. To an oven-dried 50 mL RBF under an atmosphere of argon was added ethyl vinyl ether (2.0 mL, 21 mmol) and freshly distilled THF (15 mL). The flask was cooled to –78 °C and *t*-BuLi (19 mL, 1.6 M in pentane, 30 mmol) was added dropwise via syringe over 10 min causing an intense yellow colouration, and the mixture was stirred at –78 °C for 1 h. The reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h, during which time the solution changed colour from yellow to brown; it was then cooled to –78 °C and stirred for 1 h. Neat 1-bromo-3-chloropropane (1.0 mL, 8.2 mmol) was added dropwise, causing a light purple colour that faded to colourless within seconds. The reaction mixture was stirred overnight while the acetone bath was allowed to thaw from –78 °C to ~15 °C. The resulting white slurry was cooled to 0 °C, quenched with brine (6 mL) and extracted with ether (3 x 30 mL). The combined organic layers were washed successively with water (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to yield a colourless oil (1.35 g, 90%) that was sufficiently pure to be used in the next reaction. An analytical sample was obtained by chromatography using basic alumina and eluting with 1% triethylamine/petrol. R_f 0.37 (petrol); ν_{max} 2980w, 1655m, 1276m, 1077s, 798s; δ_H (400 MHz, C_6D_6) 1.02 (3 H, t, *J* = 7.0 Hz, H7), 1.77 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.13 (2 H, t, *J* = 7.0 Hz, H3), 3.17 (2 H, t, *J* = 7.0 Hz, H5), 3.38 (2 H, q, *J* = 7.0 Hz, H6), 3.79 and 3.87 (2 x 1 H, 2 x d, *J* = 1.5 Hz, H1); δ_C (100 MHz, C_6D_6) 14.4 (C7), 30.6 (C4), 32.6 (C3), 44.2 (C5), 62.7 (C6), 81.7 (C1), 161.8 (C2); HRMS (FI^+) found 148.0658, $C_7H_{13}{}^{35}ClO$ (M^+) requires 148.0649.

5-(4-Chlorobutyl)-2,3-dihydrofuran (83)



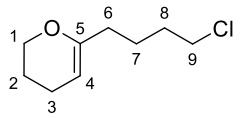
A modified literature procedure[276–280] was used. To an oven-dried 50 mL RBF under an atmosphere of argon was added dihydrofuran (0.8 mL, 10 mmol) and freshly distilled THF (8 mL). The flask was cooled to –78 °C and *t*-BuLi (8 mL, 1.5 M in pentane, 12 mmol) was added dropwise via syringe over 10 min causing an intense yellow colouration, and the reaction mixture stirred at –78 °C for 1 h. The reaction mixture was warmed to 0 °C and was stirred at this temperature for 2 h, during which time the solution changed from yellow to pale yellow, and then cooled to –78 °C and stirred for 1 h. Neat 1-chloro-4-iodobutane (0.61 mL, 5.0 mmol) was added dropwise and reaction mixture was stirred overnight while the acetone bath was allowed to thaw from –78 °C to ~15 °C. The resulting white slurry was quenched with brine (3 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow oil (824 mg, 100%) that was sufficiently pure to be used in the next reaction. R_f 0.20 (petrol); ν_{max} 2935s, 2861m, 1667s, 1005s, 725s; δ_H (400 MHz, C_6D_6) 1.41–1.49 (4 H, m, H6 and H7), 1.93–1.97 (2 H, m, H5), 2.28 (2 H, tq, *J* = 9.5 and 2.0 Hz, H2), 3.06 (2 H, t, *J* = 6.0 Hz, H8), 4.05 (2 H, t, *J* = 9.5 Hz, H1), 4.42 (1 H, app. sept, *J* = 1.0 Hz, H3); δ_C (100 MHz, C_6D_6) 23.0 (C6), 27.0 (C5), 29.9 (C2), 31.9 (C7), 44.2 (C8), 69.4 (C1), 93.6 (C3), 158.4 (C4); HRMS (FI^+) found 161.07254, $C_8H_{14}O^{35}Cl$ (MH^+) requires 161.07277.

5-(3-Chloropropyl)-2,3-dihydrofuran (84)



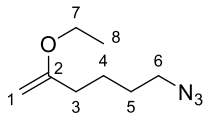
A modified literature procedure[276–280] was used. To an oven-dried 50 mL RBF under an atmosphere of argon was added dihydrofuran (1 mL, 14 mmol) and freshly distilled THF (10 mL). The flask was cooled to –78 °C and *t*-BuLi (8 mL, 1.65 M in pentane, 13 mmol) was added dropwise via syringe over 10 min causing an intense yellow colouration, and the mixture stirred at –78 °C for 1 h. The reaction mixture was warmed to 0 °C and stirred at this temperature for 2 h, during which time the solution changed colour from yellow to pale yellow; then cooled to –78 °C for and stirred for 1 h. Neat 1-chloro-3-bromopropane (0.67 mL, 6.8 mmol) was added dropwise and reaction mixture was stirred overnight while the acetone bath was allowed to thaw from –78 °C to ~15 °C. The resulting white slurry was quenched with brine (3 mL) and extracted with ether (3 x 20mL). The combined organic layers were washed successively with water (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow oil (1.07 g, 100%) that was sufficiently pure to be used in the next reaction. R_f 0.60 (ethyl acetate/ petrol, 1:10); ν_{max} 2958w, 2862w, 1668m, 1003s, 930s, 724s, 651s; δ_H (400 MHz, C_6D_6) 1.71 (2 H, app. pent, *J* = 7.0 Hz, H6), 2.10 (2 H, tq, *J* = 7.0 and 1.0 Hz, H5), 2.24 (2 H, tq, *J* = 9.0 and 2.0 Hz, H2), 3.13 (2 H, t, *J* = 6.0 Hz, H7), 3.99 (2 H, t, *J* = 9.0 Hz, H1), 4.40 (1 H, sept, *J* = 1.0 Hz, H3); δ_C (100 MHz, C_6D_6) 25.4 (C5), 29.9 (C6), 30.2 (C2), 44.2 (C7), 69.7 (C1), 94.5 (C3), 157.6 (C4); HRMS (FI^+) found 146.0502, $C_7H_{11}{}^{35}ClO$ (M^+) requires 146.0498.

6-(4-Chlorobutyl)-3,4-dihydro-2*H*-pyran (85)



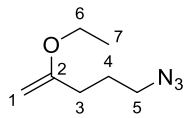
A modified literature procedure[276–280] was used. To an oven-dried 50 mL RBF under an atmosphere of argon was added dihydropyran (0.78 mL, 8.5 mmol) and freshly distilled THF (8 mL). The flask was cooled to –78 °C and *t*-BuLi (5.5 mL, 1.65M in pentane, 9.1 mmol) was added dropwise via syringe over 10 min causing an intense yellow colouration, and the reaction mixture stirred at –78 °C for 1 h. The reaction was warmed to 0 °C and stirred at this temperature for 2 h, during which time the solution to change from yellow to pale yellow, and then cooled to –78 °C for 1 h. Neat 1-iodo-4-chlorobutane (0.7 mL, 5.7 mmol) was added dropwise and reaction was stirred overnight while the acetone bath was allowed to thaw from –78 °C to ~15 °C. The resulting white slurry was cooled in ice, quenched with brine (4 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed successively with water (5 mL) and brine (5 mL) then dried (Na_2SO_4) and concentrated under reduced pressure to yield a yellow oil (1.08 g, 100%) that was sufficiently pure to be used in the next reaction. R_f 0.80 (ethyl acetate/ petrol, 1:1); ν_{max} 2932m, 2868w, 1675m, 1234m, 1062s, 762s, 649m; δ_H (400 MHz, C_6D_6) 1.40–1.51 (6 H, m, H2, H7 and H8), 1.75–1.80 (2 H, m, H3), 1.90–1.92 (2 H, m, H6), 3.08–3.12 (2 H, m, H9), 3.72 (2 H, t, *J* = 5.0 Hz, H1), 4.37 (1 H, t, *J* = 4.0 Hz, H4); δ_C (100 MHz, C_6D_6) 20.5 (C3), 22.7 (C2), 24.5 (C7), 32.2 (C8), 33.9 (C6), 44.7 (C9), 65.9 (C1), 95.5 (C4), 154.2 (C5); HRMS (FI^+) found 174.0804, $C_9H_{15}{}^{35}ClO$ (M^+) requires 174.0806.

6-Azido-2-ethoxyhex-1-ene (86)



A modified literature procedure[251,283,284] was used. To an oven-dried 50 mL RBF was added 6-chloro-2-ethoxyhex-1-ene (1.17 g, 7.19 mmol), NaN_3 (885 mg, 13.6 mmol) and DMSO (11 mL) and the reaction vessel sealed under an atmosphere of argon. The reaction slurry was stirred at 40 °C for 21 h and the reaction vessel removed from heat, quenched with ice (~40 g) and extracted with ether (3 x 50 mL). The combined organic layers were washed successively with water (10 mL) and brine (10 mL), then dried (Na_2SO_4). The solution was concentrated under reduced pressure to afford a yellow oil (1.02 g, 84%) that was sufficiently pure to be used in the next reaction. R_f 0.25 (petrol); ν_{max} 2980w, 2091s, 1653m, 1094m, 796s; δ_H (400 MHz, C_6D_6) 1.07 (3 H, t, *J* = 7.0 Hz, H8), 1.22 (2 H, app. pent, *J* = 7.0 Hz, H5), 1.39 (1 H, app. pent, *J* = 7.5 Hz, H4) 1.98 (2 H, t, *J* = 7.5 Hz, H3), 2.65 (2 H, t, *J* = 7.0 Hz, H6), 3.45 (2 H, q, *J* = 7.0 Hz, H7), 3.83 and 3.87 (2 x 1 H, 2 x d, *J* = 1.0 Hz, H1); δ_C (100 MHz, C_6D_6) 14.5 (C8), 24.6 (C5), 28.3 (C4), 34.8 (C3), 51.0 (C6), 62.6 (C7), 81.1 (C1), 162.9 (C2); HRMS (FI^+) found 170.1289, $C_8H_{16}N_3O$ (MH^+) requires 170.1288.

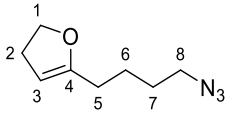
5-Azido-2-ethoxypent-1-ene (87)



A modified literature procedure[251,283,284] was used. To an oven-dried 50 mL RBF was added 6-azido-2-ethoxypent-1-ene (211 mg, 1.42 mmol), NaN_3 (146 mg, 2.27 mmol) and DMSO (2 mL). The slurry was stirred under an atmosphere of argon at 50 °C for 21 h, removed from heat, and the reaction diluted with ether (50 mL) and washed successively with water (10 x 1 mL) and brine (1 mL). The organic layer was dried

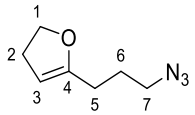
(Na_2SO_4) and concentrated under reduced pressure to afford a yellow oil (160 mg, 72%) that was sufficiently pure to be used in the next reaction. R_f 0.37 (petrol); ν_{max} 2932w, 2092s, 1654m, 1271m, 1086m, 799m; δ_H (400 MHz, C_6D_6) 1.03 (3 H, t, *J* = 7.0 Hz, H7), 1.53 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.00 (2 H, t, *J* = 7.0 Hz, H3), 2.74 (2 H, t, *J* = 7.0 Hz, H5), 3.39 (2 H, q, *J* = 7.0 Hz, H6), 3.79 and 3.84 (2 x 1 H, 2 x d, *J* = 1.5 Hz, H1); δ_C (100 MHz, C_6D_6) 14.4 (C7), 26.8 (C4), 32.4 (C3), 50.6 (C5), 62.7 (C6), 81.6 (C1), 162.0 (C2); HRMS (FI^+) found 156.0933, $C_7H_{14}N_3O$ (MH^+) requires 156.1131.

5-(4-Azidobutyl)-2,3-dihydrofuran (88)



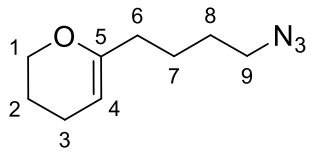
A modified literature procedure[251,283,284] was used. To an oven-dried 50 mL RBF was added 5-(4-chlorobutyl)-2,3-dihydrofuran (566 mg, 3.52 mmol), NaN_3 (355 mg, 5.64 mmol) and DMSO (6 mL). The slurry was stirred at 65 °C under an atmosphere of argon for 20 h, removed from heat, quenched with water (10 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed successively with water (3 x 2 mL) and brine (2 mL), then dried (Na_2SO_4). Solution was concentrated under reduced pressure to afford a yellow oil (497 mg, 84%) that was sufficiently pure to be used in the next reaction. R_f = 0.20 (petrol); ν_{max} 2941m, 2864m, 2091s, 1667m, 1005m, 723m; δ_H (400 MHz, C_6D_6) 1.17–1.24 (2 H, m, H7), 1.30–1.38 (4 H, m, H6), 1.94 (2 H, tq, *J* = 7.5 and 1.0 Hz, H5), 2.29 (2 H, tq, *J* = 9.5 and 2.0 Hz, H2), 2.63 (2 H, t, *J* = 7.0 Hz, H8), 4.06 (2 H, t, *J* = 9.5 Hz, H1), 4.43 (1 H, app. sept, *J* = 1.0 Hz, C3); δ_C (100 MHz, C_6D_6) 24.0 (C6), 27.6 (C5), 28.4 (C7), 30.2 (C2), 51.0 (C8), 69.7 (C1), 93.9 (C3), 158.7 (C4); HRMS (FI^+) found 168.1131, $C_8H_{14}N_3O$ (MH^+) requires 168.1131.

5-(3-Azidopropyl)-2,3-dihydrofuran (89)



A modified literature procedure[251,283,284] was used. To an oven-dried 50 mL RBF was added 5-(4-chloropropyl)-2,3-dihydrofuran (308 mg, 2.10 mmol), NaN_3 (209 mg, 3.21 mmol) and DMSO (1 mL). The slurry was stirred under argon at 60 °C for 23 h, the mixture removed from heat, then quenched with water (20 mL) and extracted with ether (3 x 30 mL). The combined organic layers were washed successively with water (8 x 1 mL) and brine (1 mL), then dried (Na_2SO_4). Solution was concentrated under reduced pressure to afford an orange oil (178 mg, 55%) that was sufficiently pure to be used in the next reaction. R_f 0.60 (ethyl acetate/ petrol, 1:10); ν_{max} 2933w, 2864w, 2095s, 1668w, 1258m, 1005m, 961m. δ_H (400 MHz, C_6D_6) 1.47 (2 H, app. pent, *J* = 7.0 Hz, H6), 1.97 (2 H, tq, *J* = 7.0 and 1.0 Hz, H5), 2.25 (2 H, tq, *J* = 9.5 and 2.0 Hz, H2), 2.72 (2 H, t, *J* = 7.0 Hz, H7), 4.01 (2 H, t, *J* = 9.5 Hz, H1), 4.39 (1 H, sept, *J* = 1.0 Hz, H3); δ_C (100 MHz, C_6D_6) 25.2 (C5), 26.2 (C6), 30.2 (C2), 50.6 (C7), 69.7 (C1), 94.4 (C3), 157.8 (C4); HRMS (FI^+) found 153.0899, $C_7H_{11}N_3O$ (M^+) requires 153.0897.

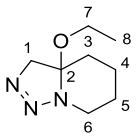
6-(4-Azidobutyl)-3,4-dihydro-2*H*-pyran (90)



A modified literature procedure[251,283,284] was used. To an oven-dried 50 mL RBF was added 6-(4-chlorobutyl)-3,4-dihydro-2*H*-pyran (529 mg, 3.03 mmol), NaN_3 (321 mg, 4.93 mmol) and DMSO (1.5 mL). The reaction was stirred at 60 °C under argon for 65 h, then removed from heat, the mixture quenched with water (25 mL) and extracted with ether (3 x 25 mL). Combined organic layers were washed successively with water

(6 x 1 mL) and brine (1 mL), then dried (Na_2SO_4). The solution was concentrated under reduced pressure to afford a yellow oil (398 mg, 72%) that was sufficiently pure to be used in the next reaction. R_f 0.80 (ethyl acetate/ petrol, 1:1); ν_{max} 2970m, 2867w, 2090s, 1739m, 1675m, 1233m, 1063m, 763m; δ_H (400 MHz, C_6D_6) 1.25 (2 H, dt, *J* = 15.0 and 7.0 Hz, H8), 1.36–1.49 (4 H, m, H2 and H7), 1.78–1.81 (2 H, m, H3), 1.92 (2 H, t, *J* = 7.5 Hz, H6), 2.68 (2 H, t, *J* = 7.0 Hz, H7), 3.74 (2 H, t, *J* = 5.0 Hz, H1), 4.39 (1 H, t, *J* = 4.0 Hz, H4); δ_C (100 MHz, C_6D_6) 20.5 (C3), 22.7 (C2), 24.3 (C7), 28.3 (C8), 34.1 (C6), 51.1 (C9), 66.0 (C1), 95.5 (C4), 154.2 (C5); HRMS (FI^+) found 181.1210, $C_9H_{15}N_3O$ (M^+) requires 181.1210.

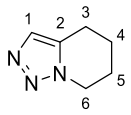
3a-Ethoxy-3,3a,4,5,6,7-hexahydro-[1,2,3]triazolo[1,5-a]pyridine (93)



To an oven-dried 14 mL Ace pressure tube was added 6-azido-2-ethoxyhex-1-ene (70 mg, 0.41 mmol), dry toluene (5.5 mL), and solid K_2CO_3 (114 mg, 0.827 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 130 °C for 4 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. The tube was removed from heat, the solution filtered, and the filtrate concentrated under reduced pressure to yield a yellow oil (69 mg, quantitative), revealed by ^{1}H-NMR spectroscopy to be 6:4 mixture of **93**/**93x**. An analytical sample of **93** was isolated by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. The product **93** was isolated as a colourless oil. R_f 0.33 (petrol/ether, 1:1); ν_{max} 2971w, 2943w, 1444w, 1316m, 1217m, 1046m, 904w; δ_H (400 MHz, C_6D_6) 0.90–0.98 (1 H, m, H3) overlays with

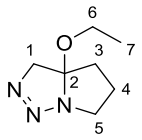
0.94 (3 H, t, *J* = 7.0 Hz, H8), 1.10–1.27 (3 H, m, H4 and H5), 1.66 (1 H, qt, *J* = 13.0 and 4.0 Hz, H4), 1.91 (1 H, dt, *J* = 13.0 and 3.0 Hz, H3), 2.71 and 2.79 (2 x 2 H, dq, *J* = 9.0 and 7.0 Hz, 2 x H7), 3.05 (1 H, td, *J* = 12.0 and 4.0 Hz, H6), 3.34 (1 H, d, *J* = 17.5 Hz, H1), 3.90–3.94 (1 H, m, *J* = 12.0 and 5.0 Hz, H6), 3.99 (1 H, d, *J* = 17.5 Hz, H1); δ_C (100 MHz, C_6D_6) 87.9 (C2), 71.3 (C1), 58.1 (C7), 42.9 (C6), 34.6 (C3), 24.9 (C5), 20.6 (C4), 15.6 (C8); HRMS (FI^+) found 170.1283, $C_8H_{16}N_3O$ (MH^+) requires 170.1288.

4,5,6,7-Tetrahydro-[1,2,3]triazolo[1,5-a]pyridine (93x)[450]



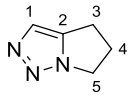
To an oven-dried 14 mL Ace pressure tube was added 6-azido-2-ethoxyhex-1-ene (61 mg, 0.36 mmol), dry toluene (5 mL) and triethylamine (3 drops). The vessel was flushed with argon, sealed with a PTFE screw cap with FETFE® O-ring and stirred at 130 °C for 1 week, during which time the colourless solution became brown (a sample after 2 d revealed 80% triazole formation and minor triazoline). The tube was removed from heat and the solution was concentrated under reduced pressure to yield an orange oil with data consistent with the literature data[450] (41 mg, 90%). R_f 0.10 (petrol/ ethyl acetate, 4:1); ν_{max} 2950m, 2868w, 2095w, 1552w, 1431m, 1236s, 990s, 811m, 645m; δ_H (400 MHz, $CDCl_3$) 1.88–1.94 (2 H, m, H4), 2.05–2.10 (2 H, m, H5), 2.84 (2 H, t, *J* = 6.5 Hz, H3) 4.37 (2 H, t, *J* = 6.0 Hz, H6) 7.44 (1 H, s, H1); δ_C (100 MHz, $CDCl_3$) 20.2 (C4), 20.2 (C3), 22.8 (C5), 46.0 (C6), 130.73 (C1), 133.2 (C2); *m/z* (ESI) 269.2 (M_2Na^+, 100%), 146.1 (MNa^+, 33%), 124.2 (MH^+, 18%).

3a-Ethoxy-3a,4,5,6-tetrahydro-3*H*-pyrrolo[1,2-c][1,2,3]triazole (94)



To an oven-dried 14 mL Ace pressure tube was added 5-azido-2-ethoxypent-1-ene (467 mg, 3.07 mmol), dry toluene (8 mL), and solid K_2CO_3 (128 mg, 0.926 mmol). The vessel was flushed with argon, sealed with a PTFE screw cap with FETFE® O-ring and stirred at 130 °C for 4 d, during which time the white slurry became brown. The tube was removed from heat, filtered, then concentrated to yield a crude mixture yellow oil (460 mg, quantitative), revealed by ^{1}H-NMR spectroscopy to be 4:1 mixture of **94/94x**. An analytical sample of **94** was isolated by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. The product **94** was isolated as a colourless oil. R_f = 0.28 (ether/ petrol, 1:1); ν_{max} 2971m, 1476w, 1443w, 1366m, 1216s, 1106s; δ_H (400 MHz, C_6D_6) 0.98 (3 H, t, *J* = 7.0 Hz, H7), 1.03–1.18 (2 H, m, H3 and H4). 1.43–1.53 (1 H, m, H4), 1.76 (1 H, dt, *J* = 12.5 and 6.5 Hz, H3), 2.90–2.98 (1 H, m, *J* = 7.0 Hz, H6), 3.12–3.23 (1 H, m, H5 and H6), 3.45 (1 H, dt, *J* = 11.5 and 6.0 Hz, H5), 3.60 and 4.10 (2 x 1 H, 2 x d, *J* = 18.5 Hz, H1); δ_C (100 MHz, C_6D_6) 15.8 (C7), 25.2 (C4), 37.3 (C3), 49.5 (C5), 58.2 (C6), 73.0 (C1), 101.3 (C2); HRMS (FI^+) found 156.1138, $C_7H_{14}N_3O$ (MH^+) requires 156.1131.

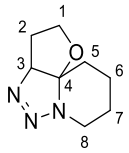
5,6-Dihydro-4*H*-pyrrolo[1,2-c][1,2,3]triazole (94x)



A 1:3 mixture of **94/94x** (26 mg), prepared as above was dissolved in methanol (1 mL) and stirred for 20 h at room temperature. The solution was concentrated under reduced pressure to afford a yellow oil (16 mg). An analytical sample was obtained by chromatography over aluminium oxide eluting with 5% ether/petrol → 5%

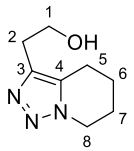
methanol/ether. R_f = 0.10 (ethyl acetate/petrol, 1:4); ν_{max} 2961m, 1654w, 1454w, 1438m, 1311m, 1224m, 1177m, 1094s, 724m; δ_H (400 MHz, $CDCl_3$) 2.80 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.92 (2 H, t, *J* = 7.0 Hz, H3), 4.33 (2 H, t, *J* = 7.0 Hz, H5), 7.39 (1 H, s, H1); δ_C (400 MHz, $CDCl_3$) 20.6 (C3), 28.3 (C4), 46.2 (C5), 126.8 (1), 141.9 (C2); HRMS (FI^+) found 110.0710, $C_5H_8N_3$ (MH^+) requires 110.0713.

3,3a,7,8,9,10-Hexahydro-2*H*-furo[3',3':4,5]triazolo[1,5-a]pyridine (95)



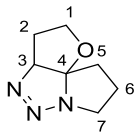
To an oven-dried 14 mL Ace pressure tube was added 5-(4-azidobutyl)-2,3-dihydrofuran (40 mg, 0.24 mmol), dry toluene (3 mL), and solid K_2CO_3 (72 mg, 0.52 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 130 °C for 3.5 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution.. The tube was removed from heat, filtered, and the filtrate concentrated to yield a yellow oil (42 mg, quantitative). An analytical sample of **95** was isolated by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f = 0.19 (petrol ether, 1:1) ν_{max} 2946m, 2864w, 1440m, 1366s, 1216s, 1032m; δ_H (400 MHz, C_6D_6) 1.10–1.21 (3 H, m, H5 and H7), 1.32 (1 H, dp, *J* =3.5 and 13.0 Hz, H6), 1.60–1.75 (3 H, m, H2, H5 and H6), 2.04 (1 H, dd, *J* = 12.0 and 5.0 Hz, H2), 3.14 (1 H, ddd, J = 12.0, 8.5 and 5.0 Hz, H1), 3.40 (1 H, td, *J* = 12.0 and 4.5 Hz, H8), 3.51 (1 H, ddd, *J* = 8.0, 7.5 and 1.0 Hz, H1), 3.94–3.98 (1 H, m , H8), 4.09 (1 H, d, *J* = 8.0 Hz, H3); δ_C (100 MHz, C_6D_6) 21.0 (C6), 25.2 (C7), 31.1 (C2), 32.8 (C5), 43.4 (C8), 65.8 (C1), 83.6 (C3), 95.0 (C4); HRMS (FI^+) found 168.1136, $C_8H_{14}N_3O$ (MH^+) requires 168.1131.

2-(4,5,6,7-Tetrahydro-[1,2,3]triazolo[1,5-a]pyridin-3-yl)ethanol (95x)



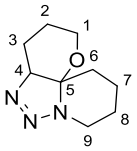
A modified literature procedure[9] was used. To an oven-dried 10 mL RBF was added 3,3a,7,8,9,10-hexahydro-2*H*-furo[3',3':4,5]triazolo[1,5-a]pyridine **(95)** (19 mg, 0.12 mmol). The oil was suspended in dry DCM (2 mL) and flask flushed with argon and the mixture cooled to –78 °C. Allyltributyl tin (38 µl, 0.11 mmol) was added via syringe, followed by TMSOTf (28 µl, 0.12 mmol) after 10 min. The reaction was stirred overnight during which time the acetone bath was allowed to thaw from –78 °C to ~12 °C, then the reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL), and extracted with DCM (3 x 7 mL). The combined organics were dried (K_2CO_3) and concentrated, to yield a clear oil with solid particles suspended within (62 mg). The solid was found to be insoluble in d_6-benzene but dissolved in $CDCl_3$, and was revealed to be the corresponding triazole (**95x**). The triazole was passed through a silica column eluting with ethyl acetate to methanol, yielding a colourless oil (7 mg, 35%). R_f 0.18 (petrol/ethyl acetate, 1:1); ν_{max} 3362br, 2949s, 2867m, 1574m, 1224m, 1052s, 668m; δ_H (400 MHz, $CDCl_3$) 1.89–1.95 (2 H, m, H6), 2.03–2.09 (2 H, m, H7), 2.75 (2 H, t, *J* = 6.5 Hz, H5), 2.83 (2 H, t, *J* = 6.0 Hz, H2), 3.97 (2 H, t, *J* = 6.0 Hz, H1), 4.35 (2 H, t, *J* = 6.0 Hz, H8); δ_C (100 MHz, $CDCl_3$) 19.8 (C5), 20.1 (C6), 22.6 (C7), 27.6 (C2), 46.2 (C8), 61.6 (C1) *note: due to a weak sample, signals for C3 and C4 were not recorded, and the sample unfortunately disposed of*; HRMS (FI^+) found 168.1130, $C_8H_{14}N_3O$ (MH^+) requires 168.1131.

2,3,3a,7,8,9-Hexahydrofuro[2,3-d]pyrrolo[1,2-c][1,2,3]triazole (96)



To an oven-dried base-washed 14 mL Ace pressure tube was added 5-(4-azidopropyl)-2,3-dihydrofuran (40 mg, 0.26 mmol), dry toluene (3 mL), and solid K_2CO_3 (72 mg, 0.52 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 130 °C for 2 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. The tube was removed from heat, filtered, and the filtrate concentrated to yield a yellow oil (38 mg, quantitative). An analytical sample of **96** was isolated by chromatography over basic alumina eluting with 1% triethylamine in 5% ether/petrol. R_f 0.20 (petrol/ether, 1:1); ν_{max} 2951w, 2872w, 1491m, 1442m, 1121s, 1029s, 991s, 843m, 676m; δ_H (400 MHz, C_6D_6) 1.08–1.16 (1 H, m, H6), 1.33–1.46 (2 H, m, H5 and H6). 1.62–1.73 (1 H, m, H2), 1.80–1.90 (2 H, m, H2 and H5), 3.12–3.23 (2 H, m, H1 and H7), 3.44–3.53 (2 H, m, H1 and H7), 4.17 (1 H, d, *J* = 9.5 Hz, H3); δ_C (100 MHz, C_6D_6) 25.4 (C6), 31.9 (C2), 33.4 (C5), 48.8 (C7), 65.1 (C1), 85.5 (C3), 107.9 (C4); HRMS (FI^+) found 126.0918, $C_8H_{14}N_3O$ (MH^+-N_2) requires 126.0913.

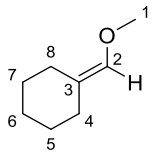
12-Oxa-6,7,8-triazatricyclo[7.4.0.0^{1,6}]tridec-7-ene (97)



To an oven-dried 14 mL Ace pressure tube was added 6-(4-azidobutyl)-3,4-dihydro-2*H*-pyran (147 mg, 0.810 mmol), dry toluene (4 mL), and solid K_2CO_3 (126 mg, 0.911 mmol). The vessel was flushed with argon, thread sealed with PTFE tape and PTFE

screw cap with FETFE® O-ring and stirred at 130 °C for 10 d, during which the white slurry became orange. The tube was removed from heat and the slurry concentrated under reduced pressure to yield an orange oil on solid K_2CO_3 that was filtered through Celite washing with petrol and concentrated to yield a yellow waxy solid (114 mg). The crude mixture was purified over basic alumina by eluting with 1% triethylamine in 10% ether/petrol yielding the pure **97** as a colourless oil (30 mg, 20%). R_f 0.30 (petrol/ether, 1:1); ν_{max} 2942s, 2859m, 1445m, 1094m, 1033s, 942m, 808m; δ_H (400 MHz, C_6D_6) 0.93–1.03 (2 H, m, H2 and H6), 1.23–1.30 (3 H, m, H7 and H8), 1.39–1.51 (2 H, m, H2 and H3), 1.57–1.69 (1 H, m, H7), 1.73 (1 H, dt, *J* = 13.0 and 3.0 Hz, H6), 1.13–1.20 (1 H, m, H3), 2.95–3.01 (1 H, m, H1), 3.24–3.31 (2 H, m, H1 and H4), 3.39–3.46 (1 H, m, H9), 3.89–3.94 (1 H, m, H9); δ_C (100 MHz, C_6D_6) 20 (C7), 21.1 (C2), 21.5 (C3), 24.8 (C8), 30.3 (C6), 42.9 (C9). 60.2 (C1), 76.4 (C4), 87.6 (C5); HRMS (FI^+) found 182.1285, $C_9H_{16}N_3O$ (MH^+) requires 182.1288.

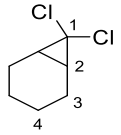
(Methoxymethylene)cyclohexane (99)[290,291]



A literature procedure[290,291] was used. To a base-washed, oven-dried 250 mL RBF was added (methoxymethyl)triphenylphosphonium chloride (4.96 g, 14.5 mmol) and freshly distilled THF (100 mL). The flask was cooled to –78 °C under argon and *t*-BuLi (12.5 mL, 1.6 M in pentane, 20.0 mmol) added dropwise over 30 min causing a rich red solution characteristic of ylide formation. After a further 30 min, the flask was warmed to room temperature and held at this temperature for 30 min, then re cooled to –78 °C. Cyclohexanone (1.0 mL; 9.6 mmol), that had been filtered through a plug of silica, was charged to the reaction flask, and the solution allowed to warm to room temperature

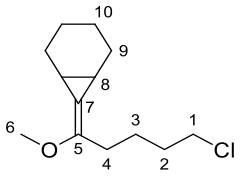
overnight. The reaction was quenched with water (50 mL) and extracted with ether (3 x 30 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to yield a crude orange oil that was purified over basic alumina by eluting with 2.5% ether/petrol, yielding pure product as a colourless oil (482 mg, 40%) with data consistent with literature data.[290,291] R_f 0.73 (petrol/ether 9:1); ν_{max} 2926m, 1686m, 1447w, 1226m, 1128s, 907s, 730s; δ_H (400 MHz, $CDCl_3$) 1.44–1.57 (6 H, br, H5, H6 and H7), 1.94 (2 H, t, *J* = 5.5 Hz, H8), 2,17 (2 H, t, *J* = 5.5 Hz, H4), 3.53 (3 H, s, H1), 5.75 (1 H, s, H2); δ_C (100 MHz, $CDCl_3$) 25.4 (C5), 26.7 (C7), 28.3 (C6), 30.5 (C8), 59.2 (C1), 118.4 (C3), 138.7 (C2); HRMS (FI^+) found 126.1042, $C_8H_{14}O$ (M^+) requires 126.1039.

7,7-Dichlorobicyclo[4.1.0]heptane (105)[307]

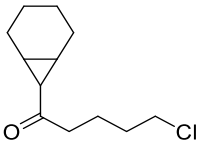


A literature procedure[307] was used. To a 25 mL RBF was added chloroform (2.4 mL), cyclohexene (0.81 mL, 9.9 mmol), cetyl trimethyl ammonium chloride solution (0.12 g, 25% wt in water, 0.09 mmol) and the solution stirred vigorously at 50 °C. Sodium hydroxide (3 g) in water (6 mL) was added dropwise over 2 min and the biphasic mixture stirred under argon for 3.5 h. The reaction was removed from heat, quenched with ice (5 g) and acidified with 10% aqueous sulphuric acid solution. The reaction was extracted with ether (3 x 25 mL), washed successively with water (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated to yield a yellow oil (1.41 g, 86%) with data consistent with the literature data.[307] δ_H (400 MHz, $CDCl_3$) 1.15–1.25 (2 H, m, H4), 1.29–1.79 (2 H, m, H4), 1.65–1.79 (4 H, m, H2 and H3), 1.91–2.00 (2 H, m, H3); δ_C (100 MHz, $CDCl_3$) 18.8 (C3), 20.2 (C4), 25.8 (C2), 67.3 (C1).

7-(5-Chloro-1-methoxypentylidene)bicyclo[4.1.0]heptane (107)



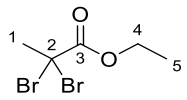
107



107x

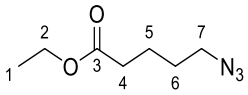
A modified literature procedure[306] was used. Finely powdered 4 Å sieves (227 mg), magnesium turnings (45 mg, 1.8 mmol) and Cp_2TiCl_2 (378 mg, 1.51 mmol) were placed in an oven-dried 50 mL RBF and dried by heating with a heat gun under 7 mbar pressure. After cooling under argon, distilled THF (6 mL) and triethylphosphite (0.5 mL, 2.9 mmol) were added to the flask and the red slurry stirred at 25 °C for 3 h, during which the a green colouration appeared indicating successful reduction before becoming to brown. 7,7-Dichlorobicyclo[4.1.0]heptane (110 mg, 0.668 mmol) was added in THF (1 mL), and 15 min later methyl 5-chloropentanoate (50 µl; 0.35 mmol) in THF (1 mL). The dark brown solution was refluxed for 2 h, the vessel removed from heat then triethylamine (0.3 mL) and hexane (20 mL) added. The reaction was quickly filtered through Celite washing with petrol, dried (K_2CO_3), filtered again and concentrated to yield a foul smelling orange solid (551 mg). The crude was purified over basic alumina eluting with 1% triethylamine/hexane yielding the product as a colourless oil (4 mg, 5%), which hydrolysed in deuterated benzene overnight from residual water, precluding full characterisation. Product degrades on silica TLC plate, R_f of tentative hydrolysis product **107x** 0.15 (petrol); ^{1}H NMR of **107** δ_H (200 MHz, C_6D_6) 1.15–1.77 (14 H, m, H2, H3, H8, H9, H10). 2.23 (2 H, t, *J* = 7.0 Hz, H4), 3.15 (2 H, t, *J* = 6.5 Hz, H1), 3.49 (3 H, s, H6).

Ethyl 2,2-dibromopropanoate (108)[315–317]



A literature procedure[315–317] was used. To an oven-dried 100 mL RBF containing diisopropylamine (1.8 mL, 13 mmol) and dry THF (40 mL) at –78 °C and under argon was added *t*-BuLi (8 mL, 1.6 M in pentane, 13 mmol) causing an intense yellow colouration. After 15 min ethyl 2-bromopropionate (1.5 mL, 11 mmol) in THF (1 mL) was added to the mixture dropwise, then 40 min later 1,2-dibromo-1,1,2,2-tetrachloroethane (5.66 g, 17.4 mmol) in THF (10 mL) added quickly and in one portion. After 1 h, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ solution (100 mL), then extracted with hexane (2 x 200 mL) and the combined organic fractions washed successively with water (10 mL) and brine (10 mL), then dried ($MgSO_4$). The solution was concentrated under reduced pressure to give a crude residue that was distilled under vacuum (11 Torr, B.p. 40 °C) affording the pure product as a colourless oil with data consistent with the literature data[315–317] (2.31 g, 77%). R_f 0.63 (ethyl acetate/ petrol, 1:4); ν_{max} 2986w, 1735s, 1257m, 907s, 728s; δH (400 MHz, $CDCl_3$) 1.37 (2 H, t, J = 1.0 Hz, H5), 2.65 (3 H, s, H1), 4.34 (2 H, q, J = 7.0 Hz, H4); δC (100 MHz, CDCl3) 13.7 (C5), 37.3 (C1), 52.3 (C2), 63.7 (C4), 166.8 (C3); HRMS (FI^+) found 259.8834, $C_5H_8{}^{79}Br_2O_2$ (M^+) requires 259.8886.

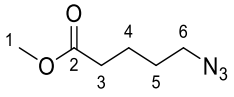
Ethyl 5-azidopentanoate (112)



A modified literature procedure[283] was used. To an oven-dried 50 mL RBF was added ethyl 5-bromopentanoate (1.0 mL, 6.3 mmol), NaN_3 (620 mg, 9.54 mmol) and DMSO (3 mL). The reaction slurry was stirred at 60 °C under argon for 16 h, then

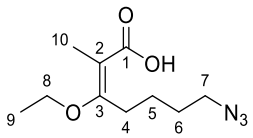
removed from heat, diluted with ethyl acetate (80 mL) and washed successively with water (6 x 2 mL) and brine (1 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless oil (1.04 g, 97%) that was sufficiently pure to be used in the next reaction. R_f 0.45 (ethyl acetate/ petrol, 1:4); ν_{max} 2940w, 2094s, 1733s, 1159m; δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, t, *J* = 7.0 Hz, H1), 1.59–1.74 (4 H, m, H5 and H6), 2.33 (2 H, t, *J* = 7.0 Hz, H4), 2.29 (2 H, t, *J* = 6.5 Hz, H7), 4.13 (2 H, q, *J* = 7.0 Hz, H2); δ_C (100 MHz, $CDCl_3$) 14.2 (C1), 22.1 (C5), 28.2 (C6), 33.6 (C4), 51.0 (C7), 60.4 (C2), 173.1 (C3); HRMS (FI^+) found 172.0958, $C_7H_{14}N_3O_2$ (MH^+) requires 172.1081.

Methyl 5-azidopentanoate (113)



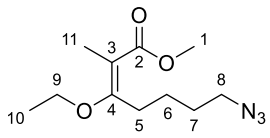
A modified literature procedure[283] was used. To an oven-dried 50 mL RBF was added methyl 5-chloropentanoate (2.0 mL, 14 mmol), NaN_3 (1.35 g, 20.8 mmol) and DMSO (4 mL). The reaction slurry was stirred at 60 °C under argon for 16 h, then removed from heat, diluted with ethyl acetate (80 mL) and washed successively with water (6 x 2 mL) and brine (1 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford a colourless oil (2.10 g, 96%) that was sufficiently pure to be used in the next reaction. R_f 0.45 (ethyl acetate/ petrol, 1:4); ν_{max} 2952w, 2093s, 1736s, 1228m; δ_H (400 MHz, $CDCl_3$) 1.59–1.75 (4 H, m, H4 and H5), 2.35 (2 H, t, *J* = 7.0 Hz, H3), 2.29 (2 H, t, *J* = 7.0 Hz, H6), 3.67 (3 H, s, H1); δ_C (100 MHz, $CDCl_3$) 22.1 (C4), 28.2 (C5), 33.4 (C3), 51.0 (C1), 51.6 (C6), 173.6 (C2). HRMS (FI^+) found 158.0900, $C_6H_{11}N_3O_2$ (M^+) requires 158.0846.

(*E*)-7-Azido-3-ethoxy-2-methylhept-2-enoic acid (114)



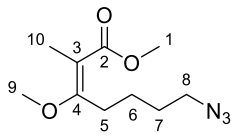
A modified literature procedure[308] was used. To a 50 mL oven-dried RBF containing ethyl 2,2-dibromopropanoate (0.1 mL, 0.7 mmol) and dry THF (5 mL) under argon and at –78 °C was added *t*-BuLi (1.8 mL, 1.6 M in pentane, 2.9 mmol) over 5 min. The yellow solution was stirred for 3 h at –78 °C then the vessel allowed to warm to 0 °C in an ice bath. After 30 min, the solution was warmed to ambient temperature and ethyl 5-azidopentanoate (83 mg, 0.48 mmol) in THF (1 mL) was added dropwise over 2 min. The resulting cloudy orange solution was stirred for 2 h, then quenched with saturated aqueous NaOH solution (5 mL, 1 M) and petrol (20 mL). The solution was extracted with water (5 x 5 mL), then the combined aqueous layers acidified with 36% aqueous HCl. The solution was extracted with DCM (3 x 20 mL) and the organics washed successively with water (2mL) and brine (2mL), then dried (Na_2SO_4). The solution was concentrated to yield a yellow oil (83 mg, 76%) that was sufficiently pure to be used in the next reaction. R_f 0.20 (ethyl acetate/ petrol, 1:9); ν_{max} 3234w, 2096m, 1671m, 1330m, 812s; δ_H (400 MHz, C_6D_6) 0.90 (H, t, *J* = 7.0 Hz, H9), 1.25–1.36 (4 H, m, H5 and H6), 2.11 (3 H, s, H10), 2.63 (2 H, t, *J* = 7.0 Hz, H4), 2.71 (2 H, t, *J* = 6.5 Hz, H7), 3.36 (4 H, q, *J* = 7.0 Hz, H8); δ_C (100 MHz, C_6D_6) 12.2 (C10), 15.1 (C9), 25.3 (C5), 27.6 (C4), 28.5 (C6), 50.9 (C7), 62.9 (C8), 105.4 (C2), 133.5 (C3), 175.4 (C1); HRMS (FI^+) found 250.1162, $C_{10}H_{17}N_3NaO_3$ (MNa^+) requires 250.1168.

(*E*)-Methyl 7-azido-3-ethoxy-2-methylhept-2-enoate (115)



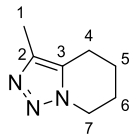
A modified literature procedure[308] was used. To a 50 mL oven-dried RBF containing ethyl 2,2-dibromopropanoate (0.2 mL, 1.4 mmol) and dry THF (10 mL) under argon and at –78 °C was added *t*-BuLi (3.6 mL, 1.6 M in pentane, 5.8 mmol) over 5 min. The yellow solution was stirred for 3 h at –78 °C then the reaction allowed to warm to 0 °C in an ice bath. After 30 min, the solution was warmed to ambient temperature and ethyl 5-azidopentanoate (168 mg, 0.97 mmol) in THF (1 mL) added quickly in one portion then stirred for 1 h. Iodomethane (0.87 mL, 14 mmol) and distilled DMPU (1.7 mL, 14.0 mmol) were added neat and the orange reaction stirred overnight. The solution was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with ether (3 x 25 mL), then washed successively with water (1 mL), saturated aqueous $NaHCO_3$ solution (1 mL) and brine (1 mL), then dried (Na_2SO_4). The solution was concentrated under reduced pressure to yield a crude yellow oil (616 mg) that was purified over silica by eluting with 0.2% triethylamine in petrol to 0.2% triethylamine in 1% ether/petrol, yielding the product as a colourless oil (92.8 mg, 40%). R_f 0.77 (petrol/ether, 1:1); ν_{max} 2981m, 2939m, 2872w, 2095s, 1734s, 1705s, 1616m, 1279s, 1112s, 770w; δ_H (400 MHz, C_6D_6) 0.95 (3 H, t, *J* = 7.0 Hz, H10), 1.33–1.45 (4 H, m, H6 and H7), 2.08 (3 H, s, H3), 2.71 (2 H, t, *J* = 7.5 Hz, H5), 2.76 (2 H, t, *J* = 6.0 Hz, H8), 3.41 (2 H, q, *J* = 7.0 Hz, H9), 3.46 (3 H, s, H1); δ_C (100 MHz, C_6D_6) 12.2 (C11), 15.2 (C10), 25.4 (C6), 27.4 (C5), 28.6 (C7), 50.8 (C8), 50.9 (C1), 62.9 (C9), 107.9 (C3), 167.6 (C4), 169.3 (C2); HRMS (FI^+) found 264.1319, $C_{11}H_{19}N_3NaO_3$ (MNa^+) requires 264.1319.

(*E*)-Methyl 7-azido-3-methoxy-2-methylhept-2-enoate (116)



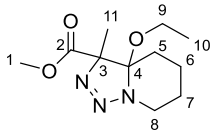
A modified literature procedure[308] was used. To a 100 mL oven-dried RBF containing ethyl 2,2-dibromopropanoate (0.45 mL, 3.3 mmol), dry THF (20 mL) and under argon and at –78 °C was added *t*-BuLi (8.25 mL, 1.6 M in pentane, 13.2 mmol) over 18 min. The yellow solution was stirred for 3 h at –78 °C then allowed to warm to 0 °C in an ice bath. After 30 min, the solution was warmed to ambient temperature and methyl 5-azidopentanoate (340 mg, 2.16 mmol) in THF (1 mL) added quickly in one portion then stirred for 1 h. Iodomethane (2 mL, 32 mmol) and HMPA (5.5 mL, 32 mmol) were added neat and the reaction stirred overnight. The solution was quenched with saturated aqueous NH_4Cl solution (6 mL), extracted with ether (3 x 40 mL), then washed successively with water (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL), then dried (Na_2SO_4). The solution was concentrated under reduced pressure to yield a crude yellow oil (3.2 g) that was purified over silica by eluting with 0.5% triethylamine in petrol/ether 40:1, yielding product as a colourless oil (200 mg, 40%). R_f 0.40 (petrol/ether, 8:1); ν_{max} 2945w, 2095s, 1735m, 1710s, 1618m, 1279m, 1115s, 812w; δ_H (400 MHz, C_6D_6) 1.30–1.38 (4 H, m, H6 and H7), 2.08 (3 H, s, H10), 2.67 (2 H, t, *J* = 7.0 Hz, H5), 2.73 (2 H, t, *J* = 6.5 Hz, H8), 3.08 (3 H, s, H9), 3.45 (3 H, s, H1); δ_C (100 MHz, C_6D_6) 10.6 (C10), 24.2 (C6), 26.1 (C5), 27.6 (C7), 49.8 (C8), 49.9 (C1), 53.7 (C9); HRMS (FI^+) found 250.1165, $C_{10}H_{17}N_3NaO_3$ (MNa^+) requires 250.1162. *Note: the sample was disposed of before a ^{13}C-NMR could be recorded featuring C2, C3 and C4.*

3-Methyl-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine (117)[451]



To an oven-dried 14 mL Ace pressure tube was added (*E*)-7-azido-3-ethoxy-2-methylhept-2-enoic acid (3.6 mg, 0.016 mmol) and dry toluene (5 mL). The vessel was flushed with argon, then sealed with a PTFE screw cap with FETFE® O-ring and stirred at 130 °C for 62 h, then concentrated under reduced pressure to yield a brown oil (1.5 mg, 69%) with data consistent with the literature data.[451] R_f 0.10 (ethyl acetate/ petrol, 1:1); ν_{max} 3016w, 2970m, 2947w, 1436m, 1359s, 1229s, 1216s, 899w; δ_H (400 MHz, C_6D_6) 0.88–0.98 (4 H, m, H5 and H6), 1.86 (2 H, t, *J* = 6.0 Hz, H4), 2.15 (3 H, s, H1), 3.63 (2 H, t, *J* = 5.5 Hz, H7). *m/z* (ESI) 138.2 (MH^+), 297.1 (M_2Na^+), 160.1 (MNa^+).

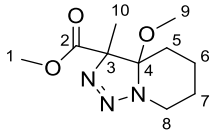
Methyl-3a-ethoxy-3-methyl-3,3a,4,5,6,7-hexahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (118)



An oven-dried 8 mL microwave tube containing (*E*)-methyl 7-azido-3-ethoxy-2-methylhept-2-enoate (94 mg, 0.39 mmol), deuterated acetonitrile (2 mL) and flushed with argon was microwaved for 72 h at 130 °C. ^{1}H-NMR spectroscopy on a reaction sample revealed 80% conversion to the product. Solution was concentrated to yield a crude oil (92 mg), and purified over basic alumina eluting with 0.5% triethylamine/petrol to 0.5% triethylamine 50% ether/methanol yielding product as a brown oil (20 mg, 21%). R_f 0.28 (petrol/ether 1:1); ν_{max} 3369br, 2948m, 2868w, 1733s, 1637m, 1445m, 1254s, 1110s, 1058s, 768w; δ_H (400 MHz, C_6D_6) 0.92 (3 H, t, *J* = 7.0 Hz, H10), 1.09–1.30 (4 H, m, H6 and H7), 1.41–1.49 (1 H, m, H5), 1.69 (3 H, s, H11), 1.93 (1

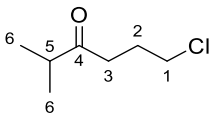
H, dt, *J* = 13.0 and 3.0 Hz, H5), 2.92–30.01 (3 H, m, H8 and H9), 3.25 (3 H, s, H1), 3.87–3.95 (1 H, m, H8); δ_C (100 MHz, C_6D_6) 14.7 (C10), 15.2 (C11), 20.3 (C6), 24.5 (C7), 30.5 (C5), 44.4 (C8), 51.9 (C1), 60.3 (C9), 87.2 (C3), 92.2 (C4), 170.3 (C2); HRMS (FI^+) found 264.1219, $C_{11}H_{19}N_3NaO_3$ (MNa^+) requires 264.1319.

Methyl 3a-methoxy-3-methyl-3,3a,4,5,6,7-hexahydro-[1,2,3]triazolo[1,5-a]pyridine-3-carboxylate (119)



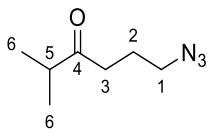
To an oven-dried 14 mL Ace pressure tube was added (*E*)-methyl 7-azido-3-methoxy-2-methylhept-2-enoate (132 mg, 0.58 mmol), dry toluene (8 mL), and solid K_2CO_3 (200 mg, 1.44 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, and stirred at 110 °C for 10 d, during which the white slurry became orange. The tube was removed from heat and the reaction slurry concentrated under reduced pressure to yield an orange oil on solid K_2CO_3 that was purified over basic alumina by eluting with 1% triethylamine in 10% ether/petrol to 5% methanol/petrol, yielding product as a colourless oil (38 mg, 29%). R_f 0.20 (petrol/ether, 1:1); ν_{max} 2948m, 2868w, 1734s, 1444m, 1256s, 1145s, 781w; δ_H (400 MHz, C_6D_6) 1.08–1.29 (4 H, m, H6 and H7), 1.36–1.40 (1 H, m, H5), 1.71 (3 H, s, H10), 1.93 (1 H, dt, *J* = 13.0 and 3.0 Hz, H5), 2.75 (3 H, s, H9), 2.90–2.97 (1 H, m , H8), 3.22 (3 H, s, H1), 3.88–3.93 (1 H, m, H8); δ_C (100 MHz, C_6D_6) 15.1 (C7), 20.2 (C10), 24.4 (C6), 30.3 (C5), 44.4 (C8). 51.9 (C1), 52.5 (C9), 87.2 (C3), 92.2 (C4), 170.2 (C2); HRMS (FI^+) found 250.1162, $C_{10}H_{17}N_3NaO_3$ (MNa^+) requires found 250.1162.

6-Chloro-2-methylhexan-3-one (128)



A modified literature procedure[332] was used. To an oven-dried 50 mL RBF was added anhydrous $FeCl_3$ (1.23 g, 7.58 mmol), 4-chlorobutanoyl chloride (3.0 mL, 27 mmol) and the contents cooled to –78 °C under an atmosphere of argon. Dry THF (80 mL) was added to the cooled flask, and 15 min later isopropyl magnesium chloride (33 mL, 2 M in THF, 66 mmol) dropwise via syringe over 1 h. After 1 h, the reaction was quenched with saturated ammonium chloride solution (30 mL) and warmed to room temperature. The solution was extracted with ether (3 x 100 mL), the organics washed with brine (30 mL), dried (Na_2SO_4) and concentrated to yield a colourless oil that was sufficiently pure to be used without purification (3.8 g, 95%). R_f 0.85 (petrol/ether, 1:1); ν_{max} 2972w, 1709m, 1467w, 907s, 727s; δ_H (400 MHz, $CDCl_3$) 1.12 (6 H, d, *J* = 7.0 Hz, H6), 2.05 (2 H, app. pent, *J* = 6.5 Hz, H2), 2.62 (1 H, sept, *J* = 7.0 Hz, H5) overlays with 2.66 (2 H, t, *J* = 7.0 Hz, H3), 3.58 (2 H, t, *J* = 6.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 18.2 (C6), 26.3 (C2), 36.8 (C4), 41.0 (C5), 44.6 (C1), 213.6 (C4); HRMS (FI^+) found 148.0655, $C_7H_{13}{}^{35}ClO$ (M^+) requires 148.0655.

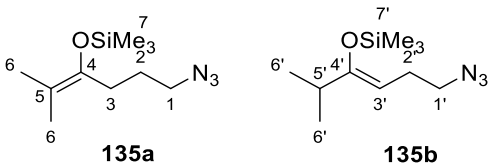
6-Azido-2-methylhexan-3-one (129)



To an oven-dried 50 mL RBF was added 6-chloro-2-methylhexan-3-one (0.65 g, 4.4 mmol), NaN_3 (440 mg, 6.77 mmol) and DMSO (3 mL), and the reaction slurry was stirred under argon at 60 °C for 21 h. The reaction was diluted with ethyl acetate (80 mL), washed successively with water (8 x 1 mL) and brine (1 mL), then dried (Na_2SO_4)

and concentrated to yield a crude yellow oil (700 mg) that was purified over silica by eluting with 30% ether in petrol yielding the product as a clear oil (640 mg, 94%). R_f 0.86 (petrol/ether, 1:1); ν_{max} 2871m, 2935w, 2876w, 2095s, 1711s, 1466m, 1258m, 1027m; δ_H (400 MHz, $CDCl_3$) 1.11 (6 H, d, *J* = 7.0 Hz, H6), 1.87 (2 H, app. pent, *J* = 7.0 Hz, H2), 2.56 (3 H, t, *J* = 7.0 Hz, H3) overlays with 2.61 (1 H, sept, *J* = 7.0 Hz, H5), 3.32 (2 H, t, *J* = 6.5 Hz, H1); δ_C (100 MHz, $CDCl_3$) 18.2 (C6), 22.9 (C2), 36.7 (C3), 41.0 (C5), 50.8 (C1), 213.5 (C4); HRMS (FI^+) found 178.0952, $C_7H_{13}N_3NaO$ (MNa^+) requires 178.0951.

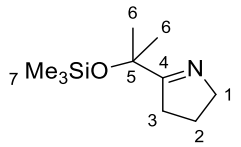
(6-Azido-2-methylhex-2-en-3-yloxy)trimethylsilane (135a) and (6-azido-2-methylhex-3-en-3-yloxy)trimethylsilane (135b)



A modified literature procedure[339–341] was used. To a base-washed and oven-dried 100 mL RBF was added dry ether (30 mL), diisopropylamine (0.82 mL, 5.8 mmol) and MeMgBr (1.8 mL, 3 M in ether, 5.4 mmol) under argon. The clear solution was stirred over night during which a cloudy grey precipitate formed. 6-Azido-2-methylhexan-3-one (600 mg, 3.86 mmol) in dry ether (4 mL) was added via syringe over 15 min and the reaction stirred for an additional 30 min. Neat TMSCl (1.47 mL, 11.6 mmol), triethylamine (1.72 mL, 12.3 mmol) and HMPA (0.33 mL, 1.9 mmol) were added, causing an intense yellow colouration that soon gave way for a colourless solution with grey solid at the bottom. After 48 h, the reaction was poured over saturated $NaHCO_3$ (30 mL), extracted with ether (3 x 40 mL) and washed successively with water (3 mL) and brine (3 mL), then dried (K_2CO_3). The solution was concentrated to afford a colourless oil, an inseparable 55:45 mixture of regioisomers in favour of (**135a**) (611 mg, 70%). Note: NMR data reported as seen for the mixture of regioisomers. Integrations are given as if

a 1:1 mixture of products for ease of reporting. R_f 0.84 (petrol/ether, 1:1); ν_{max} 2964w, 2098m, 1253m, 905s, 843m, 726.72s; δ_H (400 MHz, $CDCl_3$) 0.17 (9 H, s, H7), 0.21 (9 H, s, H7'), 1.04 (6 H, d, *J* = 7.0 Hz, H6'), 1.59 and 1.61 (2 x 3 H, 2 x s, H6), 1.74 (2 H, app. pent, *J* = 7.0 Hz, H2), 2.13–2.19 (3 H, m, H3 and H5'), 2.30 (2 H, app. q, *J* = 7.0 Hz, H2'), 3.21 (2 H, t, *J* = 7.0 Hz, H1'), 3.27 (2 H, t, *J* = 7.0 Hz, H1), 4.50 (1 H, t, *J* = 7.0 Hz, H3'); δ_C (100 MHz, $CDCl_3$) 0.56 (C7), 0.64 (C7'), 17.9 (C6), 18.6 (C6), 20.58 (C6'), 25.5 (C2'), 26.3 (C3), 28.8 (C2), 34.3 (C5'), 50.8 (C1), 51.3 (C1'), 100.5 (C3'), 111.0 (C5), 142.6 (C4), 158.5 (C4'); HRMS (FI^+) found 227.1450, $C_{10}H_{21}N_3OSi$ (M^+) requires 227.1454.

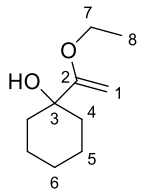
5-(2-((Trimethylsilyl)oxy)propan-2-yl)-3,4-dihydro-2*H*-pyrrole (139)



139

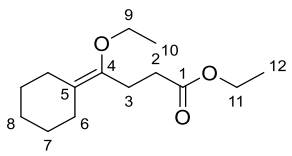
To an oven-dried base-washed 14 mL Ace pressure tube was added a 55:45 mixture of (6-azido-2-methylhex-2-en-3-yloxy)trimethylsilane **(135a)** and (6-azido-2-methylhex-3-en-3-yloxy)trimethylsilane **(135b)** prepared as above (20 mg, 0.1 mmol) and dry toluene (3 mL). The vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring and stirred at 160 °C for 20 h, then 170 °C for 28 h. The tube was removed from heat and the solution concentrated under reduced pressure to yield a brown oil (unweighed) that was a ~55/45 mixture of **139**/**135b** as determined by ^{1}H-NMR. **139** R_f 0.18 (petrol/ether, 1:1). Data given for the title compound. R_f 0.46 (ethyl acetate/ petrol, 1:1); ν_{max} 2964w, 2096m, 1668w, 1642w, 1252m, 1033m, 907s, 839s, 729s; δ_H (400 MHz, $CDCl_3$) 0.11 (9 H, s, H7), 1.45 (6 H, s, H6), 1.86 (2 H, m, H2), 2.64 (2 H, tt, *J* = 7.5 and 2.0 Hz, H3), 3.83 (2 H, tt, *J* = 7.5 and 2.0 Hz, H1). δ_C (100 MHz, $CDCl_3$) 2.1 (C7), 22.6 (C2), 28.3 (C6), 33.2 (C3), 61.0 (C1), 183.6 (C4); HRMS (FI^+) found 200.1466, $C_{10}H_{22}NOSi$ (MH^+) requires 200.1465.

1-(1-Ethoxyvinyl)cyclohexan-1-ol (148)[452]



A modified literature procedure[345] was used. To an oven-dried 100 mL round-bottom flask containing ethyl vinyl ether (2 mL, 21 mmol) and THF (13 mL) under argon at –78 °C was added *t*-BuLi (12.5 mL, 1.6 M in pentane, 20.0 mmol) dropwise via syringe pump over 1 h. After 30 min, the reaction was warmed to 0 °C, and after 15 min re-cooled to –78 °C. Cyclohexanone (1.0 mL, 9.6 mmol) was added dropwise, and the solution stirred overnight as the temperature warmed to ambient. The cloudy solution was cooled to 0 °C, quenched with brine (15 mL), and extracted successively with ether (3 x 40 mL). The combined organic layers washed with brine (10 mL), dried ($NaSO_4$), and concentrated to yield a crude oil that was sufficiently pure to be used in the next reaction and with data consistent with literature data[452] (1.7 g, quantitative). R_f 0.75 (1:1 petrol/ether); δ_H (200 MHz, C_6D_6) 1.00 (3 H, t, *J* = 7.0 Hz, H8), 1.38–1.90 (10 H, m, H4, H5, and H6), 3.38 (2 H, q, *J* = 7.0 Hz, H7), 3.84 (2 H, d, *J* = 2.5 Hz, H1), 4.34 (1 H, d, *J* = 2.5 Hz, H1).

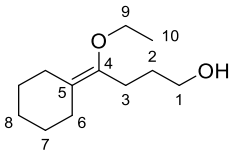
Ethyl 4-cyclohexylidene-4-ethoxybutanoate (149)[452]



A modified literature procedure[344] was used. To an oven-dried 25 mL round-bottom flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (4 mL), crude 1-(1-ethoxyvinyl)cyclohexan-1-ol (340 mg, 2.00 mmol), and a small spatula tip of hydroquinone. The set up was flushed with argon, then

placed into a pre-heated oil bath at 135 °C. Propionic acid (2 drops) was added at hourly inervals for 5 h, then the reaction heated overnight. Ethanol was observed distilling off at 78 °C. The reaction was cooled to room temperature, diluted with ether (70 mL) and washed successively with saturated aqueous NH_4Cl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated onto basic alumina. Product was obtained by purification over alumina eluting with 2% Et_3N with 5% ether in petrol, with data consistent with the literature data[452] (30 mg, 6%). R_f 0.66 (petrol/ ether, 2:1); (200 MHz, C_6D_6) 0.96 (3 H, t, *J* = 7.0 Hz, H12), 1.06 (3 H, t, *J* = 7.0 Hz, H10), 1.38–1.53 (6 H, m, H7 and H8), 2.00–2.10 (2 H, m, H6), 2.28–2.39 (2 H, m, H6), 2.42–2.61 (4 H, m, H2 and H3), 3.42 (2 H, q, *J* = 7.0 Hz, H9), 3.97 (2 H, q, *J* = 7.0 Hz, H11).

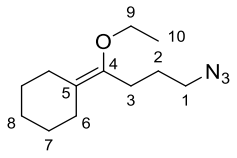
4-Cyclohexylidene-4-ethoxybutan-1-ol (150)



To an oven-dried 25 mL round-bottom flask was added ethyl 4-cyclohexylidene-4-ethoxybutanoate (30 mg, 0.12 mmol), THF (1 mL), and the solution stirred at 0 °C under argon. $LiAlH_4$ (0.2 mL, 1.0 M in THF, 0.2 mmol) was added at 0 °C, the reaction stirred for 2 h, then quenched with saturated aqueous Rochelle's salt (1 mL). The layers were separated and the aqueous layer extracted successively with ether (3 x 7 mL), the combined organic layers washed with brine (3 mL), dried (Na_2SO_4), and concentrated under vacuum to yield an oil that was purified over basic alumina eluting with 2% Et_3N and 10% ether in petrol, yielding a colourless oil of low analytical purity (22 mg, <88%). R_f 0.41 (petrol/ ether, 2:1); δ_H (200 MHz, C_6D_6) 1.09 (3 H, t, *J* = 7.0 Hz, H10), 1.30–1.78

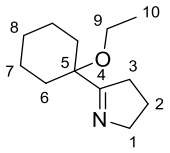
(8 H, m, H2, H7, and H8), 2.00–2.11 (2 H, m, H6), 2.19 (2 H, t, J = 7.0 Hz, H3), 2.32–2.44 (2 H, m, H6), 3.32–3.50 (4 H, m, H9 and H1).

(4-Azido-1-ethoxybutylidene)cyclohexane (151)



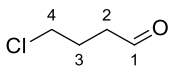
A modified literature procedure[41] was used. To a 7 mL sample vial was added 4-cyclohexylidene-4-ethoxybutan-1-ol (20 mg, 0.10 mmol) in DMF (1 mL) and the solution cooled to 0 °C under argon. Freshly recystallised CBr_4 (66 mg, 0.20 mmol), followed by PPh_3 (52 mg, 0.20 mmol) were added, causing the colourless solution to turn yellow. After 30 min at 0 °C, NaN_3 (26 mg, 0.40 mmol) was added and the reaction stirred overnight, during which the ice bath thawed from 0 °C to 15 °C. The cloudy brown solution was extracted with petrol (8 x 3 mL) until no product was observed by TLC of the DMF layer, and the combined petrol fractions washed with saturated aqueous $NaHCO_3$ (5 mL), then brine (5 mL), and dried (Na_2SO_4). The organic solution was concentrated to yield a crude oil that was purified over basic alumina eluting with 1% Et_3N and 5% ether in petrol, yielding a colourless oil (13 mg, 57%). R_f 0.88 (petrol); δ_H (400 MHz, $CDCl_3$) 1.08 (3 H, t, *J* = 7.0 Hz, H10), 1.42–1.52 (8 H, m, H2, H7, and H8), 1.99–2.03 (2 H, m, H6), 2.05 (2 H, t, J = 7.0 Hz, H3), 2.34–2.36 (2 H, m, H6), 2.83 (2 H, t, *J* = 6.5 Hz, H1), 3.39 (2 H, q, *J* = 7.0 Hz, H9); δ_C (100 MHz, C_6D_6) 23.4 (C3), 26.7 (C2), 26.9 (C6), 27.8 (C7), 28.1 (C7), 29.3 (C8), 30.4 (C6), 50.2 (C1), 64.2 (C9), 123.4 (C5), 144.5 (C4).

5-(1-Ethoxycyclohexyl)-3,4-dihydro-2*H*-pyrrole (155)



To an oven-dried 14 mL Ace pressure tube was added (4-azido-1-ethoxybutylidene)cyclohexane (6 mg, 0.03 mmol) and d_8-toluene (1 mL). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 130 °C for 3.5 d. After removing from heat and cooling, the brown reaction solution was filtered through a sintered funnel with ether, concentrated onto silica, and purified over silica eluting with 10% ether to 40% ether in petrol. The product was isolated as a colourless oil (2 mg, 78% w/w in ether, 28%). R_f 0.61 (ether); δ_H (200 MHz, $CDCl_3$) 1.19 (3 H, t, *J* = 7.0 Hz, H10), 1.48–1.74 (8 H, m, H6, H7, and H8), 1.84–1.92 (4 H, m, H2 and H6), 2.59 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3), 3.21 (2 H, q, *J* = 7.0 Hz, H9), 3.89 (2 H, tt, *J* = 7.5 and 2.0 Hz, H1). m/z (ESI) 196.2 (MH^+).

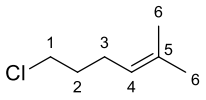
4-Chlorobutanal (158)[453]



A literature procedure[453] was used. To a 100 mL oven-dried RBF was added oxalyl chloride (2.5 mL, 30 mmol) in dry DCM (50 mL) and the flask cooled to –78 °C under argon. DMSO (4.5 mL, 63 mmol) in dry DCM (5.5 mL) were added dropwise via syringe over 100 min being sure to maintain the temperature at –78 °C. 4-Chlorobutanol (2.17 g, 20 mmol) that had been previously neutralised by washing with saturated $NaHCO_3$ and dried ($MgSO_4$) was added dropwise in DCM (3 mL) over 2 h at –78 °C. After 15 min, triethylamine (12.5 mL, 90 mmol) was added dropwise over 40 min, then the reaction left to warm to room temperature overnight. The yellow cloudy solution was

quenched with water (40 mL), extracted with DCM (3 x 70 mL), washed successively with 0.1 M aqeuous HCl solution (2 x 20 mL), saturated aqueous $NaHCO_3$ solution (30 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated to yield an orange oil (2.8 g) that was used crude in the next reaction. R_f 0.42 (petrol/ether, 1:1); ν_{max} 2958w, 1724m, 1276m, 1261m, 750s; δ_H (400 MHz, $CDCl_3$); 2.10 (2 H, app. pent, *J* = 6.5 Hz, H3), 2.67 (2 H, t, *J* = 7.0 Hz, H2), 3.60 (2 H, t, *J* = 6.5 Hz, H4), 9.81 (1 H, s, H1); δ_C (100 MHz, $CDCl_3$) 24.8 (C3), 40.9 (C2), 44.1 (C4), 200.9 (C1); HRMS (FI^+) found 106.0181, $C_4H_7{}^{35}ClO$ (M^+) requires 106.1080.

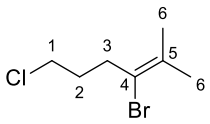
6-Chloro-2-methylhex-2-ene (159)[351,352]



A literature procedure[351,352] was used. To a 250 mL base-washed and oven-dried RBF was added dry isopropyltriphenylphosphonium iodide (10.65 g, 24.6 mmol), THF (100 mL) and the flask cooled to 0 °C under argon. *n*-BuLi (15 mL, 1.55 M in pentane, 23.2 mmol) was added dropwise over 1 h, causing an intense red colouration indicative of ylide formation. After stirring for 20 min, crude 4-chlorobutanal (2.8 g, ~20 mmol) was added neat over 50 min and after stirring for a further 2 h, the reaction was allowed to warm to ambient temperature overnight. The yellow cloudy solution was quenched with saturated NH_4Cl (30 mL), extracted with petrol (3 x 100 mL), washed successively with 0.1 M aqueous HCl solution (40 mL), saturated aqueous $NaHCO_3$ solution (40 mL) and brine (40 mL), and the volume reduced to 100 mL on a Buchi. The flask was cooled to –78 °C and the resulting precipitate filtered and washed with cold petrol, and this process of concentration/ precipitating repeated twice to remove $OPPh_3$. After concentrating to a yellow oil, the crude was purified over silica by eluting with petrol and the relevant fractions collected, yielding a colourless oil (1.06 g, 40%). R_f 0.78

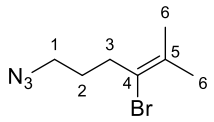
(petrol); ν_{max} 2927s, 1442s, 1377m, 1066w, 733m, 653s; δ_H (400 MHz, $CDCl_3$) 1.63 and 1.71 (2 x 3 H, 2 x s, H6), 1.81 (2 H, app. pent, *J* = 7.0 Hz, H2), 2.14 (2 H, app. q, *J* = 7.0 Hz, H3), 3.53 (2 H, t, *J* = 6.5 Hz, H1), 5.09 (1 H, t, *J* = 7.0 Hz, H4); δ_C (100 MHz, $CDCl_3$) 17.7 and 25.7 (C6), 25.2 (C3), 32.6 (C2), 44.6 (C1), 122.6 (C4), 133.1 (C5); HRMS (FI^+) found 132.0708, $C_7H_{13}{}^{35}Cl$ (M^+) requires 132.0700.

3-Bromo-6-chloro-2-methylhex-2-ene (160)



A modified literature procedure[353–355] was used. To an oven-dried 25 mL RBF was added 6-chloro-2-methylhex-2-ene (514 mg, 3.87 mmol), dry DCM (3 mL) and the flask cooled to 0 °C under argon. Bromine (0.2 mL, 4.0 mmol) in DCM (2 mL) was added dropwise, causing a brown colouration that faded on addition before persisting, and the brown reaction warmed to room temperature. After 15 min, reaction was concentrated to yield a brown oil of 4,5-dibromo-1-chloro-5-methylhexane that was immediately used crude in the next reaction. To the crude 4,5-dibromo-1-chloro-5-methylhexane was added DCM (15 mL) and DBU (1.0 mL, 6.7 mmol) and the reaction refluxed under argon overnight. After removing DCM under reduced pressure, the crude oil was purified over silica by eluting with petrol yielding the title compound as a colourless oil (464 mg, 57% over 2 steps). R_f 0.70 (petrol); ν_{max} 2959w, 2919w, 1442m, 1275m, 1261m, 908m, 814m, 750s; δ_H (400 MHz, $CDCl_3$) 1.82 and 1.89 (2 x 3 H, 2 x s, H6), 2.04 (2 H, app. pent, *J* = 6.5 Hz, H2), 2.68 (2 H, t, *J* = 7.0 Hz, H3), 3.55 (2 H, t, *J* = 6.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 20.5 and 25.4 (C6), 31.0 (C2), 34.3 (C3), 43.8 (C1), 119.9 (C4), 131.9 (C5); HRMS (FI^+) found 209.9814, $C_7H_{12}{}^{79}Br{}^{35}Cl$ (M^+) requires 209.9811.

6-Azido-3-bromo-2-methylhex-2-ene (161)

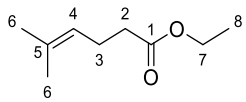


Generation 1: To an oven-dried 50 mL RBF was added 6-chloro-3-bromo-2-methylhex-2-ene (240 mg, 1.14 mmol), NaN_3 112 g, 1.71 mmol) and DMSO (3 mL) and the reaction slurry stirred for 21 h under argon at 60 °C. After diluting with ether (60 mL), the solution was washed successively with water (1 x 10 mL) and brine (1 mL), dried (Na_2SO_4) and concentrated to yield a colourless oil (198 mg, 80%) that was sufficiently pure to be used in the next reaction. R_f 0.31 (petrol); ν_{max} 2092*s*; δ_H (400 MHz, $CDCl_3$) 1.80 (3 H, s, H6), 1.85 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.89 (3 H, s, H6), 2.60 (2 H, t, *J* = 7.0 Hz, H3), 3.30 (3 H, t, *J* = 7.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 20.4 (C6), 25.4 (C6), 27.3 (C2), 34.3 (C3), 50.1 (C1), 120.0 (C4), 131.6 (C5); HRMS (FI^+) found 217.0131, $C_7H_{12}{}^{79}BrN_3$ (M^+) requires 217.0215.

Generation 2: To an oven-dried 50 mL round-bottom flask was added 6-azido-2-methylhex-2-ene (420 mg, 3.01 mmol), petrol (10 mL) and the solution cooled to 0 °C under argon. Bromine (0.15 mL, 3.01 mmol) in petrol (0.5 mL) was added dropwise to the reaction via syringe over 15 min, causing an orange colouration that subsided until persisting. The reaction was warmed to room temperature, stirred for 5 min, then cooled to 0 °C and quenched with aqueous saturated $Na_2S_2O_3$ solution (30 mL). After the orange colour faded to colourless, the layers were separated and the aqueous extracted successively with petrol (3 x 30 mL), the combined organics washed with brine (5 mL), dried ($MgSO_4$), and concentrated to yield a crude yellow oil. The crude was transferred to a 50 mL round-bottom flask with DMSO (1.0 mL) and stirred at room temperature under argon. *t*-BuOK (4.5 mL, 1.0 M in *t*-BuOH, 4.5 mmol) was added dropwise via syringe pump over 20 min, causing the colourless solution to turn brown, and stirred

overnight. The reaction was concentrated to half volume under vacuum to remove *t*-BuOH, then diluted with saturated aqueous $NaHCO_3$ (20 mL). The solution was extracted successively with ether (20 mL x 4), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was purified over silica eluting with petrol to yield a pale yellow oil (0.49 g, 74% over 2 steps). R_f 0.31 (petrol); ν_{max} 2092s; δ_H (400 MHz, $CDCl_3$) 1.80 (3 H, s, H6), 1.85 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.89 (3 H, s, H6), 2.60 (2 H, t, *J* = 7.0 Hz, H3), 3.30 (3 H, t, *J* = 7.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 20.4 (C6), 25.4 (C6), 27.3 (C2), 34.3 (C3), 50.1 (C1), 120.0 (C4), 131.6 (C5); HRMS (FI^+) found 217.0131, $C_7H_{12}{}^{79}BrN_3$ (M^+) requires 217.0215.

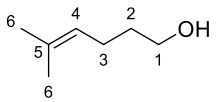
Ethyl 5-methylhex-4-enoate (162)[454]



A modified literature procedure[346–348] was used. To an oven-dried 100 mL round-bottom flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (35 mL), 2-methyl-3-buten-2-ol (2 mL, 19 mmol), and a small spatula tip of hydroquinone. The set up was flushed with argon, then placed into a pre-heated oil bath at 140 °C. 10 drops of propionic acid were added and the reaction stirred for 19 h. Ethanol was observed distilling off at 78 °C. 5 more drops of propionic acid were added, and the reaction stirred for 5 h. Finally, 0.1 mL of propionic acid was added and the reaction stirred for 19 h. Reaction completion was indicated by TLC. The reaction was cooled to room temperature, diluted with ether (100 mL) and washed successively with aqueous 0.1 M HCl (4 x 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield a crude oil that was purified over silica eluting with 1% ether in petrol, yielding a pale yellow oil (2.90 g, 86% w/w, 83%) with data consistent with the literature data.[454] R_f 0.78 (petrol/ ether, 1:1);

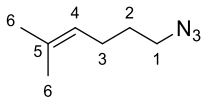
ν_{max} 1734s; δ_H (400 MHz, $CDCl_3$) 1.25 (3 H, t, *J* = 7.0 Hz, H8), 1.62 (3 H, s, H6), 1.68 (3 H, s, H6), 2.31 (4 H, m, H2 and H3), 4.12 (2 H, q, *J* = 7.0 Hz, H7), 5.09 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 14.2 (C8), 17.6 (C6), 23.6 (C5), 25.6 (C6), 34.5 (C2), 60.2 (C7), 122.4 (C4), 132.9 (C5), 173.4 (C1); m/z (ESI) 157.1 (MH^+).

5-Methylhex-4-en-1-ol (163)[455]



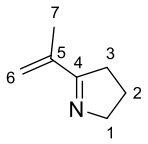
To an oven-dried 250 mL round-bottom flask was charged solid $LiAlH_4$ (900 mg, 23.7 mmol), ether (10 mL), and the slurry stirred at 0 °C under argon. A solution of ethyl 5-methylhex-4-enoate (2.90 g, 86% w/w, 15.8 mmol) in ether (10 mL) was added dropwise via syringe pump over 30 min, and the syringe washed in with further ether (5 mL). The reaction was stirred at 0 °C for 25 min, then allowed to warm to room temperature. After stirring at ambient for 2 h, the reaction was cooled to 0 °C and quenched slowly with saturated Rochelle's salt (1 mL). The solution was diluted further with saturated Rochelle's salt (60 mL) and stirred overnight. The solution was extracted with ether (3 x 20 mL), the combined organic layers washed with brine (2 mL) and dried ($MgSO_4$). The dry organic layer was concentrated under vacuum to yield a colourless oil (2.2 g, 79% w/w, 96%) with data consistent with the literature data.[455] R_f 0.35 (petrol/ ether, 1:1); ν_{max} 3326br; δ_H (400 MHz, $CDCl_3$) 1.52 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.57 (3 H, s, H6), 1.65 (3 H, d, *J* = 1.0 Hz, H6), 2.01 (2 H, app. q, *J* = 7.0 Hz, H3), 2.70 (1 H, br, OH), 3.57 (3 H, t, *J* = 6.5 Hz, C1), 5.09 (1 H, t. hept, *J* = 7.0 and 1.0 Hz, H4); δ_C (100 MHz, $CDCl_3$) 17.5 (C6), 24.3 (C3), 25.6 (C6), 32.7 (C2), 62.3 (C1), 123.9 (C4), 131.9 (C5); m/z (ESI) 115.2 (MH^+).

6-Azido-2-methylhex-2-ene (164)



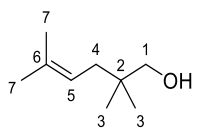
A modified literature procedure[456] was used. To an oven-dried 100 mL round-bottom flask was added 5-methylhex-4-en-1-ol (1.2 g, 79% w/w, 8.3 mmol), ether (20 mL) and triethylamine (1.4 mL, 10 mmol) and the solution cooled to 0 °C under argon. Methanesulfonyl chloride (0.8 mL, 10.0 mmol) was added dropwise via syringe over 5 min, causing a white precipitate to form. After 30 min, the reaction was warmed to ambient temperature and stirred for 3 h. The reaction was quenched with brine (15 mL), separated, and the aqueous layer extracted successively with ether (15 mL x 3). The organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated to yield a colourless oil that was used crude in the next reaction. The crude oil was transferred to a 50 mL round-bottom flask with DMSO (4 mL) and NaN_3 (1 g, 15.3 mmol) and the mixture stirred at 35 °C for 18 h. The product was extracted with petrol (80 mL) and the petrol layer washed successively with water (10 mL x 4). The combined aqueous washes were extracted with petrol (3 x 10 mL), dried ($MgSO_4$) and concentrated and the crude product purified over silica eluting with petrol, yielding a colourless oil (900 mg, 80% over 2 steps). R_f 0.76 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.62 (3 H, s, H6), 1.64 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.71 (3 H, d, *J* = 1.0 Hz, H6), 2.08 (2 H, app. q, *J* = 7.0 Hz, H3), 3.27 (3 H, t, *J* = 7.0 Hz, H1), 5.09 (1 H, t. hept, *J* = 7.0 and 1.0 Hz, H4); δ_C (100 MHz, $CDCl_3$) 17.5 (C6), 25.0 (C3), 25.7 (C6), 28.8 (C2), 50.9 (C1), 122.8 (C4), 132.9 (C5); HRMS (FI^+) found 139.1106, $C_7H_{13}N_3$ (M^+) requires 139.1109.

5-(Prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrole (171)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 6-azido-3-bromo-2-methylhex-2-ene (60 mg, 0.28 mmol) in toluene (5.5 mL), with solid K_2CO_3 (381 mg, 2.76 mmol) and sodium hydroxide (20 mg, 0.55 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil, and stirred at 150 °C for 44 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the solution was filtered through a sintered funnel with ether (20 mL), concentrated to a toluene solution, and purified over silica eluting with 0.1% triethylamine in petrol to 10% ether in petrol with 0.1% triethylamine. The volatile product was isolated as a yellow oil (35 mg, 63% w/w with triethylamine, 73%). An analytical sample was obtained by further concentration. R_f 0.33 (ether); ν_{max} 1633s; δ_H (500 MHz, C_6D_6) 1.45 (2 H, app. pent, *J* = 7.5 Hz, H3), 2.20 (3 H, app. s, H7), 2.26 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3), 3.85 (2 H, app. t, *J* = 7.5 Hz, H1), 5.16 (1 H, app. s, H6), 5.23 (1 H, s, H6); δ_C (125 MHz, C_6D_6) 19.4 (C7), 22.7 (C2), 33.6 (C3), 61.5 (C1), 119.2 (C6), 141.7 (C5), 173.5 (C4); HRMS (FI^+) found 110.09626, $C_7H_{12}N$ (MH^+) requires 110.09643.

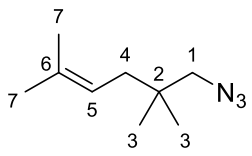
2,2,5-Trimethylhex-4-en-1-ol (173)[457]



A modified literature procedure[457] was used. To an oven-dried 100 mL RBF was added diisopropylamine (3.44 mL, 24.6 mmol), THF (10 mL) and the solution cooled to

–78 °C under argon. *n*-BuLi (15.9 mL, 1.55 M in pentane, 24.6 mmol) was added to the flask dropwise over 25 min and the solution warmed to room temperature, held for 10 min then cooled to –78 °C. Ethyl isobutyrate (3 mL, 22 mmol) was added dropwise over 15 min, then after a further 15 min prenyl chloride (2.76 mL, 24.6 mmol) added dropwise and the solution warmed to room temperature overnight. The cloudy yellow solution was cooled to 0 °C and lithium aluminium hydride solution (20 mL, 1.0 M in THF, 20 mmol) added dropwise over 20 min. After 1.5 h, reaction was quenched slowly with brine (7 mL) and stirred overnight. The solution was extracted with ether (3 x 100 mL), washed successively with water (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated to yield a yellow oil (3.11 g, 98%) with data consistent with the literature data.[457] The product was sufficiently pure to be used in the next reaction. R_f 0.74 (petrol/ether 1:1); ν_{max} 3348br, 2962m, 2926m, 2870m, 1470m, 1453m, 1378m, 1363m, 1043s; δ_H (400 MHz, $CDCl_3$) 0.86 (6 H, s, H7), 1.61 and 1.71 (2 x 3 H, 2 x s, H7), 1.93 (2 H, d, *J* = 7.5 Hz, H4), 3.31 (2 H, s, H1), 5.19 (1 H, tt, *J* = 7.5 and 1.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 17.8 and 26.0 (C7), 23.8 (C3), 36.2 (C2), 37.0 (C4), 71.9 (C1), 120.7 (C5), 133.4 (C6); HRMS (FI^+) found 142.1353, $C_9H_{18}O$ (M^+) requires 142.1352.

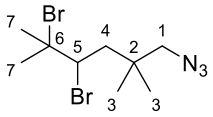
6-Azido-2,5,5-trimethylhex-2-ene (174)



A modified literature procedure[410] was used. To an oven-dried 25 mL RBF was added 2,2,5-trimethylhex-4-en-1-ol (500 mg, 3.51 mmol), pyridine (0.5 ml, 6.2 mmol) and dry DCM (5 mL) and the flask cooled to –78 °C under argon. Trifluoromethanesulfonic acid anhydride (0.88 mL, 5.23 mmol) was added dropwise,

stirred for 10 min, and the flask warmed to room temperature, during which time the solution turned from yellow to pink to purple. A TLC after 1.5 h revealed the reaction to be complete. After stirring overnight and quenching with brine (50 mL) the solution was extracted with ether (3 x 20 mL), washed with saturated $NaHCO_3$ solution (3 x 2 mL), then dried (Na_2SO_4) and concentrated to yield a red oil that was used crude in the next step. The crude oil was dissolved in DMF (2 mL) and stirred with NaN_3 (340 g, 5.23 mmol) under argon at 30 °C overnight. After diluting with ether (100 mL) the solution was washed successively with water (10 x 1 mL) and brine (1 mL), then dried (Na_2SO_4) and concentrated to yield a red oil (313 g, 53% over 2 steps). R_f 0.58 (petrol); ν_{max} 2965m, 2928m, 2096s, 1470m, 1365m, 845w; δ_H (400 MHz, $CDCl_3$) 0.91 (6 H, s, H3), 1.62 and 1.74 (2 x 3 H, 2 x s, H7), 1.94 (2 H, d, *J* = 8.0 Hz, H4), 3.09 (2 H, s, H1), 5.14 (1 H, tt, *J* = 8.0 and 1.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 17.8 and 26.1 (C7), 24.9 (C3), 36.3 (C2), 37.7 (C4), 62.1 (C1), 119.8 (C5), 124.0 (C6); HRMS (FI^+) found 140.1434, $C_9H_{18}N_3$ (MH^+-N_2) requires 140.1434.

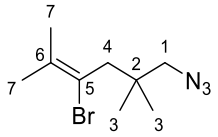
1-Azido-4,5-dibromo-2,2,5-trimethylhexane (175)



To an oven-dried 50 mL RBF was added 6-azido-2,5,5-trimethylhex-2-ene (1.12 g, 6.69 mmol), and dry DCM (7 mL) and the flask cooled to −78 °C under argon. Bromine (0.34 mL, 6.7 mmol) in DCM (1 mL) was added dropwise, causing the solution to turn brown in colour. After stirring for 2 h, the acetone bath from removed and the flask was allowed to warm to room temperature for 30 min. The reaction was concentrated to an orange oil and purified over silica eluting with petrol, yielding the title product as a yellow oil (470 mg, 20%). R_f 0.36 (petrol); ν_{max} 2964w, 2100s, 1457w, 1096m, 805w; δ_H (500 MHz, $CDCl_3$) 1.06 and 1.08 (2 x 3 H, 2 x s, H7), 1.81 and 2.00 (2 x 3 H, 2 x s, H6), 2.07

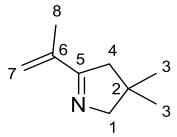
(1 H, dd, *J* = 8.5 and 16.0 Hz, H3), 2.50 (1 H, dd, *J* = 1.0 and 16.0 Hz, H3), 3.24 and 3.32 (2 x 1 H, 2 x d, J = 12.0 Hz, H1), 4.30 (1 H, d, *J* = 8.5 Hz, H4); δ_C (125 MHz, $CDCl_3$) 24.9 (C7), 25.5 (C6), 27.7 (C2), 35.2 (C6), 45.5 (C3), 59.8 (C4), 62.2 (C1), 69.5 (C5); HRMS (FI^+) found 326.9793, $C_9H_{17}{}^{79}Br_2N_3$ (M^+) requires 326.9769.

6-Azido-3-bromo-2,5,5-trimethylhex-2-ene (176)



To an oven-dried 50 mL RBF was added 1-azido-4,5-dibromo-2,2,5-trimethylhexane (116 mg, 0.51 mmol) and dry THF (6 mL) and the flask cooled to 0 °C under argon. KHMDS (4 mL, 0.5 M in toluene, 2 mmol) was added dropwise over 1 h, and the reaction stirred overnight during which the ice bath thawed to 10 °C. The reaction was quenched brine (5 mL) and then extracted with petrol (3 x 20 mL), then washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), then dried (Na_2SO_4) and concentrated to yield a crude brown oil. The crude was purified over silica by eluting with petrol, yielding the product as a colourless oil (53 mg, 42%). R_f 0.40 (petrol); ν_{max} 2925m, 2101s, 1457w, 1389w, 802w; δ_H (500 MHz, $CDCl_3$) 1.02 (6 H, s, H3), 1.79 and 1.92 (2 x 3 H, 2 x s, H7), 2.61 (2 H, s, H4), 3.26 (2 H, s, H1); δ_C (125 MHz, $CDCl_3$) 21.6 and 25.9 (C7), 25.6 (C3), 37.7 (C2), 45.9 (C4), 62.2 (C1), 116.9 (C5), 134.1 (C6); HRMS (FI^+) found 245.0535, $C_9H_{17}{}^{79}BrN_3$ (M^+) requires 245.0528.

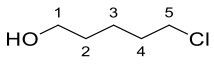
3,3-Dimethyl-5-(prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrole (178)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 6-azido-3-bromo-2,5,5-trimethylhex-2-ene (37 mg, 0.15 mmol), in toluene (3.0 mL), with

solid K_2CO_3 (210 mg, 1.52 mmol) and sodium hydroxide (12 mg, 0.30 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil, and stirred at 150 °C for 24 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the solution was filtered through a sintered funnel with ether (20 mL), concentrated to a toluene solution, and purified over silica eluting with 0.1% triethylamine in petrol to 10% ether in petrol with 0.1% triethylamine. The volatile product was isolated as a yellow oil (19 mg, 77% w/w with toluene, 71%). An analytical sample was obtained by further concentration. R_f 0.46 (petrol/ether 1:1); ν_{max} 1591s; δ_H (500 MHz, C_6D_6) 0.84 (3 H, s, H3), 2.20 (5 H, app. s, H4 and H8), 3.66 (2 H, s, H1), 5.16 (1 H, s, H7), 5.24 (1 H, s, H7); δ_C (125 MHz, C_6D_6) 19.0 (C8), 27.6 (C3), 38.1 (C2), 48.8 (C4), 74.9 (C1), 119.2 (C7), 142.1 (6). 173.2 (C5); HRMS (FI^+) found 138.12748, $C_9H_{16}N$ (MH^+) requires 138.12773.

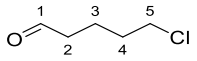
5-Chloropentan-1-ol[458]



A literature procedure[458] was used. To an oven-dried 100 mL round-bottom flask was added $LiAlH_4$ (800 mg, 21.0 mmol), ether (20 mL) and the reaction stirred at 0 °C under argon. Methyl-5-chlorovalerate (3 mL, 21 mmol) was added dropwise via syringe pump over 30 min, and the syringe washed in with ether (20 mL). After 2 h the reaction was quenched slowly with saturated aqueous Rochelle's salt (40 mL) and stirred for 14 h. The layers were separated and the aqueous layer extracted successively with ether (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated to yield a crude oil (3.03 g, 86% w/w, 100%) that was sufficiently pure to be used in the next reaction and with data consistent with literature data.[458] R_f 0.20

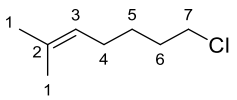
(3:1 petrol/ether); δ_H (200 MHz, $CDCl_3$) 1.50–1.64 (4 H, m, H2, H3), 1.82 (2 H, app. pent, *J* = 7.0 Hz, H4), 3.56 (2 H, t, *J* = 6.5 Hz, H2), 3.67 (2 H, t, *J* = 6.0 Hz, H1).

5-Chloropentanal (179)[459]



A modified literature procedure[460] was used. To a 250 mL oven-dried RBF was added oxalyl chloride (3.0 mL, 35 mmol) in dry DCM (100 mL) and the flask cooled to –78 °C under argon. DMSO (3.5 mL, 49 mmol) in dry DCM (8 mL) were added dropwise via syringe pump over 50 min being sure to maintain the temperature at –78 °C. After stirring for 1 h, 5-chloropentan-1-ol (2.5 g, 20.4 mmol) was added dropwise over 30 min at –78 °C, and the syringe washed in with DCM (5 mL). After 45 min, triethylamine (14 mL, 102 mmol) was added dropwise over 40 min, then the reaction left to warm to room temperature overnight. The cream solution was quenched with water (60 mL), extracted successively with petrol (4 x 20 mL), and the combined organic layers washed successively with 0.1 M HCl solution (4 x 10 mL), brine (10 mL), then dried ($MgSO_4$) and concentrated to yield an colourless oil (2.77 g, 100%) that was used crude in the next reaction and with data consistent with literature data.[459] R_f 0.46 (1:1 petrol/ether); δ_H (200 MHz, $CDCl_3$); 1.78–1.85 (4 H, m, H3 and H4), 2.47–2.54 (2 H, m, H2), 3.53–3.59 (2 H, m, H5), 9.79 (1 H, t, *J* = 1.5 Hz, H1).

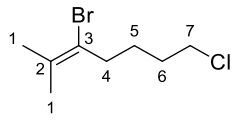
7-Chloro-2-methylhept-2-ene (180)



A modified literature procedure[351,352] was used. To an oven-dried 100 mL round-bottom flask was added isopropyltriphenylphosphonium iodide (3.28 g, 7.58 mmol), ether (40 mL) and the flask cooled to 0 °C under argon. *n*-BuLi (4.7 mL, 1.6 M in pentane,

7.5 mmol) was added dropwise over 1 h, causing an intense red colouration indicative of ylide formation. After stirring for 2 h, crude 5-chloropentanal (726 mg, 6.02 mmol) in ether (5 mL) was added dropwise via syringe pump over 40 min and the syringe washed in with ether (2 mL), and the reaction stirred overnight during with the ice bath thawed and was removed. The cream solution was quenched with brine (70 mL) and filtered through celite, washing with ether (60 mL). The solution was separated and the aqueous layer extracted successively with ether (3 x 10 mL) and dried ($MgSO_4$). The organic layer was concentrated onto silica and purified by eluting with petrol and the relevant fractions collected. The combined fractions (~14 mL) were used as is in the next reaction, though an analytical sample could be achieved by concentration. R_f 0.60 (petrol); ν_{max} 2928s, 1447m, 731s, 653s; δ_H (400 MHz, $CDCl_3$) 1.48 (2 H. app. pent, *J* = 7.5 Hz, H5), 1.61 (3 H, s, H1), 1.70 (3 H, s, H1), 1.77 (2 H, app. pent, *J* = 7.0 Hz, H6), 2.01 (2 H, app. q, *J* = 7.5 Hz, H4), 3.53 (2 H, t, *J* = 7.0 Hz, H7), 5.11 (1 H, app. t quin, *J* = 7.0 and 1.0 Hz, H3); δ_C (100 MHz, $CDCl_3$) 17.7 (C1), 25.7 (C1), 25.7 (C5), 27.2 (C4), 32.2 (C6), 45.1 (C7), 123.9 (C3), 132.0 (C2); HRMS (FI^+) found 146.0862, $C_8H_{15}{}^{35}Cl$ (M^+) requires 146.0863.

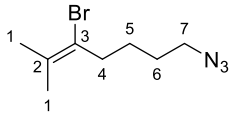
3-Bromo-7-chloro-2-methylhept-2-ene (181)



To an oven-dried 100 mL round-bottom flask was added freshly columned 7-chloro-2-methylhept-2-ene (~6.02 mmol) in pentane (14 mL) and the solution cooled to 0 °C under argon. Bromine (0.3 mL, 6 mmol) in petrol (1.7 mL) was added dropwise to the reaction via syringe over 1 min, causing an orange colouration that subsided until persisting. After 10 min, the reaction was quenched with aqueous saturated $Na_2S_2O_3$ solution (40 mL). After the orange colour faded to colourless, the layers were separated

and the aqueous extracted successively with petrol (3 x 30 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated to yield a crude yellow oil. The crude was transferred to a 50 mL round-bottom flask with DMSO (1 ml) and stirred at room temperature under argon. *t*-BuOK (9 mL, 1.0 M in *t*-BuOH, 9 mmol) was added dropwise via syringe pump over 1 h, causing the colourless solution to turn brown, and stirred for 21 h. The reaction was concentrated to half volume under vacuum to remove *t*-BuOH, then diluted with brine (30 mL). The solution was extracted successively with ether (3 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was purified over silica eluting with petrol to yield a colourless oil (0.604 g, 44% over 3 steps). R_f 0.40 (petrol); ν_{max} 2864s, 1447m, 732s, 653s; δ_H (400 MHz, $CDCl_3$) 1.64–1.82 (4 H, m, H5 and H6), 1.78 (3 H, s, H1), 1.87 (3 H, s, H1), 2.53 (2 H, t, *J* = 7.0 Hz, H4), 3.56 (2 H, t, *J* = 6.5 Hz, H7); δ_C (100 MHz, $CDCl_3$) 20.4 (C1), 25.4 (C1), 25.6 (C6), 31.5 (C5), 36.6 (C4), 44.8 (C7), 121.1 (C3), 130.7 (C2); HRMS (FI^+) found 223.9969, $C_8H_{14}{}^{79}Br^{35}Cl$ (M^+) requires 223.9967.

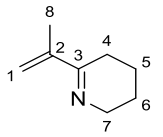
7-Azido-3-bromo-2-methylhept-2-ene (182)



To an oven-dried 25 mL round-bottom flask was added 3-bromo-7-chloro-2-methylhept-2-ene (600 mg, 2.66 mmol), NaN_3 (346 mg, 5.32 mmol) and DMSO (4 mL), and the reaction stirred at 50 °C under argon for 24 h. The reaction was diluted with petrol (20 mL) and washed successively with water (3 x 5 mL). The combined aqueous washes were extracted successively with petrol (3 x 20 mL) and the combined organics concentrated onto silica and purified eluting with petrol to yield a colourless oil (528 mg, 85%). R_f 0.43 (petrol); ν_{max} 2092s; δ_H (400 MHz, $CDCl_3$) 1.57–1.66 (4 H, m, H5 and H6), 1.78 (3 H, s, H1), 1.88 (3 H, s, H1), 2.53 (2 H, t, *J* = 6.5 Hz, H4), 3.30 (2 H, t, *J* = 6.5 Hz,

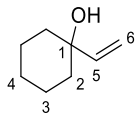
H7); δ_C (100 MHz, $CDCl_3$) 20.4 (C1), 25.4 (C1), 25.5 (C5), 27.8 (C6), 36.8 (C4), 51.4 (C7), 121.1 (C3), 130.7 (C2); HRMS (FI^+) found 124.1062, $C_8H_{14}N^+$ ($M^+–N_2Br$) requires 124.1121.

6-(Prop-1-en-2-yl)-2,3,4,5-tetrahydropyridine (183)



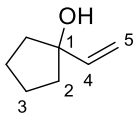
To an oven-dried 14 mL Ace pressure tube was added a 0.036 M solution of 7-azido-3-bromo-2-methylhept-2-ene (100 mg, 0.433 mmol) in toluene (12 mL) with K_2CO_3 (600 mg, 4.37 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 9 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the orange solution was filtered through a sintered funnel with ether (20 mL), concentrated to a toluene solution, and purified over silica eluting with 0.1% Et_3N in petrol to 10% ether with 0.1% Et_3N in petrol. The product was isolated as a colourless oil (17 mg, 32%). R_f 0.10 (ether); ν_{max} 2096m, 1767s, 1725s, 1695s, 1619s; δ_H (500 MHz, C_6D_6) 1.20 (2 H, app. dquin, *J* = 6.0 and 2.0 Hz, H2), 1.26–1.31 (2 H, m, H3), 2.02 (2 H, tt, *J* = 6.5 and 2.0 Hz, H4), 2.17 (3 H, s, H7), 3.70 (2 H, app. t, *J* = 5.5 Hz, H1), 5.23 (1 H, s, H8) 5.25 (1 H, s, H8); δ_C (150 MHz, C_6D_6) 18.80, (C3), 18.82 (C7), 20.9 (C2), 24.1 (C4), 48.8 (C1), 114.2 (C8), 145.6 (C6), 164.07 (C5); HRMS (FI^+) found 124.11188, $C_8H_{14}N$ (MH^+) requires 124.11208.

1-Vinylcyclohexanol (184)[461]



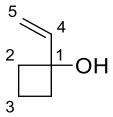
A modified literature procedure[461] was used. To a 1 L 3-neck round-bottom flask equipped with temperature probe, addition funnel and nitrogen line was added vinyl magnesium bromide (115 mL, 1.0 M in THF, 115 mmol), THF (150 mL) and the solution cooled to −10 °C internal temperature with an acetone bath. The reaction was placed under nitrogen by 3 iterations of evacuation/ back fill. Cyclohexanone (10 mL, 96 mmol) in THF (50 mL) was added dropwise via addition funnel over 10 min causing a yellow precipitate, maintaining the internal temperature below −10 °C and the funnel washed in with THF (20 mL). After stirring for 17 h, during which the acetone bath thawed 15 °C. The reaction was cooled to 4 °C and quenched with saturated aqueous NH_4Cl (500 mL), separated, and the aqueous layer extracted successively with MTBE (3 x 200 mL), then the combined organic layers washed successively with 1.0 M HCl (60 mL), saturated aqueous $NaHCO_3$ (60 mL), and brine (60 mL) then the combined aqueous washes back extracted with MTBE (200 mL). The organics were dried ($MgSO_4$) and concentrated to yield a crude oil that was sufficiently pure to be used in the next reaction. An analytical sample was obtained by purification over silica eluting with 20% MTBE in pentane, yielding an oil with data consistent with literature data.[461] R_f 0.30 (petrol/ether, 2:1); ν_{max} 3400br; δ_H (400 MHz, $CDCl_3$) 1.24–1.69 (10H, m, H2, H3 and H4), 5.03 (1 H, dd, *J* = 10.5 and 1.5 Hz, H6), 5.24 (1 H, dd, *J* = 17.5 and 1.5 Hz, H6), 5.97 (1 H, dd, *J* = 17.5 and 10.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 22.0 (C4), 25.5 (C3), 37.5 (C2), 71.7 (C1), 111.5 (C6), 146.0 (C5); HRMS (FI^+) found 126.1040, $C_8H_{14}O$ (M^+) requires 126.1045.

1-Vinylcyclopentanol (185)[462]



A literature procedure[462] was used. To an oven-dried 100 mL round-bottom flask containing vinyl magnesium bromide (17.0 mL, 1.0 M, 17.0 mmol) under argon at 0 °C was added cyclopentanone (1.0 mL, 11 mmol) in THF (2 mL) dropwise via syringe pump over 20 min and the reaction stirred stirred for 17 h as the ice bath thawed from 0 °C to 10 °C. The reaction was quenched at 0 °C with saturated aqueous Rochelle's salt (20 mL) and 0.1 M HCl (20 mL), extracted successively with ether (3 x 20 mL), then the combined organic layers washed with brine (10 mL) and dried ($MgSO_4$). The organics were concentrated to yield a crude oil that was sufficiently pure to be used in the next reaction with data consistent with literature data.[462] R_f 0.54 (3:1 petrol/ether); δ_H (200 MHz, $CDCl_3$) 1.57–1.72 (8 H, m, H2, H3), 5.04 (1 H, dd, *J* = 10.5 and 1.5 Hz, H5), 5.29 (1 H, dd, *J* = 17.0 and 1.5 Hz, H5), 6.04 (1 H, dd, *J* = 17.0 and 10.5 Hz, H5).

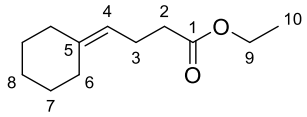
1-Vinylcyclobutanol (186)[463]



A modified literature procedure[463] was used. To an oven-dried 50 mL round-bottom flask was added cyclobutanone (0.4 mL, 5.3 mmol) and THF (2 mL) and the solution stirred at 0 °C under argon. Vinyl magnesium bromide (11 mL, 1.0 M in THF, 11 mmol) was added dropwise via syringe pump over 1 h, and the reaction stirred overnight as the ice bath thawed from 0 °C to 15 °C. The reaction was quenched with brine (10 mL), extracted successively with ether (3 x 20 mL), then the combined organic layers concentrated onto silica and purified by eluting with petrol to 10% ether in petrol, yielding a colourless oil (228 mg, 43%) consistent with literature data.[463] R_f 0.30 (1:1

petrol/ether); ν_{max} 3357br; δ_H (400 MHz, $CDCl_3$) 1.57 (1 H, d.quin, *J* = 11.5 and 8.5 Hz, H3), 1.74–1.84 (1 H, m, H3), 2.11–2.26 (4 H, m, H2), 5.06 (1 H, dd, *J* = 10.5 and 1.0 Hz, H5), 5.25 (1 H, dd, *J* = 17.0 and 1.0 Hz, H5), 6.12 (1 H, dd, *J* = 17.0 and 10.5 Hz, H4); δ_C (100 MHz, $CDCl_3$) 11.9 (C3), 35.8 (C2), 75.0 (C1), 111.2 (C5), 142.3 (C4); HRMS (FI^+) found 98.0728, $C_6H_{10}O$ (M^+) requires 98.7032.

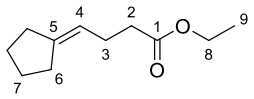
Ethyl 4-cyclohexylidenebutanoate (187)



A modified literature procedure[346–348] was used. To a 500 mL round-bottom flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (180 mL), crude 1-vinylcyclohexanol (~96.5 mmol), and a small spatula tip of hydroquinone. The set up was flushed with nitrogen, then placed into a pre-heated block at 146 °C. Propionic acid (0.4 mL, 5.3 mmol) was added and then every hour after for 5 hours (total 2.4 mL) and the reaction stirred for a further 17 h (total of 22 h). Ethanol was observed distilling off at 78 °C. Reaction completion was indicated by TLC. The reaction was cooled to room temperature, diluted with MTBE (500 mL) and washed successively with aqueous 0.1 M HCl (2 x 100 mL), saturated aqueous $NaHCO_3$ (200 mL), and brine (100 mL), and the combined aqueous washes back extracted with MTBE (100 mL). The combined organics were dried ($MgSO_4$) and concentrated to yield a crude oil that was sufficiently pure to be used in the next reaction. An analytical sample was obtained by purification over silica eluting with 10% MTBE in pentane. R_f 0.69 (petrol/ ether, 1:1); ν_{max} 1736s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* = 7.0 Hz, H10), 1.46–1.56 (6 H, m, H7 and H8), 2.05 (2 H, app. t, *J* = 5.5 Hz, H6), 2.13 (2 H, app. t, *J* = 5.5 Hz, H6), 2.31 (4 H, app. d, *J* = 3.5 Hz, H2 and H3), 4.06 (2 H, q, *J* = 7.0 Hz, H9), 5.04 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 14.2 (C10), 22.7 (C3), 26.8 (C8), 27.8 (C7), 26.6 (C7), 28.6 (C6), 34.9

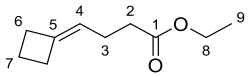
(C2), 37.0 (C6), 60.2 (C9), 119.0 (C4), 141.1 (C5), 173.5 (C1); HRMS (FI^+) found 196.1469, $C_{12}H_{20}O_2$ (M^+) requires 196.1463.

Ethyl 4-cyclopentylidenebutanoate (188)[464]



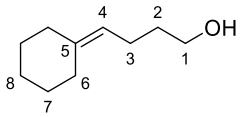
A modified literature procedure[346–348] was used. To an oven-dried 100 mL round-bottom flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (20 mL), crude 1-vinylcyclopentanol (~11.3 mmol), and a small spatula tip of hydroquinone. The set up was flushed with argon, then placed into a pre-heated oil bath at 140 °C. Propionic acid (50 µL, 0.66 mmol) was added and the reaction stirred for 6 h. Ethanol was observed distilling off at 78 °C. Further propionic acid (50 µL, 0.66 mmol) was added and the reaction stirred for 16 h. Reaction completion was indicated by TLC. The reaction was cooled to room temperature, diluted with ether (100 mL) and washed successively with 0.1 M HCl (3 x 80 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated onto silica. Pure product was obtained by purification over silica eluting with 1% ether in petrol with data consistent with literature data[464] (1.56 g, 80% w/w, 61% over 2 steps). R_f 0.82 (petrol/ ether, 3:1); ν_{max} 1736s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* = 7.0 Hz, H9), 1.57–1.69 (6 H, m, H7), 2.20 (4 H, app. q, *J* = 7.0 Hz, H6), 2.28–2.36 (4 H, m, H2 and H3), 4.11 (2 H, q, *J* = 7.0 Hz, H8), 5.21 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 14.2 (C9), 25.2 (C3), 26.3 (C7), 28.6 (C6), 33.6 (C6), 34.4 (C2), 60.2 (C8), 117.9 (C4), 144.8 (C5), 173.6 (C1); m/z (ESI) 205.1 (MNa^+), 183.1 (MH^+).

Ethyl 4-cyclobutylidenebutanoate (189)



A modified literature procedure[346–348] was used. To an oven-dried 50 mL round-bottom flask equipped with stirrer bar, distillation head and thermometer was added triethylorthoacetate (3.7 mL), 1-vinylcyclobutanol (190 mg, 1.93 mmol), and a small spatula tip of hydroquinone. The set up was flushed with argon, then placed into a pre-heated oil bath at 140 °C. 2 drops of propionic acid were added by removing the thermometer and the reaction stirred for 22 h. Ethanol was observed distilling off at 78 °C. Reaction completion was indicated by TLC. The reaction was cooled to room temperature, diluted with ether (50 mL) and washed successively with aqueous 0.1 M HCl (20 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a crude oil that was purified over silica by eluting with petrol, yielding a colourless oil (253 mg, 79%). R_f 0.60 (3:1 petrol/ether); ν_{max} 1735s, 1164s; δ_H (400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* = 7.0 Hz, H9), 1.92 (2 H, app. quin, *J* = 8.0 Hz, H6), 2.18 (2 H, app. q, *J* = 7.0 Hz, H6), 2.31 (2 H, t, *J* = 7.0 Hz, H2), 2.54–2.59 (4 H, m, H6), 4.13 (2 H, q, *J* = 8.0 Hz, H8), 5.03 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 14.2 (C9), 16.9 (C7), 23.6 (C3), 29.2 (C6), 30.8 (C6), 34.5 (C2), 60.2 (C8), 188.2 (C4), 141.6 (C5), 173.4 (C1); HRMS (FI^+) found 168.1148, $C_{10}H_{16}O_2$ (M^+) requires 168.1150.

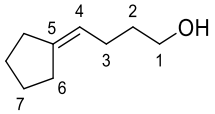
4-Cyclohexylidenebutan-1-ol (190)[465]



To a 1 L 3-neck round-bottom flask equipped with temperature probe, addition funnel and nitrogen line was added crude ethyl 4-cyclohexylidenebutanoate (~96.5 mmol), THF (150 mL) and the solution cooled to –72 °C internal temperature with an

acetone bath. The reaction was placed under nitrogen by 3 iterations of evacuation/ back fill. $LiAlH_4$ (120 mL, 1.0 M in THF, 120 mmol) was added dropwise via addition funnel keeping the temperature below –60 °C over 1 h. After 20 min, the reaction was warmed to 0 °C internal temperature, and stirred for 1 h. The reaction was cooled back down to –70 °C and slowly quenched with saturated aqueous Rochelle's salt (500 mL), maintaining the temperature below –60 °C. The reaction was allowed to warm to room temperature and the layers separated. The aqueous layer was extracted successively with MTBE (3 x 200 mL), the combined organic layers washed successively with 0.1M HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (5 mL), then the combined aqueous washes back extracted with MTBE (100 mL). The organics were dried ($MgSO_4$) and concentrated under vacuum to yield an orange oil (15.26 g, 82% w/w, 84% over 3 steps) with data consistent with the literature data.[465] R_f 0.30 (petrol/ ether, 1:1); ν_{max} 3326br; δ_H (400 MHz, $CDCl_3$) 1.47–1.55 (6 H, m, H7 and H8), 1.61 (2 H, app. quin, *J* = 7.0 Hz, H2), 2.05–2.15 (6 H, m, H6 and H3), 3.65 (2 H, t, *J* = 6.5 Hz, H1), 5.09 (1 H, t, *J* = 7.5 Hz, H4); δ_C (100 MHz, $CDCl_3$) 23.4 (C3), 26.9 (C8), 27.8 (C7), 28.6 (C6), 28.6 (C7), 33.0 (C2), 37.1 (C6), 62.7 (C1), 120.4 (C4), 140.5 (C5); HRMS (FI^+) found 154.1351, $C_{10}H_{18}O$ (M^+) requires 154.1358.

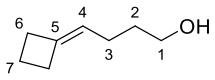
4-Cyclopentylidenebutan-1-ol (191)[466]



To an oven-dried 50 mL round-bottom flask was charged solid $LiAlH_4$ (500 mg, 13.1 mmol) and ether (5 mL), and the slurry stirred at 0 °C under argon. Ethyl 4-cyclopentylidenebutanoate (1.5 g, 80% w/w, 6.6 mmol) in ether (5 mL) was added dropwise the syringe washed in with further ether (2 mL). After 2 h, the reaction was quenched at 0 °C slowly with saturated Rochelle's salt (20 mL) and stirred for 23 h. The

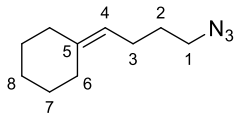
layers were separated and the aqueous layer extracted successively with ether (3 x 20 mL), the combined organic layers washed with brine (3 mL), then dried ($MgSO_4$). The dry organic layer was concentrated under vacuum to yield a colourless oil that was purified over silica eluting with 10% ether in petrol, yielding a colourless oil with data consistent with literature data[466] (945 mg, 90% w/w, 92%). R_f 0.32 (petrol/ ether, 1:1); ν_{max} 3331br; δ_H (400 MHz, $CDCl_3$) 1.55–1.69 (6 H, m, H2 and H7), 2.05 (2 H, app. q, *J* = 7.0 Hz, H3), 2.16–2.23 (4 H, m, H6), 3.64 (2 H, t, *J* = 6.5 Hz, H1), 5.25 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 25.9 (C3), 26.3 (C7), 26.3 (C7), 28.6 (C6), 32.6 (C2), 33.6 (C6), 62.8 (C1), 119.3 (C4), 144.0 (C5); m/z (ESI) 141.2 (MH^+).

4-Cyclobutylidenebutan-1-ol (192)



To an oven-dried 10 mL round-bottom flask was added ethyl 4-cyclobutylidenebutanoate (230 mg, 1.36 mmol) in THF (1 mL) and the solution stirred at 0 °C under argon. $LiAlH_4$ (1.5 mL, 1.0 M in THF, 1.5 mmol) was added dropwise via syringe over 1 min, and the reaction stirred for 13 h during which the ice bath thawed to 15 °C. The reaction was quenched slowly with saturated aqueous Rochelle's salt (1 mL), followed by brine (10 mL) and then extracted successively with ether (3 x 20 mL). The combined organic fractions were washed successively with saturated aqueous $NaHCO_3$ (10 mL), then brine (10 mL), dried (Na_2SO_4) and concentrated to yield a colourless oil (168 mg, 97%). R_f 0.37 (petrol/ether, 1:1); ν_{max} 3327br; δ_H (400 MHz, $CDCl_3$) 1.60 (2 H, app. quin, *J* = 6.5 Hz, H2), 1.89–1.99 (4 H, m, H3 and H7), 2.61–2.66 (4 H, m, H6), 3.64 (2 H, t, *J* = 6.5 Hz, H1), 5.04–5.09 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 17.0 (C7), 24.3 (C3), 29.2 (C6), 30.8 (C6), 32.6 (C2), 62.8 (C1), 129.6 (C4), 140.7 (C5); HRMS (FI^+) found 126.1041, $C_8H_{14}O$ (M^+) requires 126.1045.

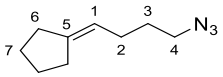
(4-Azidobutylidene)cyclohexane (193)



A modified literature procedure[456] was used. To an 500 mL 3-neck round-bottom flask equipped with temperature probe, addition funnel and nitrogen line was added crude 4-cyclohexylidenebutan-1-ol (~81.1 mmol), triethylamine (13.5 mL, 97.3 mmol), THF (150 mL) and the solution cooled to 2 °C internal temperature with a salt ice bath. The reaction was placed under nitrogen by 3 iterations of evacuation/ back fill. Methanesulfonyl chloride (7.5 mL, 97 mmol) in THF (20 mL) was added dropwise via addition funnel over 25 min, causing a cream precipitate to form and an exotherm of 8 °C. The reaction was warmed to 12 °C, stirred for 20 min then cooled in ice. The reaction was quenched with brine (300 mL), separated, and the aqueous layer extracted successively with MTBE (2 x 100 mL). The organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated to yield a yellow oil that was used crude in the next reaction. The crude oil was transferred to a 250 mL 3-neck round-bottom flask equipped with nitrogen line, temperature probe and stopped, with DMF (80 mL), NaN_3 (10.0 g, 153 mmol) and the mixture stirred at 40 °C for 15 h. The reaction was cooled in ice and diluted with brine (800 mL) causing an exotherm from 10 °C to 20 °C, and extracted successively with MTBE (5 x 150 mL) and the combined organics washed brine (50 mL), dried ($MgSO_4$) and concentrated to yield a crude brown oil that was sufficiently pure to be used in the next reaction. R_f 0.40 (petrol); ν_{max} 2092*s*; δ_H (400 MHz, $CDCl_3$) 1.47–1.58 (6 H, m, H8 and H7), 1.63 (2 H, app. quin, *J* = 7.0 Hz, H3), 2.06–2.14 (6 H, m, H2 and H6), 3.27 (2 H, t, *J* = 7.0 Hz, H4), 5.04 (1 H, t, *J* = 7.0, H1); δ_C (100 MHz, $CDCl_3$) 24.0 (C2), 26.9 (C8), 27.8 (C7), 28.6 (C6). 28.6 (C7), 29.1 (C3), 31.2 (C6),

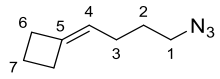
50.8 (C1), 119.4 (C4), 141.2 (C5); HRMS (FI$^+$) found 179.1478, $C_{10}H_{17}N_3$ (M^+) requires 179.1422.

(4-Azidobutylidene)cyclopentane (194)



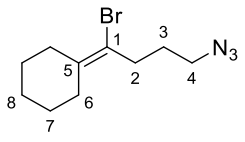
A modified literature procedure[456] was used. To an oven-dried 50 mL round-bottom flask was added 4-cyclopentylidenebutan-1-ol (870 mg, 90% w/w, 5.58 mmol), ether (20 mL) and triethylamine (1.0 mL, 7.1 mmol) and the solution cooled to 0 °C under argon. Methanesulfonyl chloride (0.6 mL, 8 mmol) was added dropwise, causing a white precipitate to form. After 35 min, the reaction was warmed to ambient temperature and stirred for 145 min. The reaction was quenched with brine (10 mL), separated, and the aqueous layer extracted successively with ether (3 x 10 mL). The organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated to yield a yellow oil that was used crude in the next reaction. The crude oil was transferred to a 50 mL round-bottom flask with DMSO (3 mL), NaN_3 (0.8 g, 12 mmol) and the mixture stirred at 35 °C for 17 h. The reaction was poured into a separating funnel with water (30 mL) and extracted successively with ether (3 x 20 mL) and the combined organics concentrated onto silica. Pure product was obtained by purification over silica eluting with petrol as a colourless oil (0.936 g, 76% w/w, 77% over 2 steps). R_f 0.38 (petrol); ν_{max} 2090s; δ_H (400 MHz, $CDCl_3$) 1.59–1.69 (6 H, m, H3 and H7), 2.07 (2 H, qt, J = 7.5 And 1.5 Hz, H2), 2.16–2.25 (4 H, m, H6), 3.27 (2 H, t, J = 7.0 Hz, H4), 5.21 (1 H, m, H1); δ_C (100 MHz, $CDCl_3$) 26.3 (C7), 26.4 (C7), 26.6 (C2), 28.6 (C3), 28.7 (C6), 33.6 (C6), 51.0 (C4), 118.2 (C1), 144.7 (C5); HRMS (FI$^+$) found 165.1254, $C_9H_{15}N_3$ (M^+) requires 165.1266.

(4-Azidobutylidene)cyclobutane (195)



A modified literature procedure[41] was used. To a 7 mL sample vial was added 4-cyclobutylidenebutan-1-ol (400 mg, 1.18 mmol) in DMF (2 mL) and the solution cooled to 0 °C under argon. Freshly recystallised CBr_4 (795 mg, 2.40 mmol), followed by PPh_3 (629 mg, 2.40 mmol), were added, causing the colourless solution to turn yellow. After 30 min at 0 °C, NaN_3 (310 mg, 4.75 mmol) was added and the reaction stirred overnight, during which the ice bath thawed from 0 °C to 15 °C. The cloudy brown solution was extracted with petrol (8 x 3 mL) until no product was observed by TLC of the DMF layer, and the combined petrol fractions washed with saturated aqueous $NaHCO_3$ (5 mL), then brine (5 mL), and dried (Na_2SO_4). The organic solution was concentrated to yield a crude oil that was purified over silica eluting with petrol, yielding a colourless oil (119 mg, 70% over 2 steps). R_f 0.40 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.55 (2 H, app. quin, *J* = 7.0 Hz, H2), 1.90–2.0 (4 H, m, H3 and H7), 2.61–2.67 (4 H, m, H6), 3.19 (2 H, t, *J* = 7.0 Hz, H1), 5.01 (1 H, m, H4); δ_C (100 MHz, $CDCl_3$) 17.0 (C7), 24.9 (C3), 28.7 (C2), 29.2 (C6), 30.89 (C6), 50.9 (C1), 118.5 (C4), 141.5 (C5); HRMS (FI^+) found 151.1113, $C_8H_{13}N_3$ (M^+) requires 151.1109.

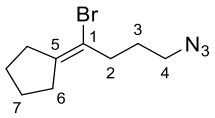
(4-Azido-1-bromobutylidene)cyclohexane (196)



To a 1 L 3-neck round-bottom flask equipped with temperature probe, addition funnel and nitrogen line was added crude (4-azidobutylidene)cyclohexane (~81.1 mmol), DCM (200 mL) and the solution cooled to 2 °C internal temperature with a salt ice bath. The reaction was placed under nitrogen by 3 iterations of evacuation/ back fill.

Bromine (4.15 mL, 81.2 mmol) in DCM (40 mL) was added dropwise to the reaction via addition funnel over 20 min, causing an orange colour with an exotherm of 5 °C. The funnel was washed in with DCM (5 mL) After 5 min, the reaction was warmed to 10 °C, stirred for 10 min, then cooled to 2 °C and quenched with aqueous saturated $Na_2S_2O_3$ solution (800 mL). The layers were separated and the aqueous extracted successively with DCM (2 x 150 mL), the combined organics washed with brine (20 mL), dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was transferred to a 500 mL 3-neck round-bottom flask equipped with temperature probe, addition funnel and nitrogen line with DMSO (150 ml) and the vessel filled with nitrogen by 3 iterations of evacuation/ backfill. *t*-BuOK (80.0 mL, 1.0 M in *t*-BuOH, 80.0 mmol) was added dropwise via addition funnel over 5 min, maintaining the internal temperature at 20 °C using an ice bath. The dark brown solution was stirred for 16 h then poured onto brine (800 mL). The solution was extracted successively with MTBE (3 x 250 mL), the combined organics washed with brine (100 mL), dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was purified over silica eluting with pentane to yield a pale yellow oil (11.0 g, 52% over 4 steps). R_f 0.21 (petrol); ν_{max} 2093s; δ_H (400 MHz, $CDCl_3$) 1.56 (6 H, br. s, H7 and H8), 1.85 (2 H, app. quin, J = 7.0 Hz, H3), 2.25–2.28 (2 H, m, H6), 2.4 (2 H, br. s, H6), 2.63 (2 H, t, J = 7.0 Hz, H2), 3.30 (3 H, t, J = 6.5 Hz, H4); δ_C (100 MHz, $CDCl_3$) 26.3 (C8), 27.2 (C7), 27.4 (C3), 27.8 (C7), 31.2 (C6), 33.9 (C2), 35.5 (C6), 50.0 (C4), 117.5 (C1), 139.2 (C5); HRMS (FI^+) found 257.0543, $C_{10}H_{16}{}^{79}BrN_3$ (M^+) requires 257.0528.

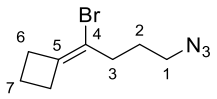
(4-Azido-1-bromobutylidene)cyclopentane (197)



To an oven-dried 50 mL round-bottom flask was added (4-azidobutylidene)cyclopentane (330 mg, 76% w/w, 1.51 mmol), petrol (3 mL) and the solution cooled to 0 °C under argon. Bromine (0.77 mL, 1.54 mmol) in petrol (1 mL) was added dropwise to the reaction via syringe over 1 min, causing an orange colouration that subsided until persisting. After 10 min, the reaction was warmed to room temperature, stirred for 7 min, then cooled to 0 °C and quenched with aqueous saturated $Na_2S_2O_3$ solution (25 mL). After the orange colour faded to colourless, the layers were separated and the aqueous extracted successively with petrol (3 x 20 mL), the combined organics washed with brine (5 mL), dried ($MgSO_4$), and concentrated to yield a crude yellow oil. The crude was transferred to a 50 mL round-bottom flask with DMSO (0.5 ml) and stirred at room temperature under argon. *t*-BuOK (2.3 mL, 1.0 M in *t*-BuOH, 2.3 mmol) was added dropwise via syringe pump over 20 min, causing the colourless solution to turn brown, and stirred for 16 h. The reaction was concentrated to half volume under vacuum to remove *t*-BuOH, then diluted with saturated aqueous $NaHCO_3$ (20 mL). The solution was extracted successively with ether (6 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was purified over silica eluting with petrol to yield a colourless oil (279 mg, 75% over 2 steps). R_f 0.17 (petrol); ν_{max} 2094s; δ_H (400 MHz, $CDCl_3$) 1.69 (2 H, app. quin , *J* = 7.0 Hz, H7), 1.78 (2 H, app. quin, *J* = 7.0 Hz, H7), 1.85 (2 H, app. quin, *J* = 6.5 Hz, H3), 2.30 (2 H, t, *J* = 7.0 Hz, H6), 2.34 (2 H, t, *J* = 7.0 Hz, H6), 2.53 (2 H, t, *J* = 7.0 Hz, H2), 3.30 (2 H, t, *J* = 6.5 Hz, H4); δ_C (100 MHz, $CDCl_3$) 26.0 (C7), 27.2 (C3), 27.8 (C7), 31.9

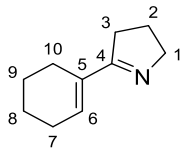
(C6), 35.1 (C2), 35.9 (C6), 50.1 (C4), 115.6 (C1), 144.1 (C5); HRMS (FI$^+$) found 243.0432, $C_9H_{14}{}^{79}BrN_3$ (M$^+$) requires 243.0371.

(4-Azido-1-bromobutylidene)cyclobutane (198)



To an oven-dried 25 mL round-bottom flask was added (4-azidobutylidene)cyclobutane (330 mg, 2.18 mmol), DCM (6 mL) and the solution cooled to 0 °C under argon. Bromine (0.11 mL, 2.2 mmol) in petrol (1.0 mL) was added dropwise to the reaction via syringe over 1 min, causing an orange colouration that subsided until persisting. The reaction was stirred at 0 °C for 5 min, then warmed to room temperature. After stirring for 30 min, the reaction was concentrated under vaccum to yield an orange oil. To the crude was added THF (5 mL) and the solution cooled to –78 °C under argon. KHMDS (7.2 mL, 0.91 M in THF, 6.5 mmol) was added dropwise via syringe pump over 20 min causing the clear orange solution to turn dark brown, and the reaction stirred overnight during which the acetone bath thawed from –78 °C to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with petrol (20 mL x 3). The combined organics were washed successively with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), then dried ($MgSO_4$), and concentrated to yield a crude brown oil. The crude was purified over silica eluting with petrol to yield a colourless oil (282 mg, 56% over 2 steps). R_f 0.31 (petrol); ν_{max} 2096s; δ_H (400 MHz, $CDCl_3$) 1.82 (2 H, app. quin, *J* = 7.0 Hz, H2), 1.94 (2 H, app. quin, *J* = 7.0 Hz, H7), 2.38 (2 H, tt, *J* = 7.0 And 1.0 Hz, H3), 2.60–2.69 (4 H, m, H6), 3.30 (2 H, t, *J* = 7.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 14.9 (C7), 26.8 (C2), 29.5 (C6), 32.1 (C6), 32.2 (C3), 150.0 (C1), 114.9 (C4), 140.4 (C5); HRMS (FI$^+$) found 229.0215, $C_8H_{12}{}^{79}BrN_3$ (M$^+$) requires 229.0215.

5-Cyclohexenyl-3,4-dihydro-2*H*-pyrrole (199)

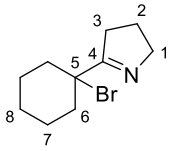


IAVBC route: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (150 mg, 0.583 mmol) in toluene (11.6 mL), K_2CO_3 (805 mg, 5.83 mmol) and NaOH (46 mg, 1.2 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 10% ether in petrol with 0.5% triethylamine. The product was isolated as a yellow oil (73 mg, 84%). R_f 0.40 (ether); ν_{max} 1642m; δ_H (500 MHz, $CDCl_3$) 1.61–1.71 (4 H, m, H8 and H9), 1.88 (2 H, app. quin, *J* = 7.5 Hz, H2), 2.21 (2 H, m, H7), 2.41 (2 H, m, H10), 2.67 (2 H, tt, *J* = 8.0 and 1.5 Hz, H3), 3.93 (2 H, t, *J* = 6.5 Hz, H1), 6.28 (1 H, m, H6); δ_C (150 MHz, CDCl3) 22.0 (C8), 22.3 (C9), 22.4 (C2), 24.9 (C10), 26.0 (C7), 33.7 (C3), 61.0 (C1), 134.6 (C6), 134.8 (C5), 175.1 (C4); m/z (ESI) HRMS (FI^+) found 149.1199, $C_{10}H_{15}N$ (M^+) requires 149.1205.

Second generation route: A modified literature procedure[418–420] was used. To a 50 mL oven-dried two-neck pear-shaped flask containing NaH (586 mg, 60% in mineral oil, 14.6 mmol) and THF (10 mL) was added methyl cyclohex-1-enecarboxylate (1.0 g, 7.3 mmol), 1-vinyl-2-pyrrolidinone (0.86 mL, 8.1 mmol), and N,N-diethylaniline (0.8 mL, 5 mmol). The reaction was refluxed for 2 h, then cooled to 0 °C and quenched slowly with water (5 mL) and 37% hydrochloric acid (4 mL). After the removal of THF under vacuum, further water (5 mL) and 37% hydrochloric acid (5 mL) were added and the

reaction refluxed for 24 h. The solution was cooled in ice, adjusted to pH 11 with aqueous NaOH solution, and extracted successively with DCM (3 x 50 mL). The combined organic layers were washed with brine (35 mL), dried ($MgSO_4$) and concentrated onto silica. The product was purified by eluting with petrol first to remove diethylaniline, then a gradient of 20–50% ether in petrol to collect the product as a pale yellow oil (770 mg, 72%). R_f 0.40 (ether); ν_{max} 1642m; δ_H (500 MHz, $CDCl_3$) 1.61–1.71 (4 H, m, H8 and H9), 1.88 (2 H, app. quin, *J* = 7.5 Hz, H2), 2.21 (2 H, m, H7), 2.41 (2 H, m, H10), 2.67 (2 H, tt, *J* = 8.0 and 1.5 Hz, H3), 3.93 (2 H, t, *J* = 6.5 Hz, H1), 6.28 (1 H, m, H6); δ_C (150 MHz, CDCl3) 22.0 (C8), 22.3 (C9), 22.4 (C2), 24.9 (C10), 26.0 (C7), 33.7 (C3), 61.0 (C1), 134.6 (C6), 134.8 (C5), 175.1 (C4); m/z (ESI) HRMS (FI^+) found 149.1199, $C_{10}H_{15}N$ (M^+) requires 149.1205.

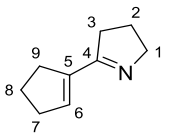
5-(1-Bromocyclohexyl)-3,4-dihydro-2*H*-pyrrole (199x)



To an oven-dried 14 mL Ace pressure tube was added (4-azido-1-bromobutylidene)cyclohexane (18 mg, 0.07 mmol), d_8-toluene (1.5 mL), and solid K_2CO_3 (40 mg, 0.29 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring and the colourless solution stirred at 130 °C for 5 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was loaded onto a silica pipette column and eluted with a gradient of neat petrol to neat ether, yielding **199** (5 mg, 48%), a colourless oil, and the title compound as a colourless oil (2 mg, 12%). R_f 0.68 (ether); ν_{max} 1625m; δ_H (500 MHz, $CDCl_3$) 1.32–1.39 (1 H, m, H8), 1.59–1066 (2 H, m, H7 and H8), 1.77–1.84 (1

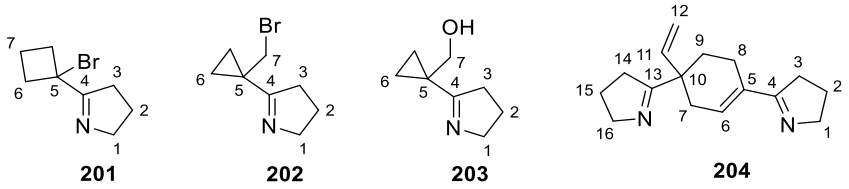
H, m, H7), 1.95 (2 H, tt, *J* = 7Hz, H2), 1.99–2.09 (1 H, m, H6), 2.72–2.32 (1 H, m, H6), 2.80 (2 H, tt, J = 7.5 and 2.0 Hz, H3), 3.91 (2 H, tt, *J* = 7.0 and 2.0 Hz, H1); δ_C (150 MHz, CDCl3) 22.7 (C2), 23.4 (C7), 25.1 (C8), 33.4 (C3), 38.8 (C6), 60.8 (C1), 69.3 (C5), 178.9 (C4); HRMS (FI^+) found 230.0533, $C_{10}H_{17}{}^{79}BrN_3$ (M^+) requires 230.0539.

5-Cyclopentenyl-3,4-dihydro-2*H*-pyrrole (200)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclopentane (100 mg, 0.411 mmol) in toluene (8.2 mL), with NaOH (32 mg, 0.82 mmol) and solid K_2CO_3 (567 mg, 4.11 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 48 h. After removing from heat and cooling, the brown reaction solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 10% ether in petrol with 0.5% triethylamine. The product was isolated as a yellow oil (43 mg, 78%). R_f 0.34 (1% MeOH in ether); ν_{max} 1680m, 1629m, 1590m, 1260s; δ_H (500 MHz, $CDCl_3$) 1.90 (2 H, app. quin, *J* = 7.5 Hz, H2), 1.96 (2 H, app. quin, *J* = 7.5 Hz, H8), 2.49–2.53 (2 H, m, H7), 2.65–2.72 (4 H, m, H3 and H9), 3.94 (2 H, t, *J* = 7.0 Hz, H1), 6.19 (1 H, app. t, *J* = 2.0 Hz, H6); δ_C (150 MHz, $CDCl_3$) 22.6 (C2), 23.2 (C8), 31.9 (C9), 33.5 (C7), 34.9 (C3), 61.3 (C1), 137.3 (C6), 140.9 (C5), 171.5 (C4); HRMS (FI^+) found 136.1116, $C_9H_{14}N$ (M^+) requires 136.1121.

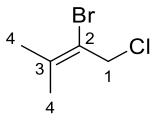
5-(1-bromocyclobutyl)-3,4-dihydro-2*H*-pyrrole (201), 5-(1-(bromomethyl)cyclopropyl)-3,4-dihydro-2*H*-pyrrole (202), (1-(3,4-dihydro-2*H*-pyrrol-5-yl)cyclopropyl)methanol (203), and 5,5'-(4-vinylcyclohex-1-ene-1,4-diyl)bis(3,4-dihydro-2*H*-pyrrole) (204)



To an oven-dried 14 mL Ace pressure tube was added (4-azido-1-bromobutylidene)cyclobutane (120 mg, 0.523 mmol), solid K_2CO_3 (722 mg, 5.23 mmol) and d_8-toluene (4 mL). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring and the colourless stirred at 140 °C for 22 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the brown reaction solution was loaded onto a silica pipette column and eluted with a gradient of neat petrol to neat ether. Compounds **201**–**204** were typically isolated in the order of 1-5 mg in yields <10%. Complete data for the compounds were assembled from separate experiments. **201**: R_f 0.78 (ether); ν_{max} 1627m; δ_H (500 MHz, $CDCl_3$) 1.86 (1 H, ddddd, *J* = 10.5 Hz, 8.5 Hz, 8.5 Hz, 6.5 and 6.5 Hz, H7), 1.99 (2 H, app. quin, *J* = 7.5 Hz, H2), 2.23–2.32 (1 H, m, H7), 2.58–2.74 (2 H, m, H6), 2.76 (2 H, tt, *J* = 8 Hz, H3), 2.89–2.96 (2 H, m, H6), 3.93 (2 H, tt, *J* = 7.0 Hz, H1); δ_C (150 MHz, $CDCl_3$); 15.9 (C7), 22.2 (C2), 32.0 (C3), 36.7 (C6), 58.9 (C5), 59.9 (C1), 177.0 (C4); HRMS (FI^+) found 202.0224, $C_8H_{13}{}^{79}BrN$ (M^+) requires 202.0226. **202**: R_f 0.55 (ether); ν_{max} 1629m; δ_H (500 MHz, C_6D_6) 0.53 (1 H, dt, *J* = 7.0 and 4.5 Hz, H6), 1.09 (1 H, dt, *J* = 7.0 and 4.5 Hz, H6), 1.40 (2 H, app. quin. *J* = 7.5 Hz, H2), 1.95 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3), 3.36 (2 H, s, H7), 3.71 (2 H, tt, *J* = 7.0 and 2.0 Hz); δ_C (150 MHz, C_6D_6) 17.7 (C6), 23.1 (C2), 30.4 (C5), 34.0 (C3), 40.4 (C7), 61.2

(C1), 175.7 (C4); HRMS (FI$^+$) found 202.0228, $C_8H_{13}{}^{79}BrN$ (M^+) requires 202.0226. **203**: R_f 0.18 (5% methanol in ether); ν_{max} 3334br, 1621m; δ_H (500 MHz, $CDCl_3$) 0.84 (1 H, dt, *J* = 6.5 and 4.5 Hz, H6), 0.99 (1 H, dt, *J* = 6.5 and 4.5 Hz, H6), 1.83 (2 H, app. quin, *J* = 7.0 Hz, H2), 2.23 (2 H, tt. *J* = 7.5 and 1.5 Hz, H2), 3.65 (2 H, s, H7), 3.85 (2 H, tt, *J* = 7.0 and 1.5 Hz); δ_C (150 MHz, $CDCl_3$) 11.6 (C6), 21.9 (C2), 26.0 (C5), 33.1 (C3), 60.8 (C1), 68.4 (C7), 180.7 (C4); HRMS (FI$^+$) found 162.0889, $C_8H_{13}NNa^+$ (M^+) requires 162.0883. **204**: R_f 0.28 (methanol/ ether, 1:10); δ_H (500 MHz, C_6D_6) 1.39–1.46 (4 H, m, H2 and H15), 1.78 (1 H, ddd, *J* = 13.5 Hz, 8.0 and 5.5 Hz, H9), 1.97 (1 H, ddd, *J* = 13.0, 6.5 and 6.5 Hz, H9), 2.16 (2 H, dq, *J* = 8.0 and 2.0 Hz, H14), 2.27 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3) overlays with (1 H, m, H7), 2.60–2.69 (1 H, m, H8), 2.81–2.87 (1 H, m, H8), 3.02 (1 H, d, *J* = 18.5, H7), 3.68 (2 H, tq, *J* = 7.0 and 1.5 Hz, H16), 3.86 (2 H, app. t, *J* = 7.0 Hz, H1), 4.97 (2 H, dd, *J* = 13.5 and 4.0 Hz, H12), 5.74 (1 H, dd, *J* = 17.5 and 10.5 Hz, H11), 6.03 (1 H, t, *J* = 4.0 Hz, H6); δ_C (150 MHz, C_6D_6) 22.7 (C8), 23.5 (C15), 23.5 (C2), 30.8 (C9), 33.5 (C14), 34.1 (C3), 34.4 (C7), 45.1 (C10), 61.3 (C16), 61.8 (C1), 114.0 (C12), 126.2 (C5), 132.1 (C6), 143.5 (C11), 173.7 (C13), 179.2 (C4); HRMS (FI$^+$) found 265.1667, $C_{16}H_{22}N_2Na^+$ (M^+) requires 265.1675.

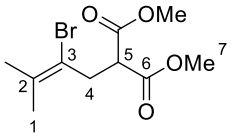
2-Bromo-1-chloro-3-methylbut-2-ene (205)



To a 25 mL round-bottom flask was added prenyl chloride (1.0 mL, 8.9 mmol), petrol 30-40 (10 mL), and the solution stirred at 0 °C under argon. Bromine (0.45 mL, 8.9 mmol) in petrol (0.55 mL) was added dropwise to the reaction, causing a brown colouration which fades before persisting. The solution was stirred for 5 min, then warmed to room temperature for 5 min. After cooling to 0 °C, the reaction was quenched with aqueous $Na_2S_2O_3$ solution (25 mL), and the aqueous layer extracted successively

with petrol (3 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to yield a colourless oil that was used crude in the next reaction. In a 250 mL round-bottom flask, the crude oil was dissolved in ethanol (10 mL) and stirred at 0 °C under argon. KOH (0.55 g, 9.8 mmol) in ethanol (10 mL) was added to the solution, causing the colourless solution to turn brown, and after 1.5 h the reaction was warmed to room temperature. After 5 min, the reaction was diluted with water (100 mL), and the aqueous solution extracted successively with DCM (3 x 30 mL). The combined organic fractions were dried ($MgSO_4$) and concentrated to yield the title compound as a yellow oil that was used crude in the next reaction (1.746 g). R_f 0.37 (petrol); ν_{max} 2976w, 1263m, 1026m, 700s; δ_H (500 MHz, $CDCl_3$) 1.90 (3 H, s, H4), 1.94 (3 H, s, H4), 4.44 (2 H, s, H1); δ_C (125 MHz, $CDCl_3$) 20.5 (C4), 25.6 (C5), 48.3 (C1), 115.6 (C2), 138.55 (C3); HRMS (FI^+) found 181.9499, $C_5H_8{}^{79}Br^{35}Cl$ (M^+) requires 181.9498.

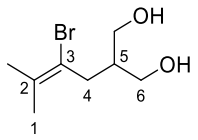
Dimethyl 2-(2-bromo-3-methylbut-2-en-1-yl)malonate (206)



A modified literature procedure[467] was used. To a 100 mL round-bottom flask was added crude 2-bromo-1-chloro-3-methylbut-2-ene (1.74 g, ~8.87 mmol), dimethyl malonate (1.0 mL, 8.9 mmol), K_2CO_3 (2.45 g, 17.7 mmol) and dry MeCN (30 mL) and the reaction refluxed under argon for 17 h. The solution was filtered, washed with ether, and the filtrate concentrated onto silica and purified eluting with 5% ether in petrol, yielding the title compound as a colourless oil (1.428 g, 58% over 3 steps). R_f 0.60 (1:1 ether/ petrol); ν_{max} 1735s; δ_H (400 MHz, $CDCl_3$) 1.80 (3 H, s, H1), 1.85 (3 H, s, H1), 3.09 (2 H, d, *J* = 7.5 Hz. H4), 3.73 (6 H, s, H7), 3.88 (1 H, t, *J* = 7.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 20.5

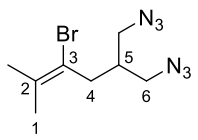
(C1), 25.5 (C1), 36.5 (C4), 50.6 (C5), 52.6 (C7), 116.7 (C3), 134.1 (C2), 169.0 (C6); HRMS (FI^+) found 301.0041, $C_{10}H_{15}{}^{79}BrO_4Na$ (MNa^+) requires 301.0051.

2-(2-Bromo-3-methylbut-2-en-1-yl)propane-1,3-diol (207)



To a 100 mL oven-dried round-bottom flask was added powdered $LiAlH_4$ (0.876 g, 22.8 mmol), dry ether (50 mL) and the solution stirred at 0 °C under argon. Dimethyl 2-(2-bromo-3-methylbut-2-en-1-yl)malonate (1.27 g, 4.57 mmol) in ether (5 mL) was added dropwise over 5 min, and the reaction stirred at 0 °C for 1 h. The solution was quenched at 0 °C with saturated aqueous Rochelle's salt solution (20 mL) and stirred for 1 h. The aqueous solution was extracted successively with ether (3 x 50 mL), the combined organics dried ($MgSO_4$) and concentrated onto silica. The product was purified by eluting with a gradient of 50% ether in petrol to pure ether, yielding a colourless oil (780 mg, 78%). R_f 0.36 (ether); ν_{max} 3269br; δ_H (400 MHz, $CDCl_3$) 1.81 (3 H, s, H1), 1.90 (3 H, s, H1), 2.14–2.22 (1 H, m, H5), 2.60 (2 H, d, *J* = 7.5 Hz. H4), 3.70 (2 H, dd, *J* = 10.5 and 6.0 Hz, H6), 3.87 (2 H, dd, *J* = 10.5 and 3.5 Hz, H6); δ_C (100 MHz, $CDCl_3$) 20.7 (C1), 25.5 (C1), 35.8 (C4), 41.0 (C5), 64.9 (C6), 119.5 (C3), 132.3 (C2), 169.0 (C6); HRMS (FI^+) found 222.0254, $C_8H_{15}{}^{79}BrO_2$ (M^+) requires 222.0250.

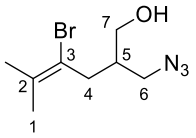
6-Azido-5-(azidomethyl)-3-bromo-2-methylhex-2-ene (208)



To a 21 mL vial containing 2-(2-bromo-3-methylbut-2-en-1-yl)propane-1,3-diol (250 mg, 1.13 mmol), and ether (12 mL) at 0 °C under argon was added triethylamine (344 µL, 2.47 mmol), followed by methanesulfonyl chloride (191 µL, 2.47 mmol), and

the reaction stirred for 5 min. After 20 min, the cloudy solution was warmed to room temperature, stirred for 30 min, then filtered, and the filtrate concentrated to yield a crude yellow oil that was used immediately in the next reaction. In a 7 mL vial, the crude oil prepared above was stirred under argon at 40 °C in DMSO (2 mL) with NaN_3 (290 mg, 4.46 mmol) for 21 h. The reaction was diluted with ether (60 mL), extracted successively with water (3 x 1 mL), and the combined aqueous layers back extracted with ether (10 mL). The combined organics were dried ($MgSO_4$), concentrated, and purified over silica eluting with 10% ether, yielding the product as a pale yellow oil (241 mg, 78%). R_f 0.94 (ether); ν_{max} 2091s; δ_H (400 MHz, $CDCl_3$) 1.82 (3 H, s, H1), 1.91 (3 H, s, H1), 2.22–2.32 (1 H, m, H5), 3.34 (2 H, dd, *J* = 12.0 and 6.5 Hz, H6), 3.46 (2 H, dd, *J* = 12.0 and 5.0 Hz, H6); δ_C (100 MHz, $CDCl_3$) 20.7 (C1), 25.6 (C1), 37.0 (C4), 37.6 (C5), 51.6 (C6), 118.0 (C3), 133.5 (C2); HRMS (FI^+) found 165.1136, $C_8H_{13}N_4$ (M^+–Br–N_2) requires 165.1135.

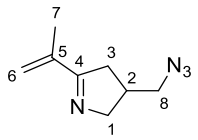
2-(Azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (209)



To a 14 mL vial containing 2-(2-bromo-3-methylbut-2-en-1-yl)propane-1,3-diol (136 mg, 0.612 mmol), and ether (2 mL) at 0 °C under argon was added triethylamine (94 μL, 0.67 mmol), followed by methane sulfonyl chloride (47 μL, 0.61 mmol), and the reaction stirred for 5 min. After 5 min, the cloudy solution was warmed to room temperature, stirred for 2.5 h, then filtered, and the filtrate concentrated to yield a crude green oil that was used immediately in the next reaction. In a 7 mL vial, the crude oil prepared above was stirred under argon at 40 °C in DMSO (0.5 mL) with NaN_3 (80 mg, 1.2 mmol) for 19 h. The reaction was diluted with ether (60 mL), extracted successively with water (3 x 1 mL), and the combined aqueous layers back extracted with ether (10

mL). The combined organics were dried ($MgSO_4$), concentrated, and purified over silica eluting with 10% ether, yielding 2-(azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (54 mg, 35%), and as a side product 6-azido-5-(azidomethyl)-3-bromo-2-methylhex-2-ene (31 mg, 18%). R_f 0.28 (2:1, petrol/ ether); ν_{max} 3354br, 2095s; δ_H (500 MHz, $CDCl_3$) 1.82 (3 H, s, H1), 1.91 (3 H, s, H1), 2.19–2.26 (1 H, m, H5), 2.58 (2 H, app. t, *J* = 8.0 Hz. H4), 3.40 (2 H, dd, *J* = 12.0 and 6.0 Hz, H6), 3.52 (2 H, dd, *J* = 12.0 and 5.0 Hz, H6), 3.63 (2 H, dd, *J* = 11.0 and 6.0 Hz, H7), 3.72 (2 H, dd, *J* = 11.0 and 4.0 Hz, H7); δ_C (125 MHz, $CDCl_3$) 20.7 (C1), 25.5 (C1), 35.8 (C4), 41.0 (C5), 51.8 (C6), 64.9 (C7), 118.8 (C3), 132.8 (C2); HRMS (FI^+) found 247.0230, $C_8H_{14}{}^{79}BrN_3O$ (M^+) requires 247.0320.

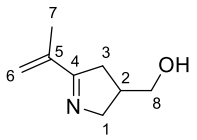
3-(Azidomethyl)-5-(prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrole (210)



To an oven-dried 14 mL Ace pressure tube was added a 0.02 M solution of 6-azido-5-(azidomethyl)-3-bromo-2-methylhex-2-ene (70 mg, 0.26 mmol) in toluene (14 mL) with K_2CO_3 (354 mg, 2.57 mmol) and NaOH (20 mg, 0.500 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the orange solution was filtered through a sintered funnel with DCM (30 mL), reduced in volume to a toluene solution, and purified over silica eluting with a gradient of 0.1% Et_3N in petrol to 0.1% Et_3N in 50% ether in petrol. The product was isolated as a yellow oil (32 mg, 76%). R_f 0.65 (ether); ν_{max} 2095s; δ_H (400 MHz, $CDCl_3$) 2.02 (3 H, s, H7), 2.54–2.68 (2H, m, H2 and H3), 2.91 (1 H, qt, *J* = 7.5 and 1.5 Hz, H3), 3.29

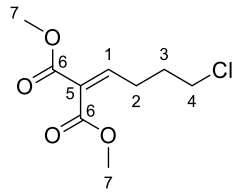
(2 H, ddd, *J* = 31.0, 12.0 and 7.0 Hz, H8), 3.76 (1 H, dd, *J* = 17.5 and 4.5 Hz, H1), 4.11 (1 H, dd, *J* = 16.5 and 8.0 Hz, H1), 5.42 and 5.49 (1 H, s, H6); δ_C (100 MHz, $CDCl_3$) 19.2 (C7), 36.8 (C2), 38.4 (C3), 55.0 (C8), 64.7 (C1), 121.4 (C6), 140.6 (C5), 173.9 (C4); HRMS (FI^+) found 165.1134, $C_8H_{13}N_4$ (M^+) requires 165.1135.

(5-(Prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrol-3-yl)methanol (211)



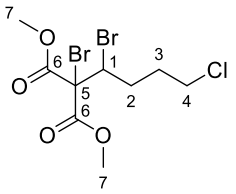
To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 2-(azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (100 mg, 0.404 mmol) in toluene (8 mL) with K_2CO_3 (557 mg, 4.04 mmol) and NaOH (30 mg, 0.81 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the orange solution was filtered through a sintered funnel with DCM (30 mL), reduced in volume to a toluene solution, and purified over silica eluting with a gradient of 0.1% Et_3N in petrol to 0.1% Et_3N in ether with 0.1% MeOH. The product was isolated as a yellow oil (46 mg, 82%). R_f 0.17 (ether); ν_{max} 3272br, 1596m; δ_H (500 MHz, $CDCl_3$) 2.00 (3 H, s, H7), 2.54–2.63 (2 H, m, H2 and H3), 2.81–2.87 (2 H, m, H3 and OH), 3.52 (2 H, ddd, *J* = 21.5 Hz, 10.5 and 8.0 Hz, H8), 3.78 (1 H, dd, *J* = 16.5 and 4.0 Hz, H1), 4.04 (1 H, app. dd, *J* = 16.5 and 7.0 Hz, H1), 5.42 and 5.46 (1 H, s, H6); δ_C (125 MHz, $CDCl_3$) 18.2 (C7), 36.5 (C3), 38.0 (C2), 62.9 (C1), 64.2 (C8), 120.4 (C6), 139.6 (C5), 173.6 (C4); HRMS (FI^+) found 140.1065, $C_8H_{14}NO$ (MH^+) requires 140.1070.

Dimethyl 2-(4-chlorobutylidene)malonate (212)



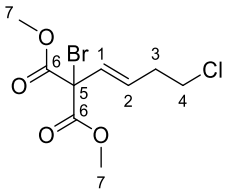
A modified literature procedure[359] was used. To a 50 mL oven-dried round-bottom flask was added carbon tetrachloride (2.5 mL) and $TiCl_4$ (1.1 mL, 10 mmol) at 0 °C under argon. Freshly distilled THF (20 mL) was added dropwise over 25 min causing a bright yellow precipitate to form. 4-Chlorobutanal (800 mg, 7.50 mmol) and dimethyl malonate (0.57 mL, 5.0 mmol) in THF (1 mL) were added dropwise over 10 min, and washed in with further THF (1 mL), followed immediately by pyridine (1.6 mL, 20 mmol) over 40 min, during which the yellow solution turned orange. After 1 h, the reaction was allowed to warm to room temperature and stirred 17 h. The reaction was quenched with water (100 mL) and extracted successively with ether (3 x 20 mL), and the combined organic layers washed with brine (10 mL), dried ($MgSO_4$) and concentrated to yield a yellow oil. The oil was purified over silica eluting with 1:8 ether in petrol, yielding a pale yellow oil (879 mg, 80%). R_f 0.39 (1:1 petrol/ ether); ν_{max} 1729s; δ_H (400 MHz, $CDCl_3$) 1.97 (2 H, app. quin, *J* = 7.0 Hz, H3), 2.49 (2 H, app. q, *J* = 7.5 Hz, H2), 2.02 (2 H, t, *J* = 6.5 Hz, H4), 3.79 (3 H, s, H7), 3.85 (3 H, s, H7), 3.01 (1 H, t, *J* = 8.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 27.1 (C3), 31.0 (C2), 43.9 (C4), 52.5 (C7), 52.6 (C7), 129.1 (C5), 148.1 (C1), 164.2 (C6), 165.6 (C6); HRMS (FI^+) found 243.0399, $C_9H_{13}{}^{35}ClNaO_4$ (MNa^+) requires 243.0395.

Dimethyl 2-bromo-2-(1-bromo-4-chlorobutyl)malonate (213)



To a 50 mL oven-dried round-bottom flask was added dimethyl 2-(4-chlorobutylidene)malonate (250 mg, 1.13 mmol), in DCM (10 mL), and the reaction stirred at 0 °C under argon. Bromine (60 µL, 1.17 mmol) in DCM (0.9 mL) was added dropwise over 10 min, causing the colourless solution to turn orange. After 10 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), extracted successively with DCM (3 x 10 mL), dried ($MgSO_4$), and concentrated to yield a crude oil. The product was purified over silica eluting with 1:8 ether in petrol, yielding a colourless oil (372 mg, 86%). R_f 0.60 (1:1 petrol/ ether); ν_{max} 1743s; δ_H (400 MHz, $CDCl_3$) 1.91–2.24 (3 H, m, H2 and H3), 2.42 (1 H, dddd, *J* = 14.0 Hz, 9.5 Hz, 6.0 Hz, and 1.5 Hz, H2), 3.85 (3 H, s, H7), 3.87 (3 H, s, H7), 4.52 (1 H, dd, *J* = 10.5 and 1.5 Hz, H1); δ_C (100 MHz, $CDCl_3$) 30.8 (C3), 33.5 (C2), 43.8 (C4), 54.3 (C7), 54.5 (C5), 55.3 (C1), 67.5 (C5), 164.7 (C6), 165.5 (C6); HRMS (FI^+) found 400.8763, $C_9H_{13}{}^{35}Cl^{79}Br_2NaO_4$ (MNa^+) requires 400.8761.

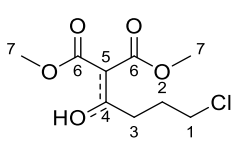
(*E*)-Dimethyl 2-bromo-2-(4-chlorobut-1-enyl)malonate (214)



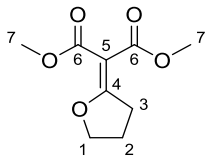
To a 14 mL sample vial was added dimethyl 2-(4-chlorobutylidene)malonate (55 mg, 0.25 mmol), in DCM (2 mL), and the reaction stirred at 0 °C under argon. Bromine (13 µL, 0.25 mmol) in DCM (0.9 mL) was added dropwise over 10 min, causing the colourless solution to turn orange. After 10 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), extracted successively with DCM (3 x 10 mL), dried

($MgSO_4$), and concentrated to yield a crude oil. In a 7 mL sample vial, DCM (1 mL) and triethylamine (70 μL, 0.50 mmol) was added to the crude dibromide, and the reaction stirred under argon for 22 h. The reaction was quenched with water (10 mL), extracted successively with DCM (3 x 5 mL), dried ($MgSO_4$), and concentrated to yield an orange oil. The crude was purified over silica eluting with 1:16 ether in petrol, yielding the title compound (18 mg, 24%), and the recovered **212** (9 m, 16% recovery) as colourless oils. R_f 0.64 (1:1 petrol/ ether); ν_{max} 1742s; δ_H (400 MHz, $CDCl_3$) 2.61 (2 H, dddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 and 1.5 Hz, H3), 3.50 (2 H, t, *J* = 7.0 Hz, H4), 3.78 (6 H, s, H7), 5.82 (1 H, dt, *J* = 15.5 and 7.0 Hz, H2), 6.07 (1 H, dt, *J* = 15.5 and 1.5 Hz, H1); δ_C (100 MHz, $CDCl_3$) 35.3 (C3), 43.0 (C4), 54.1 (C7), 59.7 (C5), 128.4 (C2), 132.1 (C1), 166.5 (C6); HRMS (FI^+) found 320.9499, $C_9H_{12}{}^{35}Cl^{79}BrNaO_4$ (MNa^+) requires 320.9500.

Dimethyl 2-(4-chloro-1-hydroxybutylidene)malonate (215) and dimethyl 2-(dihydrofuran-2(3*H*)-ylidene)malonate (216)



215

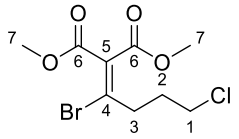


216

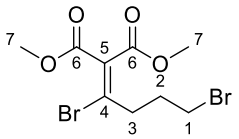
A modified literature procedure[360] was used. To a 10 mL oven-dried round-bottom flask was added anhydrous $MgCl_2$ (952 mg, 10.0 mmol) and acetonitrile (50 mL) at 0 °C under argon. Dimethyl malonate (1.14 mL, 10.0 mmol) and triethylamine (2.8 mL, 20 mmol) were added dropwise, followed 10 min later by 4-chlorobutyryl chloride (1.7 mL, 15 mmol), and the reaction stirred at 0 °C for 1 h. The reaction as warmed to ambient temperature, then after 1.5 h quenched with water (60 mL), extracted successively with ether (3 x 20 mL), washed with brine (10 mL), and dried ($MgSO_4$). Concentration and purification over silica eluting with petrol to 50% ether yielded **215**

as a 53:47 mixture of resonance isomers (1.173g, 50%) as a colourless oil, and **216** as a white solid (514 mg, 25%). **215**: R_f 0.54 (1:1 petrol/ ether); ν_{max} 1724s, 1652m, 1603m; δ_H (400 MHz, $CDCl_3$) 2.08–2.18 (4 H, m, H2 and H2'), 2.65 (2 H, app. t, *J* = 7.5 Hz, H3'), 2.84 (2 H, t, *J* = 7.0 Hz, H3), 3.59 (4 H, app. t, *J* = 6.5 Hz, H1 and H1'), 3.80 (3 H, s, H7'), 3.82 (6 H, s, H7), 3.83 (3 H, s, H7'), 4.53 (1 H, s, H5), 13.5 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 26.1 (C2), 29.4 (C2'), 31.2 (C3'), 38.7 (C3), 43.9 (C1), 44.1 (C1'), 52.3 (C7'), 52.4 (C7'), 53.3 (C7), 65.0 (C5), 134.7 (C5'), 164.8 (C6 and C6'), 181.9 (C4'), 197.8 (C4); HRMS (FI^+) found 259.0351, $C_9H_{13}{}^{35}ClNaO_5$ (MNa^+) requires 259.0344. **216**: R_f 0.13 (1:1 petrol/ ether); ν_{max} 1709s, 1625s; δ_H (400 MHz, $CDCl_3$) 2.13 (2 H, app. quin, *J* = 7.5 Hz, H2), 3.18 (2 H, t, *J* = 8.0 Hz, H3), 3.72 (3 H, s, H7), 3.80 (3 H, t, H7), 4.39 (2 H, t, *J* = 7.0 Hz, H1); δ_C (100 MHz, $CDCl_3$) 23.2 (C2), 31.8 (C3), 51.6 (C7), 52.2 (C7), 73.8 (C1), 99.5 (C5), 165.9 (C6), 166.3 (C6), 176.9 (C4); HRMS (FI^+) found 223.0584, $C_9H_{12}NaO_5$ (MNa^+) requires 223.0577.

Dimethyl 2-(1-bromo-4-chlorobutylidene)malonate (217) and dimethyl 2-(1-bromo-4-bromobutylidene)malonate (218)



217

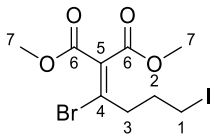


218

A modified literature procedure[361,362] was used. To an 50 mL oven-dried round-bottom flask was added DMF (8 mL) and the solution stirred at 0 °C under argon. PBr_3 (0.25 mL, 2.5 mmol) in ether (2 mL) was added dropwise over 40 min causing a white precipitate to form. 5 min later, dimethyl 2-(4-chloro-1-hydroxybutylidene)malonate (200 mg, 0.84 mmol) in DMF (1 mL) was added over 25 min, and washed in with further DMF (1 mL). An oven-dried reflux condenser was attached under argon, and the reaction heated to 40 °C for 17 h, during which the white precipitate turned orange. The reaction

as removed from heat then quenched with water (100 mL), extracted successively with ether (3 x 30 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was purified over silica eluting with 1:8 ether in petrol, yielding an inseparable 1:1 mixture of **217/218** as a yellow oil (143 mg, ~53%). R_f 0.60 (1:1 petrol/ ether); ν_{max} 1726s, 1620m; δ_H (400 MHz, $CDCl_3$) 2.15 (2 H, app. quin, *J* = 7.0 Hz, H2), 2.24 (2 H, app. quin, *J* = 7.0 Hz, H2), 3.25 (4 H, app. t, *J* = 7.5 Hz, H3), 3.46 (2 H, t, *J* = 6.5 Hz, CH_2Br), 3.60 (2 H, t, *J* = 6.5 Hz, CH_2Cl), 3.79 (3 H, s, H7), 3.79 (3 H, s, H7), 3.85 (6 H, s, H7); δ_C (100 MHz, $CDCl_3$) 31.1 (C2), 31.2 (C2), 31.7 (CH_2Br), 36.5 (C3), 37.7 (C3), 43.5 (CH_2Cl), 52.8 (C7), 52.9 (C7), 129.9 (C5), 145.9 (C4), 146.1 (C4), 162.0 (C6), 165.2 (C6); HRMS (FI^+) found 366.8980, $C_9H_{12}{}^{79}Br_2NaO_4$ (MNa^+) requires 366.8975; HRMS (FI^+) found 322.9478, $C_9H_{12}{}^{35}Cl^{79}BrNaO_4$ (MNa^+) requires 322.9479.

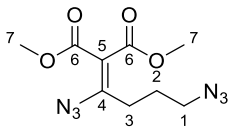
Dimethyl 2-(1-bromo-4-iodobutylidene)malonate (219)



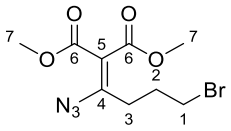
To an 25 mL oven-dried pear-shaped flask equipped with reflux condenser and $CaCl_2$ drying tube was added a 1:1 mixture of **217/218** (85 mg, 0.26 mmol), NaI (398 mg, 2.65 mmol) and acetone (10 mL). The solution was refluxed for 17 h, during which an off-white solid precipitated from the reaction. The reaction was reaction was removed from heat and concentrated to remove acetone. The solid was diluted with water (20 mL), extracted successively with ether (3 x 10 mL), the combined organics washed with brine (2 mL), dried ($MgSO_4$), and concentrated to yield a brown oil that was sufficiently pure to be used in the next reaction (80 mg, 77%). R_f 0.50 (1:1 petrol/ ether); ν_{max} 1728s, 1620m; δ_H (400 MHz, $CDCl_3$) 2.17–2.24 (2 H, app. quin, *J* = 7.0 Hz, H2), 3.19–3.25 (4 H, m, H1 and H3), 3.79 (3 H, s, H7), 3.85 (3 H, s, H7); δ_C (100 MHz, $CDCl_3$) 3.9 (C1),

32.0 (C2), 39.9 (C3), 52.8 (C7), 52.9 (C7), 130.0 (C5), 145.7 (C4), 162.0 (C6), 165.2 (C6); HRMS (FI$^+$) found 412.8863, $C_9H_{12}{}^{79}Br^{126.9}INaO_4$ (MNa$^+$) requires 412.8856.

Dimethyl 2-(1,4-diazidobutylidene)malonate (220) and Dimethyl 2-(1-azido-4-bromobutylidene)malonate (221)



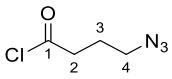
220



221

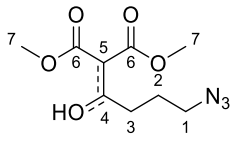
To a 7 mL sample vial was added dimethyl 2-(1-bromo-4-iodobutylidene)malonate (80 mg, 0.20 mmol), NaN_3 (20 mg, 0.30 mmol), DMF (0.5 mL) and the reaction stirred at room temperature for 3 h under argon. The reaction was diluted with brine (10 mL), extracted successively with ether (3 x 10 mL), and the combined organic layers washed with brine (5 mL). The combined organic fractions were dried ($MgSO_4$), then concentrated onto silica and purified by eluting with a gradient of petrol to 10% ether in petrol, an inseparable 1:1 mixture of products as a yellow oil (39 mg). R_f 0.44 (1:1 ether/ petrol); ν_{max} 2110s, 1716s, 1611s; δ_H (400 MHz, $CDCl_3$) 1.88–1.95 (2 H, m, H2), 2.16–2.33 (2 H, m, H2), 2.93–2.97 (2 H, m, H3), 3.00–3.04 (2 H, m, H3), 3.45 (2 H, t, *J* = 6.5 Hz, CH_2Br), 3.51 (2 H, t, *J* = 6.5 Hz, CH_2N_3) 3.75 (3 H, s, H7), 3.82 (3 H, s, H7); δ_C (100 MHz, $CDCl_3$) 27.1 (C2), 27.4 (C3), 29.1 (C3), 30.7 (C2), 32.1 (CH_2Br), 50.6 (CH_2N_3), 52.3 (C7), 52.7 (C7), 113.8 (C5), 154.7 (C4), 155.0 (C4), 163.8 (C6), 165.4 (C6); HRMS (FI$^+$) found 327.9906, $C_9H_{12}{}^{79}BrN_3NaO_4$ (MNa$^+$) requires 327.9903; HRMS (FI$^+$) found 291.0823, $C_9H_{12}N_6NaO_4$ (MNa$^+$) requires 291.0812.

4-Azidobutanoyl chloride (222)[468]



A literature procedure[468] was used. To a 50 mL oven-dried round-bottom flask was added ethyl 4-bromobutyrate (5.0 mL, 35 mmol), NaN_3 (2.72 g, 41.9 mmol) and DMF (10 mL) and the reaction stirred at room temperature under argon for 18 h. The reaction was diluted with water (100 mL), extracted successively with ether (3 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$) and concentrated into a 500 mL round-bottom flask. Methanol (40 mL), and water was added until the solution turned cloudy, followed by LiOH (3.0 g, 125.0 mmol) and the reaction stirred at room temperature for 20 h. The methanol was removed under reduced pressure, and the aqueous solution made acidic with 3N HCl (37%, 6 mL). The aqueous was extracted successively with ether (4 x 60 mL), dried ($MgSO_4$) and the solvent removed. In a 500 mL round-bottom flask, DCM (100 mL) was added to the crude, along with a drop of DMF at 0 °C under argon. Oxalyl chloride (6.0 mL, 71 mmol) was added dropwise, and after stirring for 19 h the solvent was removed to yield a yellow oil. The oil was diluted with ether (100 mL) and filtered to remove solids and concentrated to yield the final product (4.0 g, 77%) with data consistent with literature data.[468] δ_H (200 MHz, $CDCl_3$) 1.97 (2 H, app. quin, *J* = 7.0 Hz, H3), 3.03 (2 H, t, *J* = 6.5 Hz, H2), 3.41 (2 H, t, *J* = 6.5 Hz, H4).

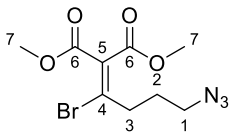
Dimethyl 2-(4-azido-1-hydroxybutylidene)malonate (223)



A modified literature procedure[360] was used. To a 250 mL oven-dried round-bottom flask was added anhydrous $MgCl_2$ (1.7 mg, 18 mmol) and acetonitrile (100 mL) at 0 °C under argon. Dimethyl malonate (1.8 mL, 16 mmol) and triethylamine (4.4 mL,

31 mmol) were added dropwise, followed 10 min later by 4-azidobutyryl chloride (3.48 g, 23.6 mmol) in MeCN (3 mL) dropwise over 45 min, and the reaction stirred at 0 °C for 1 h. The reaction as warmed to ambient temperature, then after 1 h quenched with water (150 mL), extracted successively with ether (3 x 200 mL), washed with brine (20 mL), and dried ($MgSO_4$). Concentration and purification over silica eluting with 10% ether in petrol yielded the product as an 58:42 mixture of resonance isomers as a pale yellow oil (2.66 mg, 46%). R_f 0.40 (1:1 petrol/ ether); ν_{max} 2097s, 1722s, 1651m, 1602m; δ_H (400 MHz, $CDCl_3$) 1.87–1.97 (4 H, m, H2 and H2'), 2.55 (2 H, t, *J* = 7.5 Hz, H3'), 2.73 (2 H, t, *J* = 7.0 Hz, H3), 3.32–3.37 (4 H, m, H1 and H1'), 3.79 (3 H, s, H7'), 3.81 (6 H, s, H7), 3.82 (3 H, s, H7'), 4.51 (1 H, s, H5), 13.5 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 22.7 (C2), 25.9 (C2'), 31.0 (C3'), 38.6 (C3), 50.3 (C1), 50.6 (C1'), 52.2 (C7'), 52.4 (C7'), 53.3 (C7), 64.9 (C5), 99.7 (C5'), 164.9 (C6 and C6'), 182.1 (C4'), 197.8 (C4); HRMS (FI^+) found 266.0755, $C_9H_{13}N_3NaO_5$ (MNa^+) requires 266.0747.

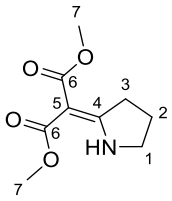
Dimethyl 2-(4-azido-1-bromobutylidene)malonate (224)



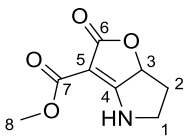
A modified literature procedure[361,362] was used. To a 50 mL oven-dried round-bottom flask was added DMF (3.4 mL) and the solution stirred at 0 °C under argon. PBr_3 (0.25 mL, 2.5 mmol) in ether (2 mL) was added dropwise over 40 min causing a white precipitate to form. 10 min later, dimethyl 2-(4-chloro-1-hydroxybutylidene)malonate (200 mg, 0.84 mmol) in DMF (1 mL) was added over 25 min, and washed in with further DMF (1 mL). An oven-dried reflux condenser was attached under argon, and the reaction heated to 45 °C for 22 h, during which the white precipitate turned green. The reaction as removed from heat then quenched with brine (60 mL), extracted successively with

ether (3 x 20 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was purified over silica eluting with 1:16 ether in petrol, yielding a yellow oil (83 mg, 22%). R_f 0.50 (1:1 petrol/ ether); ν_{max} 2098s, 1729s, 1621m; δ_H (400 MHz, $CDCl_3$) 1.96 (2 H, app. quin, *J* = 7.0 Hz, H2), 3.19 (2 H, app. t, *J* = 7.5 Hz, H3), 3.38 (2 H, t, *J* = 7.0 Hz, H1), 3.79 (3 H, s, H7), 3.86 (3 H, s, H7); δ_C (100 MHz, $CDCl_3$) 27.6 (C2), 36.2 (C3), 50.2 (C1), 52.8 (C7), 52.8 (C7), 129.8 (C5), 146.5 (C4), 162.0 (C6), 165.3 (C6); HRMS (FI^+) found 327.9910, $C_9H_{12}{}^{79}BrN_3NaO_4$ (MNa^+) requires 327.9903.

Dimethyl 2-(pyrrolidin-2-ylidene)malonate (225) and methyl 2-oxo-4,5,6,6a-tetrahydro-2*H*-furo[3,2-b]pyrrole-3-carboxylate (226)



225

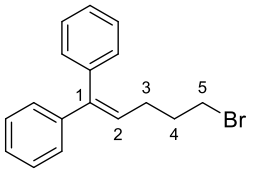


226

To an oven-dried 14 mL Ace pressure tube was added a 0.03 M solution of 2-(4-azido-1-bromobutylidene)malonate (120 mg, 0.350 mmol) in freshly distilled toluene (CaH_2) (7 mL), with solid K_2CO_3 (484 mg, 3.50 mmol). The reaction was bubbled through with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 100 °C for 11 h in a pre-heated oil bath. A white solid precipitate crashed out of the reaction solution as the colourless solution turned yellow. After removing from heat and cooling, the reaction was filtered to collect the precipitate, a white solid, which was dried under high vacuum **226** (24 mg; 60%). The filtrate was concentrated and purified over silica, eluting a gradient of petrol to 25% ether, yielding a red oil **225** (9 mg, 20%) with data consistent with the literature data.[469] **225**: R_f 0.34 (ether); ν_{max} 3308br, 1642s, 1573s;

δ_H (500 MHz, $CDCl_3$) 2.05 (2 H, app. quin, *J* = 7.5 Hz, H2), 3.13 (2 H, t, *J* = 8.0 Hz, H3), 3.62 (2 H, t, *J* = 7.5 Hz, H5), 3.73 (3 H, s, H7), 3.75 (3 H, s, H7), 9.66 (1 H, br, NH); δ_C (150 MHz, $CDCl_3$) 20.6 (C2), 33.5 (C3), 46.5 (C1), 49.9 (C7), 50.2 (C7), 85.7 (C5), 167.0 (C6), 169.3 (C6), 172.9 (C4); m/z (ESI) 200.1 (MH^+), 222.1 (MNa^+). **226**: M.p 235 °C; R_f 0.13 (8:1 ether/ methanol); ν_{max} 3165br, 1739m, 1702m, 1636s; δ_H (500 MHz, $CDCl_3$) 2.13 (1 H, dddd, *J* = 11.5 Hz, 11.5 Hz, 11.0 and 8.5 Hz, H2), 2.61 (1 H, ddd, *J* = 11.5 Hz, 7.0 and 4.5 Hz, H2), 3.83 (3 H, s, H8), 3.83 (1 H, ddd, *J* = 11.0, 11.0 and 4.5 Hz, H1), 3.90 (1 H, ddd, *J* = 11.5 Hz, 9.0 and 3.0 Hz, H1), 5.00 (1 H, ddd, *J* = 120 Hz, 7.0 and 1.0 Hz, H3), 6.91 (1 H, br, NH); δ_C (150 MHz, $CDCl_3$) 31.3 (C2), 49.5 (C1), 50.5 (C8), 76.4 (C3), 84.7 (C5), 162.8 (C7), 169.7 (C6), 179.6 (C4); HRMS (FI^+) found 206.0429, $C_8H_9NNaO_4$ (MNa^+) requires 206.0424.

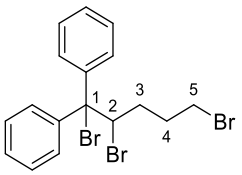
(5-Bromopent-1-ene-1,1-diyl)dibenzene (228)



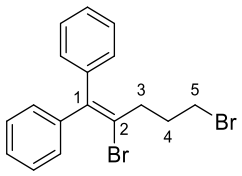
A modified literature procedure[470] was used. To an oven-dried 250 mL round-bottom flask was added ether (80 mL), phenyl lithium (15 mL, 1.9 M in ether, 28 mmol) and the solution stirred at –78 °C under argon. Ethyl 5-bromovalerate (1.8 mL, 11.4 mmol) was added dropwise over 10 min, the reaction stirred for 2 h, then quenched with saturated aqueous NH_4Cl (60 mL). The aqueous phase was extracted with ether (3 x 50 mL), and the combined organic fractions washed with brine (10 mL), dried ($MgSO_4$) and concentrated into a 500 mL round-bottom flask equipped with a reflux condenser. The crude alcohol was dissolved in isopropanol (200 mL) with 20% aqueous sulphuric acid (20 mL) and refluxed for 3 h. The reaction was removed from heat, cooled to room temperature, and concentrated to remove IPA. The aqueous solution was diluted with

saturated aqueous $NaHCO_3$ (100 mL), extracted successively with DCM (4 x 60 mL), the combined organic layers washed with brine (20 mL) then dried ($MgSO_4$). The organic solution was concentrated to yield a crude oil that was purified over silica eluting with petrol, yielding a colourless oil (2.77 g, 80% over 2 steps). R_f 0.65 (8:1 petrol/ ether); ν_{max} 1493m, 1443m, 1243m, 1073w, 759s, 697s; δ_H (400 MHz, $CDCl_3$) 2.02 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.28 (2 H, app. q, *J* = 7.5 Hz, H3), 3.40 (2 H, t, *J* = 7.0 Hz, H5), 6.07 (1 H, t, *J* = 7.5 Hz, H2), 7.19–7.42 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.5 (C3), 33.1 (C4), 33.1 (C5), 127.1, 127.1, 127.2, 127.6 (C2), 128.2, 128.3, 129.8, 138.9 (C1), 142.4, 143.0; HRMS (FI^+) found 300.0513, $C_{17}H_{17}{}^{79}Br$ (M^+) requires 300.0514.

(1,2,5-Tribromopentane-1,1-diyl)dibenzene (229) and (2,5-dibromopent-1-ene-1,1-diyl)dibenzene (230)



229

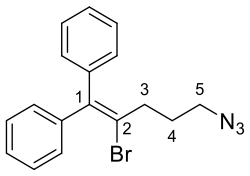


230

To an oven-dried 100 mL round-bottom flask was added (5-bromopent-1-ene-1,1-diyl)dibenzene (1.0 g, 3.3 mmol), DCM (40 mL) and the solution stirred at 0 °C under argon. Bromine (0.17 mL; 3.3 mmol) in DCM (0.8 mL) was added dropwise via syringe, and after 10 min the reaction quenched with saturated aqueous $Na_2S_2O_3$ (50 mL). The aqueous layer was extracted successively with DCM (3 x 30 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), and concentrated into a 100 mL round-bottom flask. To the crude oil was added DCM (40 mL), propionic acid (0.12 mL, 1.65 mmol), and the reaction stirred under argon at room temperature for 3 d. The reaction was quenched with saturated aqueous $NaHCO_3$ (80 mL), the aqueous layer extracted successively with DCM (3 x 50 mL), and the combined organics washed with brine (15 mL), dried ($MgSO_4$) and concentrated onto silica. Eluting over silica with 1% ether in

petrol, yielded **230** as a white solid (749 mg, 60%), and unreacted tribromide **229** as a white solid (396 mg, 26%). **230:** M.p 54 °C; R_f 0.78 (8:1 petrol/ ether); ν_{max} 1492w, 1442w, 1248w, 1075w, 761m, 699s; δ_H (400 MHz, $CDCl_3$) 2.25 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.73 (2 H, app. t, *J* = 7.5 Hz, H3), 3.38 (2 H, t, *J* = 6.5 Hz, H5), 7.17–7.35 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 32.2 (C4), 32.2 (C5), 37.3 (C3), 125.6 (C2), 127.3, 127.5, 128.1, 128.5, 128.7, 129.0, 140.6 (C1), 143.0, 143.3; HRMS (FI^+) found 379.9601, $C_{17}H_{16}{}^{79}Br_2$ (M^+) requires 379.9599. **229:** M.p 70 °C; R_f 0.33 (petrol/ ether, 8:1); ν_{max} 1492m, 1448m, 1158m, 1061m, 699s; δ_H (400 MHz, $CDCl_3$) 1.72–1.81 (1 H, m, H3), 1.89–2.20 (1 H, m, H4), 2.02–2.12 (1 H, m, H3), 2.19–2.30 (1 H, m, H4), 3.32–3.40 (2 H, m, H5), 5.12 (1 H, dd, *J* = 10.5 and 2.0 Hz, H2), 7.20–7.39 (6 H, m, Ar-H), 7.50–7.53 (2 H, m, Ar-H), 7.58–7.61 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 31.4 (C4), 31.5 (C3), 32.5 (C5), 65.6 (C2), 80.0 (C1), 125.4, 125.6, 127.2, 128.4, 128.6, 142.3, 143.0, 146.5; HRMS (FI^+) found 379.9632, $C_{17}H_{16}{}^{79}Br_2$ (M^+ –HBr) requires 379.9613.

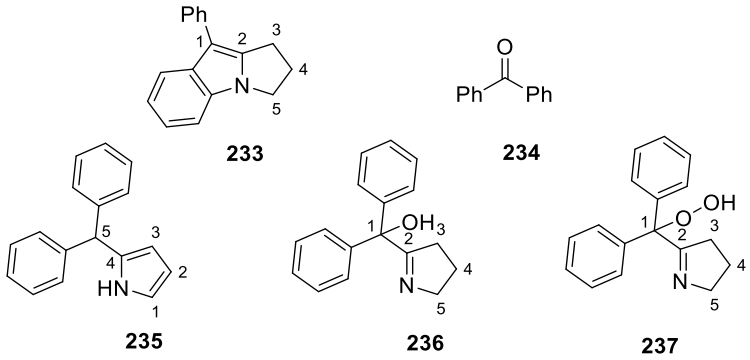
(5-Azido-2-bromopent-1-ene-1,1-diyl)dibenzene (231)



To a 14 mL sample vial was added (2,5-dibromopent-1-ene-1,1-diyl)dibenzene (736 mg, 1.93 mmol), NaN_3 (151 mg, 2.32 mmol), DMF (5 mL) and the reaction stirred at room temperature for 18 h under argon. The reaction was diluted with brine (50 mL) and extracted successively with ether (20 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$), then concentrated onto silica and purified by eluting with petrol, yielding a pale yellow oil (629 mg, 95%). R_f 0.16 (petrol); ν_{max} 2095s; δ_H (400 MHz, $CDCl_3$) 1.96 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.65 (2 H, app. t, *J* = 7.5 Hz, H3), 3.27 (2 H, t, *J* = 6.5 Hz, H5), 7.17–7.35 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 28.2

(C4), 35.8 (C3), 50.3 (C5), 126.4 (C2), 127.3, 127.5, 128.1, 128.5, 128.6, 129.0, 140.7 (C1), 142.9, 143.1; HRMS (FI$^+$) found 313.0471, $C_{17}H_{16}{}^{79}BrN$ (M^+-N_2) requires 313.0461.

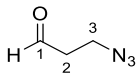
9-Phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]indole (233),[471] benzophenone (234),[472] 2-benzhydryl-1*H*-pyrrole (235),[473] (3,4-dihydro-2*H*-pyrrol-5-yl)diphenylmethanol (236), and 5-(hydroperoxydiphenylmethyl)-3,4-dihydro-2*H*-pyrrole (237)



Typical experimental: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (5-azido-2-bromopent-1-ene-1,1-diyl)dibenzene (120 mg, 0.350 mmol) in freshly distilled toluene (CaH_2) (7 mL), plus solid K_2CO_3 (484 mg, 3.50 mmol). The reaction was bubbled through with argon, thread sealed with a PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 8 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the dark brown reaction solution was filtered to remove K_2CO_3 and concentrated onto silica. Eluting with a gradient of 1% ether to 50% ether in petrol yielded typically 5 products; **233** orange oil (<4 mg, <5%), **234** orange oil (4 mg, 6%), **235** orange oil (4 mg, 5%), **236** off-white solid (33 mg, 38%), and **237** brown oil (variable 0-10%). **233**: Consistent with literature data.[471] R_f 0.5 (1:8 ether/ petrol); δ_H (200 MHz, $CDCl_3$) 2.67 (2 H, q, *J* = 7.0 Hz, H4), 3.21 (2 H, t, *J* = 7.0 Hz, H3), 4.15

(2 H, t, *J* = 7.0 Hz, H5), 7.08–7.69 (9 H, m, Ar-H). **234**: Consistent with literature data.[472] R_f 0.4 (1:8 ether/ petrol); δ_H (200 MHz, $CDCl_3$) 7.45–7.65 (6 H, m, Ar-H), 7.80–7.84 (4 H, m, Ar-H). **235**: Consistent with literature data.[473] R_f 0.29 (1:8 ether/ petrol); ν_{max} 3429m, 1493m, 1451m, 1029m, 722s, 1643m; δ_H (500 MHz, $CDCl_3$) 5.48 (1 H, s, H5), 5.81–5.83 (1 H, m, H3), 6.16–6.17 (1 H, m, H2), 7.71–6.73 (1 H, m, H1), 7.19–7.21 (4 H, m, Ar-H), 7.22–7.26 (2 H, m, Ar-H), 7.29–7.33 (4 H, m, Ar-H); δ_C (150 MHz, $CDCl_3$) 49.5 (C5), 106.9 (C3), 107.2 (C2), 116.1 (C1), 125.6, 127.5, 127.8, 132.6 (C4), 142.0; m/z (ESI) 234.1 (MH^+). **236**: M.p 60 °C; R_f 0.36 (1:1 ether/ petrol); ν_{max} 3400br, 1643m; δ_H (400 MHz, $CDCl_3$) 2.07 (2 H, app. pent, *J* = 7.5 Hz, H4), 2.52 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3), 3.95 (2 H, tt, *J* = 7.5 and 2.0 Hz, H5), 5.73 (1 H, br, OH), 7.29-7.37 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 24.3 (C4), 35.0 (C3), 59.3 (C5), 80.0 (C1), 127.6, 127.6, 128.1, 143.6, 181.5 (C2); HRMS (FI^+) found 274.1200, $C_{17}H_{17}NNaO$ (MNa^+) requires 274.1202. **237**: R_f 0.36 (1:1 ether/ petrol); δ_H (500 MHz, $CDCl_3$) 1.93 (2 H, app. pent, *J* = 7.5 Hz, H4), 2.41 (2 H, tt, *J* = 8.0 and 2.0 Hz, H3), 4.04 (2 H, tt, *J* = 7.0 and 2.0 Hz, H5), 7.31-7.38 (10 H, m, Ar-H); δ_C (150 MHz, $CDCl_3$) 22.1 (C4), 38.2 (C3), 60.3 (C5), 90.6 (C1), 127.7, 128.1, 128.4, 139.9, 182.0 (C2); HRMS (FI^+) found 290.1144, $C_{17}H_{17}NNaO_2$ (MNa^+) requires 290.1151.

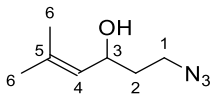
3-Azidopropanal (238)[474]



A literature procedure[475] was used. To an oven-dried 100 mL round-bottom flask was added glacial acetic acid (15 mL, 262 mmol), acrolein (2 mL, 30 mmol) and the reaction stirred at 0 °C. To the frozen solution was added NaN_3 (2.91 g, 45.0 mmol) in water (25 mL) dropwise via syringe pump over 1 h. The reaction was warmed to room temperature then extracted successively with ether (3 x 50 mL). The combined aqueous fractions were washed with saturated aqueous Na_2CO_3 (3 x 20 mL), brine (20 mL), then

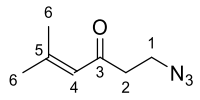
dried ($MgSO_4$) and concentrated to yield a pale yellow solution (4.6 g, 46% w/w, 71%) that was sufficiently pure to be used in the next reaction and with data consistent with literature data.[474] R_f 0.50 (1:1 petrol/ether); δ_H (400 MHz, $CDCl_3$) 2.72 (2 H, t, *J* = 6.5 Hz, H2), 3.60 (2 H, t, *J* = 6.5 Hz, H3), 9.78 (1 H, s, H1); δ_C (100 MHz, $CDCl_3$) 43.7 (C2), 44.4 (C3), 199.2 (C1).

1-Azido-5-methylhex-4-en-3-ol (239)



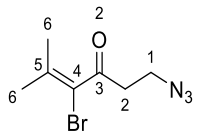
To an oven-dried 250 mL round-bottom flask was added THF (20 mL) and crude 3-azidopropanal (4.5 g, 46% w/w, 21 mmol) and the reaction stirred at –78 °C under argon. 2-methyl-1-propenyl magnesium bromide (46 mL, 0.5 M in THF, 23 mmol) dropwise over 1 h. After 1 h the acetone bath was removed and the reaction stirred at room temperature for 2 h. The reaction was quenched at 0 °C with saturated aqueous Rochelle's salt (100 mL) and the reaction stirred overnight. The layers were separated and the aqueous layer extracted successively with ether (3 x 30 mL). The combined organics were washed successively with 0.1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), then brine (10 mL) and dried ($MgSO_4$). The dry organic solution as concentrated onto silica and purified by eluting with 5% ether in petrol, yielding a colourless oil (1.94 g, 60%). R_f 0.63 (1:1 petrol/ether); ν_{max} 3371br, 2096s; δ_H (400 MHz, $CDCl_3$) 1.66–1.88 (2 H, 3, H2), 1.71 (3 H, d, *J* = 1.5 Hz, H6), 1.75 (3 H, d, *J* = 1.5 Hz, H6), 3.33 (1 H, ddd, *J* = 12.5, 6.5, and 6.5 Hz, H1), 3.45 (1 H, t, *J* = 12.0, 7.0, and 7.0 Hz, H1), 4.51 (1 H, ddd, *J* = 8.0, 8.0 and 5.5 Hz, H3), 5.18 (1 H, d pent, *J* = 9.0 and 1.5 Hz, H4); δ_C (100 MHz, $CDCl_3$) 18.2 (C6), 25.8 (C6), 36.2 (C2), 48.2 (C1), 66.1 (C3), 127.0 (C4), 136.2 (C5); HRMS (FI^+) found 155.1057, $C_7H_{13}N_3O$ (M^+) requires 155.1059.

1-Azido-5-methylhex-4-en-3-one (240)



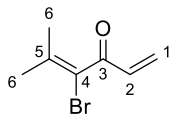
A modified literature procedure[460] was used. To a 100 mL oven-dried RBF was added oxalyl chloride (0.25 mL, 2.9 mmol) in dry DCM (10 mL) and the flask cooled to –78 °C under argon. DMSO (0.41 mL, 5.8 mmol) in dry DCM (1 mL) were added dropwise via syringe pump over 40 min being sure to maintain the temperature at –78 °C. After stirring for 1 h, 1-azido-5-methylhex-4-en-3-ol (400 mg, 2.57 mmol) in DCM (4 mL) was added dropwise over 30 min at –78 °C, and the syringe washed in with DCM (4 mL). After 30 min, triethylamine (1.8 mL, 13 mmol) was added dropwise over 15 min, then the reaction left to warm to room temperature overnight. The cream solution was quenched with water (10 mL), extracted successively with DCM (3 x 20 mL), and the combined organic fractions washed successively with 0.1 M HCl solution (10 mL) and brine (10 mL). The combined aqueous fractions were back extracted with DCM (20 mL), and the combined organics then dried ($MgSO_4$) and concentrated to yield a brown oil that was purified over silica eluting with 5% ether in petrol, yielding a pale yellow oil (324 mg, 82%). R_f 0.71 (1:1 petrol/ether); ν_{max} 2096s, 1687s, 1619s; δ_H (400 MHz, $CDCl_3$) 1.91 (3 H, s, H6), 2.17 (3 H, s, H6), 2.68 (2 H, t, *J* = 6.5 Hz, H2), 3.56 (2 H, t, *J* = 6.5 Hz, H1), 6.07 (1 H, app.t, *J* = 1.0 Hz, H4); δ_C (100 MHz, $CDCl_3$) 20.97 (C6), 27.7 (C6), 42.6 (C2), 46.1 (C1), 123.2 (C4), 157.1 (C5), 197.2 (C3); HRMS (FI^+) found 153.0899, $C_7H_{11}N_3O$ (M^+) requires 153.0902.

1-Azido-4-bromo-5-methylhex-4-en-3-one (241)



To an oven-dried 50 mL round-bottom flask was added 1-azido-5-methylhex-4-en-3-one (225 mg, 1.47 mmol), DCM (5 mL) and the solution cooled to 0 °C under argon. Bromine (0.83 mL, 1.6 mmol) in DCM (0.5 mL) was added dropwise to the reaction via syringe over 10 min, causing an orange colouration that subsided until persisting. The reaction was warmed to room temperature, stirred for 10 min, then cooled to 0 °C. Triethylamine (0.45 mL, 3.2 mmol) was added causing white fumes, and stirred for 20 min. The reaction was concentrated under vacuum and the solid residue diluted with 0.1 M HCl (10 mL), then extracted with petrol (3 x 25 mL), then dried (Na_2SO_4) and concentrated to yield a yellow oil. The oil was purified over silica eluting with 1% ether in petrol, yielding a pale yellow oil (145 mg, 42%). R_f 0.78 (2:1, petrol/ ether); ν_{max} 2101s, 1684m; δ_H (400 MHz, $CDCl_3$) 2.05 (3 H, s, H6), 2.10 (3 H, s, H6), 3.09 (2 H, t, *J* = 6.5 Hz, H2), 3.59 (2 H, t, *J* = 6.5 Hz, H1); δ_C (100 MHz, $CDCl_3$) 20.2 (C6), 26.1 (C6), 39.8 (C2), 45.4 (C1), 115.8 (C4), 146.1 (C5), 194.8 (C3); HRMS (FI^+) found 231.006, $C_7H_{10}{}^{79}BrN_3O$ (M^+) requires 231.007.

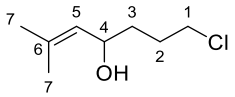
4-Bromo-5-methylhexa-1,4-dien-3-one (242)



To a 7 mL sample vial was added 1-azido-4-bromo-5-methylhex-4-en-3-one (30 mg, 0.13 mmol), K_2CO_3 (178 mg, 1.29 mmol), and toluene (1 mL) and the reaction stirred at room temperature under argon for 3 d. The reaction was filtered through celite and concentrated to yield a crude oil (17 mg) of which the sole product was 4-bromo-5-

methylhexa-1,4-dien-3-one by ^{1}H-NMR. The oil was purified over silica eluting with petrol to yield a colourless oil (2 mg, 8%). R_f 0.75 (1:1, petrol/ ether); ν_{max} 1735s, 1684m; δ_H (500 MHz, $CDCl_3$) 1.95 (3 H, s, H6), 2.03 (3 H, s, H6), 5.93 (1 H, dd, *J* = 10.5 and 1.5 Hz, H1), 6.35 (1 H, dd, *J* = 17.5 and 1.5 Hz, H1), 6.71 (1 H, dd, *J* = 17.5 and 10.5 Hz, H2); δ_C (150 MHz, $CDCl_3$) 22.4 (C6), 25.3 (C6), 114.5 (C4),130.6 (C1), 134.4 (C2), 142.4 (C5), 189.8 (C3); HRMS (FI^+) found 187.9836, $C_7H_9{}^{79}BrO$ (M^+) requires 187.9837.

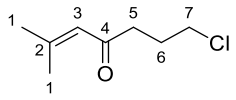
7-Chloro-2-methylhept-2-en-4-ol (244)



A modified literature procedure[476] was used. To a 100 mL oven-dried 2-neck round-bottom flask was added magnesium turnings (4.08 mg, 17.0 mmol), freshly distilled THF (34 mL), and 1-bromo-2-methylprop-1-ene (1.9 mL, 19 mmol). A drop of iodomethane was added to initiate the reaction, and the solution refluxed until the magnesium turnings had been consumed (~4 h). The cloudy grey solution was cannulated immediately into the next reaction. To a 100 mL oven-dried round-bottom flask was added freshly prepared (2-methylprop-1-enyl)magnesium bromide (34 mL, 0.5 M in THF, 17 mmol) and the solution stirred at 0 °C under argon. Freshly distilled 4-chlorobutanal (840 mg, 7.92 mmol) in THF (2 mL) was added dropwise over 5 min, and washed in with further THF (2 mL). After 1 h, the reaction was warmed to ambient temperature, then after a further hour quenched with saturated aqueous NH_4Cl (60 mL). The aqueous layer was extracted successively with ether (3 x 20 mL), washed with brine (10 mL), dried ($MgSO_4$) and concentrated to yield a yellow oil that was sufficiently pure to be used in the next reaction (1.1 g, 76%). An analytical sample was obtained by purification over silica eluting with 10% ether in petrol. R_f 0.17 (2:1 petrol/ ether); ν_{max} 3355br; δ_H (400 MHz, $CDCl_3$) 1.53–1.90 (4 H, m, H2 and H3), 1.69 (3 H, d, *J* = 1.5 Hz, H7),

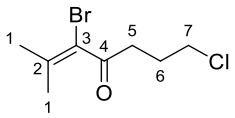
1.73 (3 H, d, *J* = 1.5 Hz, H7), 3.57 (2 H, td, *J* = 6.5 Hz, 6.5 and 1.5 Hz, H1), 4.38 (1 H, ddd, *J* = 9.0 Hz, 6.5 and 6.5 Hz, H4), 5.18 (1 H, d sept, *J* = 9.0 and 1.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 18.2 (C7), 25.8 (C7), 28.7 (C2), 34.8 (C3), 45.1 (C1), 68.0 (C4), 127.7 (C5), 135.7 (C6); HRMS (FI^+) found 162.0809, $C_8H_{15}{}^{35}ClO$ (M^+) requires 162.0811.

7-Chloro-2-methylhept-2-en-4-one (245)



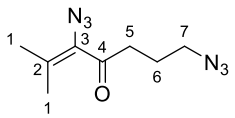
A modified literature procedure[460] was used. To a 100 mL oven-dried round-bottom flask was added oxalyl chloride (0.85 mL, 10.1 mmol) in dry DCM (20 mL) and the flask cooled to –78 °C under argon. DMSO (1.5 mL, 21 mmol) in dry DCM (2 mL) were added dropwise via syringe pump over 35 min being sure to maintain the temperature at –78 °C. 7-Chloro-2-methylhept-2-en-4-ol (1.1 g, 6.8 mmol) in DCM (1.5 mL) was added dropwise over 1 h, and after 15 min, triethylamine (3.8 mL, 27 mmol) was added dropwise over 20 min. Then the reaction left to warm to room temperature overnight, and the cream solution quenched with water (50 mL), extracted successively with DCM (3 x 20 mL), and the combined organic layers washed successively with 0.1 M HCl solution (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), then dried ($MgSO_4$) and concentrated to yield an orange oil. The product was purified over silica eluting with 5% ether in petrol, yielding an orange oil (423 mg, 39%). R_f 0.54 (2:1 petrol/ ether); ν_{max} 1687s, 1622s; δ_H (400 MHz, $CDCl_3$) 1.89 (3 H, s, H1), 2.06 (2 H, app. pent, *J* = 6.5 Hz, H6), 2.15 (3 H, s, H1), 2.61 (2 H, t, *J* = 7.0 Hz, H5), 3.59 (2 H, dt, *J* = 6.5 and 1.0 Hz, H7), 6.08 (1 H, sextet, *J* = 1.5 Hz, H3); δ_C (100 MHz, $CDCl_3$) 20.8 (C1), 25.7 (C6), 27.7 (C1), 40.7 (C5), 44.7 (C7), 123.6 (C3), 155.8 (C2), 199.4 (C4); HRMS (FI^+) found 160.0652, $C_8H_{13}{}^{35}ClO$ (M^+) requires 160.0655.

7-Chloro-3-bromo-2-methylhept-2-en-4-one (246)



To a 25 mL oven-dried round-bottom was added 7-chloro-2-methylhept-2-en-4-one (200 mg, 1.24 mmol), DCM (4 mL) and the solution stirred at 0 °C under argon. Bromine (64 μL, 1.1 mmol) in DCM (0.9 mL) was added dropwise to the reaction, causing the colourless solution to turn brown, and after 10 min quenched with saturated aqueous $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted successively with DCM (3 x 10 mL), dried ($MgSO_4$), and concentrated into a 7 mL sample vial. DCM (2 mL) and triethylamine (0.26 mL, 1.9 mmol) were added, and the reaction stirred at room temperature under argon for 6 h. The reaction was concentrated onto silica, and the product purified by eluting with 1% ether in petrol, yielding a yellow oil (164 mg, 55%). R_f 0.62 (2:1 petrol/ ether); ν_{max} 1684s, 1589m; δ_H (400 MHz, $CDCl_3$) 2.03 (3 H, s, H1), 2.05 (3 H, s, H1), 2.09 (2 H, app. pent, *J* = 6.5 Hz, H6), 3.00 (2 H, t, *J* = 7.0 Hz, H5), 3.61 (2 H, t, *J* = 6.5 Hz, H7); δ_C (100 MHz, $CDCl_3$) 23.0 (C1), 26.8 (C1), 27.0 (C6), 38.5 (C5), 44.3 (C7), 117.1 (C3), 145.2 (C2), 198.1 (C4); HRMS (FI^+) found 237.9759, $C_8H_{12}{}^{79}Br^{35}ClO$ (M^+) requires 237.9760.

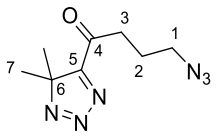
3,7-Diazido-2-methylhept-2-en-4-one (247)



To a 7 mL sample vial was added 7-chloro-3-bromo-2-methylhept-2-en-4-one (90 mg, 0.37 mmol), NaN_3 (100 mg, 1.5 mmol), and DMF (0.4 mL) and the reaction stirred under argon at 40 °C for 20.5 h. The reaction was diluted with ether (60 mL), washed successively with water (3 x 1 mL), dried ($MgSO_4$) and concentrated to yield a crude oil. The product was purified over silica eluting with 1% ether in petrol, yielding

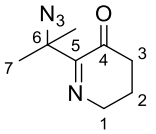
recovered starting material (11 mg, 12% recovery), and the title product as a yellow oil (13 mg, 19% B.R.S.M). R_f 0.41 (2:1 petrol/ ether); ν_{max} 2105s, 1686m; δ_H (500 MHz, $CDCl_3$) 1.95 (2 H, app. pent, *J* = 7.0 Hz, H6), 1.96 (3 H, s, H1), 2.08 (3 H, s, H1), 2.76 (2 H, t, *J* = 7.0 Hz, H5), 3.37 (2 H, t, *J* = 6.5 Hz, H7); δ_C (150 MHz, $CDCl_3$) 21.5 (C6), 22.0 (C1), 23.3 (C1), 38.6 (C5), 50.7 (C7), 132.0 (C3), 139.3 (C2), 197.0 (C4); HRMS (FI^+) found 231.0966, $C_8H_{12}N_6NaO$ (MNa^+) requires 231.0965.

4-Azido-1-(4,4-dimethyl-4*H*-1,2,3-triazol-5-yl)butan-1-one (248)



To a standard NMR tube was added 3,7-diazido-2-methylhept-2-en-4-one (13 mg, 53 μmol), and deuterated toluene (1 mL). The tube was sealed with an NMR cap and stirred at 50 °C for 29 h. The reaction was shown to be a 1:2:2 mixture of **247**/**248**/**249** by ^{1}H-NMR analysis. The NMR data for the title compound is as follows. δ_H (700 MHz, $CDCl_3$) 1.39 (6 H, s, H7), 2.03 (2 H, app pent, *J* = 7.0 Hz, H2), 3.04 (2 H, t, *J* = 7.0 Hz, H3), 3.42 (2 H, t, *J* = 7.0 Hz, H1); δ_C (175 MHz, $CDCl_3$) 22.6 (C2), 24.7 (C7), 37.2 (C3), 40.4 (C6), 50.4 (C1), 179.9 (C5), 192.9(C4).

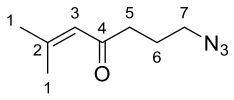
2-(2-Azidopropan-2-yl)-5,6-dihydropyridin-3(4*H*)-one (249)



To a standard NMR tube was added 3,7-diazido-2-methylhept-2-en-4-one (13 mg, 53 μmol), and deuterated toluene (1 mL). The tube was sealed with an NMR cap and stirred at 90 °C for 7 h. The reaction was concentrated onto silica, then purified over silica by eluting with a gradient of pure petrol to 25% ether in petrol, yielding the product as a yellow oil (6 mg, 63%). R_f 0.66 (ether); ν_{max} 2099m, 1622m; δ_H (700 MHz,

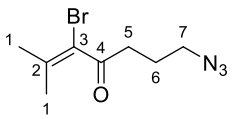
$CDCl_3$) 1.55 (6 H, s, H7), 2.11 (2 H, app pent, *J* = 6.0 Hz, H2), 2.54 (2 H, t, *J* = 6.0 Hz, H3), 3.98 (2 H, t, *J* = 5.5 Hz, H1); δ_C (175 MHz, $CDCl_3$) 23.5 (C2), 25.1 (C7), 38.0 (C3), 49.9 (C1), 64.3 (C6), 165.5 (C5), 190.75(C4); HRMS (FI^+) found 203.0898, $C_8H_{12}N_4NaO$ (MNa^+) requires 203.0903.

7-Azido-2-methylhept-2-en-4-one (250)



To a 7 mL sample vial was added 7-chloro-2-methylhept-2-en-4-one (526 mg, 3.27 mmol), NaN_3 (400 mg, 6.15 mmol), and DMF (1 mL) and the reaction stirred under argon at 50 °C for 44 h. The reaction was diluted with ether (100 mL), washed successively with water (3 x 2 mL), dried ($MgSO_4$) and concentrated to yield a crude oil. The product was purified over silica eluting with 5% ether in petrol, yielding a pale yellow oil (356 mg, 65%). R_f 0.55 (2:1 petrol/ ether); ν_{max} 2093s, 1686s, 1619s; δ_H (400 MHz, $CDCl_3$) 1.87 (2 H, app. pent, *J* = 7.0 Hz, H6), 1.90 (3 H, s, H1), 2.16 (3 H, s, H1), 2.52 (2 H, t, *J* = 7.0 Hz, H5), 3.33 (2 H, t, *J* = 6.5 Hz, H7), 6.07 (1 H, sextet, *J* = 1.0 Hz, H3); δ_C (100 MHz, $CDCl_3$) 20.8 (C1), 23.2 (C6), 27.7 (C1), 40.6 (C5), 50.9 (C7), 123.5 (C3), 155.9 (C2), 199.4 (C4); HRMS (FI^+) found 190.0947, $C_8H_{13}{}^{35}ClNaO$ (MNa^+) requires 190.0951.

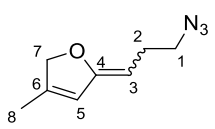
7-Azido-3-bromo-2-methylhept-2-en-4-one (251)

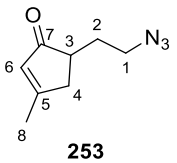


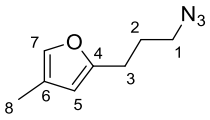
To a 50 mL oven-dried round-bottom was added 7-azido-2-methylhept-2-en-4-one (359 mg, 2.14 mmol), DCM (20 mL) and the solution stirred at 0 °C under argon. Bromine (0.11 mL, 2.1 mmol) in DCM (0.8 mL) was added dropwise to the reaction, causing the colourless solution to turn brown, and after 10 min quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The aqueous layer was extracted successively with DCM (3 x

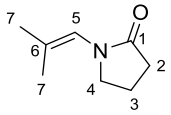
20 mL), dried ($MgSO_4$), and concentrated into a 14 mL sample vial. DCM (10 mL) and triethylamine (0.6 mL, 4.3 mmol) were added, and the reaction stirred at room temperature under argon for 19 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), extracted successively with DCM (3 x 20 mL), dried (10 mL) and concentrated onto silica. The product was purified by eluting with 1% ether in petrol, yielding a yellow oil (349 mg, 66%). R_f 0.33 (4:1 petrol/ ether); ν_{max} 2097s, 1684s; δ_H (500 MHz, $CDCl_3$) 1.92 (2 H, app. pent, *J* = 7.0 Hz, H6), 2.03 (3 H, s, H1), 2.06 (3 H, s, H1), 2.92 (2 H, t, *J* = 7.0 Hz, H5), 3.36 (2 H, t, *J* = 6.5 Hz, H7); δ_C (150 MHz, $CDCl_3$) 23.0 (C1), 23.6 (C6), 26.8 (C1), 38.4 (C5), 50.7 (C7), 117.1 (C3), 145.3 (C2), 198.0 (C4); HRMS (FI^+) found 268.0063, $C_8H_{12}{}^{79}BrN_3NaO$ (MNa^+) requires 268.0056.

2-(3-Azidopropylidene)-4-methyl-2,5-dihydrofuran (252), 5-(2-azidoethyl)-3-methylcyclopent-2-en-1-one (253), 2-(3-azidopropyl)-4-methylfuran (254), and 1-(2-methylprop-1-en-1-yl)pyrrolidin-2-one (255)[477,478]





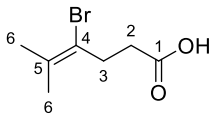




To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 7-azido-3-bromo-2-methylhept-2-en-4-one (70 mg, 0.28 mmol) in toluene (5.7 mL), with solid K2CO3 (342 mg, 2.48 mmol). The reaction was bubbled through with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. After removing from heat and cooling, the reaction was filtered to remove K_2CO_3 was concentrated to a crude brown oil. ^{1}H-NMR of this oil revealed a 3.5:2.5:2.0:1.0 ratio of **252**:**253**:**254**:**255**. The compounds were purified over silica

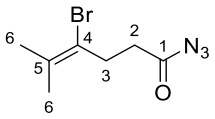
eluting a gradient of petrol to pure ether, yielding **254**, a colourless oil (10 mg, 21%), **253**, an orange oil (10 mg, 21%), and **255**, a yellow oil (4 mg, 10%). **252** was not observed after chromatography and was characterised from the crude mixture. **252**: δ_H (400 MHz, $CDCl_3$) 1.86 (3 H, d, *J* = 1.0 Hz, H8), 2.41 (2 H, ap. q, *J* = 7.0 Hz, H2), 3.28 (2 H, t, J = 7.0 Hz, H1), 4.21 (1H, t, *J* = 7.5 Hz, H3), 4.77–4.79 (2 H, m, H7), 5.77 (app. sext, *J* = 1.5 Hz, H5); δ_C (100 MHz, $CDCl_3$) 12.6 (C8), 30.6 (C2), 51.5 (C1), 79.1 (C7), 89.5 (C7), 89.5 (C3), 120.6 (C5), 142.5 (C6), 162.0 (C4). **253**: R_f 0.50 (1:1 petrol/ ether); ν_{max} 2098s, 1695s, 1623m; δ_H (500 MHz, $CDCl_3$) 1.64 (1 H, dddd, *J* = 14.0 Hz, 9.0 Hz, 7.0 Hz, and 7.0 Hz, H2), 2.09 (1 H, dddd, *J* = 14.0 Hz, 7.0 Hz, 7.0 Hz, and 5.5 Hz, H2), 2.15 (3 H, s, H8), 2.31 (1 H, d nonet, *J* = 18.5 and 1.0 Hz, H4), 2.47–2.52 (1 H, 3, H3), 2.83 (1 H, q sextet, *J* = 18.5 Hz, 7.0 Hz, and 1.0 Hz, H4), 3.45 (2 H, td, *J* = 7.0 and 2.5 Hz, H1), 5.94 (1 H, s, H6); δ_C (150 MHz, $CDCl_3$) 18.4 (C8), 29.3 (C2), 38.8 (C4), 43.0 (C3), 48.8 (C1), 128.8 (C6), 176.2 (C5), 209.6 (C7); HRMS (FI^+) found 188.0800, $C_8H_{11}N_3NaO$ (MNa^+) requires 188.0794. **254**: R_f 0.74 (1:1 petrol/ ether); ν_{max} 2097s; δ_H (400 MHz, C_6D_6) 1.47 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.79 (3 H, d, *J* = 1.0 Hz, H8), 2.33 (2 H, t, *J* = 7.5 Hz, H3), 2.64 (2 H, t, *J* = 7.0 Hz, H1), 5.56 (1 H, s, H5), 6.91 (1 H, s, H7); δ_C (100 MHz, C_6D_6) 9.4 (C8), 24.9 (C3), 27.1 (C2), 50.0 (C1), 108.2 (C5), 120.2 (C6), 137.7 (C7), 154.5 (C4); HRMS (FI^+) found 165.0907, $C_8H_{11}N_3O$ (M^+) requires 165.0902. **255**: Consistent with literature data.[477,478] R_f 0.16 (ether); ν_{max} 1693s; δ_H (700 MHz, $CDCl_3$) 1.69 (3 H, s, H7), 1.76 (3 H, s, H7), 2.08 (2 H, app. pent, *J* = 7.5 Hz, H3), 2.43 (2 H, t, *J* = 8.0 Hz, H2), 3.58 (2 H, t, *J* = 7.0 Hz, H4), 5.91 (1 H, s, H5); δ_C (175 MHz, $CDCl_3$) 17.2 (C7), 17.7 (C3), 22.1 (C7), 29.7 (C2), 48.2 (C4), 118.3 (C5), 127.7 (C6), 173.6 (C1); m/z (ESI) 140.1 (MH^+), 162.1 (MNa^+).

4-Bromo-5-methylhex-4-enoic acid (256)



To an oven-dried 50 mL round-bottom flask was added ethyl 5-methylhex-4-enoate (320 mg, 1.55 mmol), DCM (10 mL) and the reaction stirred to 0 °C under argon. Bromine (80 µL, 1.5 mmol) in DCM (1 mL) was added dropwise via syringe causing an orange colouration that subsided until persisting. After 15 min the reaction was warmed to room temperature and stirred for 15 min, then concentrated to yield an orange oil. KOH (420 mg, 7.50 mmol) in MeOH (20 mL) was added to the oil and stirred for 18 h, causing the clear solution to turn cloudy. The reaction was heated to 40 °C for 8 h then stirred at room temperature for 14 h. The reaction was concentrated under vacuum, then diluted with water (50 mL) and neutralised with 0.1 M HCl. The aqueous solution was extracted with ether (3 x 20 mL), dried ($MgSO_4$), and concentrated to yield a yellow oil. The product was purified over silica eluting with 10% ether in petrol to yield a colourless oil (111 mg, 34%). R_f 0.75 (ether); ν_{max} 1709s, 1684m; δ_H (400 MHz, $CDCl_3$) 1.81 (3 H, s, H6), 187 (3 H, s, H6), 2.63 (2 H, t, *J* = 7.5 Hz, H3), 2.83 (2 H, t, *J* = 7.5 Hz, H2), 11.36 (1 H, br, OH); δ_C (100 MHz, $CDCl_3$) 20.4 (C6), 25.4 (C6), 32.5 (C2), 32.9 (C3), 119.0 (C4), 132.1 (C5), 178.9 (C1); HRMS (FI^+) found 204.9872, $C_7H_{10}{}^{79}BrO_2$ (M^+) requires 204.9870.

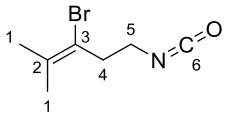
4-Bromo-5-methylhex-4-enoyl azide (257)



To a 7 mL sample vial was added 4-bromo-5-methylhex-4-enoic acid (65 mg, 0.31 mmol), toluene (2 mL) and the reaction stirred at room temperature under argon. DPPA (0.75 mL, 0.35 mmol) was added via syringe followed by triethylamine (0.50 mL, 0.36

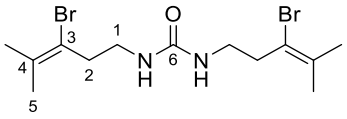
mmol) and the reaction stirred for 1 h. The reaction was concentrated onto silica and purified by eluting with 2% ether in petrol, yielding a colourless oil (44 mg, 60%) that needed to be stored at –20 °C to slow down the Curtius rearrangement. R_f 0.79 (1:1 petrol/ ether); ν_{max} 2136s, 1717s; δ_H (400 MHz, C_6D_6) 1.40 (3 H, s, H6), 1.66 (3 H, s, H6), 2.27 (2 H, t, *J* = 7.5 Hz, H3), 2.54 (2 H, t, *J* = 7.5 Hz, H2); δ_C (100 MHz, C_6D_6) 19.7 (C6), 24.9 (C6), 32.2 (C2), 35.2 (C3), 119.0 (C4), 131.9 (C5), 178.2 (C1); HRMS (FI^+) found 231.0004, $C_7H_{10}{}^{79}BrN_3O$ (M^+) requires 231.0007.

3-Bromo-5-isocyanato-2-methylpent-2-ene (258)



To a base-washed and oven-dried 7 mL sample vial was added 4-bromo-5-methylhex-4-enoyl azide (33 mg, 0.14 mmol), in benzene (3 mL). The reaction was stirred at 60 °C under argon for 16 h, then concentrated to yield a yellow oil (25 mg, 75%). R_f 0.81 (7:1 petrol/ ether); ν_{max} 2269s; δ_H (400 MHz, C_6D_6) 1.36 (3 H, s, H1), 1.69 (3 H, s, H1), 2.13 (2 H, t, *J* = 6.0 Hz, H4), 2.86 (2 H, t, *J* = 6.0 Hz, H5); δ_C (100 MHz, C_6D_6) 20.3 (C1), 25.4 (C1), 38.8 (C4), 41.4 (C5), 117.3 (C3), 135.0 (C2), 181.3 (C6); HRMS (FI^+) found 202.9946, $C_7H_{10}{}^{79}BrNO$ (M^+) requires 202.9946.

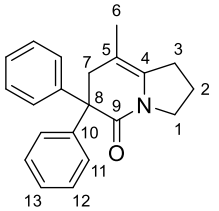
1,3-Bis(3-bromo-4-methylpent-3-enyl)urea (259)



To a 7 mL sample vial was added 4-bromo-5-methylhex-4-enoyl azide (30 mg, 0.13 mmol), K_2CO_3 (178 mg, 1.29 mmol) in benzene (3 mL). The reaction was stirred at 60 °C under argon for 17 h, then filtered through celite and concentrated to yield a white solid (20 mg, 40%). R_f 0.10 (6:1 petrol/ ether); ν_{max} 3318m, 1619s, 1579s; δ_H (400 MHz,

$CDCl_3$) 1.79 (6 H, s, H1), 1.88 (6 H, s, H1), 2.72 (4 H, t, *J* = 6.5 Hz, H2), 3.36 (4 H, q, *J* = 6.5 Hz, H1), 4.58 (2 H, *J* = 5.5 Hz, NH); δ_C (100 MHz, $CDCl_3$) 19.5 (C5), 24.4 (C5), 36.9 (C2), 37.9 (C1), 117.2 (C3), 132.1 (C4), 157.0 (C6); HRMS (FI^+) found 382.0099, $C_{13}H_{22}{}^{79}Br_2N_2O$ (M^+) requires 382.0099.

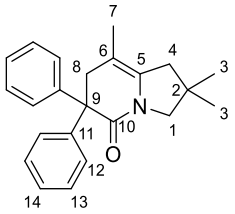
8-Methyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (265)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 6-azido-3-bromo-2-methylhex-2-ene (100 mg, 0.458 mmol) in toluene (9 mL), K_2CO_3 (633 mg, 4.58 mmol) and NaOH (36 mg, 0.92 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 44 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the PTFE screw cap was replaced with a septum and the brown slurry stirred at room temperature under argon. Freshly prepared diphenylketene (266 mg, 1.37 mmol) in toluene (2 mL) was added dropwise over 50 min, causing the yellow solution to turn a bright yellow. After stirring for 15 h, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with a gradient of 0.5% triethylamine in petrol to 0.5% triethylamine and 25% ether in petrol. The product was isolated as a white crystalline solid (112 mg, 80%). M.p 156–160 °C; R_f 0.28 (petrol/ether, 1:1); ν_{max} 2964w, 1651s (amide), 1395m, 1260m, 1021m, 800m, 728s; δ_H (400 MHz, C_6D_6) 1.11 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.49 (3 H, app. pent, *J* = 1.0 Hz, H6),

1.80 (2 H, ddd, *J* = 7.5 Hz, 3.5 and 2.0 Hz, H3), 2.67 (2 H, oct, *J* = 1.0 Hz, H7), 3.52 (2 H, app. t, *J* = 7.0 Hz, H1), 7.05 (2 H, tt, *J* = 7.5 and 1.0 Hz, H13), 7.13–7.18 (4 H, m, H13), 7.38–7.41 (4 H, m, H11); δ_C (100 MHz, $CDCl_3$) 17.2 (C6), 22.1 (C2), 27.1 (C3), 42.1 (C7), 46.3 (C1), 56.9 (C8), 104.7 (C5), 126.7 (C13), 127.9 (C11), 128.4 (C12), 133.2 (C4), 142.9 (C10), 169.6 (C9); HRMS (FI^+) found 326.1500, $C_{21}H_{21}NONa$ (MNa^+) requires 326.1515.

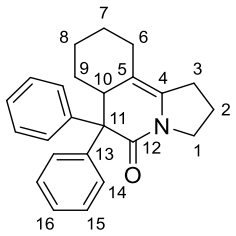
2,2,8-Trimethyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (266)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of 6-azido-3-bromo-2,5,5-trimethylhex-2-ene (50 mg, 0.20 mmol) in toluene (4 mL), K_2CO_3 (280 mg, 2.02 mmol) and NaOH (20 mg, 0.50 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 24 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the PTFE screw cap was replaced with a septum and the brown slurry stirred at 0 °C under argon. Freshly prepared diphenylketene (118 mg, 0.609 mmol) in toluene (2 mL) was added dropwise over 35 min, causing the yellow solution to turn a bright yellow. After stirring for 15 h, during which the ice bath thawed and was removed, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 0.5% triethylamine and 5–20% ether in petrol. The product was isolated as a yellow viscous oil (63 mg, 91%). R_f 0.60 (petrol/ether, 1:1); ν_{max} 2957w, 1658s (amide), 1397m, 1035w,

698s; δ_H (400 MHz, C_6D_6) 0.57 (3 H, s, H3), 1.52 (2 H, s, H7), 1.71 (2 H, s, H4), 2.70 (2 H, s, H8), 3.35 (2 H, s, H1), 7.06 (2 H, tt, *J* = 7.5 and 1.0 Hz, H14), 7.14–7.18 (4 H, m, H14), 7.40–7.42 (4 H, m, H14); δ_C (100 MHz, $CDCl_3$) 17.6 (C7), 26.3 (H3), 36.1 (C2), 41.7 (C4), 42.1 (C8), 56.6 (C9), 58.5 (C1), 105.7 (C6), 126.7 (C14), 127.9 (C12), 128.4 (C13), 133.4 (C5), 142.7 (C11), 169.9 (C10); HRMS (FI^+) found 354.1821, $C_{23}H_{25}NONa$ (MNa^+) requires 326.1828.

6,6-Diphenyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one (267)



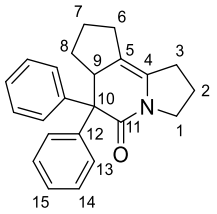
One pot: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (50 mg, 0.19 mmol) in toluene (3.8 mL), K_2CO_3 (267 mg, 1.93 mmol) and NaOH (40 mg, 0.96 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the PTFE screw cap was replaced with a septum and the yellow slurry stirred at 40 °C under argon. Freshly prepared diphenylketene (180 mg, 0.926 mmol) in toluene (2 mL) was added dropwise over 30 min, causing the yellow solution to turn a bright yellow. After stirring for 16 h, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 5–20% ether in petrol with 0.5% triethylamine. The product was isolated as a low density white

solid foam (54 mg, 80%). M.p 52 °C; R_f 0.28 (1:1 petrol/ ether); ν_{max} 1651s; δ_H (400 MHz, C_6D_6) 0.92–1.18 (6 H, m, H2, H9, H7 and H8), 1.51–1.54 (1 H, m, H8), 1.60–1.63 (1 H, m, H7), 1.87–2.00 (3 H, m, H3 and H6), 2.19–2.23 (1 H, m, H6), 2.68 (1 H, app. d, *J* = 11.5 Hz, H10), 3.34 (1 H, ddd, *J* = 11.5 Hz, 8.0 and 5.5 Hz, H1), 3.52 (1 H, ddd, *J* = 11.5, 7.5, and 7.0 Hz, H1), 7.05 (2 H, tq, J = 7.5 and 1.5 Hz, H16), 7.13–7.18 (4 H, m, H15), 7.46 (2 H, app. d, *J* = 7.5 Hz, H14), 7.75 (2 H, app. d, *J* = 7.5 Hz, H14); δ_C (100 MHz, C_6D_6) 21.1(C2), 26.7 (C3), 27.0 (C8), 28.8 (C7), 30.5 (C6), 31.4 (C9), 46.3 (C1), 49.3 (C10), 59.4 (C11), 112.2 (C5), 125.9 (C16), 127.0 (C4), 127.2 (C15), 129.2 (C14), 130.6 (C14), 143.4 (C13), 144.2 (C13), 167.7 (C12); HRMS (FI^+) found 366.1812, $C_{24}H_{25}NNaO$ (MNa^+) requires 366.1828.

Two pot: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (50 mg, 0.19 mmol) in toluene (3.8 mL), K_2CO_3 (267 mg, 1.93 mmol) and NaOH (40 mg, 0.96 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, reaction was filtered through a sintered funnel with toluene (10 mL) into an oven-dried 50 mL round-bottom flask and the yellow solution stirred at 40 °C under argon. Freshly prepared diphenylketene (180 mg, 0.926 mmol) in toluene (2 mL) was added dropwise over 30 min, causing the yellow solution to turn a bright yellow. After stirring for 15 h, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 5–20% ether in petrol with 0.5% triethylamine. The product was isolated as a low density white solid foam (51 mg, 77% over 2 steps). M.p 52 °C; R_f 0.28 (1:1 petrol/ ether); ν_{max} 1651s; δ_H (400 MHz, C_6D_6) 0.92–1.18 (6 H, m, H2, H9, H7 and H8), 1.51–1.54 (1 H, m, H8), 1.60–

1.63 (1 H, m, H7), 1.87–2.00 (3 H, m, H3 and H6), 2.19–2.23 (1 H, m, H6), 2.68 (1 H, app. d, *J* = 11.5 Hz, H10), 3.34 (1 H, ddd, *J* = 11.5 Hz, 8.0, and 5.5 Hz, H1), 3.52 (1 H, ddd, *J* = 11.5, 7.5, and 7.0 Hz, H1), 7.05 (2 H, tq, J = 7.5 and 1.5 Hz, H16), 7.13–7.18 (4 H, m, H15), 7.46 (2 H, app. d, *J* = 7.5 Hz, H14), 7.75 (2 H, app. d, *J* = 7.5 Hz, H14); δ_C (100 MHz, C_6D_6) 21.1(C2), 26.7 (C3), 27.0 (C8), 28.8 (C7), 30.5 (C6), 31.4 (C9), 46.3 (C1), 49.3 (C10), 59.4 (C11), 112.2 (C5), 125.9 (C16), 127.0 (C4), 127.2 (C15), 129.2 (C14), 130.6 (C14), 143.4 (C13), 144.2 (C13), 167.7 (C12); HRMS (FI^+) found 366.1812, $C_{24}H_{25}NNaO$ (MNa^+) requires 366.1828.

6,6-Diphenyl-2,3,6a,7,8,9-hexahydro-1*H*-cyclopenta[g]indolizin-5(6*H*)-one (268)



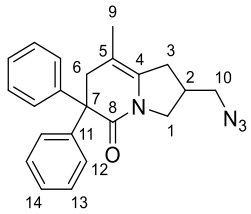
One pot: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclopentane (50 mg, 2.0 mmol) in toluene (4 mL), K_2CO_3 (283 mg, 2.04 mmol) and NaOH (40 mg, 1.0 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 48 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the PTFE screw cap was replaced with a septum and the brown slurry stirred at 0 °C under argon. Freshly prepared diphenylketene (120 mg, 0.612 mmol) in toluene (2 mL) was added dropwise over 40 min, causing the yellow solution to turn a bright yellow. After stirring for 15 h, during which the ice bath thawed and was removed, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated

onto silica, and purified over silica eluting with 5–20% ether in petrol with 0.5% triethylamine. The product was isolated as an orange amorphous solid (52 mg, 77%). M.p 160 °C; R_f 0.20 (1:1 petrol/ ether); ν_{max} 1645s; δ_H (400 MHz, C_6D_6) 1.21–1.36 (3 H, m, H2 and H7), 1.50–1.59 (2 H, m, H7 and H8), 1.75 (1 H, app. dq, *J* = 11.5 and 6.5 Hz, H8), 1.97–2.01 (2 H, m, H3), 2.02–2.09 (1 H, m, H6), 2.16 (1 H, dd, *J* = 16.0 and 8.0 Hz, H6), 3.37–3.42 (1 H, m, H10), 3.45–3.56 (2 H, m, H1), 7.03 (1 H, app. t. *J* = 7.0 Hz, H15), 7.10 (2 H, app. t. *J* = 7.5 Hz, H14), 7.13 (1 H, app. t. *J* = 7.0 Hz, H15), 7.22 (2 H, app. t. *J* = 7.5 Hz, H14), 7.35 (2 H, app. d. *J* = 8.0 Hz, H13), 7.52 (2 H, app. d. *J* = 8.0 Hz, H13); δ_C (100 MHz, C_6D_6) 22.5 (C2), 26.0 (C7), 27.4 (C3), 28.0 (C8), 28.3 (C6), 46.5 (C1), 50.3 (C9), 60.0 (C10), 114.2 (C5), 127.4 (C15), 127.4 (C14), 127.9 (C15), 128.1 (C14), 129.8 (C4), 130.9 (C13), 131.1 (C13), 140.5 (C12), 145.4 (C12), 169.7 (C11); HRMS (FI^+) found 352.1673, $C_{23}H_{23}NNaO$ (MNa^+) requires 352.1672.

Two pot: To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclopentane (50 mg, 2.0 mmol) in toluene (4 mL), K_2CO_3 (283 mg, 2.04 mmol) and NaOH (40 mg, 1.0 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 48 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the brown reaction was filtered through a sintered funnel with ether (10 mL) into an oven-dried 50 mL round-bottom flask and stirred at 0 °C under argon. Freshly prepared diphenylketene (120 mg, 0.612 mmol) in toluene (4 mL) was added dropwise over 20 min, causing the yellow solution to turn a bright yellow. After stirring for 17 h, during which the ice bath thawed and was removed, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over

silica eluting with 5–20% ether in petrol with 0.5% triethylamine. The product was isolated as an orange amorphous solid (44 mg, 65% over 2 steps). M.p 160 °C; R_f 0.20 (1:1 petrol/ ether); ν_{max} 1645s; δ_H (400 MHz, C_6D_6) 1.21–1.36 (3 H, m, H2 and H7), 1.50–1.59 (2 H, m, H7 and H8), 1.75 (1 H, app. dq, *J* = 11.5 and 6.5 Hz, H8), 1.97–2.01 (2 H, m, H3), 2.02–2.09 (1 H, m, H6), 2.16 (1 H, dd, *J* = 16.0 and 8.0 Hz, H6), 3.37–3.42 (1 H, m, H10), 3.45–3.56 (2 H, m, H1), 7.03 (1 H, app. t. *J* = 7.0 Hz, H15), 7.10 (2 H, app. t. *J* = 7.5 Hz, H14), 7.13 (1 H, app. t. *J* = 7.0 Hz, H15), 7.22 (2 H, app. t. *J* = 7.5 Hz, H14), 7.35 (2 H, app. d. *J* = 8.0 Hz, H13), 7.52 (2 H, app. d. *J* = 8.0 Hz, H13); δ_C (100 MHz, C_6D_6) 22.5 (C2), 26.0 (C7), 27.4 (C3), 28.0 (C8), 28.3 (C6), 46.5 (C1), 50.3 (C9), 60.0 (C10), 114.2 (C5), 127.4 (C15), 127.4 (C14), 127.9 (C15), 128.1 (C14), 129.8 (C4), 130.9 (C13), 131.1 (C13), 140.5 (C12), 145.4 (C12), 169.7 (C11); HRMS (FI^+) found 352.1673, $C_{23}H_{23}NNaO$ (MNa^+) requires 352.1672.

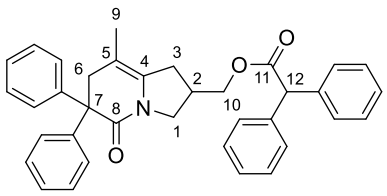
2-(Azidomethyl)-8-methyl-6,6-diphenyl-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (269)



To an oven-dried 14 mL Ace pressure tube was added a 0.026 M solution of 6-azido-5-(azidomethyl)-3-bromo-2-methylhex-2-ene (50 mg, 0.18 mmol) in toluene (7 mL) with K_2CO_3 (255 mg, 1.84 mmol) and NaOH (15 mg, 0.368 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat

and cooling, the screw cap was replaced with a septa with argon balloon, and the reaction stirred at 40 °C. Diphenylketene (106 mg, 0.546 mmol) in toluene (2 mL) was added dropwise over 20 min, and the reaction stirred for 22 h. After filtering through a sinter with DCM (30 mL), the reaction was concentrated onto silica and purified over silica, eluting with a gradient of 0.1% Et_3N in petrol to 0.1% Et_3N in ether, yielding the product as a yellow oil (38 mg, 58%). R_f 0.34 (1:1, petrol/ ether); ν_{max} 2097s, 1655m; δ_H (400 MHz, $CDCl_3$) 1.76 (3 H, s, H9), 2.27 (1 H, dd, *J* = 15.5 and 4.0 Hz, H3), 2.36–2.46 (1 H, m, H2), 3.56–3.63 (1 H, m, H3), 2.90 (2 H, dd, *J* = 24.5 and 17.5 Hz, H6), 3.09 (2 H, ddd, *J* = 23.5 Hz, 12.0 and 7.0 Hz, H10), 3.55 (1 H, dd, *J* = 12.0 and 5.0 Hz, H1), 3.83 (1 H, dd, *J* = 12.0 and 7.0 Hz, H1), 7.12–7.32 (10 H, m, H12, H13 and H14); δ_C (100 MHz, $CDCl_3$) 17.7 (C9), 30.9 (C3), 35.4 (C2), 42.1 (C6), 49.1 (C1), 53.6 (C10), 56.7 (C7), 106.1 (C5), 126.8 (C13), 126.9 (C13), 128.0 (C12), 128.1 (C12), 128.3 (C14), 128.4 (C14), 131.6 (C4), 141.9 (C11), 143.1 (C11), 169.9 (C8); HRMS (FI^+) found 381.1679, $C_{22}H_{24}N_4ONa$ (MNa^+) requires 381.1686.

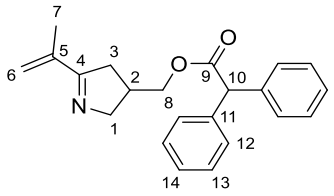
(8-Methyl-5-oxo-6,6-diphenyl-1,2,3,5,6,7-hexahydroindolizin-2-yl)methyl 2,2-diphenylacetate (270)



To an oven-dried 14 mL Ace pressure tube was added a 0.030 M solution of 2-(azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (38 mg, 0.15 mmol) in toluene (5 mL) with K_2CO_3 (212 mg, 1.54 mmol) and NaOH (12 mg, 0.31 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly

disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the screw cap was replaced with a septa with argon balloon, and the reaction stirred at 70 °C. Diphenylketene (130 mg, 0.670 mmol) in toluene (2 mL) was added dropwise over 20 min, and the reaction stirred at 70 °C for 24 h. After filtering through a sinter with DCM (30 mL), the reaction was concentrated onto silica and purified over silica, eluting with a gradient of 0.1% Et_3N in petrol to 0.1% Et_3N in ether, yielding the product as a yellow oil (60 mg, 74%). R_f 0.40 (1:1, petrol/ ether); ν_{max} 1735s, 1655m; δ_H (500 MHz, $CDCl_3$) 1.70 (3 H, s, H9), 2.12 (1 H, d, *J* = 11.0 Hz, H3), 2.45–2.55 (2 H, m, H2 and H3), 2.88 (2 H, s, H6), 3.49 (1 H, dd, *J* = 12.0 and 5.5 Hz, H1), 3.79 (1 H, dd, *J* = 12.0 and 7.0 Hz, H1), 3.90 (1 H, dd, *J* = 11.0 and 7.5 Hz, H10), 3.99 (1 H, dd, *J* = 11.0 and 6.5 Hz, H10), 5.01 (1 H, s, H12), 7.14–7.35 (20H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 17.6 (C9), 29.9 (C3), 34.5 (C2), 41.9 (C6), 48.5 (C1), 56.8 (C7), 57.0 (C12), 65.8 (C10), 105.86 (C5), 126.8, 126.9, 127.4, 127.9, 128.0, 128.2, 128.3, 128.6 and 128.7 (Ar-C), 131.7 (C4), 142.3 and 142.8 (Ar-C), 169.8 (C8), 172.3 (C11); HRMS (FI^+) found 550.2334, $C_{36}H_{33}NNaO_3$ (MNa^+) requires 550.2353.

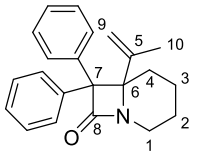
(5-(Prop-1-en-2-yl)-3,4-dihydro-2*H*-pyrrol-3-yl)methyl 2,2-diphenylacetate (271)



To an oven-dried 14 mL Ace pressure tube was added a 0.03 M solution of 2-(azidomethyl)-4-bromo-5-methylhex-4-en-1-ol (50 mg, 0.20 mmol) in toluene (7 mL) with K_2CO_3 (279 mg, 2.02 mmol) and NaOH (16 mg, 0.40 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150

°C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the screw cap was replaced with a septa with argon balloon, and the reaction stirred at room temperature. Diphenylketene (90 mg, 0.46 mmol) in toluene (2 mL) was added dropwise over 20 min, and the reaction stirred for 16 h. After filtering through a sinter with DCM (30 mL), the reaction was concentrated onto silica and purified over silica, eluting with a gradient of 0.1% Et_3N in petrol to 0.1% Et_3N in ether, yielding the product as a yellow oil (28 mg, 41%). R_f 0.28 (1:1, petrol/ ether); ν_{max} 1733s, 1597m; δ_H (400 MHz, $CDCl_3$) 1.92 (3 H, s, H7), 2.39 (1 H, dd, *J* = 16.5 and 4.5 Hz, H3), 2.59–2.76 (2 H, m, H2 and H3), 3.67 (1 H, dd, *J* = 17.0 and 4.5 Hz, H1), 3.97 (1 H, dd, *J* = 17.0, and 8.0 Hz, H1), 4.04 (1 H, ddd, *J* = 15.0, 11.0, and 7.0 Hz, H8), 4.95 (1 H, s, H10), 5.24 and 5.37 (1 H, s, H6), 7.20–7.30 (10 H, m, H12, H13 and H14); δ_C (100 MHz, $CDCl_3$) 19.2 (C7), 36.0 (C2), 37.5 (C3), 57.2 (C10), 64.0 (C1), 67.3 (C8), 121.3 (C6), 127.3 (C12), 128.6 (C11 and C13), 138.5 (C5), 140.5 (C11), 172.4 (C9), 173.9 (C4); HRMS (FI^+) found 334.1795, $C_{22}H_{24}NO_2$ (MH^+) requires 334.1802.

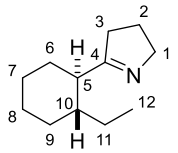
7,7-Diphenyl-6-(prop-1-en-2-yl)-1-azabicyclo[4.2.0]octan-8-one (272)



To an oven-dried 14 mL Ace pressure tube was added a 0.036 M solution of 7-azido-3-bromo-2-methylhept-2-ene (50 mg, 0.22 mmol) in toluene (6 mL) with K_2CO_3 (298 mg, 2.16 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 9 d in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3

throughout the solution. After removing from heat and cooling, the PTFE screw cap was replaced with a septum and the orange suspension stirred at 40 °C under argon. Freshly prepared diphenylketene (83 mg, 0.42 mmol) in toluene (2 mL) was added dropwise over 50 min, causing the yellow solution to turn a bright yellow. After stirring for 17 h, the cloudy solution was filtered through a sintered funnel with ether (30 mL), concentrated onto silica, and purified over silica eluting with 1:16 ether in petrol. The product was isolated as a white solid (24 mg, 35%). M.p 106 °C; R_f 0.41 (2:1 petrol/ ether); ν_{max} 1746s; δ_H (500 MHz, C_6D_6) 0.81–1.14 (4 H, m, H2 and H3), 1.22 (1 H, dt, *J* = 13.0, and 3.0 Hz, H4), 1.27 (3 H, s, H10), 1.92 (1 H, d, *J* = 12.5, H4), 2.43 (1 H, br, H1), 3.86 (1 H, dd, *J* = 13.5 and 6.0 Hz, H1), 4.77 (1 H, br, H9), 4.8 (1 H, br, H9), 6.93–6.96 (1 H, m, Ar-H), 7.00–7.04 (2 H, m, Ar-H), 7.08 (1 H, app. t, *J* = 7.5 Hz, Ar-H), 7.21 (2 H, app. t, *J* = 7.5 Hz,, Ar-H), 7.91 (2 H, br, Ar-H), 7.50 (2 H, br, Ar-H); δ_C (150 MHz, C_6D_6) 20.3 (C10), 20.4 (C3), 24.7 (C2), 33.8 (C4), 37.4 (C1), 70.3 (C7), 77.2 (C6), 116.3 (C9), 127.0 (ArC), 127.1 (ArC), 128.5 (ArC), 128.6 (ArC), 129.1 (ArC), 129.4 (ArC), 139.6 (ArC), 145.5 (C5), 168.8 (C8); HRMS (FI^+) found 340.1661, $C_{22}H_{23}NNaO$ (MNa^+) requires 340.1672.

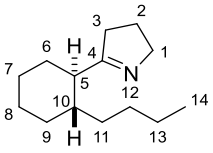
(±)-*Trans* 5-(2-ethylcyclohexyl)-3,4-dihydro-2*H*-pyrrole (274)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (60 mg, 0.23 mmol) in toluene (4.6 mL), K_2CO_3 (321 mg, 2.32 mmol) and NaOH (23 mg, 0.58 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the

insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction was filtered through a sintered funnel into an oven-dried 50 mL round-bottom flask washing with THF (10 mL) and the flask sealed with a septa. The clear pale yellow solution was stirred at 0 °C under argon, and ethylmagnesium bromide (0.35 mL, 3.0 M in ether, 1.1 mmol) was added dropwise. After stirring for 5 min, the septa was replaced with an oven-dried condenser and the reaction was heated to 40 °C in an oil bath under argon for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and saturated aqueous Rochelle's salt (2 mL) and the layers separated. The aqueous layer was extracted with ether (2 x 15 mL), the combined organics washed with brine (5 mL), dried ($MgSO_4$) and concentrated onto silica. The product was purified over silica by eluting with 0.5% triethylamine in petrol, yielding an orange oil (37 mg, 90% over 2 steps). R_f 0.24 (ether); ν_{max} 1637m; δ_H (500 MHz, C_6D_6) 0.81–0.85 (1 H, m, H6), 0.86 (3 H, t, *J* = 7.5 Hz, H12), 1.05–1.77 (12 H, m, H2, H6, H7, H8, H9, H10, H11), 2.02–2.11 (2 H, m, H3), 2.32 (1 H, td, *J* = 11.0 and 3.5 Hz, H5), 3.73–3.77 (2 H, m, H1); δ_C (150 MHz, C_6D_6) 10.7 (C12), 22.3 (C2), 25.9 (C8), 26.1 (C7), 27.0 (C11), 30.6 (C6), 31.1 (C9), 34.3 (C3), 41.1 (C10), 47.7 (C5), 60.3 (C1), 180.0 (C4); HRMS (FI^+) found 180.1747, $C_{12}H_{22}N$ (MH^+) requires 180.1747.

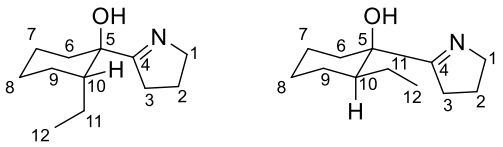
(±)-*Trans* 5-(2-butylcyclohexyl)-3,4-dihydro-2*H*-pyrrole (275)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (23 mg, 0.58 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring,

wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction was filtered through a sintered funnel into an oven-dried 50 mL round-bottom flask washing with THF (15 mL) and the flask sealed with a septa. The clear pale yellow solution was degassed with argon for 5 min, then stirred at room temperature under argon. Butylithium (0.30 mL, 2.0 M in pentane, 0.60 mmol) was added dropwise via syringe pump over 5 min causing an intense yellow colouration. After stirring for 2 h, a TLC revealed the reaction to be incomplete, and further butyllithium (0.3 mL, 2.0 M in pentane, 0.60 mmol) was added dropwise via syringe pump over 5 min and the reaction stirred for 15 h. The reaction was cooled to 0 °C and quenched with degassed water (6 mL) and the layers separated. The aqueous layer was extracted with ether (2 x 20 mL), the combined organics washed with brine (5 mL), dried (Na_2SO_4) and concentrated onto silica. The product was purified over silica by eluting with 0–10% ether in petrol, yielding a yellow oil (57 mg, 71% over 2 steps). R_f 0.30 (ether); ν_{max} 1636m; δ_H (400 MHz, $CDCl_3$) 0.85 (3 H, t, *J* = 7.0 Hz, H14), 0.90–1.05 (2 H, m), 1.09–1.45 (9 H, m), 1.68–1.91 (6 H, m), 2.21 (1 H, ddd, *J* = 11.0 and 3.0 Hz, H5), 2.40 (2 H, app. t, *J* = 7.5 Hz, H3), 3.70–3.85 (2 H, m, H1); δ_C (100 MHz, $CDCl_3$) 14.1 (C14), 22.4 (C2), 22.9 (C13), 25.9, 26.2, 28.7, 31.1, 31.4, 34.1, 34.2 (C3), 39.6 (C10), 48.7 (C10), 48.8 (C5), 60.2 (C1), 181.9 (C4); HRMS (FI^+) found 208.2053, $C_{14}H_{26}N$ (MH^+) requires 208.2060.

(±)-1-(3,4-Dihydro-2*H*-pyrrol-5-yl)-2-ethylcyclohexanol (277)

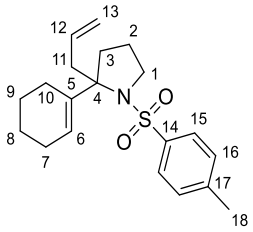


277-*cis* **277-*trans***

To a 10–20 mL Biotage microwave vial was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (30 mg, 0.75 mmol). The reaction vessel was flushed with nitrogen, crimped shut, and the colourless solution stirred at 155 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with THF (10 mL) and the clear pale yellow solution stirred at 40 °C under nitrogen. Ethylmagnesium bromide (0.5 mL, 3.0 M in ether, 1.5 mmol) was added dropwise. After stirring for 1 h, further ethylmagnesium bromide (0.5 mL, 3.0 M in ether, 1.5 mmol) was added. After 2 h, the reaction was cooled to room temperature and air bubbled through the solution until the volume reduced by half (3 h). Water (20 mL) was added, the layers separated and the aqueous layer extracted successively with ether (3 x 20 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$) and concentrated into a 50 mL round-bottom flask. DCM (5 mL), tosyl chloride (80 mg, 0.425 mmol) and triethylamine (0.06 mL, 0.425 mmol) were added and the reaction stirred at room temperature under nitrogen for 22 h. The reaction was concentrated onto silica and purified over silica using a Biotage™ cartridge by eluting with 0–20% ether in pentane, yielding two separate products as pale yellow oils. **227-*cis*** (27 mg, 36% over 3 steps). **227-*trans*** (35 mg, 46% over 3 steps). **227-*trans*** solidified on standing into a white solid. **227-*cis***: R_f 0.40 (1:1 MTBE/ hexane); ν_{max} 3434br, 1637m; δ_H (400 MHz, $CDCl_3$) 0.83 (3 H, t, *J* = 7.5 Hz, H12),

0.99–1.20 (2 H, m , H11), 1.21–1.36 (2 H, m, H7 and H8), 1.46–1.60 (3 H, m, H6 and H9), 1.67–1.84 (3 H, m, H7, H8 and H9), 2.01 (2 H, app. pent, *J* = 7.5 Hz, H2), 2.42 (1 H, tddd, *J* = 17.0 Hz, 7.5 Hz, 7.5 and 1.5 Hz, H3), 2.54 (1 H, tddd, *J* = 17.0 Hz, 8.0, 8.0, and 1.5 Hz, H3), 3.80–3.86 (2 H, m, H1), 4.15 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 12.0 (C12), 21.2 (C9), 22.8 (C11), 23.9 (C2), 25.9 (C7), 25.9 (C8), 32.9 (C3), 37.2 (C6), 44.4 (C10), 59.1 (C1), 75.1 (C5), 183.9 (C4); HRMS (FI^+) found 196.1687, $C_{12}H_{22}NO$ (MH^+) requires 196.1696. **227-*trans***: M.p 96 °C; R_f 0.19 (1:1 MTBE/ hexane); ν_{max} 3388br, 1633m; δ_H (400 MHz, $CDCl_3$) 0.87 (3 H, t, *J* = 7.0 Hz, H12), 0.83–0.92 (1 H, m, H11), 1.17–1.67 (7 H, m , H6, H7, H9, H10 and H11), 1.76–1.94 (4 H, m, H2, H6 and H8), 2.50–2.56 (2 H, m, H3), 3.65–3.80 (2 H, m, H3), 3.65–3.80 (2 H, m, H1); δ_C (100 MHz, $CDCl_3$) 12.4 (C12), 21.8 (C11), 22.9 (C7), 23.0 (C9), 23.5 (C2), 25.8 (C8), 35.4 (C6), 36.0 (C3), 47.4 (C10), 58.8 (C1), 75.3 (C5), 182.6 (C4); HRMS (FI^+) found 196.1690, $C_{12}H_{22}NO$ (MH^+) requires 196.1696.

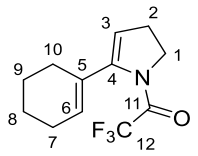
2-Allyl-2-cyclohexenyl-1-tosylpyrrolidine (279)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (150 mg, 0.583 mmol) in toluene (11.5 mL), K_2CO_3 (805 mg, 5.83 mmol) and NaOH (46 mg, 1.16 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with THF (10

mL) into a 50 mL round-bottom flask and the clear pale yellow solution stirred at 50 °C under nitrogen. Allylmagnesium chloride (2.0 mL, 2.0 M in THF, 4.0 mmol) was added dropwise and the reaction heated for 20 h. The reaction was cooled to 0 °C, quenched with water (20 mL), and the aqueous layer extracted successively with ether (3 x 20 mL). The combined organics were washed with brine (5 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. DCM (5 mL), tosyl chloride (220 mg, 1.16 mmol) and K_2CO_3 (160 mg, 1.16 mmol) were added and the reaction stirred at 40 °C under nitrogen for 22 h. The reaction was filtered to remove K_2CO_3, concentrated, and purified over silica eluting with 1–15% ether in petrol, yielding a yellow oil that solidified to an off-white solid (156 mg, 78% over 3 steps). M.p 65 °C; R_f 0.58 (1:1 ether/ hexane); ν_{max} 1154s; δ_H (500 MHz, $CDCl_3$) 1.29 (1 H, dddd, *J* = 9.5, 9.5, 9.5, and 5.5 Hz, H9), 1.43 (1 H, dddd, *J* = 10.0 Hz, 10.0 Hz, 7.0 and 7.0 Hz, H8), 1.54–1.60 (2 H, m, H8 and H9), 1.72–1.79 (3 H, m, H2 and H10), 1.86–1.98 (3 H, m, H3 an H10), 2.05 (2 H, d, *J* = 2.5 Hz, H7), 2.42 (3 H, s, H18), 2.68 (1 H, dd, *J* = 14.0 and 8.5 Hz, H11), 3.03 (1 H, dd, *J* = 14.0 and 5.5 Hz, H11), 3.46 (2 H, t, *J* = 7.0 Hz, H1), 5.04–5.10 (2 H, m, H13), 5.67–5.75 (2 H, m, H6 and H12), 7.27 (2 H, d, *J* = 8.0 Hz, H16), 7.27 (2 H, d, *J* = 8.0 Hz, H15); δ_C (150 MHz, $CDCl_3$) 21.4 (C18), 22.0 (C8), 22.7 (C9), 22.9 (C2), 25.2 (C10), 25.2 (C7), 36.6 (C3), 41.7 (C11), 50.1 (C1), 73.0 (C4), 117.9 (C13), 123.0 (C6), 127.2 (C15), 129.1 (C16), 135.4 (C12), C138.5 (C14), 138.7 (C17), 142.4 (C5); HRMS (FI^+) found 368.1655, $C_{20}H_{27}NNaO_2S$ (MNa^+) requires 368.1655.

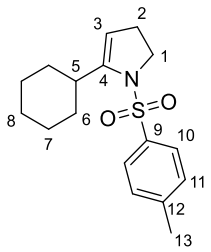
1-(5-Cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)-2,2,2-trifluoroethanone (281)



To a 10–20 mL Biotage microwave vial was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (30 mg, 0.75 mmol). The reaction vessel was flushed with nitrogen, crimped shut, and the colourless solution stirred at 155 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with DCM (20 mL) into a 50 mL round-bottom flask and the reaction cooled to –78 °C under nitrogen. Triethylamine (0.06 mL, 0.425 mmol) and trifluoroacetic anhydride (60 μL, 0.42 mmol) were added and the reaction stirred for 10 min. The acetone bath was removed and the reaction stirred for 19 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl (20 mL), the layers separated, and the aqueous layer extracted successively with DCM (2 x 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated onto silica. The product was purified over silica using a Biotage™ cartridge by eluting with 0–5% ether in pentane, yielding a pale yellow oil (88 mg, 92% over 2 steps). R_f 0.70 (2:5 ether/ hexane); ν_{max} 1696s; δ_H (500 MHz, C_6D_6) 1.47–1.53 (2 H, m, H8), 1.63–1.68 (2 H, m, H9), 1.73 (2 H, ddd, *J* = 8.0 and 3.0 Hz, H2), 1.98 (2 H, br s, H7), 2.11 (2 H, br s, H10), 3.34 (2 H, t, *J* = 8.0 Hz, H1), 4.48 (1 H, t, *J* = 3.0 Hz, H3), 5.74 (1 H, s, H6); δ_C (150 MHz, C_6D_6) 22.3 (C8), 22.6 (C9), 25.5 (C7), 28.0 (C10), 28.3 (C2), 48.1 (C1), 113.5 (C3), 116.7 (C12, q, *J* =

289.0 Hz), 126.6 (C6), 131.42 (C5), 146.9 (C4), 152.8 (C11, q, *J* = 36.0 Hz); HRMS (FI$^+$) found 268.0923, $C_{12}H_{14}{}^{19}F_3NNaO$ (MNa^+) requires 268.0920.

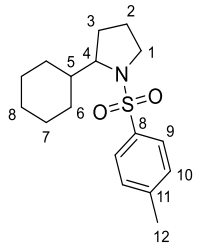
5-Cyclohexyl-1-tosyl-2,3-dihydro-1*H*-pyrrole (283)



To a 10–20 mL Biotage microwave vial was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (30 mg, 0.75 mmol). The reaction vessel was flushed with nitrogen, crimped shut, and the colourless solution stirred at 155 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with THF (20 mL) into a 50 mL round-bottom flask and stirred at 0 °C under nitrogen. $LiAlH_4$ (5 mL, 1.0 M in THF, 5 mmol) was added dropwise, and the reaction stirred for 17 h, during which the ice bath thawed and was removed. The reaction was cooled to 0 °C and quenched with brine (20 mL) and the layers separated. The aqueous layer was extracted with ether (3 x 20 mL), the combined organic fractions washed with brine (10 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. Triethylamine (0.10 mL, 0.717 mmol), tosyl chloride (80 mg, 0.42 mmol) and DCM (10 mL) were added and the reaction stirred at room temperature for 20 h. The reaction was concentrated onto silica and purified over silica using a Biotage™ cartridge by eluting with 0–5% ether in pentane, yielding a white solid (75 mg, 63% over 3 steps). The solid was stable at –20 °C, and hydrolysed readily in $CDCl_3$. M.p 58 °C; R_f 0.63 (2:5 ether/ hexane); ν_{max} 1159s; δ_H (400 MHz, C_6D_6)

1.03–1.17 (3 H, m, H6 and H8), 1.42 (2 H, qt, *J* = 13.0 and 3.0 Hz, H7), 1.54 (2 H, tt, *J* = 8.0 and 2.0 Hz, H2), 1.64 (1 H, m, H8), 1.71 (2 H, dt, *J* = 13.5 and 3.0 Hz, H7), 2.27 (2 H, d, *J* = 12.0 Hz, H6), 3.10 (1 H, app. t, *J* = 11.5 Hz, H5), 3.65 (2 H, t, *J* = 8.5 Hz, H1), 4.67 (1 H, ddd, *J* = 2.5, 2.5 and 1.5 Hz, H3), 6.75 (2 H, d, *J* = 8.0 Hz, H11), 7.72 (2 H, d, *J* = 8.0 Hz, H10); δ_C (100 MHz, C_6D_6) 20.7 (C13), 26.3 (C7), 26.5 (C8), 26.9 (C2), 32.5 (C6), 37.6 (C5), 51.0 (C1), 110.2 (C3), 127.2 (C10), 129.2 (C11), 135.8 (C9), 142.6 (C12), 150.6 (C4); HRMS (FI^+) found 328.1348, $C_{17}H_{23}NNaO_2S$ (MNa^+) requires 328.1342.

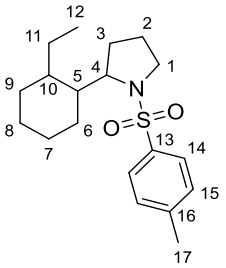
2-Cyclohexyl-1-tosylpyrrolidine (284)



To a 10–20 mL Biotage microwave vial was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (30 mg, 0.75 mmol). The reaction vessel was flushed with nitrogen, crimped shut, and the colourless solution stirred at 155 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with THF (20 mL) into a 50 mL round-bottom flask and stirred at 0 °C under nitrogen. $LiAlH_4$ (5 mL, 1.0 M in THF, 5 mmol) was added dropwise, and the reaction stirred for 1 h and then heated to 80 °C for 18 h. The reaction was cooled to 0 °C and quenched with aqueous saturated Rochelle's salt (20 mL) and the layers separated. The aqueous layer was extracted with MTBE (3 x 20 mL), the combined organic fractions washed with brine (10 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. THF (10 mL) was added, the reaction

stirred at 0 °C under nitrogen, and $LiAlH_4$ (3 mL, 1.0 M in THF, 3 mmol) was added dropwise. The reaction was stirred for 4 h during which the ice bath thawed and was removed. After cooling to 0 °C, brine (20 mL) was added and the layers separated. The aqueous layer was extracted with ether (3 x 20 mL), the combined organic fractions washed with brine (10 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. Triethylamine (0.10 mL, 0.72 mmol), tosyl chloride (80 mg, 0.42 mmol) and DCM (10 mL) were added and the reaction stirred at room temperature for 21 h. The reaction was concentrated onto silica and purified over silica using a Biotage™ cartridge by eluting with 0–5% ether in pentane, yielding a white solid (63 mg, 53% over 4 steps). M.p 92 °C; R_f 0.55 (2:5 ether/ hexane); ν_{max} 1158s; δ_H (400 MHz, $CDCl_3$) 0.88–1.43 (8H, m), 1.64–1.80 (7 H, m), 2.43 (3 H, s, H13), 3.28 (2 H, t, *J* = 6.5 Hz, H1), 3.51–3.55 (1 H, m, H4), 7.31 (2 H, d, *J* = 8.0 Hz, H11), 7.72 (2 H, d, *J* = 8.0 Hz, H10); δ_C (100 MHz, $CDCl_3$) 21.5 (C13), 24.6 (C2), 26.1, 26.4, 26.6 (C2), 27.0, 27.5, 30.4 (C6), 42.3 (C5), 49.1 (C1), 65.2 (C4), 127.5 (C10), 129.5 (C11), 135.2 (C12), 143.1 (C9); HRMS (FI^+) found 330.1491, $C_{17}H_{25}NNaO_2S$ (MNa^+) requires 330.1498.

2-(2-Ethylcyclohexyl)-1-tosylpyrrolidine (285)

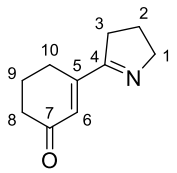


To a 10–20 mL Biotage microwave vial was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol) in toluene (8 mL), K_2CO_3 (535 mg, 3.87 mmol) and NaOH (30 mg, 0.75 mmol). The reaction vessel was flushed with nitrogen, crimped shut, and the colourless solution stirred at 155 °C for 27 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble

K_2CO_3 throughout the solution. After removing from heat and cooling, the yellow reaction solution was filtered through a sintered funnel with THF (10 mL) into a 50 mL round-bottom flask and stirred at 40 °C under nitrogen. Ethylmagnesium bromide (0.5 mL, 3.0 M in ether, 5 mmol) was added dropwise, and the reaction stirred for 2 h. The reaction was cooled to 0 °C and quenched with brine (20 mL) and the layers separated. The aqueous layer was extracted with MTBE (2 x 20 mL), the combined organic fractions washed with brine (10 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. THF (50 mL) was added, the reaction stirred at 0 °C under nitrogen, and $LiAlH_4$ (5 mL, 1.0 M in THF, 5 mmol) was added dropwise. The reaction was stirred for 16 h during which the ice bath thawed and was removed. Further $LiAlH_4$ (1.0 mL, 1.0 M in THF, 1.0 mmol) was added, and after 5 h cooled to 0 °C, quenched with brine (20 mL) and the layers separated. The aqueous layer was extracted with MTBE (3 x 20 mL), the combined organic fractions washed with brine (10 mL), dried (Na_2SO_4) and concentrated into a 50 mL round-bottom flask. Triethylamine (0.10 mL, 0.72 mmol), tosyl chloride (80 mg, 0.42 mmol) and DCM (10 mL) were added and the reaction stirred at room temperature for 15 h. The reaction was concentrated onto silica and purified over silica using a Biotage™ cartridge by eluting with 0–5% ether in pentane, yielding a viscous colourless oil (55 mg, 42% over 4 steps) as an inseparable mixture of diastereoisomers (4:3:1) of unknown stereochemistry. R_f 0.50 (1:1 ether/ hexane); ν_{max} 1159s; δ_H (400 MHz, $CDCl_3$) 0.85–0.92 (m, H12), 0.94–2.01 (m), 2.41 (s), 2.42 (s), 3.18–3.49 (m), 3.67–3.71 (m, H1), 3.73–3.77 (m, H1), 3.81–3.85 (m, H1), 7.30 (d, *J* = 7.5 Hz, H15), 7.69–7.72 (m); δ_C (100 MHz, $CDCl_3$) 9.9, 11.2, 11.4, 13.1, 16.3, 19.1, 19.2, 21.7, 22.8, 23.4, 24.1, 24.4, 24.8, 25.1, 25.3, 25.5, 25.6, 25.7, 260, 27.3, 27.7, 29.0, 29.6, 35.6, 38.7, 41.0, 43.3, 44.7, 46.5, 47.0, 48.6, 61.5, 62.6, 62.7, 126.0, 126.5, 126.6, 128.6, 128.6, 134.4, 142.1 *Note: reported as seen for*

mixture of diastereomers; HRMS (FI$^+$) found 358.1806, $C_{19}H_{29}NNaO_2S$ (MNa$^+$) requires 358.1811.

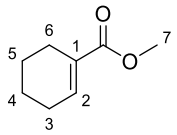
3-(3,4-Dihydro-2*H*-pyrrol-5-yl)cyclohex-2-en-1-one (286)



To an oven-dried 14 mL Ace pressure tube was added a 0.05 M solution of (4-azido-1-bromobutylidene)cyclohexane (150 mg, 0.581 mmol) in toluene (10 mL), K_2CO_3 (800 mg, 5.81 mmol) and NaOH (46 mg, 1.2 mmol). The reaction vessel was flushed with argon, thread sealed with PTFE tape and PTFE screw cap with FETFE® O-ring, wrapped in cotton wool/ aluminium foil and the colourless solution stirred at 150 °C for 30 h in a pre-heated oil bath. Stirring was maintained vigorously to evenly disperse the insoluble K_2CO_3 throughout the solution. After removing from heat and cooling, the reaction was filtered, and concentrated to yield a yellow oil that was used crude in next reaction. To a 7 mL sample vial was added crude 5-cyclohexenyl-3,4-dihydro-2H-pyrrole (~0.581 mmol), DMSO (1 mL), and the vessel flushed with argon. The reaction was heated to 60 °C for 44 h. After cooling, the reaction was diluted with ether (20 mL), washed successively with brine (2 x 1 mL), the combined aqueous washes back-extracted with ether (3 x 1 mL). The combined organic layers were dried ($MgSO_4$), concentrated to yield a crude orange oil, and purified over silica eluting with petrol to 50% ether in petrol. The product was isolated as pale yellow crystals (17 mg, 18% over 2 steps). M.p 48 °C; R_f 0.21 (ether); ν_{max} 1676s, 1590m; δ_H (500 MHz, $CDCl_3$) 1.99 (2 H, app. pent, *J* = 7.5 Hz, H2), 2.07 (2 H, app. pent, *J* = 6.0 Hz, H9), 2.48 (2 H, t, *J* = 6.5 Hz, H8), 2.75 (4 H, m, H10 and H3), 4.07 (2 H, tt, *J* = 7.5 and 2.0 Hz, H1), 6.27 (1 H, s, H6); δ_C (125 MHz, $CDCl_3$) 22.4

(C9), 22.5 (C2), 25.3 (C10), 34.0 (C3), 37.9 (C8), 62.3 (C1), 130.6 (C6), 154.0 (C5), 174.3 (C4), 200.9 (C7); HRMS (FI^+) found 186.0891, $C_{10}H_{13}NNaO$ (MNa^+) requires 186.0889.

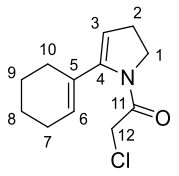
Methyl cyclohex-1-enecarboxylate (287)[421]



A literature procedure[421] was used. To a 100 mL oven-dried two-neck round-bottom flask equipped with a reflux condenser and containing cyclohexanecarboxylic acid (6.83 g, 53.3 mmol), was added thionyl chloride (4.60 mL, 63.9 mmol) dropwise, and the reaction stirred at 90 °C for 2 h under argon. After cooling to 80 °C, red phosphorus (82 mg, 2.7 mmol) was added, followed by bromine (3.30 mL, 63.9 mmol) dropwise at a rate to maintain the temperature below 100 °C. After heated at 100 °C for 7 h, the reaction was cooled to 0 °C, methanol (40 mL) added dropwise, and the reaction heated to reflux for 1 h. The reaction was quenched with cold water (100 mL) and extracted successively with ether (3 x 150 mL). The combined organic layers were washed with 1 M aqueous $Na_2S_2O_3$ (40 mL), saturated aqueous $NaHCO_3$ (40 mL), dried ($MgSO_4$) and concentrated to yield a yellow oil that was used crude in the next step. In a 100 mL oven-dried round bottom flask, crude methyl 1-bromocyclohexane carboxylate (~53.3 mmol) and quinoline (10 mL, 85 mmol) were heated to 120 °C together for 2 h under argon. The reaction was cooled in ice, quenched with 0.1 M aqueous HCl solution (100 mL), and extracted successively with petrol (3 x 100 mL). The combined organic layers were washed with 0.1 M aqeous HCl solution (3 x 10 mL), dried ($MgSO_4$) and concentrated to yield a crude oil that was purified over silica, eluting with petrol to 10% ether in petrol. The final product was isolated as a yellow oil (6.72 g, 90%) with data consistent with the literature data,[421] and used in the synthesis of **199**. R_f 0.80 (1:1

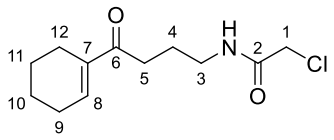
petrol/ ether); δ_H (200 MHz, $CDCl_3$) 1.54–1.72 (4 H, m, H4 and H5), 2.15–2.30 (2 H, m, H3 and H6), 3.73 (3 H, s, H7), 6.99 (1 H, sept, *J* = 2.0 Hz, H2).

2-Chloro-1-(5-cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)ethanone (288)



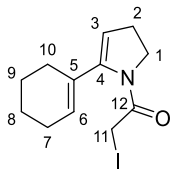
To a 14 mL sample vial was added 5-cyclohexenyl-3,4-dihydro-2*H*-pyrrole (300 mg, 2.01 mmol), toluene (8 mL), 4 Å sieves (800 mg), and the mixture stirred under argon at 0 °C. Pyridine (180 µL, 2.21 mmol), and chloro acetylchloride (160 µL, 2.01 mmol) were added to the solution, which became turgid and immobile, before regaining mobility after 5 min. After 1 h, the solution was warmed to ambient temperature, and stirred for a further 1 h. The reaction was filtered through a sinter, washed with petrol, and reduced in volume under vacuum to a concentrated toluene solution. The product containing solution was quickly purified over silica, eluting with a gradient of 0.5% triethylamine in petrol to 20% ether with 0.5% triethylamine in petrol, yielding the product as a pale yellow solid (442 mg, 97%). M.p 40 °C; R_f 0.61 (ether); ν_{max} 1669s, 1408s, 1282s; δ_H (400 MHz, $CDCl_3$) 1.65–1.70 (4 H, m, H8 and H9), 2.13 (4 H, br, H7 and H8), 2.50 (2 H, br, H2), 4.11 (4 H, br, H1 and H12), 5.27 (1 H, br, H3), 5.74 and 5.92 (1 H, br, H6); HRMS (FI^+) found 248.0815, $C_{12}H_{16}{}^{35}ClNNaO$ (MNa^+) requires 248.0813. *Note: Due to rotameric broadening and instability in both $CDCl_3$ and C_6D_6, a ^{13}C carbon could not be recorded. However, the decomposition product 2-chloro-N-(4-cyclohexenyl-4-oxobutyl)acetamide* ***(289)*** *was fully characterised.*

2-Chloro-*N*-(4-cyclohexenyl-4-oxobutyl)acetamide (289)



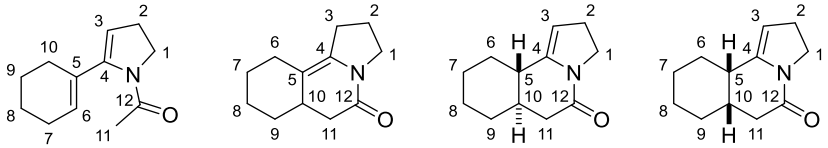
To a 7 mL sample vial was added 5-cyclohexenyl-3,4-dihydro-2*H*-pyrrole (100 mg, 0.670 mmol), toluene (4 mL), and the mixture stirred under argon at 0 °C. Pyridine (60 µL, 0.74 mmol), and chloro acetylchloride (53 µL, 0.67 mmol) were added to the solution, which became turgid and immobile, before regaining mobility after 5 min. After 1 h, the solution was warmed to ambient temperature, and stirred for a further 1 h. The reaction was filtered through a sinter, washed with petrol, and stirred for 26 h with 0.1 M aqueous HCl solution (1 mL). The solution was diluted with brine (5 mL), extracted successively with ether (3 x 10 mL), the combined organic layers dried (Na_2SO_4) and concentrated onto silica. The product was purified by eluting with a gradient of petrol to pure ether, yielding the product as a white solid (124 mg, 76%). M.p 55°C; R_f 0.23 (ether); ν_{max} 3283m, 1665s, 1558m; δ_H (400 MHz, $CDCl_3$) 1.51–1.59 (4 H, m, H10 and H11), 1.86 (2 H, app. pent, *J* = 7.0 Hz, H4), 2.12–2.22 (4 H, m, H9 and H12), 3.31 (2 H, app. q, *J* = 6.5 Hz, H3), 6.86 (1 H, br, NH), 6.90 (1 H, s, H8); δ_C (125 MHz, $CDCl_3$) 21.5 (H11), 21.9 (H10), 23.1 (C12), 23.7 (C4), 26.1 (C9), 34.2 (C3), 39.7 (C3), 42.6 (C1), 139.0 (C7), 140.4 (C8), 166.0 (C2), 200.6 (C6); HRMS (FI^+) found 244.1099, $C_{12}H_{19}{}^{35}ClNO_2$ (MH^+) requires 244.1110.

1-(5-(Cyclohex-1-en-1-yl)-2,3-dihydro-1*H*-pyrrol-1-yl)-2-iodoethan-1-one (290)



A modified literature precedure[363] was used: To a foil-wrapped 7 mL sample vial was added 2-chloro-*N*-(4-cyclohexenyl-4-oxobutyl)acetamide (93 mg, 0.41 mmol), NaI (61 mg, 0.41 mmol), and the mixture stirred in acetone for 18 h under argon. The precipitate of NaCl was removed by filtration, and the filtrate concentrated to afford the product as a brown oil (128 mg, 97% yield) that was unstable to chromatography and used immediately in the next reaction. δ_H (200 MHz, $CDCl_3$) 1.67 (4 H, br, H8 and H9), 2.18 (2 H, br, H7 and H10), 2.47 (2 H, br, H2), 3.37–3.99 (4 H, m, H1 and H11), 5.17 and 5.31 (1 H, br, H3), 5.73 and 6.02 (1 H, br, H6).

1-(5-(Cyclohex-1-en-1-yl)-2,3-dihydro-1*H*-pyrrol-1-yl)ethan-1-one (291a), 2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one (291b), (6aR,10aS)-2,6,6a,7,8,9,10,10a-octahydropyrrolo[2,1-a]isoquinolin-5(3*H*)-one (291c), and (6aS,10aS)-2,6,6a,7,8,9,10,10a-octahydropyrrolo[2,1-a]isoquinolin-5(3*H*)-one (291d)



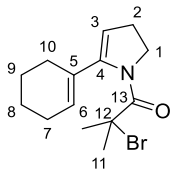
291a **291b** **291c** **291d**

A modified literature precedure[422–426] was used: To an oven-dried two-neck 100 mL round-bottom flask was added a 0.025 M solution 2-iodo-*N*-(4-cyclohexenyl-4-oxobutyl)acetamide (128 mg, 0.403 mmol) in degassed toluene (16 mL) and the solution

heated to 100 °C. A 0.02 M solution of Bu_3SnH (0.125 mL, 0.444 mmol) and AIBN (7 mg, 0.04 mmol) in degassed toluene (20 mL) was added dropwise over 1.5 h, and the reaction heated at reflux for 17.5 h. The reaction was removed from heat, and stirred with saturated aqueous KF solution (20 mL) for 3 h, and then extracted successively with DCM (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield a crude solid that was purified over silica eluting with a gradient of 0.5% triethylamine in petrol to 50% ether and 0.5% triethylamine in petrol. Products **291a–291d** were isolated as a yellow oil in a ratio of 1:2:2.3:1.5 (61 mg, 77% combined). Separate analytical samples were obtained by further chromatography. **291a**: R_f 0.53 (1% MeOH in ether); ν_{max} 1667s, 1649s, 1622s, 1397s; δ_H (500 MHz, C_6D_6) 1.25–2.05 (13 H, m, H2, H7, H8, H9, H10 and H11), 3.01 and 4.02 (1 H, br, H1), 4.84 (1 H, t, *J* = 3.0 Hz, H3), 5.72 (1 H, br, H6); HRMS (FI^+) found 214.1204, $C_{12}H_{17}NNaO$ (MNa^+) requires 214.1202. *Note: Due to rotameric broadening and instability in both $CDCl_3$ and C_6D_6, a ^{13}C carbon of **291a** could not be recorded.* **291b**: R_f 0.46 (1% MeOH in ether); ν_{max} 1658s, 1398s; δ_H (500 MHz, C_6D_6) 0.74–0.82 (1 H, m, H9), 0.97–1.13 (2 H, m, H7 and H8), 1.22 (2 H, app. pent, H2), 1.45–1.59 (3 H, m, H7, H8 and H9), 1.65 (1 H, app. t, *J* = 14.5 Hz, H6), 1.95–2.05 (4 H, m, H3, H10 and H11), 2.09 (1 H, app. d, *J* = 14.5 Hz, H6), 2.58 (1 H, dd, *J* = 21.5 and 13.0 Hz, H11), 3.43 (1 H, dt, *J* = 11.5 and 7.0 Hz, H1), 3.53 (1 H, dt, *J* = 11.5 and 7.0 Hz, H1); δ_C (125 MHz, C_6D_6) 21.4 (C2), 25.7 (C8), 26.3 (C7), 26.9 (C3), 28.0 (C6), 34.7 (C10), 34.9 (C9), 38.9 (C11), 45.1 (C1), 108.1 (C5), 131.2 (C4), 165.7 (C12); HRMS (FI^+) found 192.1380, $C_{12}H_{18}NO$ (MH^+) requires 192.1383. **291c**: R_f 0.33 (1% MeOH in ether); ν_{max} 1643s, 1432m, 1408s; δ_H (500 MHz, C_6D_6) 0.50 (1 H, dddd, *J* = 12.9 Hz, 12.9 Hz, 11.5 and 4.0 Hz, H9), 0.84–1.01 (4 H, m, H6, H7, H8 and H10), 1.26–1.51 (4 H, m, H5, H7, H8 and H9), 1.67–1.71 (1 H, m, H6), 1.80 (1 H, dd, *J* = 16.5 and 12.5 Hz, H11), 2.01–2.13 (2 H, m, H2), 2.33 (1 H, dd, *J* = 16.5 and 4.0 Hz, H11) 3.68 (1 H, dddd, *J* = 12.0 Hz, 11.5, 7.5

and 1.0 Hz, H1), 3.68 (1 H, dddd, *J* = 13.0 Hz, 11.0 Hz, 6.0 and 0.5 Hz, H1), 4.40 (1 H, dd, *J* = 5.0 and 2.5 Hz, H3); δ_C (125 MHz, C_6D_6) 24.4 (C8), 24.6 (C7), 25.9 (C2), 27.6 (C6), 31.3 (C9), 35.3 (C10), 37.5 (C5), 38.9 (C11), 43.7 (C1), 100.1 (C3), 143.8 (C4), 164.5 (C12); HRMS (FI^+) found 214.1198, $C_{12}H_{17}NNaO$ (MNa^+) requires 214.1202. **291d**: R_f 0.33 (1% MeOH in ether); ν_{max} 1665s, 1409m; δ_H (500 MHz, C_6D_6) 0.88–1.02 (2 H, m, H7 and H9), 1.10–1.22 (3 H, m, H6, H7 and H8), 1.27–1.43 (3 H, m, H8, H9 and H10), 1.57–1.62 (1 H, m, H6), 2.03–2.14 (3 H, m, H2 and H5), 1.95 (1 H, dd, *J* = 17.0 and 5.0 Hz, H11), 2.00 (1 H, dd, *J* = 17.0 and 4.5 Hz, H11), 3.53 (2 H, m, H1), 4.42 (1 H, dd, *J* = 4.5 and 2.5 Hz, H1); δ_C (125 MHz, C_6D_6) 20.8 (C8), 23.6 (C9), 25.7 (C2), 26.6 (C6), 27.3 (C7), 32.5 (C5), 32.8 (C10), 36.7 (C11), 43.6 (C1), 102.1 (C3), 141.5 (C4), 163.9 (C12); HRMS (FI^+) found 214.1203, $C_{12}H_{17}NNaO$ (MNa^+) requires 214.1202.

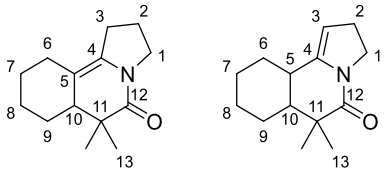
2-Bromo-1-(5-cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)-2-methylpropan-1-one (292)



To a 14 mL sample vial was added 5-cyclohexenyl-3,4-dihydro-2*H*-pyrrole (640 mg, 4.29 mmol), toluene (10 mL), 4 Å sieves (1 g), and the mixture stirred under argon at 0 °C. Pyridine (380 µL, 4.72 mmol), and α-bromoisobutyryl bromide (550 µL, 4.50 mmol) were added to the solution, which became turgid and immobile, before regaining mobility after 5 min. After 10 min, the solution was warmed to ambient temperature, and stirred for a further 1 h. The reaction was filtered through a sinter, washed with petrol, and reduced in volume under vacuum to a concentrated toluene solution. The product containing solution was quickly purified over silica, eluting with a gradient of 0.5% triethylamine in petrol to 20% ether with 0.5% triethylamine in petrol, yielding

the product as a white solid (1.16 g, 90%). M.p 90 °C; R_f 0.65 (ether); ν_{max} 1643s, 1624s, 1388s; δ_H (500 MHz, C_6D_6) 1.55 (1 H, dddd, *J* = 12.5 Hz, 6.0 Hz, 2.5 and 2.5 Hz, H9), 1.70 (1 H, dddd, *J* = 12.0 Hz, 6.0, 3.0 and 3.0 Hz, H8), 1.78 (6 H, s, H11), 2.00 (2 H, ddd, *J* = 7.5 Hz, 7.5 and 3.0 Hz, H2), 2.03–2.07 (1 H, m, H7), 2.21 (1 H, dddd, *J* = 8.5, 4.0, 2.5, and 2.5 Hz, H10), 3.86 (2 H, t, *J* = 8.0 Hz, H1), 5.07 (1 H, t, *J* = 3.0 Hz, H3), 5.83 (1 H, app. sept, *J* = 2.0 Hz, H6); δ_C (125 MHz, C_6D_6) 21.4 (C9), 21.7 (C8), 24.5 (C7), 26.5 (C10), 28.1 (C2), 31.0 (C11), 50.8 (C1), 57.9 (C12), 110.2 (C3), 123.0 (C6), 131.4 (C5), 148.5 (C4), 167.2 (C13); HRMS (FI^+) found 298.0800, $C_{14}H_{21}{}^{79}BrNO$ ($MH+^+$) requires 298.0801.

6,6-Dimethyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one (293a) and 6,6-dimethyl-2,6,6a,7,8,9,10,10a-octahydropyrrolo[2,1-a]isoquinolin-5(3*H*)-one (293b)

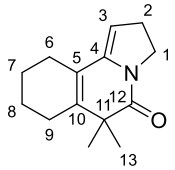


293a **293b**

A modified literature precedure[422–426] was used: To an oven-dried two-neck 100 mL round-bottom flask was added a 0.025 M solution 2-bromo-1-(5-cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)-2-methylpropan-1-one (200 mg, 0.673 mmol) in degassed toluene (27 mL) and the solution heated to 100 °C. A 0.043 M solution of Bu_3SnH (0.235 mL, 0.875 mmol) and AIBN (11 mg, 67 μmol) in degassed toluene (20 mL) was added dropwise over 1 h, and the reaction heated at reflux for 22 h. The reaction was removed from heat, and stirred with saturated aqueous KF solution (40 mL) for 3 h, and then extracted successively with DCM (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield a crude solid that was purified over silica eluting with a gradient of 0.5% triethylamine in petrol to 20% ether and 0.5% triethylamine in petrol.

Products **293a**+**293b** were isolated as a yellow oil in a ratio of 2.3:1 (106 mg, 72% combined). Separate analytical samples were obtained by further chromatography where possible. **293a**: R_f 0.40 (2:1 ether/petrol); ν_{max} 1658s, 1641s, 1408s; δ_H (500 MHz, C_6D_6) 0.98 (1 H, dq, *J* = 12.5 and 3.5 Hz, H9), 1.05–1.11 (2 H, m, H7 and H8), 1.17 (3 H, s, H13), 1.25 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.32 (3 H, s, H13), 1.54–1.67 (3 H, m, H7, H8 and H9), 1.74 (1 H, tdq, *J* = 14.0 Hz, 5.0 and 1.5 Hz, H6), 1.82 (1 H, app. d sept, *J* = 12.0 and 2.0 Hz, H10), 2.02 (2 H, m, *J*, H3), 2.15 (1 H, app. d pent, *J* = 14.0 and 2.0 Hz, H6), 3.47 and 3.55 (1 H, dt, *J* = 11.5 and 7.0 Hz, H1); δ_C (125 MHz, C_6D_6) 20.3 (C13), 21.5 (C2), 25.3 (C13), 26.1 (C8), 26.9 (C3), 27.0 (C7), 27.5 (C9), 29.0 (C6), 40.7 (C11), 45.7 (C1), 47.5 (C10), 108.5 (C5), 130.0 (C4), 172.3 (C12); HRMS (FI^+) found 220.1693, $C_{14}H_{22}NO$ (MH^+) requires 220.1696. *Note:* ***293b*** *was characterised as a minor product that co-eluted with* ***293a****. Reported is the partial spectra of* ***293b*** *obscured by* ***293a****.* **293b**: R_f 0.39 (2:1 ether/petrol); δ_H (500 MHz, C_6D_6) 1.01 and 1.32 (3 H, s, H13), 3.73 (1 H, ddd, *J* = 12.5 Hz, 11.5 and 7.5 Hz, H1), 3.87 (1 H, ddd, *J* = 12.5, 11.0, and 6.5 Hz, H1), 4.43 (1 H, app. q, *J* = 2.5 Hz, H3); δ_C (125 MHz, C_6D_6) 20.3 and 23.4 (C13), 25.2 (C1), 101.0 (C3).

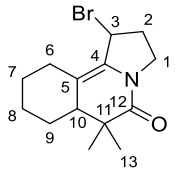
6,6-Dimethyl-2,3,7,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(6*H*)-one (294)



A modified literature procedure[427,428] was used. To a 10 mL oven-dried round-bottom flask was added 2-bromo-1-(5-cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)-2-methylpropan-1-one (100 mg, 0.336 mmol), CuBr (53 mg, 0.36 mmol), and degassed DCM (2.5 mL) and the insoluble mixture stirred at room temperature under argon. TMEDA (56 μL, 0.37 mmol) was added to the reaction, which instantly turned clear and

colourless and was stirred for 10 min, during which a green tint appeared in the solution. The reaction as heated to reflux for 2 h 20 min during which the solution turned brown, and then filtered through a plug of silica and concentrated to yield a crude oil. The oil was purified over basic alumina eluting with a gradient of 2.5% triethylamine in petrol, up to 40% ether in 2.5% triethylamine in petrol, separating the recovered starting material (16 mg) from the purified product, a yellow oil (71 mg, 78%, 92% B.R.S.M). R_f 0.43 (ether); ν_{max} 1720m, 1666s; δ_H (400 MHz, C_6D_6) 1.36 (6 H, s, H13), 1.36–1.40 (4 H, m, H7 and H8), 1.77 (2 H, br, H9), 1.99 (2 H, app. tt, *J* = 6.5 and 2.0 Hz, H6), 2.11 (2 H, app. tdt, *J* = 9.0, 3.0, and 1.0 Hz, H2), 3.80 (2 H, app. t, *J* = 9.0 Hz, H1), 4.56 (1 H, t, *J* = 3.0 Hz, H3); δ_C (100 MHz, C_6D_6) 21.9 (C7), 22.7 (C8), 24.2 (C9), 24.3 (C6), 25.3 (C13), 27.0 (C2), 44.0 (C11), 44.8 (C1), 102.0 (C3), 117.9 (C5), 140.5 (C4), 140.7 (C10), 170.1 (C12); HRMS (FI^+) found 218.1538, $C_{14}H_{20}NO$ (MH^+) requires 218.1539.

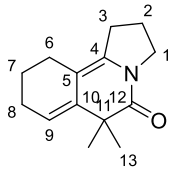
1-Bromo-6,6-dimethyl-2,3,6,6a,7,8,9,10-octahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one (295)



A modified literature procedure[427,428] was used. To a 7 mL sample vial was added 2-bromo-1-(5-cyclohexenyl-2,3-dihydro-1*H*-pyrrol-1-yl)-2-methylpropan-1-one (100 mg, 0.336 mmol), CuBr (15 mg, 0.10 mmol), and degassed DCM (2.5 mL) and the insoluble mixture stirred at room temperature under argon. PMDTA (21 µL, 0.10 mmol) was added to the reaction, which instantly turned which instantly turned a clear green that darkened over 15 min. The reaction was filtered through a pipette of silica and concentrated to yield a pale yellow oil as a 1:1.3 inseparable mixture of diastereoisomers (90 mg, 90%). The product was unstable to full column chromatography with either

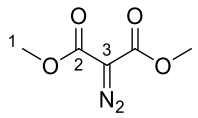
silica or alumina due to the lability of the alkl bromide moiety leading to dehydrobromination. R_f 0.24 (2:1 petrol/ether); ν_{max} 1605s; δ_H (400 MHz, $CDCl_3$) 1.02, 1.05, 1.15 and 1.18 (3 H, s, H13), 1.07–1.46 (3 H, m, H7, H8 and H9), 1.69–1.83 (3 H, m, H7, H8 and H9), 1.87–2.04 (3 H, m, H6 and H10), 2.17–2.29 (2 H, m, H2), 2.53 (1 H, app. t, *J* = 7.0 Hz, H6), 3.61–3.71 (1 H, m, H1), 3.90–4.02 (1 H, m, H1), 5.12 (1 H, d, *J* = 4.5 Hz, H3), 5.18 (1 H, d, *J* = 5.0 Hz, H3); δ_C (100 MHz, $CDCl_3$) 20.0, 20.3, 25.3 and 25.5 (C13), 25.6 and 25.8 (C8), 25.9 and 27.1 (C7), 27.1 and 27.8 (C9), 29.1 and 29.7 (C6), 34.6 and 34.7 (C2), 40.6 and 40.8 (C11), 43.6 and 43.7 (C1), 46.9 and 47.0 (C3), 47.7 and 47.9 (C10), 116.9 and 117.2 (C5), 131.2 and 131.6 (C4), 172.9 and 173.2 (C12); HRMS (FI^+) found 298.0796, $C_{14}H_{21}{}^{79}BrNO$ (MH^+) requires 298.0801.

6,6-Dimethyl-2,3,6,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one (296)



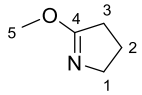
When purified over silica in the absence of triethylamine, or dissolved in $CDCl_3$, 6,6-dimethyl-2,3,7,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(6*H*)-one **(294)** would partially isomerise to 6,6-dimethyl-2,3,6,8,9,10-hexahydropyrrolo[2,1-a]isoquinolin-5(1*H*)-one ~1:1 ratio, which could be isolated by chromatography for characterisation. R_f 0.33 (ether); ν_{max} 1660s, 1410m; δ_H (500 MHz, C_6D_6) 1.19 (2 H, app. pent, *J* = 7.0 Hz, H2), 1.51 (6 H, s, H12), 1.57 (2 H, app. pent, *J* = 6. 0 Hz, H7), 1.81–1.86 (4 H, m, H3 and H8), 2.11 (2 H, tt, *J* = 6.5 and 1.0 Hz, H6), 3.47 (2 H, t, *J* = 7.0 Hz, H1), 5.44 (1H, t, *J* = 4.0 Hz, H9); δ_C (125 MHz, C_6D_6) 20.3 (C2), 21.7 (C7), 24.9 (C6), 25.1 (C3), 26.4 (C8), 26.6 (C13), 42.9 (C11), 45.1 (C1), 118.1 (C9), 122.9 (C5), 130.7 (C4), 140.3 (C10), 171.7 (C12); HRMS (FI^+) found 240.1358, $C_{14}H_{19}NNaO$ (MNa^+) requires 240.1359.

Dimethyl 2-diazomalonate (297)[431]



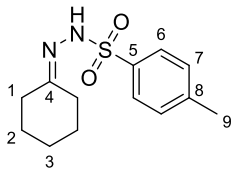
A literature procedure[431] was used. To an oven-dried 250 mL round-bottom flask was added 4-acetamidobenzenesulfonyl azide (1.90 g, 7.90 mmol), dry acetonitrile (30 mL), triethylamine (1.20 mL, 8.70 mmol), and the mixture stirred at 0 °C under argon. Dimethyl malonate (0.90 mL, 7.9 mmol) was added dropwise over 40 min, and the reaction stirred at room temperature for 21 h. The resulting white precipitate was filtered and washed with 1:1 petrol/ ether (2 x 200 mL). The filtrate was concentrated to yield a yellow oil, that was purified by distillation collecting at 40 °C (70 °C bath temperature) at 0.1 Torr, yielding a yellow oil (1.2 g, 96% yield) with data consistent with the literature data.[431] δ_H (400 MHz, $CDCl_3$) 3.82 (6 H, s, H1).

5-Methoxy-3,4-dihydro-2*H*-pyrrole (298)[432]



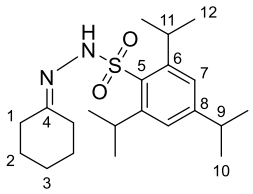
A literature procedure[432] was used. To an oven-dry 50 mL round bottom flask was added 2-pyrrolidinone (3.0 mL, 39 mmol) and dimethyl sulphate (3.7 mL, 39 mmol) and the mixture heated to 60 °C for 22 h. The reaction was removed from heat and poured onto saturated K_2CO_3 (100 mL), extracted successively with ether (3 x 50 mL), the combined organic layers dried (K_2CO_3) and concentrated to yield a colourless oil. The product was purified by distillation, collecting product between room temperature (20 Torr) and 60 °C (100 Torr) bath temperature as a colourless oil (1.519 g, 38% yield) with data consistent with the literature data.[432] δ_H (400 MHz, $CDCl_3$) 2.00 (2 H, app. t, J = 7.5 Hz, H2), 2.42 (2 H, app. pent, J = 8.0 Hz, H3), 3.63 (2 H, app. t, J = 7.0 Hz, H1), 3.77 (3 H, s, H5).

N′-Cyclohexylidene-4-methylbenzenesulfonohydrazide (300)[436]



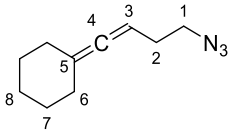
A literature procedure[436] was used. To an oven-dried 100 mL round-bottom flask was added cyclohexanone (1.55 mL, 15.0 mmol), tosyl hydrazide (2.9 g, 15 mmol), methanol (30 mL), and 10% aqueous HCl solution (0.1 mL). The reaction was attached with a reflux condenser and $CaCl_2$ drying tube and refluxed for 18 h. The reaction was cooled in ice, concentrated to remove solvent, then recrystallized from hot ethanol, yielding the product as a white solid (2.44 g, 60% yield) with data consistent with the literature data.[436] δ_H (400 MHz, $CDCl_3$) 1.57 (6 H, br, H2 and H3), 2.23 (2 H, br, H1), 2.42 (3 H, s, H9), 7.30 (2 H, d, *J* = 8.0 Hz, H7), 7.84 (2 H, d, *J* = 8.0 Hz, H6).

N′-Cyclohexylidene-2,4,6-triisopropylbenzenesulfonohydrazide (304)[438]



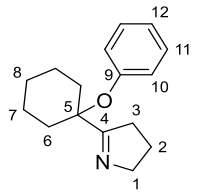
A literature procedure[438] was used. To a 20 mL sample vial was added cyclohexanone (0.315 mL, 3.04 mmol), trisylhydrazide (1.00 g, 3.04 mmol), methanol (3 mL), and 37% aqueous HCl (5 drops). The reaction was stirred for 1 h 15 min at room temperature, then stored at –20 °C for 23 h. The cloudy pink solution was filtered and washed with cold methanol. The precipitate was tried by three successive azeotropes with toluene, yielding the product as a white solid (758 mg, 66% yield) with data consistent with the literature data.[438] δ_H (400 MHz, $CDCl_3$) 1.57 (6 H, br, H2 and H3), 2.23 (2 H, br, H1), 2.42 (3 H, s, H9), 7.30 (2 H, d, *J* = 8.0 Hz, H7), 7.84 (2 H, d, *J* = 8.0 Hz, H6).

(4-Azidobut-1-en-1-ylidene)cyclohexane (312)



To a 10–20 mL Biotage microwave vial was added (4-azido-1-bromobutylidene)cyclohexane (50 mg, 0.19 mmol), Cs_2CO_3 (126 mg, 0.387 mmol), phenol (27 mg, 0.30 mmol), and BrettPhos generation 1 pre-catalyst (2 mg, 2.5 μmol), and the reaction vessel crimped and flushed with nitrogen. Toluene (2 mL) was added, and the white solution stirred at 60 °C for 16 h. The reaction was removed from heat, quenched with brine (5 mL), extracted successively with MTBE (3 x 10 mL), dried (Na_2SO_4), and concentrated to yield a crude oil. The oil was purified over silica, eluting with 2% MTBE in pentane, yielding the title product as a colourless oil (27 mg, 80%). R_f 0.36 (1:99, ether/petrol); ν_{max} 2094s; δ_H (400 MHz, $CDCl_3$) 1.47–1.66 (6 H, m, H7 and H8), 2.06–2.18 (4 H, m, H6), 2.26 (2 H, dt, *J* = 7.0 and 6.5 Hz, H2), 3.21 (2 H, t, *J* = 7.0 Hz, H1). 4.91–5.06 (1H, m, H3); δ_C (100 MHz, $CDCl_3$) 26.1 (C8), 27.4 (C6), 28.8 (C7), 31.5 (C2), 50.7 (C1), 84.8 (C3), 103.8 (C5), 199.0 (C4); HRMS (FI^+) found 177.1266, $C_{10}H_{15}N_3$ (M^+) requires 177.1266.

5-(1-Phenoxycyclohexyl)-3,4-dihydro-2*H*-pyrrole (316)



To a 10–20 mL Biotage microwave vial was added (4-azido-1-bromobutylidene)cyclohexane (100 mg, 0.387 mmol), Cs_2CO_3 (252 mg, 0.774 mmol), phenol (54 mg, 0.58 mmol), and BrettPhos generation 1 pre-catalyst (4 mg, 5 μmol), and the reaction vessel crimped and flushed with nitrogen. Toluene (4 mL) was added, and the white solution stirred at 100 °C for 16 h, then 120 °C for 18 h. The reaction was

removed from heat, quenched with brine (20 mL), extracted successively with MTBE (3 x 10 mL), dried (Na_2SO_4), and concentrated to yield a crude oil. The oil was purified over silica, eluting with 0–30% MTBE in pentane, yielding the title product as a colourless oil (10 mg, 10%), and 5-cyclohexenyl-3,4-dihydro-2H-pyrrole **(199)** (24 mg, 42%). R_f 0.44 (1:1, ether/petrol); ν_{max} 1635m, 1569m, 1492m, 1224s; δ_H (400 MHz, $CDCl_3$) 1.25–1.34 (1 H, m, H8), 1.51–1.70 (5 H, m, H7 and H8), 1.79 (2 H, td, *J* = 12.0 and 4.5 Hz, H6), 1.88 (2 H, app. pent, *J* = 7.5 Hz, H2). 2.24 (2 H, br d, *J* = 12.5 Hz, H3), 2.64 (2 H, tt, *J* = 7.5 and 2.0 Hz, H3), 3.95 (2 H, tt, *J* = 7.5 and 2.0 Hz, H1), 6.83–6.86 (2 H, m, H10), 6.93 (1 H, tt, *J* = 7.5 and 1.0 Hz, H12), 7.21 (2 H, dd, *J* = 8.5 and 7.5 Hz, H11); δ_C (100 MHz, $CDCl_3$) 21.3 (C7), 22.5 (C2), 25.4 (C8), 33.0 (C6), 33.7 (C3), 61.1 (C1), 80.0 (C5), 117.9 (C10), 121.0 (C12), 129.2 (C11), 155.8 (C9), 183.5 (C4); HRMS (FI^+) found 244.1696, $C_{16}H_{22}NO$ (MH^+) requires 244.1699.

4 References

(1) Balucani, N. *Chem. Soc. Rev.* **2012**, *41*, 5473.

(2) Burton, A. S.; Stern, J. C.; Elsila, J. E.; Glavin, D. P.; Dworkin, J. P. *Chem. Soc. Rev.* **2012**, *41*, 5459.

(3) Watson, J. D.; Crick, F. H. C. *Nature* **1953**, *171*, 964.

(4) Cobb, M. *Cell* **2013**, *153*, 503.

(5) Dahm, R. *Hum. Genet.* **2008**, *122*, 565.

(6) Clayton, J.; Dennis, C. *50 Years of DNA*; Palgrave Macmillan, 2003; pp. 1–120.

(7) Fischer. H; Kirstahler. A. *Justus Liebigs Ann. Chem* **1928**, *466*, 178.

(8) Wilson, M. T.; Reeder, B. J. *Exp. Physiol.* **2008**, *93*, 128.

(9) Fattorusso, E.; Taglialatela-Scafati, O. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; 1st Ed.; Wiley VCH, 2007; pp. 1–665.

(10) Hesse, M. *Alkaloids: Natures Curse or Blessing?*; 1st Ed.; Wiley VCH, 2002; pp. 1–414.

(11) Komeilizadeh, H. *Iran. J. Pharm. Res.* **2006**, *4*, 229.

(12) Dua, R.; Shrivastava, S.; Sonwane, S. K.; Srivastava, S. K. *Advan. Biol. Res.* **2011**, *5*, 120.

(13) Bartholow, M. http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012.

(14) Lamberth, C.; Dinges, J. *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Wiley VCH, 2012; pp. 1–302.

(15) Evans, D. A.; Ripin, D. H. http://evans.rc.fas.harvard.edu/pdf/evans_pKa_table.pdf.

(16) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151.

(17) Al-Ajlouni, A. M.; Günyar, A.; Zhou, M.-D.; Baxter, P. N. W.; Kühn, F. E. *Eur. J. Inorg. Chem.* **2009**, *2009*, 1019.

(18) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8.

(19) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(20) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774.

(21) Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III*; Wiley VCH, 2011; pp. 1–770.

(22) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II: More Targets, Strategies, Methods*; Wiley VCH, 2003; pp. 1–685.

(23) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; Wiley VCH, 1996; pp. 1–821.

(24) Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014**, *79*, 2809.

(25) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discov. Today* **2011**, *16*, 164.

(26) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(27) Griess, P. *Proc. R. Soc. London* **1864**, *13*, 375.

(28) Curtius, T. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023.

(29) Turnbull, K.; Scriven, E. F. V. *Chem. Rev.* **1988**, *88*, 297.

(30) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed. Engl.* **2005**, *44*, 5188.

(31) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. *Chem. Commun. (Camb).* **2014**, *50*, 11440.

(32) Chiba, S. *Synlett* **2011**, *2012*, 21.

(33) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831.

(34) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chemistry* **2009**, *15*, 7830.

(35) Abbe, G. L. *Chem. Rev.* **1969**, *69*, 345.

(36) Nguyen, M. T.; Sengupta, D.; Ha, T.-K. *J. Phys. Chem.* **1996**, *100*, 6499.

(37) Yang, X.; Kiran, B.; Wang, X.; Wang, L.; Box, P. O.; Mucha, M.; Jungwirth, P. *J. Phys. Chem. A* **2004**, *108*, 7820.

(38) Loibner, H.; Zbiral, E. *Helv. Chim. Acta.* **1976**, *59*, 2100.

(39) Silverman, R. B.; Gomez-Vidal, J. A. *Org. Lett.* **2001**, *3*, 2481.

(40) Simonl, C.; Malkleit, S.; Hosztafi, S. *Tetrahedron Lett.* **1993**, *34*, 6475.

(41) Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem* **2000**, *65*, 7110.

(42) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107.

(43) Robiette, R.; Tran, T.-V.; Cordi, A.; Tinant, B.; Marchand-Brynaert, J. *Synthesis (Stuttg).* **2010**, *18*, 3138.

(44) Tingoli, M.; Tiecco, M.; Chianelli, D.; Balducci, R.; Temperini, A. *J. Org. Chem.* **1991**, *56*, 6809.

(45) Chabaud, L.; Landais, Y. *Tetrahedron Lett.* **2003**, *44*, 6995.

(46) Wiley, J.; Biekert, E.; Janeiro, R. De. *J. Am. Chem. Soc.* **1965**, *87*, 4203.

(47) Sharma, A.; Hartwig, J. F. *Nature* **2014**, *517*, 600.

(48) Bandgar, B. P.; Pandit, S. S. *Tetrahedron Lett.* **2002**, *43*, 3413.

(49) Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403.

(50) Padwa, A.; Brodney, M. a.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.

(51) Kauer, J. C.; Carboni, R. A. *J. Am. Chem. Soc.* **1967**, *89*, 2633.

(52) Capitosti, S. M.; Hansen, T. P.; Brown, M. L. *Org. Lett.* **2003**, *5*, 2865.

(53) Chehade, K. a. H.; Spielmann, H. P. *J. Org. Chem.* **2000**, *65*, 4949.

(54) Miller, D. R.; Swenson, D. C.; Gillan, E. G. *J. Am. Chem. Soc.* **2004**, *126*, 5372.

(55) Wilson, W. S.; Nissan, R. A.; Lowe-Ma, C. K. *J. Org. Chem* **1990**, *55*, 3755.

(56) Curtius, T. *J. fer Prakt. Chemie* **1894**, *50*, 275.

(57) Linke, S.; Tisue, G. T.; Lwowski, W. *J. Am. Chem. Soc.* **1967**, *89*, 6308.

(58) Tarwade, V.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 8189.

(59) Zabalov, M. V.; Tiger, R. P. *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 2270.

(60) Wentrup, C.; Bornemann, H. *European J. Org. Chem.* **2005**, *2005*, 4521.

(61) Smith, P. A. S. *Org. React. N. Y.* **1946**, *3*, 377.

(62) Menger, F. M.; Bian, J.; Azov, V. A. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2581.

(63) Hemantha, H.; Chennakrishnareddy, G.; Vishwanatha, T.; Sureshbabu, V. *Synlett* **2009**, *2009*, 407.

(64) Bolshan, Y.; Tomaszewski, M. J.; Santhakumar, V. *Tetrahedron Lett.* **2007**, *48*, 4925.

(65) Sun, X.; Rai, R.; Deschamps, J. R.; Mackerell, A. D.; Faden, A. I.; Xue, F. *Tetrahedron Lett.* **2014**, *55*, 842.

(66) Overman, L. E.; Roos, J.; Petty, B. *Org. Synth.* **1979**, *59*, 1.

(67) Czako, B.; Kurti, L. *Strategic Applications of Named Reactions in Organic Synthesis*; Academic Press, 2005; p. 116.

(68) Chen, F.; Su, B.; Wang, Q. *Org. Chem. Front.* **2014**, *1*, 674.

(69) Cheng, X.; Waters, S. P. *Org. Lett.* **2013**, *15*, 4226.

(70) Stevens, K.; Tyrrell, A. J.; Skerratt, S.; Robertson, J. *Org. Lett.* **2011**, *13*, 5964.

(71) Schmidt, K. F. *Angew. Chem* **1923**, *36*, 511.

(72) Aube, J.; Frank, K. E.; Milligan, G. L.; Gracias, V. *Tetrahedron* **1997**, *53*, 16241.

(73) Aube, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965.

(74) Aube, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635.

(75) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951.

(76) Boyer, J. H.; Morgan, L. R. *J. Org. Chem* **1959**, *24*, 561.

(77) Aube, J.; Li, S.; Huh, C.; Coombs, T.; Wrobleski, A. *Org. React.* **2012**, *78*, 1.

(78) Schultz, A. G.; Wang, A.; Alva, C.; Sebastian, A.; Glick, S. D.; Deecher, D. C.; Bidlack, J. M. *J. Med. Chem* **1996**, *39*, 1956.

(79) Kuhn, L. P.; DiDomenico, J. *J. Am. Chem. Soc.* **1950**, *72*, 5777.

(80) Andrieux, J.; Plat, M. M.; Adam, G. *Tetrahedron Lett.* **1983**, *24*, 3609.

(81) Andrieux, J.; Alberici, G. F.; Adam, G.; Plat, M. I. M. *Tetrahedron Lett.* **1983**, *24*, 1937.

(82) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320.

(83) Pearson, W. H.; Fang, W. *J. Org. Chem* **2000**, *65*, 7158.

(84) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **2001**, *57*, 5081.

(85) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583.

(86) Pearson, W. H.; Hutta, D. a.; Fang, W. *J. Org. Chem.* **2000**, *65*, 8326.

(87) Aube, J.; Milligan, G. L.; Mossman, C. J. *J. Am. Chem. Soc.* **1995**, *117*, 10449.

(88) Su, B.; Chen, F.; Wang, Q. *J. Org. Chem.* **2013**, *78*, 2775.

(89) Kapat, A.; Nyfeler, E.; Giuffredi, G. T.; Renaud, P. *J. Am. Chem. Soc.* **2009**, *131*, 17746.

(90) Smith, B. T.; Wendt, J. A.; Aube, J. *Org. Lett.* **2002**, *4*, 2577.

(91) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974.

(92) Iyengar, R.; Schildknegt, K.; Aube, J. *Org. Lett.* **2000**, *2*, 1625.

(93) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Am. Chem. Soc.* **2005**, *70*, 10645.

(94) Aube, J.; Desai, P.; Schildknegt, K.; Agrios, K. A.; Mossman, C.; Milligan, G. L.; February, R. V. *J. Am. Chem. Soc.* **2000**, *122*, 7226.

(95) Gracias, V.; Milligan, G. L.; Aube, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047.

(96) Aube, J.; Gracias, V.; Milligan, G. L. *J. Org. Chem.* **1996**, *61*, 10.

(97) Trost, B. M. *Reduction: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; 1st Ed.; 1992; pp. 1–1039.

(98) Gaoni, Y. *J. Org. Chem* **1994**, *59*, 6853.

(99) Chakraborty, T. K.; Laxman, P. *Tetrahedron Lett.* **2003**, *44*, 4989.

(100) Ali, Y.; Richardson, A. C. *Carbohydr. Res.* **1967**, *5*, 441.

(101) Rolla, F. *J. Org. Chem* **1982**, *47*, 4327.

(102) Firouzabadi, H.; Adibi, M.; Zeynizadeh, B. *Synth. Commun.* **1998**, *28*, 1257.

(103) Fringuelli, F.; Pizzo, F.; Vaccaro, L.; Chimica, D.; Elce, V. *Synthesis (Stuttg).* **2000**, *5*, 646.

(104) Firouzabadi, H.; Tamami, B.; Kiasat, a. R. *Synth. Commun.* **2000**, *30*, 587.

(105) Ranu, B. C.; Sarkar, A.; Chakraborty, R. *J. Org. Chem.* **1994**, *59*, 4114.

(106) Salunkhe, A. M.; Veeraraghavan Ramachandran, P.; Brown, H. C. *Tetrahedron* **2002**, *58*, 10059.

(107) Goulaouic-dubois, C.; Hesse, M. *Tetrahedron Lett.* **1995**, *36*, 7427.

(108) Benati, L.; Bencivenni, G.; Leardini, R.; Nanni, D.; Minozzi, M.; Spagnolo, P.; Scialpi, R.; Zanardi, G. *Org. Lett.* **2006**, *8*, 2499.

(109) Kamal, A.; Laxman, E.; Arifuddin, M. *Tetrahedron Lett.* **2000**, *41*, 7743.

(110) Kirk, B. D. N.; Wilson, M. A. *J. Chem. Soc. D.* **1970**.

(111) Staudinger, H.; Meyer, J. *Helv. Chim. Acta.* **1919**, *2*, 635.

(112) Tian, W. Q.; Wang, Y. A. *J. Org. Chem* **2004**, *69*, 4299.

(113) Lingamurthy, M.; Rajender, A.; Rao, B. V. *Tetrahedron: Asymmetry* **2014**, *25*, 860.

(114) Long, B.; Tang, S.; Chen, L.; Qu, S.; Chen, B.; Liu, J.; Maguire, A. R.; Wang, Z.; Liu, Y.; Zhang, H.; Xu, Z.; Ye, T. *Chem. Commun.* **2013**, *49*, 2977.

(115) Lee, S.-J.; Youn, S.-H.; Cho, C.-W. *Org. Biomol. Chem.* **2011**, *9*, 7734.

(116) Dixon, D. J.; Núñez, M. G.; Farley, A. J. M. *J. Am. Chem. Soc.* **2013**, *135*, 16348.

(117) Bräse, S.; Banert, K. *Organic Azides: Syntheses and Applications*; 2010; p. 439.

(118) Williams, D. R.; Shamim, K.; Reddy, J. P.; Amato, G. S.; Shaw, S. M. *Org. Lett.* **2003**, *5*, 3361.

(119) Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamotot, Y.; Engineering, M. *Tetrahedron* **1998**, *54*, 7997.

(120) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112.

(121) Saxon, E.; Bertozzi, C. *Science.* **2000**, *287*, 2007.

(122) Köhn, M.; Breinbauer, R. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3106.

(123) Saxon, E.; Armstrong, J. I.; Bertozzi, C. R. *Org. Lett.* **2000**, *2*, 2141.

(124) Palacios, F.; Retana, A.; Marigorta, E.; Santos, J. *Eur. J. Inorg. Chem.* **2001**, *13*, 2401.

(125) Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem* **1986**, *51*, 3176.

(126) Lopes, Â. S. J.; Cardoso, A. L.; Pinho, T. M. V. D. *Tetrahedron* **2001**, *57*, 6203.

(127) Sjo, Å. *J. Org. Chem* **2003**, *68*, 9958.

(128) Farney, E. P.; Yoon, T. P. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 793.

(129) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem* **1999**, *64*, 2852.

(130) Jin, L.-M.; Xu, X.; Lu, H.; Cui, X.; Wojtas, L.; Zhang, X. P. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 5309.

(131) Morimoto, Y.; Matsuda, F.; Shimhama, H. *Tetrahedron* **1996**, *52*, 10609.

(132) Gao, G.; Jones, J. E.; Vyas, R.; Harden, J. D.; Zhang, X. P. *J. Org. Chem* **2006**, *71*, 6655.

(133) Stokes, B. J.; Driver, T. G. *European J. Org. Chem.* **2011**, 4071.

(134) Driver, T. G. *Nat. Chem.* **2013**, *5*, 736.

(135) Sunberg, R. J.; Russel, H. R.; Ligon, W. V; Lin, L. *J. Org. Chem* **1972**, *37*, 719.

(136) Smith, P. A. S.; Rowe, C. D.; Hansen, D. W. *Tetrahedron Lett.* **1983**, *24*, 5169.

(137) Shin, K.; Baek, Y.; Chang, S. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 8031.

(138) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591.

(139) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141.

(140) Xiao, W.; Wei, J.; Zhou, C.-Y.; Che, C.-M. *Chem. Commun. (Camb).* **2013**, *49*, 4619.

(141) Suárez, J. R.; Chiara, J. L. *Chem. Commun. (Camb).* **2013**, *49*, 9194.

(142) Sharpless, K. B.; Kolb, H. C.; Finn, M. G. *Angew. Chemie Int. Ed.* **2001**, *40*, 2004.

(143) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128.

(144) Tang, W.; Becker, M. L. *Chem. Soc. Rev.* **2014**, *43*, 7013.

(145) Huisgen, R. *Proc. Chem. Soc.* **1961**, *October*, 357.

(146) Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565.

(147) Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1231.

(148) Kumar, K. A. *Int. J. ChemTech Res.* **2013**, *5*, 3032.

(149) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781.

(150) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.

(151) Das, R.; Majumdar, N.; Lahiri, A. *IJRPC* **2014**, *4*, 467.

(152) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717.

(153) Rostovtsev, V. V; Green, L. G.; Fokin, V. V; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2596.

(154) Clarke, D.; Mares, W.; Mcnab, H. *J. Chem. Soc., Perkin Trans 1* **1997**, 1799.

(155) Howell, S. J.; Spencer, N.; Philp, D. *Tetrahedron* **2001**, *57*, 4945.

(156) Chen, J.; Rebek, J. *Org. Lett.* **2002**, *4*, 327.

(157) Głowacka, I. E. *Tetrahedron: Asymmetry* **2009**, *20*, 2270.

(158) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem* **2002**, *67*, 3057.

(159) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

(160) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *European J. Org. Chem.* **2006**, 51.

(161) Appukkuttan, P.; Dehaen, W.; Fokin, V. V; Eycken, E. Van Der. *Org. Lett.* **2004**, *6*, 4223.

(162) Zhang, C.; Huang, B.; Chen, Y.; Cui, D.-M. *New J. Chem.* **2013**, *37*, 2606.

(163) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Vol 5.; Pergamon, Oxford, 1984; pp. 669–732.

(164) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249.

(165) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905.

(166) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278.

(167) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207.

(168) Xu, L.; Li, Y.; Li, Y. *Asian J. Org. Chem.* **2014**, *3*, 582.

(169) Golas, P. L.; Matyjaszewski, K. *Chem. Soc. Rev.* **2010**, *39*, 1338.

(170) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197.

(171) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.

(172) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923.

(173) Yap, A. H.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3035.

(174) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem* **2006**, *71*, 8680.

(175) Boz, E.; Tüzün, N. Ş. *J. Organomet. Chem.* **2013**, *724*, 167.

(176) Li, R.; Jansen, D. J.; Datta, A. *Org. Biomol. Chem.* **2009**, *7*, 1921.

(177) Sau, M.; Rodriguex-Escrich, C.; Paricas, M. *Org. Lett.* **2011**, *13*, 5044.

(178) Kumar, I.; Mir, N. a.; Rode, C. V.; Wakhloo, B. P. *Tetrahedron: Asymmetry* **2012**, *23*, 225.

(179) Brawn, R. a; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett.* **2010**, *12*, 336.

(180) Chowdhury, C.; Mukherjee, S.; Das, B. *J. Org. Chem* **2009**, *74*, 3612.

(181) Lamaty, F.; Martinex, J.; Toupet, L.; Declerck, V. *J. Org. Chem* **2009**, *74*, 2004.

(182) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439.

(183) Oliva, A. I.; Christmann, U.; Font, D.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Perica, M. A. *Org. Lett.* **2008**, *10*, 1617.

(184) Vekariya, R. H.; Liu, R. *Org. Lett.* **2014**, *16*, 1844.

(185) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 2818.

(186) Shechter, H.; Bleiholder, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 2131.

(187) Wedegaertner, D. K.; Kattak, R. K.; Harrison, I.; Cristie, S. K. *J. Org. Chem.* **1991**, *56*, 4463.

(188) Feldman, K. S.; Iyer, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 4590.

(189) Feldman, K. S.; Iyer, M. R.; Hester, D. K. *Org. Lett.* **2006**, *8*, 3113.

(190) Lo, C. S.; Faza, O. N.; Feldman, K. S.; Iyer, M. R.; Ii, D. K. H. *J. Am. Chem. Soc.* **2007**, *129*, 7638.

(191) Feldman, K. S.; Iyer, M. R.; Lo, C. S.; Faza, O. N. *J. Org. Chem* **2008**, *73*, 5090.

(192) Feldman, K. S.; Ii, D. K. H.; Lopez, C. S.; Faza, O. N. *Org. Lett.* **2008**, *10*, 1665.

(193) Feldman, K. S.; Antoline, J. F. *Org. Lett.* **2012**, *14*, 934.

(194) Feldman, K. S.; Antoline, J. F. *Tetrahedron* **2013**, *69*, 1434.

(195) Wolff, L. *Justus Liebigs Ann. Chem* **1912**, *394*, 68.

(196) Alder, V. K.; Stein, G.; Finzenhagen, H. *Justus Liebigs Ann. Chem* **1931**, *485*, 211.

(197) Alder, K.; Stein, G. *Justus Liebigs Ann. Chem* **1933**, *501*, 1.

(198) Chattaway, F. D.; Parkes, G. D. *J. Chem. Soc., Trans.* **1925**, *127*, 1307.

(199) Fieser, L. F.; Hartwell, J. L. *J. Am. Chem. Soc.* **1935**, *57*, 1479.

(200) Oehlschlager, A. C.; Zalkow, L. H. *J. Org. Chem* **1963**, *28*, 3303.

(201) Scheiner, P.; Schomaker, J. H.; Deming, S.; Libbey, W. J.; Nowack, G. P. *J. Am. Chem. Soc.* **1965**, *87*, 306.

(202) Nicholas, P. P. *J. Org. Chem* **1975**, *40*, 3396.

(203) Marsh, F. D.; Hermes, M. E. *J. Am. Chem. Soc.* **1964**, *86*, 4506.

(204) Scheiner, P. *J. Org. Chem* **1965**, *30*, 7.

(205) Scheiner, P. *J. Org. Chem* **1967**, *32*, 2022.

(206) Reddy, D. S.; Judd, W. R.; Aube, J. *Org. Lett.* **2003**, *5*, 3899.

(207) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988.

(208) Scheiner, P. *Tetrahedron* **1968**, *24*, 2757.

(209) Suman, K.; Srinu, L.; Thennarasu, S. *Org. Lett.* **2014**, *16*, 3732.

(210) Peng, W.; Zhu, S. *Tetrahedron* **2003**, *59*, 4395.

(211) Zhu, S.; Peng, W. *Synlett* **2002**, *2*, 187.

(212) Zanirato, P. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1420.

(213) Zaragoza, F.; Petersen, S. V. *Tetrahedron* **1996**, *52*, 10823.

(214) Harju, K.; Vahermo, M.; Mutikainen, I.; Yli-kauhaluoma, J. *J. Comb. Chem* **2003**, *5*, 826.

(215) Pocar, B. D.; Stradi, R.; Rossi, L. M.; Organica, C.; Farmacia, F. *J. Chem. Soc., Perkin Trans 1* **1972**, 619.

(216) Li, W.; Jia, Q.; Du, Z.; Wang, J. *Chem. Commun. (Camb).* **2013**, *49*, 10187.

(217) Pocar, B. D.; Stradi, R.; Rossi, L. M.; Organica, C.; Farmacia, F. *J. Chem. Soc., Perkin Trans 1* **1972**, 769.

(218) Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. *Synthesis (Stuttg).* **2005**, 2497.

(219) Huisgen, R.; Mobius, L.; Szeimies, G. *Chem. Ber* **1965**, *98*, 1138.

(220) Chabala, J. C.; Christensen, B. G.; Ratcliffe, R. W.; Woods, M. F. *Tetrahedron Lett.* **1985**, *26*, 5407.

(221) Dahl, R. S.; Finney, N. S. *J. Am. Chem. Soc.* **2004**, *126*, 8356.

(222) Wang, Y.; Xie, Y.; Qu, H.; Wang, H.; Pan, Y.; Huang, F. *J. Org. Chem* **2014**, *79*, 4463.

(223) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem* **2005**, *70*, 6526.

(224) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*, 10155.

(225) Janreddy, D.; Kavala, V.; Kuo, C.-W.; Chen, W.-C.; Ramesh, C.; Kotipalli, T.; Kuo, T.-S.; Chen, M.-L.; He, C.-H.; Yao, C.-F. *Adv. Synth. Catal.* **2013**, *355*, 2918.

(226) Logothetis, A. L. *J. Am. Chem. Soc.* **1965**, *87*, 749.

(227) Fusco, R.; Garanti, L.; Zecchi, G. *J. Org. Chem* **1975**, *40*, 1906.

(228) Padwa, A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123.

(229) Schultz, A.; Ravichandran, R. *J. Org. Chem* **1980**, *45*, 5008.

(230) Pearson, M. J.; Branch, C. L. *J. Chem. Soc., Chem. Comm* **1981**, 946.

(231) Kozikowski, A. P.; Park, P. *J. Org. Chem* **1984**, *49*, 1676.

(232) Sha, C.; Hseub, T. *J. Chem. Soc., Chem. Comm* **1984**, 492.

(233) Liu, J.-M.; Young, J.-J.; Li, Y.-J.; Sha, C.-K. *J. Org. Chem* **1986**, *51*, 1120.

(234) Sha, C.; Ouyang, S.; Hsieh, D.; Chang, R.; Chang, S. *J. Org. Chem* **1986**, *51*, 1490.

(235) Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1987**, *28*, 97.

(236) Hassner, A.; Andisik, D.; Amarasekara, A. *J. Org. Chem* **1988**, *53*, 27.

(237) Bennett, R. B.; Choi, J.; Montgomery, W. D.; Cha, J. K. *J. Chem. Soc., Chem. Comm* **1989**, *111*, 2580.

(238) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7571.

(239) Pearson, W. H.; Bergmeier, S. C.; Heidt, P. C. *Tetrahedron Lett.* **1990**, *31*, 5441.

(240) Moss, W.; Bradbury, R. H.; Hales, N. J.; Gallaghera, T. *J. Chem. Soc., Chem. Comm* **1990**, 51.

(241) Moss, W.; Wakefield, E.; Mahon, B. M. F.; Mloy, K. C.; Bradbury, R. H.; Park, A.; Sk, M. *Tetrahedron* **1992**, *48*, 7551.

(242) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **1994**, *50*, 12293.

(243) Schkeryantz, J. M.; Pearson, W. H. *Tetrahedron* **1996**, *52*, 3107.

(244) Pearson, W. H.; Suga, H. *J. Org. Chem* **1998**, *63*, 9910.

(245) Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, *38*, 4347.

(246) Molander, G. A.; Bibeau, C. T. *Tetrahedron Lett.* **2002**, *43*, 5385.

(247) Ducray, R.; Ciufolini, M. A. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4688.

(248) Guo, Z.; Schultz, A. G. *Tetrahedron Lett.* **2004**, *45*, 919.

(249) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D.; April, R. V. *J. Org. Chem* **2007**, *72*, 4886.

(250) Zhou, Y.; Murphy, P. V. *Org. Lett.* **2008**, *10*, 3777.

(251) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A. *J. Org. Chem.* **2010**, *75*, 5289.

(252) de Miguel, I.; Herradón, B.; Mann, E. *Adv. Synth. Catal.* **2012**, *354*, 1731.

(253) De Miguel, I.; Velado, M.; Herradón, B.; Mann, E. *Adv. Synth. Catal.* **2013**, *355*, 1237.

(254) Hemming, K.; Chambers, C. S.; Jamshaid, F.; O'Gorman, P. A. *Molecules* **2014**, *19*, 16737.

(255) Bhattacharya, D.; Ghorai, A.; Pal, U.; Chandra Maiti, N.; Chattopadhyay, P. *RSC Adv.* **2014**, *4*, 4155.

(256) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem* **1992**, *57*, 6783.

(257) De Miguel, I.; Velado, M.; Herradón, B.; Mann, E. *European J. Org. Chem.* **2012**, 4347.

(258) Schultz, A. G.; Myong, S. O.; Sha, C.; Dittami, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 3273.

(259) Hudlicky, T.; Frazier, J.; Kwart, L. *Tetrahedron Lett.* **1985**, *26*, 3523.

(260) Hudlicky, T.; Frazier, J.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L. D.; Beal, C. *J. Am. Chem. Soc.* **1986**, *108*, 3755.

(261) Pearson, W. H. *Tetrahedron Lett.* **1985**, *26*, 3527.

(262) Pearson, W. H.; Poon, Y.-F.; Glans, Jeffrey, H.; Celebuski, J. E.; Dixon, B. R. *Tetrahedron Lett.* **1986**, *27*, 6301.

(263) Pearson, W. H.; Poon, Y. *Tetrahedron Lett.* **1989**, *30*, 6661.

(264) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.; Poon, Y.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719.

(265) Uhle, F. C. *Tetrahedron Lett.* **1964**, *42*, 3099.

(266) Uhle, F. C. *J. Org. Chem* **1967**, *32*, 1596.

(267) Zha, X.; Sun, H.; Hao, J.; Zhang, Y. *Chem. Biodivers.* **2007**, *4*, 25.

(268) Zha, X. M.; Zhang, F. R.; Shan, J. Q.; Zhang, Y. H.; Liu, J. O.; Sun, H. Bin. *Chinese Chem. Lett.* **2010**, *21*, 1087.

(269) Ciufolini, M. a.; Chen, M.; Lovett, D. P.; Deaton, M. V. *Tetrahedron Lett.* **1997**, *38*, 4355.

(270) Yao, L.; Smith, B. T.; Aube, J. *J. Org. Chem.* **2004**, *69*, 1720.

(271) Padwa, A.; Ku, A.; Ku, H.; Mazzu, A. *J. Org. Chem.* **1978**, *43*, 66.

(272) Feast, G. C. Thesis: Aziridination of Tethered Allenes, 2011, Robertson, J group, Oxford.

(273) Feast, G. C.; Page, L. W.; Robertson, J. *Chem. Commun. (Camb).* **2010**, *46*, 2835.

(274) Robertson, J.; Feast, G. C.; White, L. V; Steadman, V. A; Claridge, T. D. W. *Org. Biomol. Chem.* **2010**, *8*, 3060.

(275) Zhurakovskyi, O. Thesis: Pericyclic and Related Rearrangements for the Synthesis of Nitrogen Heterocyclic Ring Systems, 2013, Robertson, J group, Oxford.

(276) Baldwin, J. E.; Hofle, G. A.; Lever, W. J. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(277) Kocienski, P. J.; Pritchard, M.; Wadman, S. N.; Whitby, R. J.; Yeates, C. L. *J. Chem. Soc., Perkin Trans 1.* **1992**, *24*, 3419.

(278) Hedenstrom, E.; Edlund, H.; Lund, S.; Abersten, M.; Persson, D. *J. Chem. Soc. Perkin Trans. 1* **2002**, *15*, 1810.

(279) Le Ménez, P.; Brion, J.-D.; Lensen, N.; Chelain, E.; Pancrazi, A.; Ardisson, J. *Synthesis (Stuttg).* **2003**, 2530.

(280) Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735.

(281) Krawczuk, P. Baran Group Meeting. Directed Metalation : A Survival Guide.

(282) Lever, W. O. J. *Tetrahedron* **1976**, *32*, 1943.

(283) Khoukhi, N.; Vauitier, M.; Carrie, R. *Tetrahedron* **1987**, *43*, 1811.

(284) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Struct.* **2008**, *892*, 210.

(285) Wiberg, K. B. *Angew. Chemie Int. Ed.* **1986**, *25*, 312.

(286) Baldwin, J. E. *J. Chem. Soc., Chem. Comm* **1976**, 734.

(287) Thorpe, J. F.; Ingold, C. K.; Beesley, R. M. *J. Chem. Soc., Trans* **1915**, *107*, 1080.

(288) Kim, S.; Lee, J. M. *Synth. Commun.* **1991**, *21*, 25.

(289) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623.

(290) Wittig, G.; Boll, W.; Kruck, K.-H. *Chem. Ber.* **1962**, *95*, 2514.

(291) Baumann, T.; Vogt, H.; Bräse, S. *European J. Org. Chem.* **2007**, *2007*, 266.

(292) Boeckman, R. J.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

(293) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.

(294) Petasis, N.; Bzowej, E. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

(295) Takai, K.; Utimoto, K.; Oshima, K.; Okazoe, T. *J. Org. Chem* **1987**, *52*, 4410.

(296) Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2763.

(297) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.

(298) Takeda, T.; Norie, I.; Fujiwara, T. *Chem. Lett.* **1998**, 741.

(299) Takeda, T.; Sasaki, R.; Fujiwara, T. *J. Org. Chem.* **1998**, *63*, 7286.

(300) Takeda, T.; Endo, Y.; Reddy, A. C. S.; Sasaki, R.; Fujiwara, T. *Tetrahedron* **1999**, *55*, 2475.

(301) Takeda, T.; Rahim, A.; Takamori, M.; Yanai, K.; Fujiwara, T. *Polyhedron* **2000**, *19*, 593.

(302) Takeda, T.; Shimane, K.; Ito, K.; Saeki, N.; Tsubouchi, A. *Chem. Commun.* **2002**, 1974.

(303) Takeda, T.; Shono, T.; Ito, K.; Sasaki, H.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 7897.

(304) Takeda, T. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 195.

(305) Takeda, T. *Chem. Rec.* **2007**, *7*, 24.

(306) Shono, T.; Nagasawa, T.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2007**, *48*, 3521.

(307) Joshi, G. C.; Singh, N.; Pande, L. M. *Tetrahedron Lett.* **1972**, 1461.

(308) Shindo, M.; Kita, T.; Kumagai, T.; Matsumoto, K.; Shishido, K. *J. Am. Chem. Soc.* **2006**, *128*, 1062.

(309) Yaji, K.; Shindo, M. *Tetrahedron* **2010**, *66*, 9808.

(310) Umezu, S.; Shindo, M. *Tetrahedron Lett.* **2013**, *54*, 6871.

(311) Shindo, M.; Mori, S. *Synlett* **2008**, *2008*, 2231.

(312) Yoshikawa, T.; Shindo, M. *Org. Lett.* **2009**, *11*, 5378.

(313) Yoshikawa, T.; Mori, S.; Shindo, M. *ChemInform* **2009**, *40*, 2092.

(314) Shindo, M. *Tetrahedron* **2007**, *63*, 10.

(315) Shindo, M.; Ato, Y. S.; Oretsune, R. K.; Oshikawa, T. Y.; Atsumoto, K. M. *Chem. Pharm. Bull.* **2003**, *51*, 477.

(316) Shindo, M.; Matsumoto, K.; Shishido, K.; Eklov, B.; Denmark, S. *Org. Synth.* **2009**, *Coll. Vol.*, 577.

(317) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.

(318) Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1985**, *107*, 2099.

(319) Houk, K. N.; Kirmse, W.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 7989.

(320) Mori, S.; Shindo, M. *Org. Lett.* **2004**, *6*, 3945.

(321) Seebach, D.; Mukhopadhyay, T. *Helv. Chim. Acta.* **1982**, *65*, 385.

(322) Dehmlow, E. V.; Rao, Y. R. *Synth. Commun.* **1988**, *18*, 487.

(323) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; 2nd ed.; Oxford University Press, 2012; pp. 356, 453, 466, 590.

(324) Mayr, H.; Breugst, M.; Ofial, A. R. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 6470.

(325) Hammond, S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(326) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462.

(327) Olmstead, H. D.; Gall, M.; Czuba, L. J.; House, H. O. *J. Org. Chem.* **1969**, *34*, 2324.

(328) Fleming, I.; Paterson, I. *Synthesis (Stuttg).* **1979**, 736.

(329) Beutelman, H. P.; Xie, L.; Saunders, W. H. *J. Org. Chem.* **1989**, *54*, 1703.

(330) Rubottom, G. M.; Mott, R. C.; Krueger, D. S. *Synth. Commun.* **1977**, *7*, 327.

(331) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; 2nd ed.; Oxford University Press, 2012; p. 600.

(332) Scheiper, B.; Bonnekessel, M.; Krause, H.; Furstner, A. *J. Org. Chem.* **2004**, *69*, 3943.

(333) Scott Smith, R.; Kochi, J. K. *J. Org. Chem.* **1976**, *41*, 502.

(334) Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

(335) Furstner, A.; Leitner, A. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 609.

(336) Turner, J. V.; Orban, J.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099.

(337) Smietana, M.; Mioskowski, C. *Org. Lett.* **2001**, *3*, 1037.

(338) Ishino, Y.; Kita, Y.; Maekawa, H.; Ohno, T.; Yamasaki, Y.; Miyata, T.; Nishiguchi, I. *Tetrahedron Lett.* **1999**, *40*, 1349.

(339) Holton, R. A.; Krafft, M. E. *Tetrahedron Lett.* **1983**, *24*, 1345.

(340) Peese, K. M.; Gin, D. Y. *Chemistry* **2008**, *14*, 1654.

(341) Cheng, H. M.; Tian, W.; Peixoto, P. a; Dhudshia, B.; Chen, D. Y.-K. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 4165.

(342) Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*; 2nd ed.; Oxford University Press, 2012; p. 949.

(343) Johnson, W. S.; Wethemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(344) Herradón, B.; Valverde, S.; Bao, R. *Synlett* **1992**, 217.

(345) Patra, D.; Ghosh, S. *J. Chem. Soc., Perkin Trans 1.* **1995**, 2635.

(346) Eng, H. M.; Myles, D. C. *Tetrahedron Lett.* **1999**, *40*, 2275.

(347) Nanda, T.; Das, T.; Jana, N.; Bhunya, R. *Synlett* **2009**, *8*, 1237.

(348) Wang, G.; Zou, Y.; Li, Z.; Wang, Q.; Goeke, A. *J. Org. Chem.* **2011**, *76*, 5825.

(349) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984.

(350) Wu, L.; Chen, Y.; Luo, J.; Sun, Q.; Peng, M.; Lin, Q. *Tetrahedron Lett.* **2014**, *55*, 3847.

(351) Tadashi, M.; Sato, H.; Fukuzawa, A. *Tetrahedron Lett.* **1987**, *28*, 4303.

(352) Snyder, S. A.; Tang, Z.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744.

(353) Robertson, J.; Stork, G.; Yamashitalc, A. *Tetrahedron Lett.* **1994**, *35*, 1481.

(354) McPhail, A. T. *J. Org. Chem* **1988**, *53*, 3170.

(355) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans 1.* **1988**, 2847.

(356) Carey, F. A.; Sundberg, R. J. *Advances Organic Chemistry: Part A: Structure and Mechanisms*; 5th ed.; Springer, 2007; pp. 633–634.

(357) Kim, H.; Gwinn, W. D. *Tetrahedron Lett.* **1964**, *37*, 2535.

(358) Olah, G. a.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69.

(359) Liu, Q.; Rovis, T.; Perreault, S. *J. Am. Chem. Soc.* **2008**, *130*, 14066.

(360) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622.

(361) Cervera, M.; Moreno-manas, M.; Pleixats, R. *Tetrahedron* **1990**, *46*, 7885.

(362) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorganic Med. Chem.* **2004**, *12*, 4285.

(363) Finkelstein, H. *Berichte der Dtsch. Chem. Gesellschaft* **1910**, *43*, 1528.

(364) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.

(365) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077.

(366) Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686.

(367) Singh, P. N. D.; Carter, C. L.; Gudmundsdóttir, A. D. *Tetrahedron Lett.* **2003**, *44*, 6763.

(368) Patonay, T.; Jeko, J.; Juhász-Tóth, É. *European J. Org. Chem.* **2008**, 1441.

(369) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(370) Rigby, J. H.; Qabar, M. *Synth. Commun.* **1990**, *20*, 2699.

(371) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. *Chem. Commun. (Camb).* **2008**, 5474.

(372) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.

(373) Singh, P.; Bisetty, K. *Int. J. Org. Chem.* **2012**, *2*, 121.

(374) Behforouz, M.; Ahmadian, M. *Tetrahedron* **2000**, *56*, 5259.

(375) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.

(376) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.

(377) Neely, J. M.; Rovis, T.; Neely, J. M.; Rovis, T. *Org. Chem. Front.* **2014**, *1*, 1010.

(378) Cuellar, M. A.; Natalia, Q.; Vera, V.; Salas, C. O.; Estevex, J. C.; Estevez, R. J. *Synlett* **2015**, *26*, A.

(379) Kubo, A.; Tamura, F.; Kitahara, Y. *Tetrahedron Lett.* **1997**, *38*, 4441.

(380) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704.

(381) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(382) Martı, N.; Grau-Martinez, A.; Sanchez, L.; Seoane, C.; Torres, M. *J. Org. Chem.* **1998**, *63*, 8074.

(383) Palacios, F.; Vicario, J.; Aparicio, D. *Tetrahedron Lett.* **2007**, *48*, 6747.

(384) Chakrabarty, M.; Sarkar, S.; Khasnobis, S.; Harigaya, Y.; Sato, N.; Arima, S. *Synth. Commun.* **2002**, *32*, 2295.

(385) Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669.

(386) Denmark, S. E.; Stiff, G. M. *J. Org. Chem.* **2000**, *65*, 5875.

(387) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690.

(388) Palacios, F.; Pascual, S.; Oyarzabal, J.; Retana, A. M. O. De; Farmacia, F. De. *Org. Lett.* **2002**, *4*, 769.

(389) Yamasaki, Y.; Maekawa, T. I.; Ishihara, T.; Kyoto, F. *Chem. Lett.* **1985**, 1387.

(390) He, X.; Xiao, Y.; Du, W.; Chen, Y. *Chem. Eur. J.* **2015**, *21*, 1.

(391) Zheng, J. C.; Liao, W. W.; Tang, Y.; Sun, X. L.; Dai, L. X. *J. Am. Chem. Soc.* **2005**, *127*, 12222.

(392) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2005**, *7*, 5393.

(393) Esquivias, J.; Go, R.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 7451.

(394) Ma, C.; Gu, J.; Teng, B.; Zhou, Q. Q.; Li, R.; Chen, Y. C. *Org. Lett.* **2013**, *15*, 6206.

(395) Langlois, Y.; Pouilhes, A.; Kouklovsky, C. *J. Am. Chem. Soc.* **1990**, *112*, 6672.

(396) Shea, K. J.; Svoboda, J. J. *Tetrahedron Lett.* **1986**, *27*, 4837.

(397) Pouilhi, A.; Kouklovsky, C.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1987**, *28*, 6183.

(398) Sridharan, V.; Perumal, P. T.; Avendaño, C.; Menéndez, J. C. *Org. Biomol. Chem.* **2007**, *5*, 1351.

(399) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. - A Eur. J.* **2003**, *9*, 466.

(400) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001.

(401) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, a M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.

(402) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646.

(403) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.

(404) Rodrõ, E.; Palacios, F.; Aparicio, D. *Tetrahedron* **2001**, *57*, 3131.

(405) Palacios, F.; Ochoa De Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767.

(406) Hayashi, K.; Tanimoto, H.; Zhang, H.; Morimoto, T.; Nishiyama, Y.; Kakiuchi, K. *Org. Lett.* **2012**, *14*, 5728.

(407) Burke, M. D.; Schreiber, S. L. *Angew. Chemie - Int. Ed.* **2004**, *43*, 46.

(408) Buonora, P.; Olsen, J.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.

(409) Frignuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; Wiley VCH, 2002; p. 66.

(410) Motorina, I. a; Grierson, D. S. *Tetrahedron Lett.* **1999**, *40*, 7215.

(411) Smith, L. I.; Hoehn, H. H.; Drake, N. L.; Williams, J. *Org. Synth.* **1955**, *Coll. Vol.*, 356.

(412) Sakamoto, M.; Miyazawa, K.; Kuwabara, K.; Tomimatsu, Y. *Heterocycles* **1979**, *12*, 231.

(413) Elliott, M. C.; Monk, A. E.; Kruiswijk, E.; Hibbs, D. E.; Jenkins, R. L.; Jones, D. V. *Synlett* **1999**, *9*, 1379.

(414) Shieh, C. H.; Brady, W. T. *J. Org. Chem.* **1983**, *48*, 2499.

(415) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465.

(416) Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron* **2001**, *57*, 10139.

(417) Elliott, M. C.; Kruiswijk, E. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3157.

(418) Brandange, S.; Lindblom, L. *Acta. Chem. Scand. B 30* **1976**, *1*, 93.

(419) Jacob III, P. *J. Org. Chem.* **1982**, *47*, 4165.

(420) Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7014.

(421) Sasaki, I.; Doi, H.; Hashimoto, T.; Kikuchi, T.; Ito, H.; Ishiyama, T. *Chem. Commun.* **2013**, *49*, 7546.

(422) Bremner, J. B.; Sengpracha, W. *Tetrahedron* **2005**, *61*, 5489.

(423) Nishio, T.; Iseki, K.; Araki, N.; Miyazaki, T. *Helv. Chim. Acta* **2005**, *88*, 35.

(424) Baker, R. S.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 2815.

(425) Goodall, K.; Parsons, A. F. *Tetrahedron Lett.* **1997**, *38*, 491.

(426) Goodall, K.; Parsons, A. F. *J. Chem. Soc., Perkin Trans 1.* **1994**, 3257.

(427) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619.

(428) Clark, A. J.; Wilson, P. *Tetrahedron Lett.* **2008**, *49*, 4848.

(429) Hamdi, N.; Fischmeister, C.; Dixneuf, P. H.; Nievas, A. R. *J. Heterocycl. Chem.* **2006**, *43*, 499.

(430) Toumi, B.; Harizi, A. *Tetrahedron Lett.* **2006**, *47*, 6685.

(431) Courtney, A. K.; Martin, S. F. *Org. Synth.* **1997**, *74*, 229.

(432) Schann, S.; Bruban, V.; Pompermayer, K.; Feldman, J.; Pfeiffer, B.; Renard, P.; Scalbert, E.; Bousquet, P.; Ehrhardt, J. D. *J. Med. Chem.* **2001**, *44*, 1588.

(433) Fulton, J. R.; Aggarwal, V. K.; De Vicente, J. *European J. Org. Chem.* **2005**, 1479.

(434) Sha, Q.; Wei, Y. *Synthesis (Stuttg).* **2013**, *45*, 413.

(435) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 7219.

(436) Cuevas-Yañez, E.; Serrano, J. M.; Huerta, G.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron* **2004**, *60*, 9391.

(437) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735.

(438) Chamberlin, R. A.; Bond, T. F. *J. Org. Chem.* **1978**, *43*, 154.

(439) De Boer, T. J.; Backer, H. J. *Org. Synth.* **1956**, *36*, 16.

(440) Wan, Z.; Jones, C. D.; Koenig, T. M.; Pu, Y. J.; Mitchell, D. *Tetrahedron Lett.* **2003**, *44*, 8257.

(441) Ma, D.; Cai, Q.; Xie, X. *Synlett* **2005**, 1767.

(442) Vukga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *European J. Org. Chem.* **2009**, 3513.

(443) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

(444) Evano, G.; Blanchard, N.; Toumi, M. *Reactions* **2008**, 3054.

(445) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.

(446) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

(447) Wu, X.; Fors, B. P.; Buchwald, S. L. *Angew. Chemie - Int. Ed.* **2011**, *50*, 9943.

(448) Bruno, N. C.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 2876.

(449) Salvi, L.; Davis, N. R.; Ali, S. Z.; Buchwald, S. L. *Org. Lett.* **2012**, *14*, 170.

(450) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *European J. Org. Chem.* **1998**, *6*, 1219.

(451) Orgdnica, D. D. Q.; Farmacia, F. De; Valencia, U. De. *Tetrahedron* **1999**, 12881.

(452) Clohessy, T. Part II Thesis: Preparation and Reactions of Functionalised ω-azidoalkenes., 2013, Robertson, J group, Oxford.

(453) Laemmerhold, K. M.; Breit, B. *Angew. Chemie Int. Ed.* **2010**, *49*, 2367.

(454) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Chem. Commun. (Camb).* **2006**, 2483.

(455) Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, S. P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1277.

(456) Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578.

(457) Hodgson, D. M.; Ying, K. C.; Nuzzo, I.; Freixas, G.; Kulikiewicz, K. K.; Cleator, E.; Paris, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4456.

(458) Ausín, C.; Kauffman, J. S.; Duff, R. J.; Shivaprasad, S.; Beaucage, S. L. *Tetrahedron* **2010**, *66*, 68.

(459) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D.; Tn, K. *Org. Lett.* **2011**, *13*, 3988.

(460) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(461) Schmidt, B. *J. Org. Chem.*, **2004**, *69*, 7672.

(462) Albrecht, U.; Langer, P. *Tetrahedron* **2007**, *63*, 4648.

(463) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773.

(464) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692.

(465) Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2005**, *127*, 6946.

(466) Bajgrowicz, J. A, Bourdin, T. B, Gygax, P, *Eur. Pat. Appl*. 1067118, 10 Jan 2001.

(467) Millán, A.; Álvarez De Cienfuegos, L.; Miguel, D.; Campaña, A. G.; Cuerva, J. M. *Org. Lett.* **2012**, *14*, 5984.

(468) Vang, T.; Xie, Y.; Liu, W. H.; Vidović, D.; Liu, Y.; Wu, S.; Smith, D. H.; Rinderspacher, A.; Chung, C.; Gong, G.; Mustelin, T.; Landry, D. W.; Rickert, R. C.; Schürer, S. C.; Deng, S. X.; Tautz, L. *J. Med. Chem.* **2011**, *54*, 562.

(469) Roth, M.; Gotschi, E. *Helv. Chim. Acta.* **1971**, *54*, 710.

(470) Rodes, S. R, Garcia, D. N, Lopez, O. B, Alvarez De Mon, S. M, De La Hera, M. A, Munoz, M. A, Ledo, G. F. PCT Int. Appl., 2012069442, 31 May 2012.

(471) Kern, N.; Hoffmann, M.; Weibel, J.; Pale, P. *Org. Lett.* **2013**, *15*, 836.

(472) Yuan, Y.; Liu, W. *Synlett* **2011**, *4*, 559.

(473) McCubbin, J. A.; Krokhin, O. V. *Tetrahedron Lett.* **2010**, *51*, 2447.

(474) Ashley, G. W.; Burlingame, M.; Desai, R.; Fu, H.; Leaf, T.; Licari, P. J.; Tran, C.; Abbanat, D.; Bush, K.; Macielag, M. *J. Antibiot. (Tokyo).* **2006**, *59*, 392.

(475) Boyer, B. Y. J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248.

(476) Seyferth, D. *Org. Synth.* **1959**, *39*, 10.

(477) Zezza, C. A.; Smith, M. B. *Synth. Commun.* **1987**, *17*, 729.

(478) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809.

(479) Bérdy, J. *J. Antibiot. (Tokyo).* **2005**, *58*, 1.

(480) Gulder, T. a M.; Moore, B. S. *Angew. Chemie - Int. Ed.* **2010**, *49*, 9346.

(481) Williams, P. G.; Buchanan, G. O.; Feling, R. H.; Kauffman, C. a.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2005**, *70*, 6196.

(482) Flitsch, W.; Hampel, K.; Mohenhorst, M. *Tetrahedron Lett.* **1987**, *28*, 4395.

(483) Flitsch, W.; Mohenhorst, M. *Liebigs Ann. Chem.* **1990**, 397.

(484) Chopard, P. A.; Hudson, R. F. *J. Org. Chem.* **1963**, 2446.

(485) Pettersson, B.; Hasimbegovic, V.; Bergman, J. *J. Org. Chem.* **2011**, *76*, 1554.

(486) Tashiro, S.; Matsuoka, K.; Minoda, A.; Shionoya, M. *Angew. Chemie - Int. Ed.* **2012**, *51*, 13123.

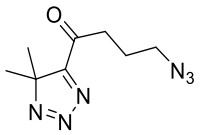
(487) Jacobi, P. a.; DeSimone, R. W.; Ghosh, I.; Guo, J.; Leung, S. H.; Pippin, D. *J. Org. Chem.* **2000**, *65*, 8478.

(488) Meduna, V.; Sawlewicz, P.; Vogt, R. *Synth. Commun.* **1989**, *19*, 1487.

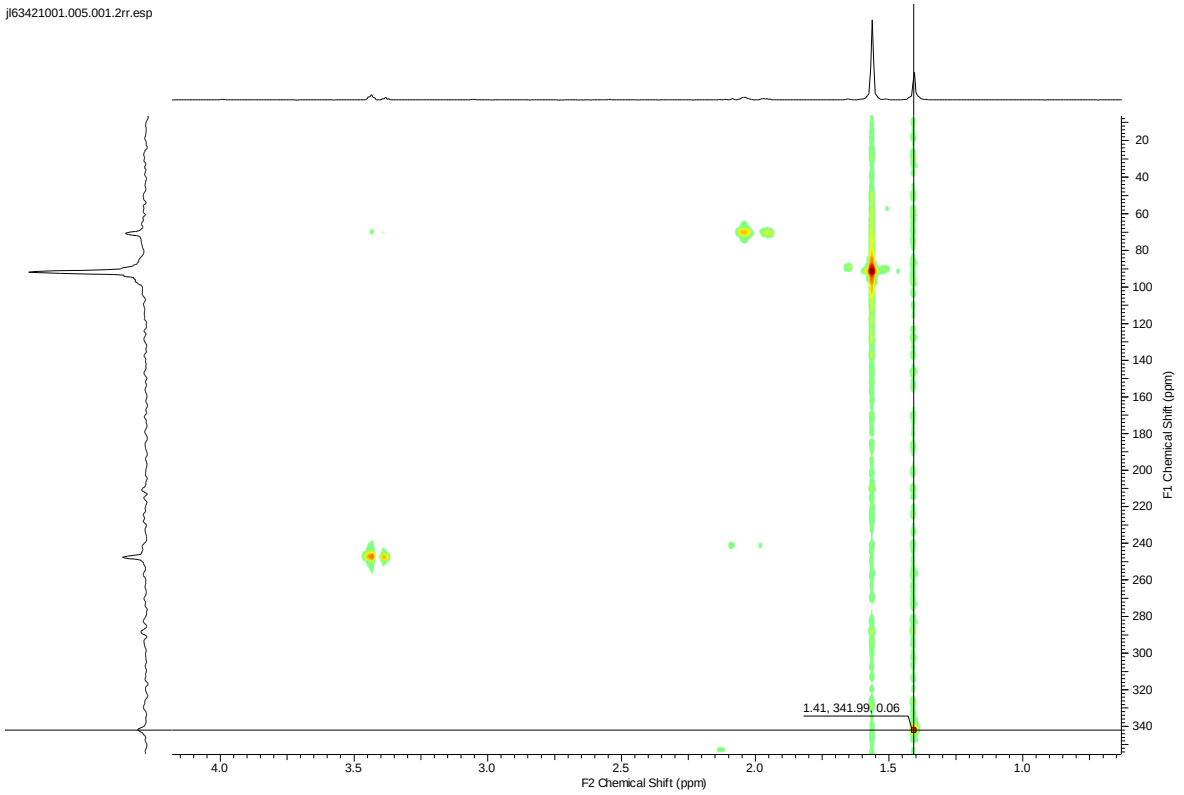
(489) Shaner, C. E.; Ferrence, G. M.; Mitchell, T. A. *Synlett* **2013**, *24*, 1861.

6 Appendix

6.1 ^{15}N–^{1}H HMBC correlation for compound 248



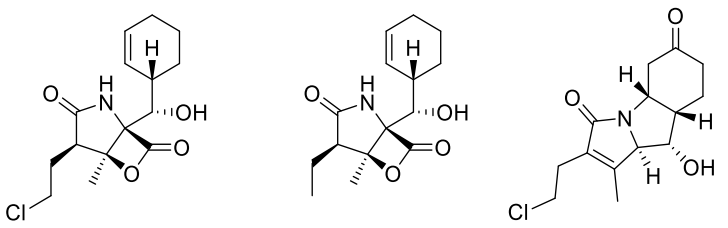
AV700 ($CDCl_3$), 10/1/14, ^{15}N–^{1}H HMBC tuned for 5 Hz *J*-coupling.



6.2 Towards the total synthesis of salinosporamide C

6.2.1 Introduction to salinosporamide C

Bacteria belonging to the order Actinomycetales provide one of the most prolific resources for the identification of lead pharmaceutical compounds.[479] Of particular merit has been salinosporamide A **318**, a marine natural product produced by the actinomycete *Salinispora tropica* that has shown to be a potent proteasome inhibitor in the treatment of cancer (Figure 21).[480] Closer examination of the producing organism led to the isolation of salinosporamide B **319** and salinosporamide C **320** as potential therapeutic agents[481] Despite being isolated in 2005,[481] as of 2014 there has not been a reported total synthesis of salinosporamide C **320**. Because of its small and interesting pyrrolidine-containing structure, the Robertson group set upon synthesising this secondary metabolite.



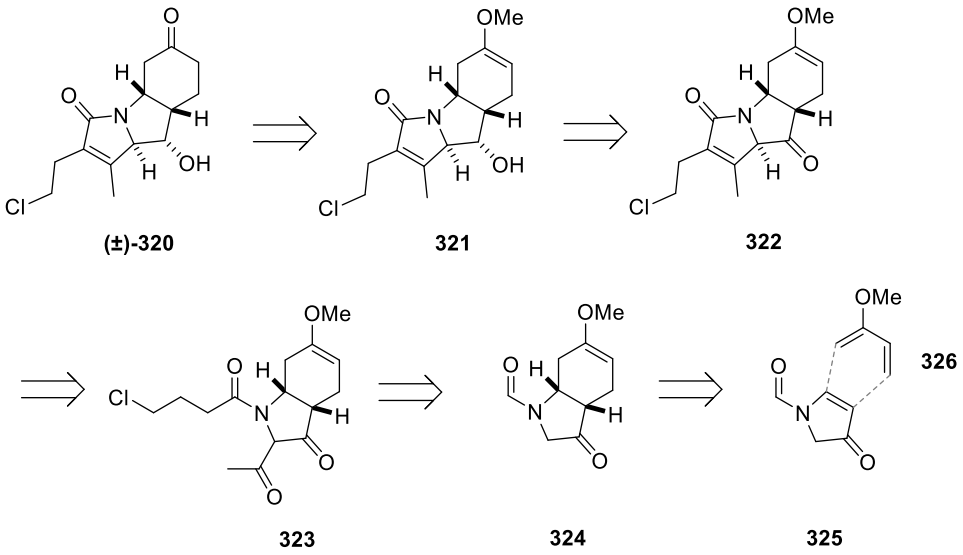
318 *salinosporamide A* | **319** *salinosporamide B* | **320** *salinosporamide C*

Figure 21: Salinosporamide A, B and C

6.2.2 First generation route

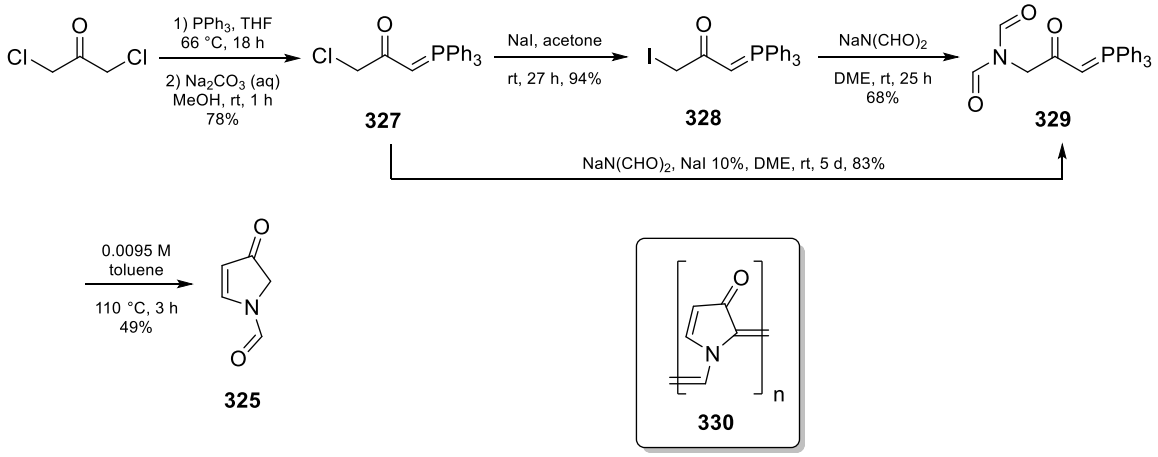
A retrosynthetic analysis of **(±)-320** is shown in Scheme 119. In a forward sense, an unprecedented Diels–Alder reaction between pyrrolone **325** and 2-methoxybutadiene **326** would provide the *cis*-fused bicyclic compound **324** in the key step. Acylation and trans-acylation would yield aldol-precursor **323**, which may undergo a regioselective aldol condensation to yield compound **322**, containing the

basic skeleton of salinosporamide C. Finally, a stereoselective reduction would provide **321**, which upon acidification would yield **(±)-320**.



Scheme 119: Retrosynthetic analysis of (±)-320.

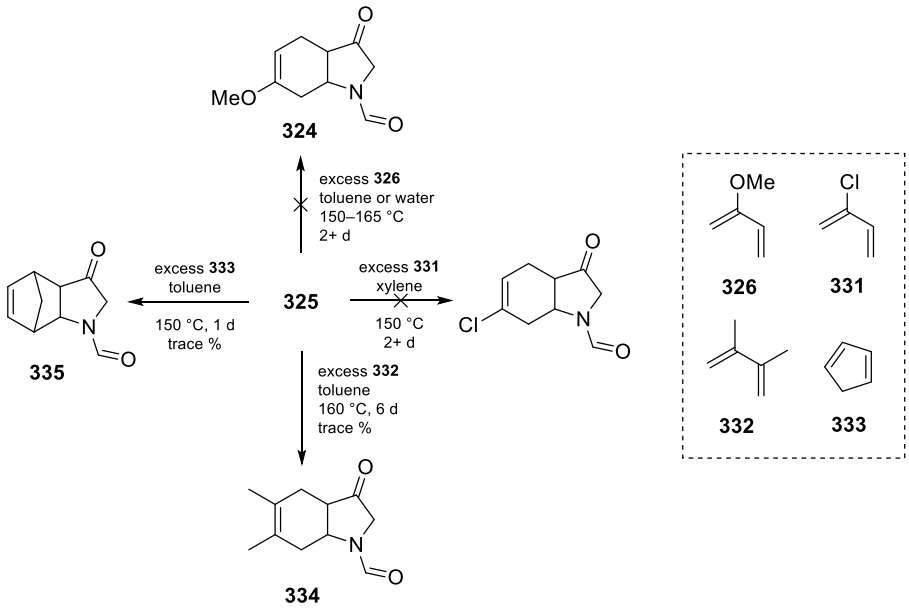
In order to test this hypothesis, we sought to prepare pyrrolone **325** based on a procedure by Flitsch *et al.*[482,483] Dichloroacetone was converted to phosphorane **327**,[484,485] which was converted to formimide **329** via either the iodide **328**, or directly using catalytic NaI (Scheme 120).



Scheme 120: Preparation of pyrrolone 325.

The intramolecular Wittig reaction of formimide **329** was found to require very high dilutions (0.0095 M) to supress an undesired side-product and provide pyrrolone **325** in an acceptable yield. The natural acidity of compound **325** at the α-position resulted in product condensation under the reaction conditions, precipitating a red "brick-dust" tentatively assigned as oligomer product **330**. Base-washed glassware was found to supress this process, suggesting an acid catalysed reaction. Practically, a dilution of 0.0095 M translates to 1.11 g of **329** in 300 mL of toluene, yielding 156 mg of **325** in a 49% yield. Thus, the preparation of **325** was highly atom and solvent inefficient. At a higher concentration of 0.024 M, **325** was prepared in only a 10% yield. Aside from dilution issues, the separation of product from triphenylphosphine oxide required a lengthy, tedious column, due to the similar R_f values of both species.

With the proposed dienophile **325** in hand, the key Diels–Alder reaction towards *cis*-bicycle **324** could be tested. The pyrrolone was found to be entirely inert towards cycloaddition with either 2-methoxybutadiene **326**, or synthetic equivalent chloroprene **331** up to temperatures of 150–165 °C (Scheme 121). Instead, the electron-rich dienes dimerised or polymerised preferentially under elevated temperatures. Activation with Lewis acids (Et_2AlCl, TMSOTf, $SnBr_4$, $SnCl_4$, $BF_3.Et_2O$, $InCl_3$) or Brønsted acids with a range of pKa values (propionic acid, $Cl_2HCCOOH$, Cl_3CCOOH, F_3CCOOH, TsOH, F_3CSO_2OH) led to no conversion, or served only to decompose the diene component.

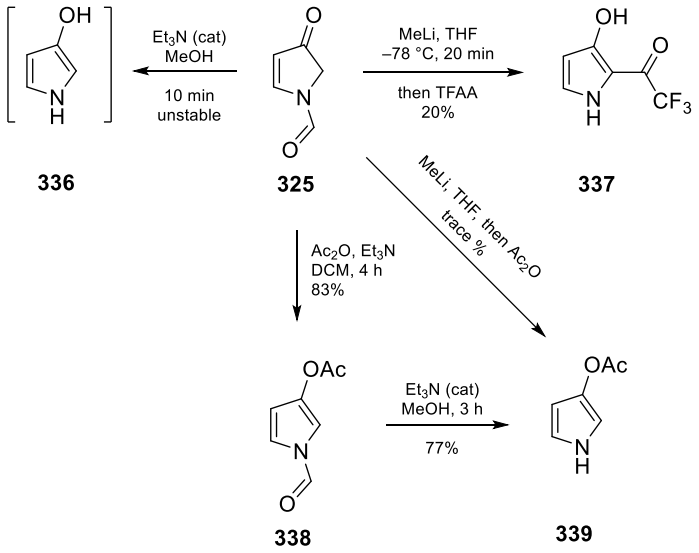


Scheme 121: Diels–Alder reactivity of pyrroline 325.

Traces of cycloaddition products could be detected and partially characterised following prolonged heating of **325** with dienes 2,3-dimethylbutadiene **332** and cyclopentadiene **333**, although high temperatures (150–160 °C) and long reaction times (days) were required (Scheme 121). The analytical purity of the products **334** (HRMS (FI^+) found 194.11761, $C_{11}H_{16}NO_2$ (MH^+) requires 194.11756) and **335** (HRMS (FI^+) found 178.08627, $C_{10}H_{12}NO_2$ (MH^+) requires 178.08626) was very low, contaminated with diene dimerisation products, which were the major component of the reaction.

It would appear that pyrrolone **325** is an extremely poor dienophile, likely due to the conjugated nitrogen at the 1-position increasing the electron density of the olefin. The formamide group therefore does not remove enough electron density from the nitrogen centre to produce a sufficiently electron-poor dienophile. Because of this, electron-rich dienes such as **331** and **326** undergo a self Diels–Alder reaction in preference to a Diels–Alder with **325**. Qualitatively, pyrrolone **325** *can* undergo a (4+2) reaction with unactivated dienes (**332** and **333**), though only traces products were detected amongst diene dimerisation products after extensive heating.

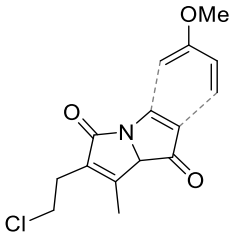
It was thought that if the dienophile could be made more electron-deficient, the pyrrolone would become a more reactive participant in a Diels–Alder reaction with 2-methoxybutadiene **326**. Pyrrolone **325** could be readily de-formylated with catalytic Et_3N in MeOH over 10 min, however the resulting 3-hydroxypyrrole **336** was entirely unstable, instantaneously polymerising upon formation (Scheme 122). Such instability had also been noted by Flitsch.[483]



Scheme 122: Attempted trans-acylation of pyrrolone 325.

Attempting to intercept **336** and trans-acylate *in situ*, **325** was de-formylated with MeLi and acylated with TFAA in an effort to make a more electron-deficient amide (Scheme 122). However the pyrrole was found to *C*-acylate to yield **337**. On a separate occasion, **325** was found to *O*-acylate with Ac_2O to afford **338**, which was stable towards deprotection, yielding **339**. Under identical conditions, deformylation of **325** with MeLi followed by acylation with Ac_2O yielded trace quantities of **339**, in direct contrast to **337**. *C*-acylation with the hard-electrophile TFAA is likely governed by electrostatics and an early transition state, while the softer Ac_2O may *O*-acylate through a late transition state governed by product stability. Alternatively, the pyrrolone may *O*-acylate with TFAA but then readily rearrange *in situ* to the *C*-acylated product.

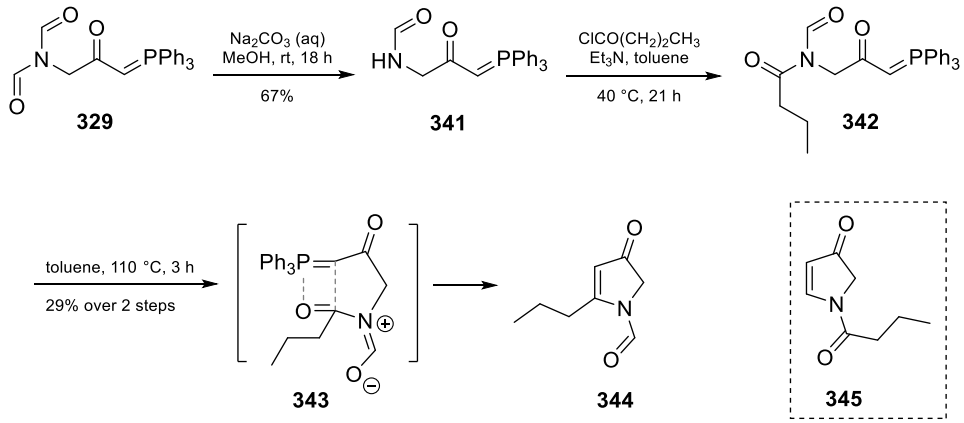
In a final change of tactic, it was thought that if the nitrogen could be brought out of conjugation with the enone, the dienophile could be made less electron rich and the Diels–Alder reaction may proceed. To this end, we attempted the synthesis of pyrrolizine **340** (Figure 22).



340

Figure 22: Theoretical dienophile 340.

Having already demonstrated that **325** could not be *C*-acylated with Ac_2O, nor transacylated (Scheme 122), we attempted to build in the model *N*-butyryl system **345** *en route* to **340** during the intramolecular Wittig reaction (Scheme 123). Compound **329** was first de-formylated to yield **341**, which upon acylation with butyryl chloride yielded **342**. It was predicted that the more electrophilic formamide carbonyl might participate in the subsequent intramolecular Wittig reaction to form **345**, however the opposite was found to be the case. Presumably, the formamide carbonyl is made unreactive through extreme resonance **343**, allowing the remaining amide carbonyl to react. Thus, the undesired isomer **344** was isolated solely. Similar reactivity had been reported by Flitsch using mixed formamide/carbamate substrates.[483]

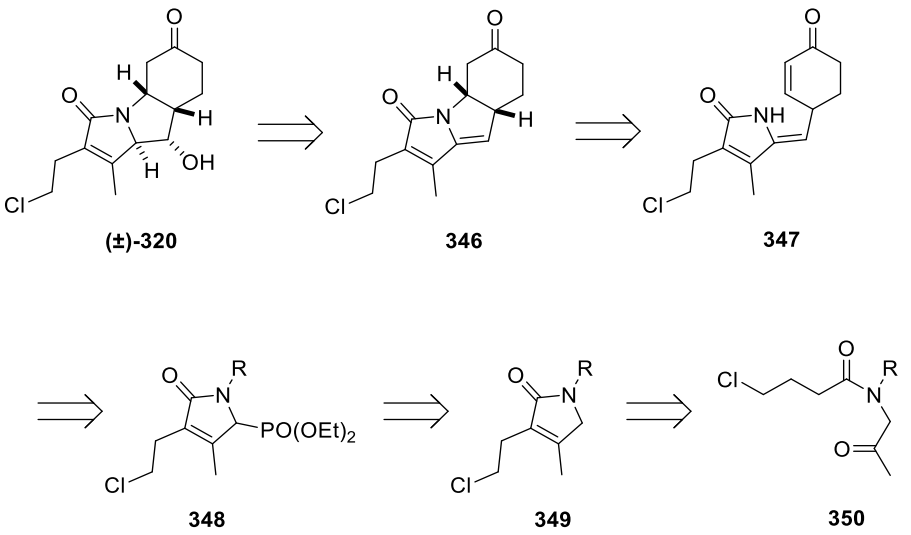


Scheme 123: Wittig reaction using mixed formamide/amide ylide 342.

With the formation of pyrrolone **325** proving inefficient and unscalable, plus its inherent unreactivity as a dienophile, we decided to pursue other strategies towards **(±)-320** .

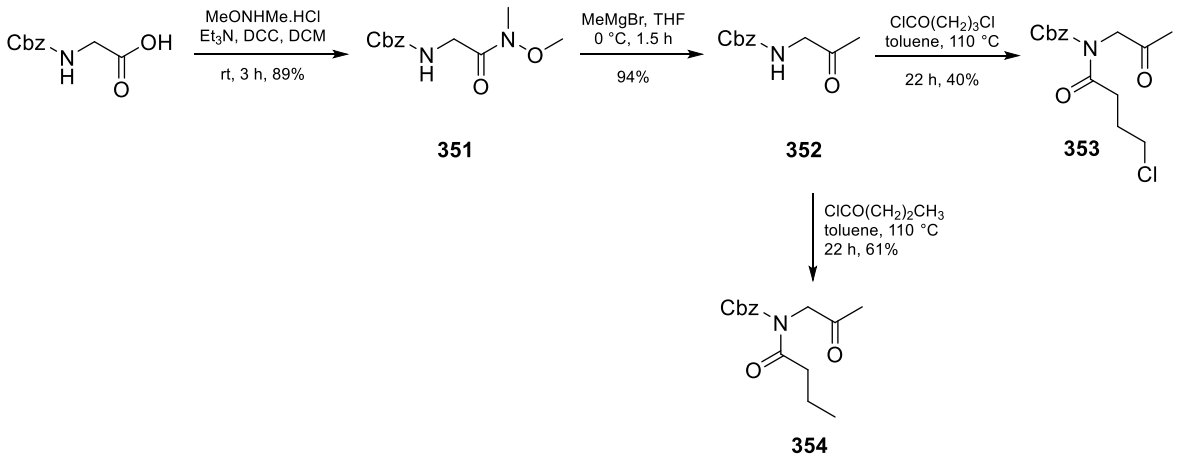
6.2.3 Second generation route

An alternative retrosynthetic analysis towards **(±)-320** is shown in Scheme 124. In the key step, an intramolecular conjugate addition in compound **347** would yield skeleton **346** *en route* to **(±)-320**. Based on the structures of salinosporamide A and B (Figure 21), such a reaction may be biomimetic in concept. Enamide **347** was anticipated as the olefination product of phosporane **348**, arising from intramolecular aldol product **349**.



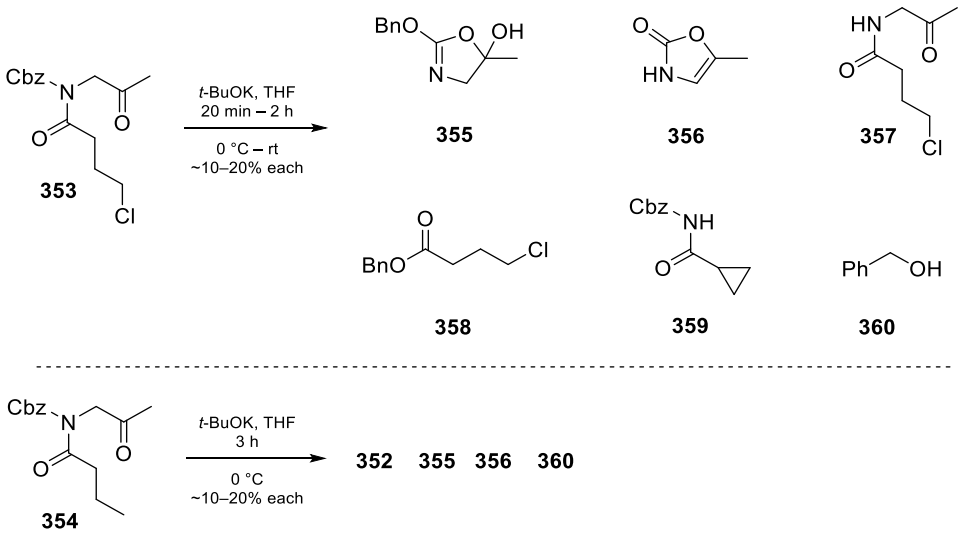
Scheme 124: Second generation retrosynthetic analysis of (±)-320.

To begin, a preparation of protected intramolecular aldol-precursor **350** was required. With benzyl-protected glycine available in-lab, the amino acid was converted to α-amino acetone derivative **352** using a literature procedure (Scheme 125).[486] *N*-acylation of **352** was ineffective when mediated with base (NaH, LHMDS, K_2CO_3), but successful when conducted in the absence of base, presumably autocatalysed by the liberated HCl. Using this protocol, chlorobutyryl amide derivative **353**, and de-chlorinated test compound **354** were prepared.



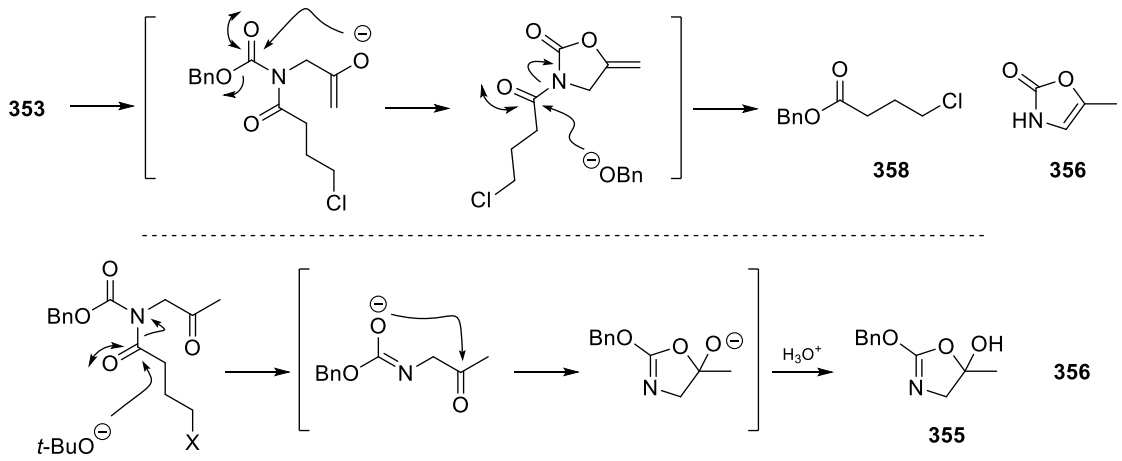
Scheme 125: Preparation of aldol precursors 353 and 354.

Compound **353** was inert towards cyclisation mediated by weak bases (Et_3N, 2,6-lutidine) or by acid (HCl, *p*-TSA, propionic acid). When treated with stronger bases however (1–2 eq. *t*-BuOK, DBU, LHMDS, NaOH, MeOK), **353** was found to cleave and/or cyclise into a variety of undesired decomposition products **355–360** (Scheme 126). Similarly, compound **354** decomposed to many of the same compounds under identical conditions.



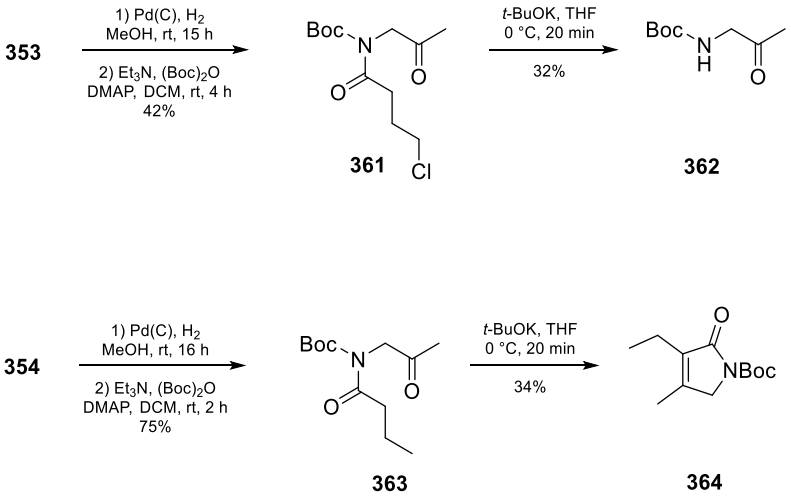
Scheme 126: Decomposition of 353 and 354 under basic conditions.

It appeared that the benzyl carbamate group was too reactive within substrates **353** and **354**, with participation from this group leading to many of the decomposition products (Scheme 127).



Scheme 127: Decomposition of 353 and 354 under basic conditions.

Jacobi *et al*. reported a successful related cyclisation with the use of a Boc-protected amide (similar to **350 → 349**, Scheme 124).[487] Presumably, the bulky *tert*-butyl group supresses participation from the carbamate carbonyl, in contrast to the more accessible Cbz group. Boc-protected analogues **361** and **363** were prepared from Cbz-protected **353** and **354** respectively by hydrogenolysis and Boc protection of the intermediate amide (Scheme 128). When treated with *t*-BuOK using Jacobi's procedure,[487] chlorobutyryl amide derivative **361** was found to de-acylate to yield compound **362** (attempted once). Butyryl amide derivative **363** however was successfully cyclised to yield the desired model compound **364**. If the cyclisation of **361** reproducibly leads to undesired de-acylation, then the required alkyl chloride tether (**349**) would need to be introduced in a protected form, should this route be pursued further.



Scheme 128: Preparation and reactivity of Boc-protected amides 361 and 363.

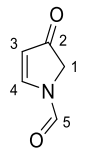
6.2.4 Conclusions

In conclusion, two separate strategies were investigated in an effort to assemble salinosporamide C **(±)-320**. In the first strategy (Section **6.2.2**) inefficiencies in the production of key intermediate **325**, and its reluctance to participate as a dienophile in a Diels–Alder reaction prevented completion of this route. Ideally, early total synthesis intermediates would require a robust preparation that could be conducted on large scale. Dilution issues in the production of **325** would render this olefination route impractical on scale.

In the second strategy (Section **6.2.3**), the availability of Cbz-protected glycine led to undesired participation from the carbamate-protecting group during the key cyclisation of **353** and **354** (Scheme 126). The use of a more bulky Boc-protecting group showed proof of concept (**363** → **364**), though the desired alkyl chloride may need to be introduced in a protected form. Future research into this strategy would require a more efficient construction of intermediate **363** and **361** (or a suitable equivalent) that does not require the interchange of protecting groups.

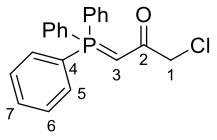
6.2.5 Experimental

3-Oxo-2,3-dihydro-1*H*-pyrrole-1-carbaldehyde (325)[482,483]



A modified literature procedure[482,483] was used. To a 500 mL, base-washed and oven-dried RBF was added a 0.0095 M solution of *N*-formyl-*N*-(2-oxo-3-(triphenylphosphanylidene)propyl)formamide (1.11 g, 2.85 mmol) in toluene (300 mL) under an atmosphere of argon. The reaction was refluxed for 3 h, during which time the colourless solution turned red and a red precipitate dropped out of solution. The reaction was filtered, concentrated, and purified over a long silica column, eluting with 0.1–0.4% MeOH in DCM, yielding a white solid with data consistent with the literature data[482,483] The product was a mixture of rotamers by ^{1}H-NMR analysis (156 mg, 49%). M.p 120 °C; R_f 0.45 (3:0.1 ether/MeOH); ν_{max} 3059w, 3093w, 2965w, 2932w, 1660s, 1540s; δ_H (500 MHz, $CDCl_3$) 4.11 and 4.18 (2 H, s, H1), 5.80 and 5.87 (1 H, d, *J* = 4.0 Hz, H3), 8.24 and 8.67 (1 H, d, *J* = 4.0 Hz, H4), 8.36 and 8.51 (1 H, s, H5); δ_C (150 MHz, $CDCl_3$) 51.1 and 52.3 (C1), 153.9 and 156.0 (C4), 157.3 and 156.3 (C5), 197.1 (C2); HRMS (FI$^+$) found 111.0323, $C_5H_5NO_2$ (M^+) requires 111.0320.

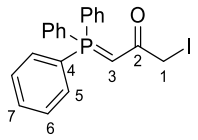
Triphenylchloracetonylphosphorane (327)[484,485]



A literature procedure[484,485] was used. To a 500 mL RBF was added 1,3-dichloroacetone (15 g, 0.12 mol), triphenylphosphine (29.5 g, 0.112 mol), and THF (200 mL) under an atmosphere of argon. The reaction was refluxed for 18 h, during which time a white precipitate formed. The precipitate was collected by filtration, washed with

petrol, then added to a 500 mL RBF containing methanol (150 mL), water (150 mL), and Na_2CO_3 (6.28 g, 590 mmol) at 0 °C. After warming to ambient temperature and stirring for 1 h, water (300 mL) was added to the clear solution, causing a white precipitate to form. After leaving to settle for 30 min, the white precipitate was collected by filtration, washed with ether (50 mL), petrol (50 mL), and dried by thrice concentration from toluene to yield a white solid with data consistent with the literature data[484,485] (32 g, 78%). M.p 170 °C; ν_{max} 1575s, 1434s, 1393s, 1105s; δ_H (400 MHz, $CDCl_3$) 4.03 (2 H, s, H1), 4.29 (1 H, d, *J* = 24.0 Hz, H3), 7.47–7.51 (6 H, m, H6), 7.56–7.61 (3 H, m, H7), 7.64–7.69 (6 H, m, H5); δ_C (100 MHz, $CDCl_3$) 47.3 and 47.5 (C1), 50.8 and 51.9 (C3), 125.8 and 126.7 (C4), 128.9 and 129.05 (C6), 132.3 and 132.3 (C7), 133.0 and 133.2 (C5), 185.2 and 185.3 (C2); m/z (ESI) 353.0 (MH^+).

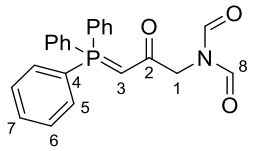
Triphenyliodoacetonylphosphorane (328)



A modified literature procedure[363] was used. To a 1 L RBF was added triphenylchloracetonylphosphorane (10.48 g, 290 mmol) and acetone (600 mL) under an atmosphere of argon. The flask was wrapped in foil to exclude light. To the flask was added NaI (4.46 g, 290 mmol) and the reaction stirred at ambient temperature for 27 h. The reaction was filtered, and the filtrate concentrated to yield a crude light brown solid that was sufficiently pure to be used in the next reaction (12.5 g, 94%). M.p 130 °C; ν_{max} 1544s, 1435s, 1381s, 1152s; δ_H (700 MHz, $CDCl_3$) 3.85 (2 H, s, H1), 4.12 (1 H, d, *J* = 24.0 Hz, H3), 7.47–7.49 (6 H, m, H6), 7.56–7.59 (3 H, m, H7), 7.64–7.67 (6 H, m, H5); δ_C (175 MHz, $CDCl_3$) 9.6 and 6.7 (C1), 51.4 and 52.1 (C3), 125.9 and 126.5 (C4), 128.9 and 129.0

(C6), 132.7 (C7), 133.0 and 133.1 (C5), 185.5 (C2); HRMS (FI^+) found 445.0202, $C_{21}H_{19}O^{127}I^{31}P$ (MH^+) requires 445.0213.

N-Formyl-*N*-[2-oxo-3-(triphenyl-l5-phosphanylidene)propyl]formamide (329)[482,483]

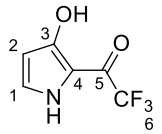


Method one: To a 250 mL RBF was added triphenyliodoacetonylphosphorane (12.0 g, 270 mmol), sodium formamide (3.56 g, 0.037 mol), and DME (60 mL) under an atmosphere of argon. The flask was wrapped in foil to exclude light and the reaction stirred at ambient temperature for 25 h. The reaction was quenched with brine (80 mL), extracted successively with ether (4 x 60 mL), dried (Na_2SO_4), and concentrated to yield a crude brown solid. The brown colouration could be removed by carefully washing the solid with cold acetone, yielding an off white solid with data consistent with the literature data[482,483] (7.13 g, 68%). M.p 150 °C; ν_{max} 1665s, 1548s, 1304s; δ_H (700 MHz, $CDCl_3$) 3.72 (1 H, br, H3), 4.44 (1 H, br, H1), 7.45–7.48 (6 H, m, H6), 7.55–7.57 (3 H, m, H7), 7.59–7.62 (6 H, m, H5), 8.91 (2 H, br, H8); δ_C (175 MHz, $CDCl_3$) 44.8 and 44.9 (C1), 49.6 and 50.2 (C3), 126.1 and 126.7 (C4), 128.9 and 128.9 (C6), 132.3 (C7), 133.0 and 133.1 (C5), 160.8 and 164.3 (C8), 182.49 and 184.7 (C2); m/z (ESI) 390.2 (MH^+).

Method two: To a 250 mL RBF was added triphenylchloracetonylphosphorane (10.0 g, 0.028 mol), sodium formamide (2.83 g, 290 mmol), NaI (423 mg, 2.83 mmol), and DME (35 mL) under an atmosphere of argon. The flask was wrapped in foil to exclude light and the reaction stirred at ambient temperature for 5 d. The reaction was quenched with water (250 mL), extracted successively with ether (4 x 150 mL), dried (Na_2SO_4), and concentrated to yield a crude brown solid. The brown colouration could

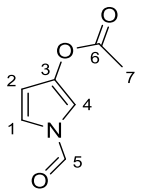
be removed by carefully washing the solid with cold acetone, yielding an off white solid with data consistent with the literature data[482,483] (9.27 g, 83%). M.p 150 °C; ν_{max} 1665s, 1548s, 1304s; δ_H (700 MHz, $CDCl_3$) 3.72 (1 H, br, H3), 4.44 (1 H, br, H1), 7.45–7.48 (6 H, m, H6), 7.55–7.57 (3 H, m, H7), 7.59–7.62 (6 H, m, H5), 8.91 (2 H, br, H8); δ_C (175 MHz, $CDCl_3$) 44.8 and 44.9 (C1), 49.6 and 50.2 (C3), 126.1 and 126.7 (C4), 128.9 and 128.9 (C6), 132.3 (C7), 133.0 and 133.1 (C5), 160.8 and 164.3 (C8), 182.49 and 184.7 (C2); m/z (ESI) 390.2 (MH^+).

2,2,2-Trifluoro-1-(3-hydroxy-1*H*-pyrrol-2-yl)ethan-1-one (337)



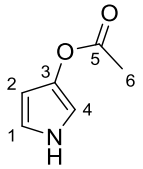
To a 15 mL oven-dried RBF was added 3-oxo-2,3-dihydro-1*H*-pyrrole-1-carbaldehyde (27 mg, 0.24 mmol) and THF (3 mL) under an atmosphere of argon and the solution cooled to –78 °C. MeLi (0.3 mL, 1.6 M in ether, 0.5 mmol) was added dropwise, and the reaction stirred for 10 min before warming to room temperature. After 10 min, the reaction was cooled to –78 °C and TFAA added (66 μL, 0.48 mmol). After allowing to warm to room temperature overnight, the reaction was quenched with water (10 mL), extracted successively with DCM (3 x 15 mL), dried (Na_2SO_4), and concentrated to a brown oil. The title compound was isolated following chromatography over silica with DCM as a yellow oil (9 mg, 20%). R_f 0.30 (DCM); δ_H (500 MHz, $CDCl_3$) 6.00 (1 H, t, *J* = 2.5 Hz, H2), 7.03 (1 H, t, *J* = 3.5 Hz, H1), 3.38 (1 H, br, OH), 9.36 (1 H, br, NH); δ_C (150 MHz, $CDCl_3$) 98.2 (C2), 111.6 (C3), 115.9 (C6, q, *J* = 288.0 Hz), 128.9 (C1), 161.4 (C4), 168.0 (C5, q, *J* = 36.0 Hz); HRMS (FI^-) found 178.01154, $C_6H_3NO_2{}^{19}F_3$ (M^-) requires 178.01214.

1-Formyl-1*H*-pyrrol-3-yl acetate (338)



To a 14 mL sample vial was added 3-oxo-2,3-dihydro-1*H*-pyrrole-1-carbaldehyde (115 mg, 1.39 mmol) and DCM (10 mL) under an atmosphere of argon and the solution cooled to 0 °C. Acetic anhydride (0.27 mL, 2.9 mmol) and Et_3N (0.40 mL, 2.9 mmol) were added and the reaction warmed to to room temperature. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted successively with DCM (3 x 15 mL), dried ($MgSO_4$), and concentrated to a brown oil. The title compound was isolated following chromatography over silica with DCM as a yellow oil (178 mg, 85%). The compound solidified on freezing. M.p 30 °C; R_f 0.50 (DCM); ν_{max} 3184w, 1754s, 1709s; δ_H (500 MHz, $CDCl_3$) 2.27 (3 H, s, H7), 6.32 (1 H, br, H2), 6.97, 7.33, and 7.50 (2 H, br, H1 and H4), 8.80 (1 H, s, H5); δ_C (150 MHz, $CDCl_3$) 19.9 (C7), 104.5 (C3), 107.8 (C2), 113.6 (C1), 117.8 (C4), 157.6 (C5), 166.9 (C6); HRMS (FI^+) found 153.0426, $C_7H_7NO_3$ (M^+) requires 153.0426.

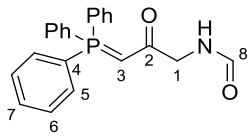
1*H*-Pyrrol-3-yl acetate (339)



To a 7 mL sample vial was added 1-formyl-1*H*-pyrrol-3-yl acetate (100 mg, 0.653 mmol) and MeOH (2 mL) under an atmosphere of argon and the solution stirred at room temperature. Et_3N (1 drop) was added, and after 3 h, the reaction was concentrated to a brown oil. The title compound was isolated following chromatography over silica with DCM as a colourless oil that solidified in the freezer (63 mg, 77%). M.p = 40 °C; R_f 0.50

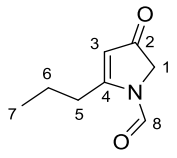
(DCM); ν_{max} 3393br, 1743s; δ_H (400 MHz, $CDCl_3$) 2.25 (3 H, s, H6), 6.09 (1 H, dd, *J* = 4.5 and 3.0 Hz, C4), 6.62 (1 H, dd, *J* = 5.0 and 3.0 Hz, C1), 6.80 (1 H, dd, *J* = 4.0 and 2.0 Hz, C2), 8.09 (1 H, br, NH); δ_C (100 MHz, $CDCl_3$) 21.0 (C6), 101.2 (C4), 107.2 (C2), 115.9 (C1), 137.5 (C3), 169.2 (C5); HRMS (FI^+) found 125.0478, $C_6H_7NO_2$(MH^+) requires 125.0477.

N-(2-Oxo-3-(triphenylphosphoranylidene)propyl)formamide (341)



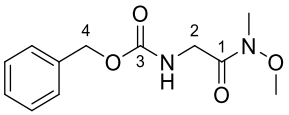
A modified literature procedure[488] was used. To a 7 mL sample vial was added *N*-formyl-*N*-(2-oxo-3-(triphenylphosphanylidene)propyl)formamide (136 mg, 0.349 mmol), MeOH (2 mL) and saturated aqueous Na_2CO_3 (0.1 mL) under an atmosphere of argon. The reaction was stirred at ambient temperature for 18 h, then diluted with brine (10 mL), extracted successively with ethyl acetate (3 x 20 mL), dried ($MgSO_4$), and concentrated to yield a crude yellow solid. The yellow colouration could be removed by carefully washing the solid with cold acetone, yielding an off white solid (85 mg, 67%). M.p 200 °C; R_f 0.10 (3:0.1 ether/MeOH); ν_{max} 3223br, 1668s, 1521s; δ_H (400 MHz, $CDCl_3$) 3.74 (1 H, br d, *J* = 21.5 Hz, H3), 40.1 (2 H, d, *J* = 4.5 Hz, H1), 7.00 (1 H, br, NH), 7.46–7.50 (6 H, m, H6), 7.56–7.64 (9 H, m, H5 and H7), 8.08 (1 H, s, H8); δ_C (100 MHz, $CDCl_3$) 44.8 and 45.0 (C1), 49.4 and 50.5 (C3), 125.9 and 126.8 (C4), 128.9 and 129.0 (C6), 132.4 (C7), 132.9 and 133.0 (C5), 160.9 (C8), 184.8 (C2); HRMS (FI^+) found 362.12982, $C_{22}H_{21}NO_2P$ (MH^+) requires 362.13044.

3-Oxo-5-propyl-2,3-dihydro-1*H*-pyrrole-1-carbaldehyde (344)



To a 7 mL sample vial was added *N*-(2-oxo-3-(triphenylphosphoranylidene)propyl)formamide (41 mg, 0.11 mmol), toluene (1 mL), and Et_3N (19 μL, 0.14 mmol) under an atmosphere of argon. Butyryl chloride (15 μL, 0.14 mmol) was added and the reaction heated to 40 °C for 21 h. The reaction was filtered, washed with ether (3 x 10 mL), and concentrated to yield a crude brown oil that was used immediately in the next reaction. The crude product was refluxed in toluene (20 mL) for 3 h, during which time the yellow solution turned orange, and was concentrated and purified over silica eluting with 0.1–0.3% MeOH in DCM. The title compound was isolated as a yellow oil, and as a mixture of rotamers by ^{1}H-NMR analysis (5 mg, 29% over 2 steps). R_f 0.36 (3:0.1 ether/MeOH); ν_{max} 1679s, 1556s; δ_H (400 MHz, $CDCl_3$) 1.02 (3 H, t, *J* = 7.0 Hz, H7), 1.77 (2 H, app sext, *J* = 7.5 Hz, H6), 2.40 (1 H, t, *J* = 7.0 Hz, H5), 2.53 (1 H, t, *J* = 7.5 Hz, H5), 4.10 (2 H, d, *J* = 10.5 Hz, H1), 5.71 (1 H, dd, *J* = 25.0 and 3.5 Hz, H3), 8.26 (1 H, d, *J* = 2.5 Hz, H8), 8.76 (1 H, d, *J* = 3.5 Hz, H8); δ_C (100 MHz, $CDCl_3$) 12.7 (C7), 16.7 and 167.0 (C6), 33.6 and 35.4 (C5), 51.2, 51.9 and 52.6 (C1), 110.0 and 110.2 (C3), 154.4, 154.7, and 155.7 (C8), 167.3 (C4), 197.3 (C2); HRMS (FI$^+$) found 153.0796, $C_8H_{11}NO_2$ (M^+) requires 153.0790.

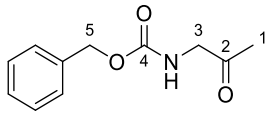
Benzyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (351)[486]



A literature procedure[486] was used. To a 100 mL RBF was added *N*,*O*-dimethylhydroxylamine hydrochloride (1.39 g, 14.3 mmol), DCM (50 mL), and the

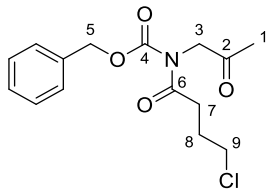
solution cooled to 0 °C under argon. Et_3N (2 mL, 14 mmol), and ((benzyloxy)carbonyl)glycine (3 g, 14 mmol), were added successively, followed by DCC (3.24 g, 15.7 mmol) and the reaction stirred at 0 °C for 30 min. After warming to room temperature and stirring for 3 h, the solution as filtered, concentrated, and purified over silica eluting with 2:1 ether/ petrol, affording the title compound as a white solid with data consistent with the literature data[486] (3.21 g, 89%). R_f 0.11 (2:1 ether/petrol); ν_{max} 1716s, 1665s; δ_H (400 MHz, $CDCl_3$) 3.21 (3 H, s, NMe), 3.72 (3 H, s, OMe), 4.15 (2 H, d, *J* = 4.5 Hz, H2), 5.13 (2 H, s, H4), 5.58 (1 H, br, NH), 7.29–7.39 (5 H, m, ArH); m/z (ESI) 275.0 (MNa^+).

Benzyl (2-oxopropyl)carbamate (352)[486]



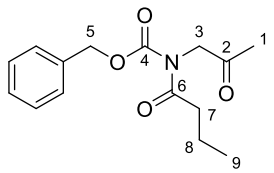
A literature procedure[486] was used. To a 100 mL RBF was added benzyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (940 mg, 3.73 mmol), THF (10 mL), and the solution cooled to 0 °C under argon. MeMgBr (3.7 mL, 3.0 M in ether, 11 mmol) was added dropwise over 5 min, and the reaction warmed to room temperature. After 1.5 h, the reaction as quenched with 0.1 M aqueous HCl (15 mL), filtered, and extracted successively with DCM (3 x 20 mL). The combined organic fractions were died ($MgSO_4$), concentrated, and purified over silica eluting with 2:1 ether/petrol affording the title compound as a white solid with data consistent with the literature data[486] (728 mg, 94%). M.p 60 °C; R_f 0.31 (2:1 ether/petrol); ν_{max} 1702s, 1586s; δ_H (400 MHz, $CDCl_3$) 2.18 (3 H, s, H1), 4.10 (2 H, d, *J* = 4.5 Hz, H3), 5.12 (2 H, s, H5), 5.54 (1 H, br, NH), 7.29–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 27.1 (C1), 51.2 (C3), 67.0 (C5), 128.1 and 128.5 (ArC), 136.3 (ArC), 156.1 (C4), 202.9 (C2); m/z (ESI) 230.0 (MNa^+).

Benzyl (4-chlorobutanoyl)(2-oxopropyl)carbamate (353)



A modified literature procedure[489] was used. To a 25 mL pear-shaped flask was added benzyl (2-oxopropyl)carbamate (428 mg, 2.07 mmol), toluene (2 mL), and 4-chlorobutyryl chloride (0.70 mL, 6.2 mmol). A condenser with $CaCl_2$ drying tube was attached to the flask and the reaction refluxed for 22 h. The reaction was removed from heat, concentrated, and purified over silica eluting with 0.1% Et_3N and 20% ether in petrol affording the title compound as a colourless oil (258 mg, 40%). R_f 0.37 (1:1 ether/petrol); ν_{max} 1741s, 1698s; δ_H (400 MHz, $CDCl_3$) 2.08–2.15 (5 H, m, H1 and H8), 3.16 (2 H, t, *J* = 7.0 Hz, H7), 3.59 (2 H, t, *J* = 6.0 Hz, H9), 4.57 (2 H, s, H3), 5.19 (2 H, s, H5), 7.29–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 26.9 (C8), 27.7 (C1), 35.0 (C7), 44.2 (C9), 53.1 (C3), 69.0 (C5), 128.3 (ArC), 128.8 (ArC), 134.7 (ArC), 153.4 (C4), 174.4 (C6), 201.3 (C2); HRMS (FI^+) found 334.0811, $C_{15}H_{18}NO_4{}^{35}ClNa$ (MNa^+) requires 334.0817.

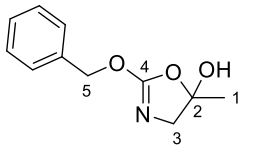
Benzyl butyryl(2-oxopropyl)carbamate (354)



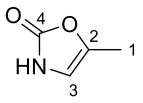
To a 25 mL pear-shaped flask was added benzyl (2-oxopropyl)carbamate (312 mg, 1.50 mmol), toluene (2 mL), and butyryl chloride (0.46 mL, 4.4 mmol). A condenser with $CaCl_2$ drying tube was attached to the flask and the reaction refluxed for 22 h. The reaction was removed from heat, concentrated, and purified over silica eluting with 0.1% Et_3N and 20% ether in petrol affording the title compound as a yellow oil (258 mg, 61%). R_f 0.60 (1:1 ether/petrol); ν_{max} 1796m, 1741s, 1701s; δ_H (400 MHz, $CDCl_3$) 2.08–

2.15 (5 H, m, H1 and H8), 3.16 (2 H, t, *J* = 7.0 Hz, H7), 3.59 (2 H, t, *J* = 6.0 Hz, H9), 4.57 (2 H, s, H3), 5.19 (2 H, s, H5), 7.29–7.39 (5 H, m, ArH); δ_C (100 MHz, $CDCl_3$) 13.6 (C9), 18.3 (C8), 26.9 (C1), 39.7 (C7), 53.0 (C3), 68.8 (C5), 128.3 (ArC), 128.7 (ArC), 134.8 (ArC), 153.6 (C4), 172.9 (C6), 201.5 (C2); HRMS (FI^+) found 300.1200, $C_{15}H_{19}NO_4Na$ (MNa^+) requires 300.1206.

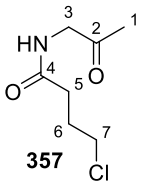
5-Hydroxy-5-methyl-4,5-dihydrooxazol-2-yl benzoate (355), 5-methyloxazol-2(3*H*)-one (356), 4-chloro-*N*-(2-oxopropyl)butanamide (357), benzoic 4-chlorobutanoic anhydride (358), benzyl (cyclopropanecarbonyl)carbamate (359), and benzyl alcohol (360).



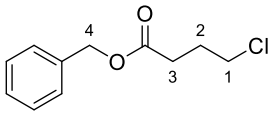
355



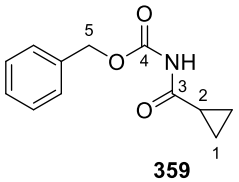
356



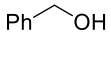
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359

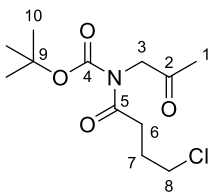


360

To a 10 mL RBF was added benzyl (4-chlorobutanoyl)(2-oxopropyl)carbamate (50–100 mg), THF (4–5 mL) and the solution cooled to –10 °C under argon. *t*-BuOK (1–2 eq., 1.0 M in THF) was added, and after 20 min–2 h the reaction quenched with brine, extracted successively with DCM, dried ($MgSO_4$), and concentrated to yield a crude oil. The oil was purified over silica eluting with 10–20% ether in petrol, yielding the title compounds (~10–20% each). **355**: R_f 0.14 (ether); ν_{max} 3284br, 1750s; δ_H (500 MHz, $CDCl_3$) 1.67 (3 H, s, H1), 3.50 (2 H, dd, *J* = 57.5 and 11.0 Hz, H3), 4.61 (2 H, dd, *J* = 28.0 and 11.0 Hz, H5), 6.33 (1 H, br, OH), 7.21–7.30 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 22.9 (C1), 33.2 (C3), 50.8 (C5), 104.8 (C2), 126.7 (ArC), 126.9 (ArC), 127.5 (ArC), 136.1 (ArC),

157.5 (C4); HRMS (FI$^+$) found 230.0786, $C_{11}H_{13}NO_3Na$ (MNa$^+$) requires 230.0788. **356**: R_f 0.14 (ether); ν_{max} 3254br, 1745s; δ_H (500 MHz, $CDCl_3$) 2.10 (3 H, s, H1), 6.22 (1 H, s, H3), 8.93 (1 H, br, NH); δ_C (125 MHz, $CDCl_3$) 10.5 (C1), 106.3 (C2), 137.4 (C3), 156.5 (C4); HRMS (FI$^+$) found 122.0231, $C_4H_5NO_2Na$ (MNa$^+$) requires 122.0212. **357**: R_f 0.06 (ether); ν_{max} 3323br, 1729s, 1654s; δ_H (500 MHz, $CDCl_3$) 2.13 (2 H, app. quin, *J* = 6.5 Hz, H6), 2.22 (1 H, s, H1), 2.44 (2 H, t, *J* = 7.0 Hz, H5), 3.62 (2 H, t, *J* = 6.5 Hz, H7), 4.17 (2 H, d, *J* = 4.5 Hz, H3), 6.27 (1 H, br, NH); δ_C (125 MHz, $CDCl_3$) 26.3 (C1), 26.9 (C6), 31.8 (C5), 43.3 (C5), 43.3 (C7), 48.8 (C3), 170.7 (C4), 201.8 (C2); HRMS (FI$^+$) found 200.0445, $C_7H_{12}NO_2{}^{35}ClNa$ (MNa$^+$) requires 200.0449. **358**: R_f 0.75 (2:1 petrol/ether); ν_{max} 1731s; δ_H (500 MHz, $CDCl_3$) 2.13 (2 H, app. quin, *J* = 6.5 Hz, H2), 2.57 (2 H, t, *J* = 7.0 Hz, H3), 3.61 (2 H, t, *J* = 6.5 Hz, H1), 5.15 (1 H, s, H5), 7.33–7.40 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 26.6 (C2), 30.2 (C3), 43.0 (C1), 65.4 (C5), 127.1 (ArC), 127.3 (ArC), 127.6 (ArC), 134.8 (ArC), 171.5 (C4); HRMS (FI$^+$) found 212.0604, $C_{11}H_{13}O_2{}^{35}ClNa$ (M$^+$) requires 212.0598. **359**: R_f 0.80 (1:1 petrol/ether); ν_{max} 2957w, 1726s; δ_H (500 MHz, $CDCl_3$) 0.87–0.90 (2 H, m, H1), 1.03–1.06 (2 H, m, H1), 1.65–1.70 (1 H, m, H2), 5.13 (1 H, s, H5), 7.33–7.40 (5 H, m, ArH); δ_C (125 MHz, $CDCl_3$) 7.5 (C1), 11.9 (C2), 65.2 (C5), 127.1 (ArC), 127.3 (ArC), 127.5(ArC), 134.1 (ArC), 154.1 (C4), 171.5 (C3); HRMS (FI$^+$) found 242.2840, $C_{12}H_{13}NO_2Na$ (MNa$^+$) requires 242.0788. **360**: Consistent with a laboratory sample. R_f 0.33 (1:1 petrol/ether); δ_H (500 MHz, $CDCl_3$) 1.81(1 H, br, OH), 4.70 (2 H, s, $ArCH_2$), 7.33–7.40 (5 H, m, ArH).

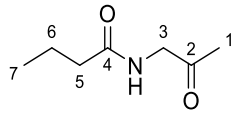
tert-Butyl (4-chlorobutanoyl)(2-oxopropyl)carbamate (361)



To a 25 mL RBF was added benzyl (4-chlorobutanoyl)(2-oxopropyl)carbamate (563 mg, 1.81 mmol), 10% w/w Pd on carbon (100 mg) and MeOH (15 mL). The reaction

was put under argon by 10 x vacuum/argon balloon iterations, and then put under hydrogen under the same manner using a hydrogen balloon. After stirring for 15 h the reaction was put under argon using 10 x vacuum/argon balloon iterations, filtered through celite, and concentrated to yield a white solid. In a 14 mL sample vial, this solid was dissolved in DCM (8 mL) and treated successively with Et_3N (250 µL, 1.809 mmol), $(Boc)_2O$ (780 mg, 3.619 mmol), and DMAP (221 mg, 1.809 mmol). After stirring at room temperature for 4 h, the reaction was concentrated and purified over silica, eluting with 10% ether in petrol, yielding the title product as a colourless oil (213 mg, 42%). R_f 0.50 (1:1 ether/petrol); ν_{max} 1741s, 1694m; δ_H (500 MHz, $CDCl_3$) 1.50 (9 H, s, H10), 2.13 (2 H, t, J = 7.0 Hz, H7), 2.17 (3 H, s, H1), 3.14 (2 H, t, J = 7.0 Hz, H6), 3.62 (2 H, t, J = 6.0 Hz, H8), 4.52 (2 H, s, H3); δ_C (125 MHz, $CDCl_3$) 26.8 (C1), 27.8 (C7), 27.9 (C10), 35.1 (C6), 44.4 (C8), 53.3 (C3), 83.9 (C9), 152.1 (C4), 174.6 (C5), 201.6 (C2); HRMS (FI^+) found 300.0967, $C_{12}H_{20}NO_4{}^{35}ClNa$ (MNa^+) requires 300.0973.

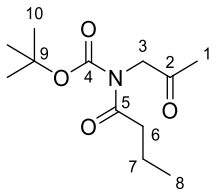
N-(2-Oxopropyl)butyramide (362)



To a 10 mL RBF was added tert-Butyl (4-chlorobutanoyl)(2-oxopropyl)carbamate (20 mg, 72 µmol), THF (2 mL) and the solution cooled to –10 °C under argon. *t*-BuOK (0.14 mL, 1.0 M in THF, 0.14 mmol) was added, and after 20 min the reaction quenched with brine (4 mL), extracted successively with DCM (3 x 10mL), dried ($MgSO_4$), and concentrated to yield a crude oil. The oil was purified over silica eluting with 10–20% ether in petrol, yielding the title compound as a colourless oil (28 mg, 34%). R_f 0.23 (1:1 ether/petrol); ν_{max} 3300m, 1721s, 1640s, 1552s; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, t, J = 7.5 Hz, H7), 1.65 (2 H, app. sext, J = 7.5 Hz, H6), 2.19 (3 H, s, H1), 2.21 (2 H, t, J = 7.5 Hz, H5), 4.15 (2 H, d, J = 4.5 Hz, H3), 6.28 (1 H, br, NH); δ_C (100 MHz,

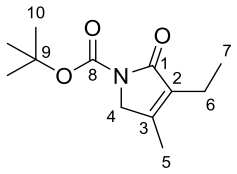
$CDCl_3$) 13.7 (C7), 19.0 (C6), 27.3 (C1), 38.2 (C5), 49.8 (C3), 173.0 (C4), 203.1 (C2); HRMS (FI^+) found 166.0836, $C_7H_{13}NO_2Na$ (MNa^+) requires 166.0838.

tert-Butyl butyryl(2-oxopropyl)carbamate (363)



To a 25 mL RBF was added benzyl butyryl(2-oxopropyl)carbamate (177 mg, 0.630 mmol), 10% w/w Pd on carbon (70 mg) and MeOH (4 mL). The reaction was put under argon by 10 x vacuum/argon balloon iterations, and then put under hydrogen under the same manner using a hydrogen balloon. After stirring for 16 h the reaction was put under argon using 10 x vacuum/argon balloon iterations, filtered through celite, and concentrated to yield a white solid. In a 14 mL sample vial, this solid was dissolved in DCM (8 mL) and treated successively with Et3N (90 μL, 0.630 mmol), $(Boc)_2O$ (274 mg, 1.26 mmol), and DMAP (81 mg, 0.630 mmol). After stirring at room temperature for 2 h, the reaction was concentrated and purified over silica, eluting with 10% ether in petrol, yielding the title product as a colourless oil (115 mg, 75%). R_f 0.77 (1:1 ether/petrol); ν_{max} 1799w, 1741s, 1698m; δ_H (500 MHz, $CDCl_3$) 0.97 (3 H, t, J = 7.5 Hz, H8), 1.49 (9 H, s, H10), 1.69 (2 H, t, J = 7.5 Hz, H7), 2.16 (3 H, s, H1), 2.92 (2 H, t, J = 7.5 Hz, H6), 2.51 (2 H, s, H3); δ_C (125 MHz, $CDCl_3$) 13.7 (C8), 18.4 (C7), 26.8 (C1), 27.9 (C10), 39.9 (C6), 53.2 (C3), 83.5 (C9), 152.3 (C4), 175.7 (C5), 201.9 (C2); HRMS (FI^+) found 266.1359, $C_{12}H_{21}NO_4Na$ (MNa^+) requires 266.1363.

tert-Butyl 3-ethyl-4-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (364)



A modified literature procedure[487] was used. To a 10 mL RBF was added *tert*-butyl butyryl(2-oxopropyl)carbamate (89 mg, 0.37 mmol), THF (4 mL) and the solution cooled to –10 °C under argon. *t*-BuOK (0.73 mL, 1.0 M in THF, 0.73 mmol) was added, and after 20 min the reaction quenched with brine (5 mL), extracted successively with DCM (3 x 10mL), dried ($MgSO_4$), and concentrated to yield a crude oil. The oil was purified over silica eluting with 10–20% ether in petrol, yielding the title compound as a colourless oil (28 mg, 34%). R_f 0.40 (1:1 ether/petrol); ν_{max} 1772s, 1727s, 1713s; δ_H (500 MHz, $CDCl_3$) 1.06 (3 H, t, *J* = 7.5 Hz, H7), 1.56 (9 H, s, H10), 2.01 (3 H, s, H5), 2.28 (2 H, t, *J* = 7.5 Hz, H6), 4.09 (2 H, s, H4); δ_C (125 MHz, $CDCl_3$) 12.8 (C7), 13.1 (C6), 16.7 (C5), 28.1 (C10), 52.8 (C4), 82.5 (C9), 134.5 (C2), 148.7 (C8), 149.9 (C3), 169.9 (C1); HRMS (FI^+) found 248.12540, $C_{12}H_{19}NO_3Na$ (MNa^+) requires 248.12571.