# Catalytic Reductions and Synthesis

# Applications of Organic Azides

Ben Scrafield, MSci

Thesis submitted to the University of Nottingham for the degree of

Doctor of Philosophy

March 2022

## Acknowledgements

First of all, I must thank my supervisor, Prof. Ross Denton, for his support and insight – without which, this thesis would not exist. It is from my colleagues from the Denton group, former and current, that I have learnt much of what I now purport to know, and I thank them for making this experience enjoyable. In particular, I would like to thank James Wilson and Nick Atkinson for their help and advice over the last four years. For earlier contributions to this work, I thank Dr. Jan Saska, Prof. Jie An, Dr. Charlotte Chapman, and Dr. Emma Stoll. Many thanks go to Dr. Liam Ball and Alessio Calcatelli, whose work helped to guide this project. The Paton group are gratefully acknowledged for their contributions to our understanding of this chemistry. I owe a debt of immense gratitude to the technical staff of the School of Chemistry, and specifically to Dr. Kevin Butler, Lola Ogunyemi, Shazad Aslam, and Ben Pointer-Gleadhill.

To my friends and family, I hope that this esoteric document holds some interest. I thank you all for your support and patience throughout this experience. Finally, I thank my long-suffering partner Isaac, who more or less kept me alive during the more fraught portions of my PhD, and made the less fraught portions all the more enjoyable.

Ben Scrafield
University of Nottingham

## Abstract

Known for over a century, organic azides are compounds of significant interest. Organic azides are potentially very useful compounds – they can be considered to function as 'protected' amines. In spite of certain hazards associated with these compounds, research into the chemistry of azides remains active. Chapter 1 of this thesis provides an overview of this considerable body of research in terms of the properties of organic azides, methods for their preparation, and aspects of their reactivity.

The primary aim of this project was to examine the scope and utility of a catalytic azide reduction. Previous catalytic methods display certain practical limitations, which are overcome by the new system. As discussed in Chapter 2, this work included preparing a variety of azides and examining their reactivity in the catalytic azide reduction. This chemistry was then extended to include post-reduction transformations. Chapter 3 details our attempts to apply this method in the preparation of small molecule targets of interest.

## Contents

## List of Abbreviations

| | |
|---|---|
| 3c-4e | three centre-four electron |
| 10-P-5 | 10-electron five-coordinate phosphorus |
| ABX | 1-azido-1λ$^3$-benzo[*d*][1,2]iodaoxol-3(1*H*)-one |
| Ac | acetyl |
| ADHD | attention deficit hyperactivity disorder |
| ADMP | 2-azido-1,3-dimethylimidazolinium hexafluorophosphate |
| AE | atom economy |
| API | active pharmaceutical ingredient |
| APN | (azidophenyl)propiolonitrile |
| Ar | unspecified aromatic group |
| ax | axial |
| AZT | azidothymidine |
| BDE | bond dissociation energy |
| Boc | *tert*-butoxycarbonyl |
| Bn | benzyl |
| b.p. | boiling point |
| bpy | 2,2'-bipyridyl |
| Bu | butyl |
| Bz | benzoyl |
| Cbz | benzyloxycarbonyl |
| CDI | 1,1'-carbonyldiimidazole |
| COSY | correlation spectroscopy |
| CuAAC | copper-catalysed azide-alkyne cycloaddition |
| d | doublet |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| dap | 2,9-di-(*para*-anisyl)-1,10-phenanthroline |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DHQ-MEQ | *O*-(4-methylquinolin-2-yl)dihydroquinine |
| DIPEA | diisopropylethylamine |
| DFT | density functional theory |
| DKR | dynamic kinetic resolution |

| | |
|---|---|
| DLP | dilauroyl peroxide |
| DMF | *N*,*N*-dimethylformamide |
| DMAP | 4-dimethylaminopyridine |
| DMM | dimethoxymethane |
| DMSO | dimethyl sulfoxide |
| DOSY | diffusion-ordered spectroscopy |
| DPPA | diphenylphosphoryl azide |
| d.r. | diastereomeric ratio |
| DTBHN | di-*tert*-butylhyponitrite |
| E | unspecified electrophile |
| e.e. | enantiomeric excess |
| eq | equatorial |
| equiv. | equivalents |
| ESI-TOF | electrospray ionisation time-of-flight |
| Et | ethyl |
| EWG | unspecified electron-withdrawing group |
| Fmoc | fluorenylmethyloxycarbonyl |
| FTIR | Fourier-transform infrared |
| HAT | hydrogen atom transfer |
| hept | heptet |
| HFIP | hexafluoroisopropanol |
| HMBC | heteronuclear multiple bond correlation |
| HOMO | highest occupied molecular orbital |
| HRMS | high-resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence |
| Hz | hertz |
| HX | Brønsted acid |
| IR | infrared |
| *J* | scalar coupling constant |
| KHMDS | potassium hexamethyldisilazane |
| L.A. | Lewis acid |
| LUMO | lowest unoccupied molecular orbital |
| M | molarity |
| m | multiplet |
| *m*-CPBA | *meta*-chloroperbenzoic acid |

| | |
|---|---|
| Me | methyl |
| MesAcr | 9-mesityl-10-acridinium |
| Ms | methanesulfonyl |
| *m/z* | mass-to-charge ratio |
| NBS | *N*-bromosuccinimide |
| NFSI | *N*-fluorobenzenesulfonimide |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser effect spectroscopy |
| Nu | unspecified nucleophile |
| Ph | phenyl |
| Phth | phthalimido |
| pin | pinacolato |
| PMHS | polymethylhydrosiloxane |
| PMI | process mass intensity |
| PNBSA | *para*-nitrobenzenesulfonyl azide |
| ppm | parts per million |
| Pr | propyl |
| PTAD | 4-phenyl-1,2,4-triazolidine-3,5-dione |
| *p*-Tol | *para*-tolyl |
| q | quartet |
| R | unspecified chemical group |
| Rh6G | rhodamine 6G |
| RME | reaction mass efficiency |
| r.r. | regioisomeric ratio |
| r.t. | room temperature |
| s | singlet |
| SCE | saturated calomel electrode |
| SET | single electron transfer |
| t | triplet |
| T3P | propanephosphonic acid anhydride |
| TBDPS | *tert*-butyldiphenylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TMDS | tetramethyldisiloxane |
| TMG | 1,1,3,3-tetramethylguanidine |

| | |
|---|---|
| TMGA | 1,1,3,3-tetramethylguanidinium azide |
| TMP | 5,10,15,20-tetramesitylporphyrin |
| TMS | trimethylsilyl |
| Tris | 1,3,5-triisopropylbenzenesulfonyl |
| Ts | *para*-toluenesulfonyl |
| THF | tetrahydrofuran |
| TLC | thin-layer chromatography |
| VT | variable temperature |
| X | unspecified atom |
| $\chi_P$ | Pauling electronegativity |

# 1. Introduction

## 1.1: Properties of Organic Azides

The azide functional group ($N_3$) occupies a unique place in the field of organic synthesis. While the azide group can be easily and inexpensively installed and can react to give a wide variety of useful products, its reactivity presents legitimate and sometimes prohibitive safety concerns: some organic azides are explosive, and inorganic azides are often both explosive[1] and acutely toxic. In spite of the safety issues associated with azides, however, their considerable utility has ensured that research into their preparation and applications has continued to grow: over 3,000 small molecules containing the azide group were found by a ChEMBL[2,3] search of the medicinal chemistry literature, and – in recent years – over 2,000 papers referring to this class of compounds have been published, annually (see Figure 1).

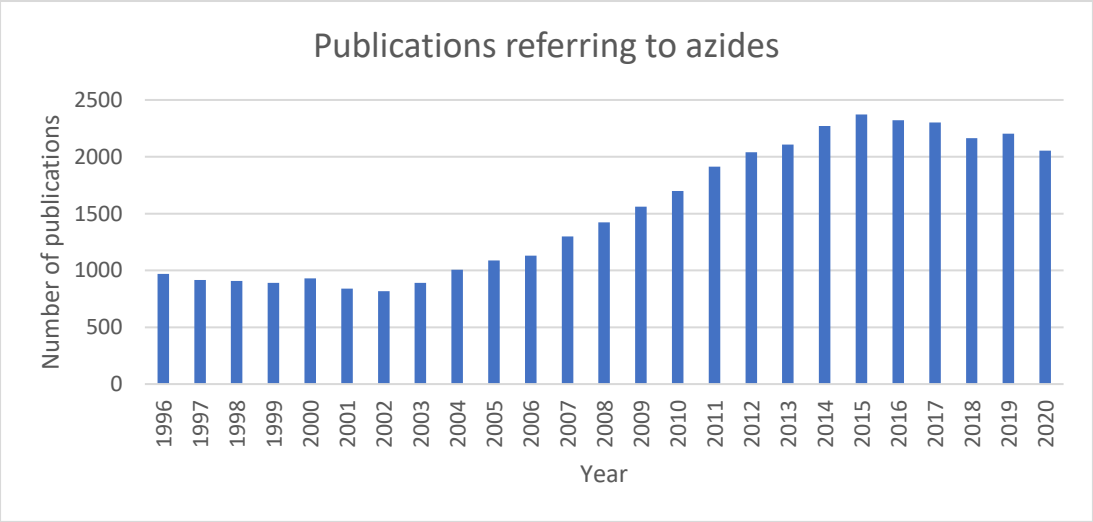
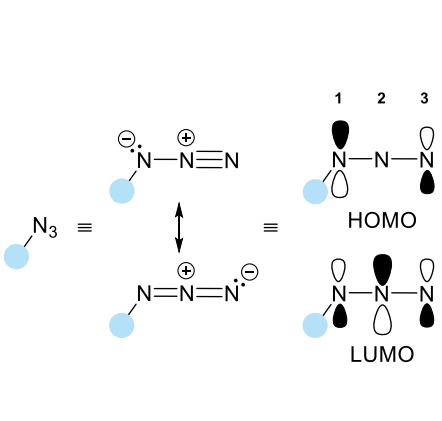



***Figure 1.*** *Publication titles/abstracts referring to azides over the last 25 years – found by searching the terms 'azide', 'azides', 'azido', and 'azidation' using Web of Science.*[4]

The utility of azides emerges directly from their fundamental physicochemical properties. As the azide group cannot be represented by a single uncharged, closed-shell structure, the $N_3$ group is typically

represented by one or more ionic resonance forms, each of which is understood to contribute to the ground state.[5,6] Crystallographic data,[7–9] hyperpolarised $^{15}N$ NMR spectra,[10] molecular mechanics/dynamics,[11] and *ab initio* calculations[12] corroborate this model – the N1-N2 bond is shown to be longer than the N2-N3 bond, N2 bears significant positive charge, and negative charge is accumulated at N1 and N3. The electronic structure of the azide group can be understood in terms of frontier molecular orbital (FMO) theory:[13–15] the HOMO of a generic azide should have 1 node at N2, and the LUMO should have 2 nodes, found between the atoms (see Figure 2). More detailed analysis of the FMOs was provided by Houk,[16] who showed that the largest lobe of the HOMO is located at N1, with a negligible amount at N2, and that significant LUMO coefficients are found at each N atom. Although – in electronic terms – azides are 1,3-dipoles[17], they do not generally display considerable polarity, as evidenced by small dipole moments[6,18] and Hammett parameters ($\sigma_m$ = 0.37, $\sigma_p$ = 0.08).[19] DFT and reactivity studies[20] show that azides can engage in intramolecular hydrogen bonding; this affects the charge distribution on the N atoms and, as a result, the reactivity of the azide group.




| = | $CO_2H$ | HO, NH, O, N, O, O | $NO_2$, O |
|---|---|---|---|
| $r_{N1-N2}$ (Å) | 1.23 | 1.24 | 1.26 |
| $r_{N2-N3}$ (Å) | 1.12 | 1.12 | 1.11 |
| $\angle_{C-N1-N2}$ (°) | 116.4 | 114.5 | 111.9 |
| $\angle_{N1-N2-N3}$ (°) | 172.5 | 173.0 | 174.0 |
| $\nu_{(N=N=N)}$ ($cm^{-1}$) | 2101 | 2105 | 2133 |

***Figure 2.*** *Structural and electronic properties of azides*

Due to its ability to liberate dinitrogen spontaneously,[21] the azide functional group is an explosophore.[22,23] As with other high-energy functional groups, the explosivity of an organic azide is greatly affected by the rest of the molecule – in general, low molecular weight azides are known to be extremely hazardous,[12,24] whereas heavier (organic) azides can display much greater stability. In practice, the relative nitrogen content of a molecule is used as a presumed index of its stability: as a general guideline, compounds with $(N_C + N_O)/N_N \geq 3$ are considered safe to isolate and store in their pure forms (where $N_X$ is the number of X atoms in the molecule).[6,25] Empirical methods for predicting the thermochemical profile of a given azide have been developed,[26] based on existing calorimetric data, but this existing data is limited: the stabilities of individual compounds have been investigated, but – to date – there is only one systematic calorimetric study[27] of a range of organic azides, which is restricted largely to sulfonyl azides. Precisely how explosive organic azides are, compared to other high-energy compounds (especially those of industrial relevance, such as nitro compounds,[28,29] diazo compounds,[27] tetrazoles, and diazonium salts[30]), remains an open question.

## 1.2: Preparation of Organic Azides

No naturally occurring organic azides are known;[i] as a result, the azide functionality must be introduced into a molecule by one of a number of synthesis methods.[6,31–37] Early methods for the preparation of organic azides involved construction of the $N_3$ group from a 'two-nitrogen'

[i] Literature searched using Web of Science,[4] Reaxys,[481] and Coconut[482]

precursor, *e.g.*, by the addition of ammonia[38] or sulfonamides[39] to diazonium salts, or by the oxidation of hydrazines with nitrous acid.[40,41] Most modern approaches to these compounds tend to involve addition of the entire azide group to a molecule, in a single step, using a discrete azide reagent. Sources of the azide moiety include both inorganic compounds such as hydrazoic acid ($HN_3$; p$K_a$ = 4.6 ($H_2O$); 7.9 (DMSO))[42] and metal azides[43], and azido-main group compounds including sulfonyl azides,[44] silyl azides,[45,46] phosphoryl azides,[44,47,48] and azidoiodanes[49,50] (see Figure 3). Ultimately, the majority of these azide reagents are prepared from sodium azide ($NaN_3$), an inexpensive but acutely toxic salt that is produced on a large scale (hundreds of tons per year).[25,51]

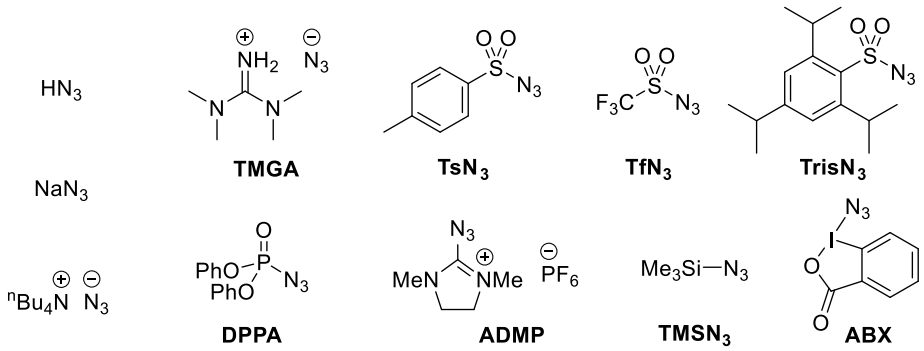



***Figure 3.*** *Reagents used as azide sources, including common abbreviations (bolded)*

## 1.2.1: Nucleophilic azidations

The azide anion, most commonly accessed from sodium azide, is a moderately strong nucleophile.[52] As a result, organic azides can be prepared by addition of the azide anion to a wide variety of carbon electrophiles. Suitable electrophiles include alkyl halides/sulfonates,[53,54] epoxides and aziridines,[55–57] 'onium' cations,[58–60] aryldiazonium salts,[61–63] activated haloarenes/heteroaromatics,[64,65] α,β-unsaturated carbonyl

compounds,[66,67] acyl halides/anhydrides,[68] Pd(II)-π-allyl complexes,[69–71] and Au(I)-allene complexes.[72,73] Chlorinated solvents[25] and methyl- or ethylammonium salts[74] are often incompatible with sodium azide due to their electrophilicity – these compounds will react to form hazardous, low molecular weight azides. Less reactive electrophile precursors such as alcohols and carboxylic acids can be activated *in situ* with appropriate nucleophilic or pro-nucleophilic azide reagents; examples of this strategy include azidation of alcohols with ADMP[75] or under Mitsunobu conditions,[76–79] and azidation of alkoxides[80] and carboxylates[47] with DPPA.

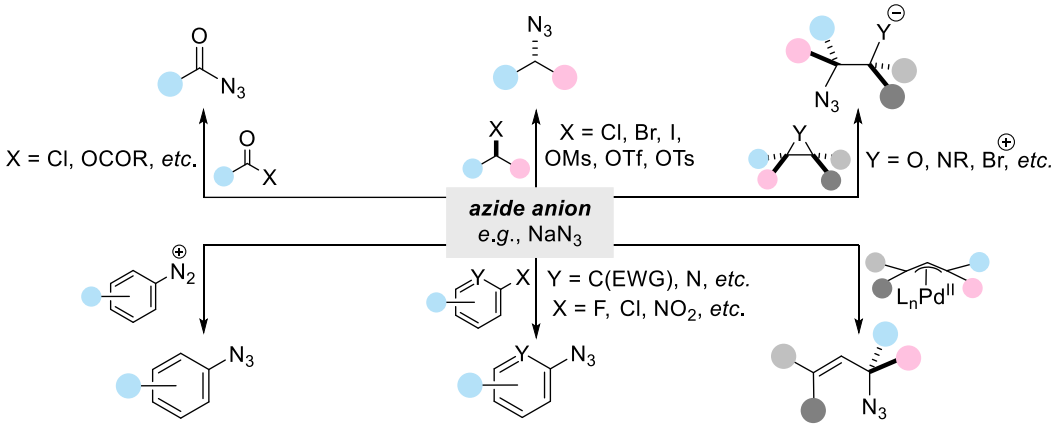
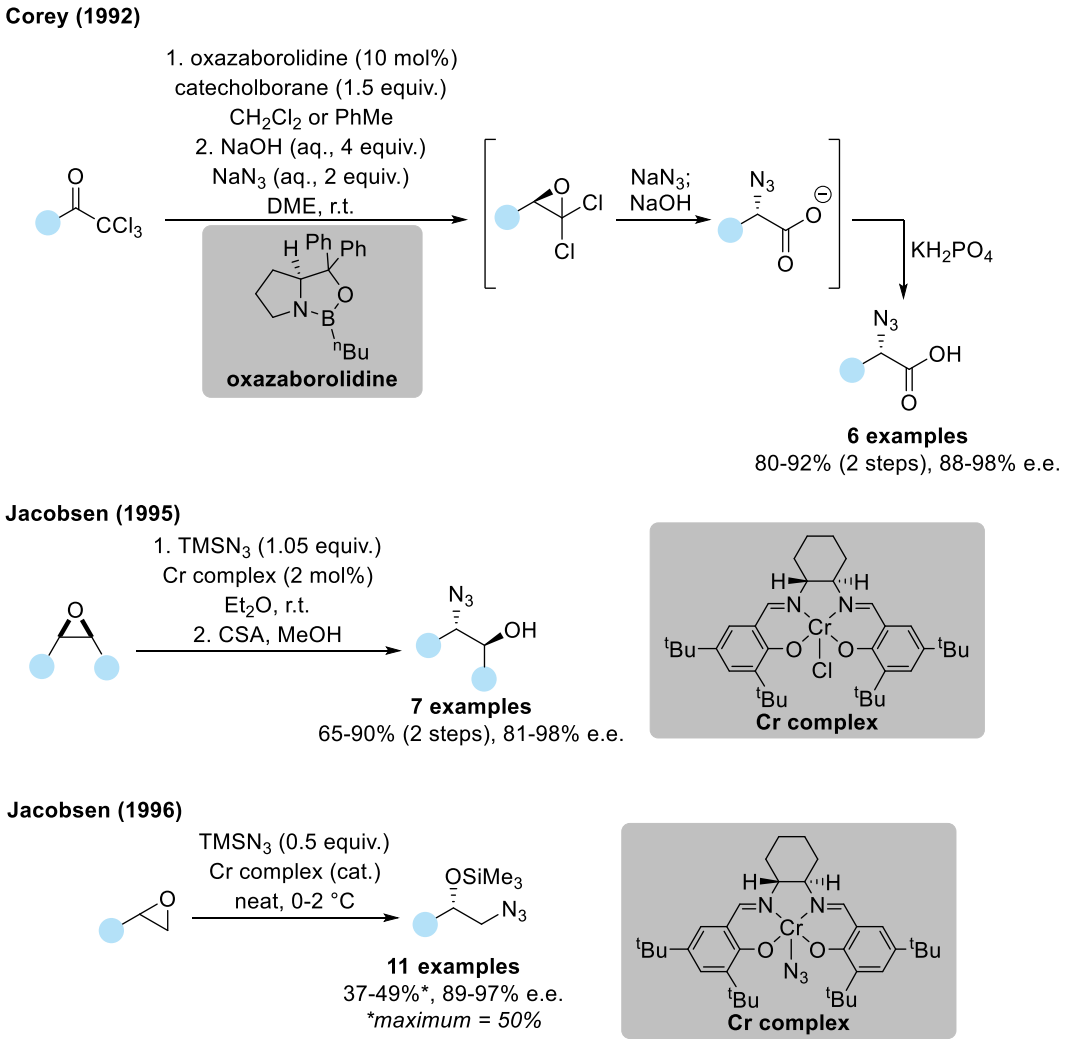



***Figure 4.*** *Nucleophilic azidations with sources of the azide anion*

Asymmetric C–N bond formation by nucleophilic azidation is well established.[35] Many azidations at $sp^3$ carbon centres proceed *via* $S_N2$-type mechanisms and – as such – are stereospecific for the product with inversion of stereochemistry at the substituted carbon.[81,82] Enantiopure and enantiomerically enriched alcohols can be used to prepare electrophiles such as alkyl halides[83–85] and sulfonates[86,87] with high optical purity, and are themselves widely available both from the chiral pool[88,89] and from achiral precursors *via* a wide variety of asymmetric transformations, some of which (*e.g.*, hydrogenation) are performed on large industrial scales.[90–92]

Research into asymmetric epoxidation is also represented by a large body of literature[93,94]: high yields and enantiomeric excesses can be achieved *via* a number of methods, of which some of the most commonly used are the Sharpless[95,96], Jacobsen-Katsuki[97–99], Shi[100,101], and Jørgensen[102] epoxidations. As a result of the diversity of available methods for asymmetric epoxidation, enantiomerically enriched 1,2-azido alcohols can be prepared with relative ease. Notable applications of this chemistry include the Corey-Link amino acid synthesis[103] and the Jacobsen group's work in the areas of dynamic kinetic resolution (DKR) of racemic terminal epoxides[104] and desymmetrisation of *meso* epoxides[105] (see Scheme 1).




***Scheme 1.*** *Syntheses of enantiomerically enriched azides* via *epoxides*

### 1.2.2: Radical azidations

Azidation *via* radical pathways has emerged, over the last 25 years, as a powerful, complementary approach to nucleophilic azidation.[32,37] The azidyl radical itself ($N_3^{\bullet}$) has electrophilic character,[106] and undergoes rapid hydrogen atom transfer (HAT)[107] with weak, nucleophilic X–H bonds;[108] hydrazoic acid ($HN_3$) has an N–H bond strength of 92 kcal·mol$^{-1}$,[108,109] but can itself undergo HAT with nucleophilic radicals to form strong X–H bonds.[110] Epimerisation of unactivated 3° C–H bonds is enabled by a combination of these two processes: the azidyl radical can reversibly abstract a hydrogen atom, leading to the thermodynamically preferred ratio of epimers for the reactive position.[111] The azidyl radical also reacts with carbon-carbon π-bonds to give carbon-centred radicals, which can then participate in a wide variety of propagation and/or termination processes.[112–118]

Direct formation of $N_3^{\bullet}$ from the azide anion is possible under oxidising conditions ($E_{1/2}(N_3^{\bullet}/N_3^{-})$ = +1.08 V ($H_2O$)[119]; +0.87 V (MeCN)[110], both *vs*. SCE), but high [$N_3^{\bullet}$] leads to dimerisation and fragmentation to give $N_2$.[120] Azide species with weak X–$N_3$ bonds – for example, diazidoiodanes[121] or azide-aminoxyl adducts[122] – can be used to generate small, steady-state concentrations of $N_3^{\bullet}$, by homolytic bond fission with light or heat. Typically, these labile azide compounds must themselves be generated *in situ* from other azide sources by ligand exchange.[123] More conveniently, common azide reagents can undergo redox processes (single-electron transfer; SET) to generate homolytically fissile intermediates: the azidyl

radical can be liberated upon single-electron oxidation of silyl azides or single-electron reduction of azidoiodanes (see Figure 5).

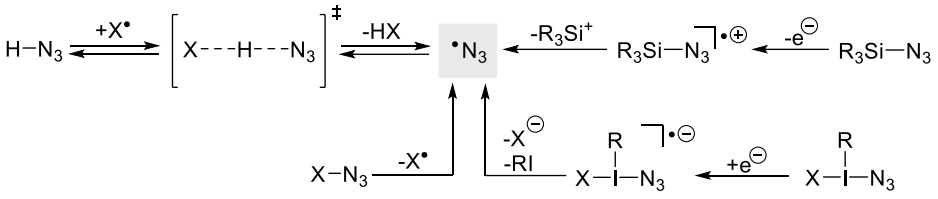
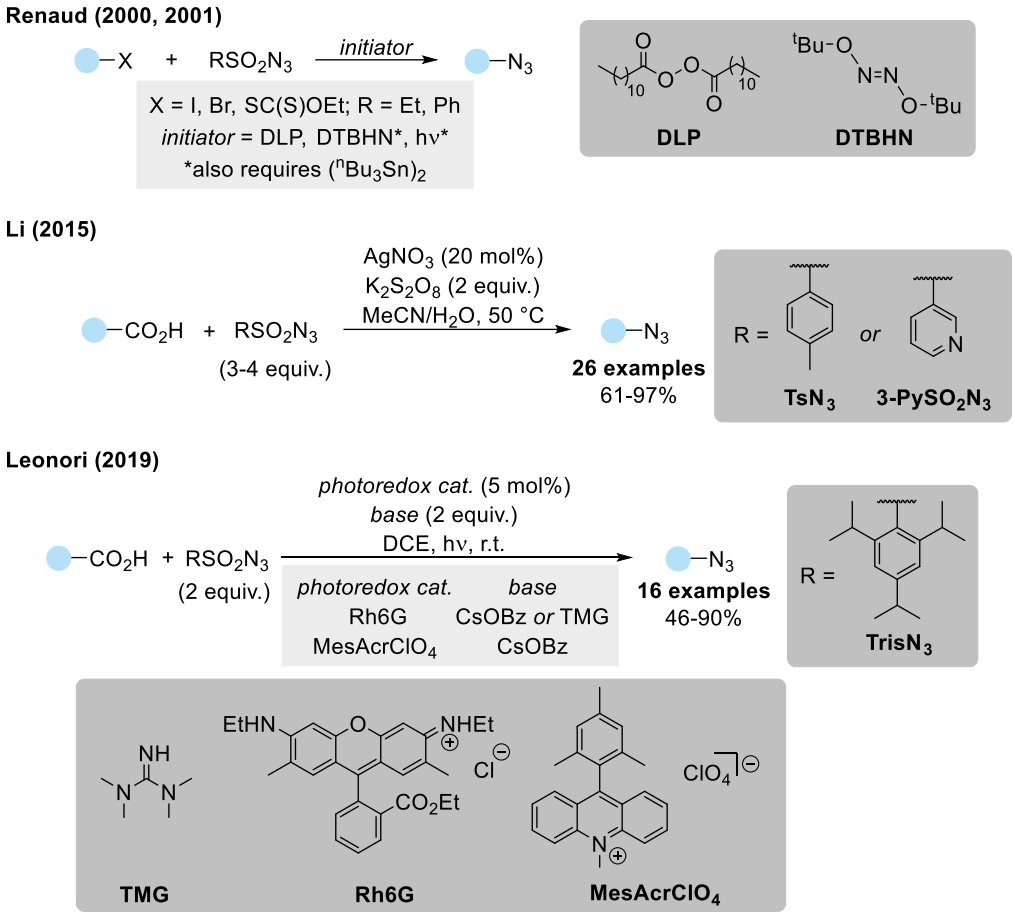



***Figure 5.*** *Generation of the azidyl radical, $N_3^{\bullet}$*

While azide reagents such as silyl and sulfonyl azides tend not to undergo homolysis under redox–neutral conditions, these reagents readily participate in azide transfer to carbon-centred radicals, probably *via* associative mechanisms.[124,125] Since many methods are known for the generation of carbon-centred radicals, this has become the pre-eminent strategy for radical azidation reactions. Following early observations[126,127] that alkyl radicals could react with sulfonyl azides, the Renaud group were the first to develop practical methods for this kind of azidation, demonstrating the effectiveness of sulfonyl azides for azide transfer to alkyl radicals generated *in situ* from alkyl halides and dithiocarbonates.[128,129] Since these key publications, a large number of variations on this azidation strategy have been disclosed: azidation is known to proceed both with different alkyl radical precursors and different azide sources.[106,130–133] A recent innovation in this area is the direct use of carboxylic acids as radical precursors. Methods for decarboxylative azidation, the first of which was published by Li in 2015,[134] are attractive because carboxylic acids are abundant, often inexpensive, and typically very stable starting materials. The Leonori group have since demonstrated

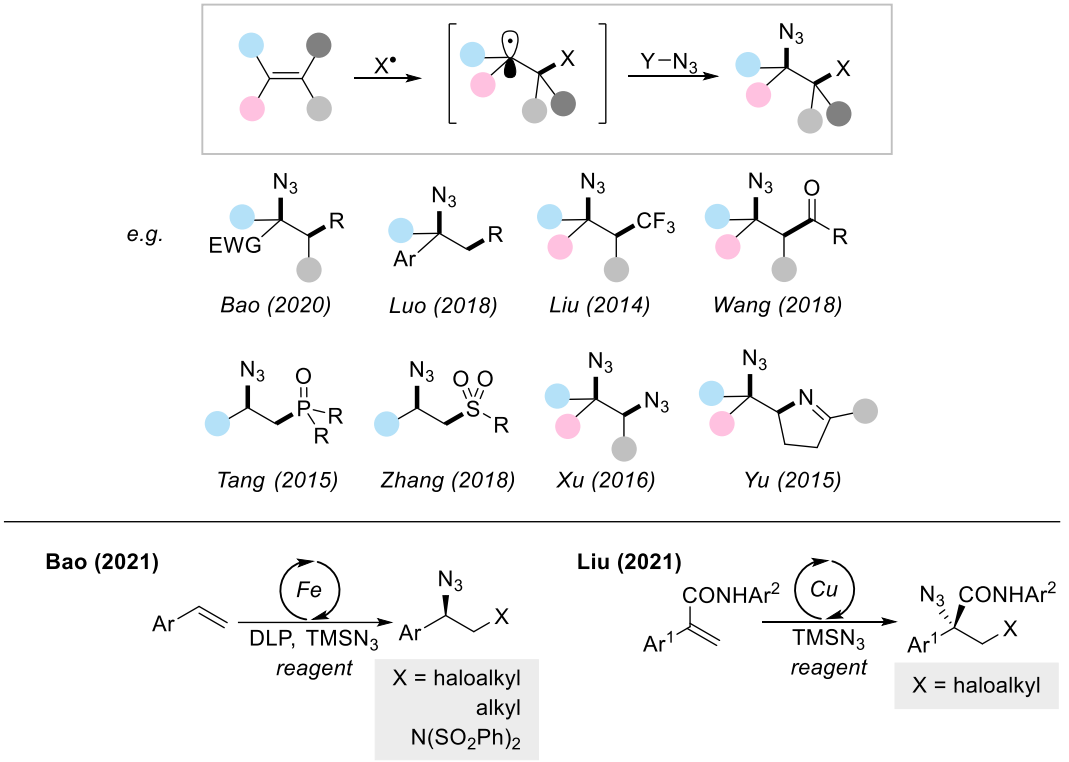
that this chemistry can be achieved under metal-free conditions, with photoredox catalysis.[135]




***Scheme 2.*** *Generation of alkyl radicals and addition to azide sources*

Alkene 'azidofunctionalisation', *i.e.*, addition of a generic radical to a carbon-carbon π-bond followed by azide transfer to the resultant radical, is an especially prominent radical azidation manifold (see Scheme 3).[32,37,136–143] Azidations of this kind can be effected with either preformed azide transfer agents, as in the Renaud chemistry, or with reactive azide intermediates generated *in situ*; where transition metals are used to catalyse azidofunctionalisation reactions, it is typically understood that C–N bond formation occurs from an organometallic-azide complex formed *in situ*. Attempts to render this kind of azidation asymmetric represent the state of the art: at the time of writing, the first examples of asymmetric

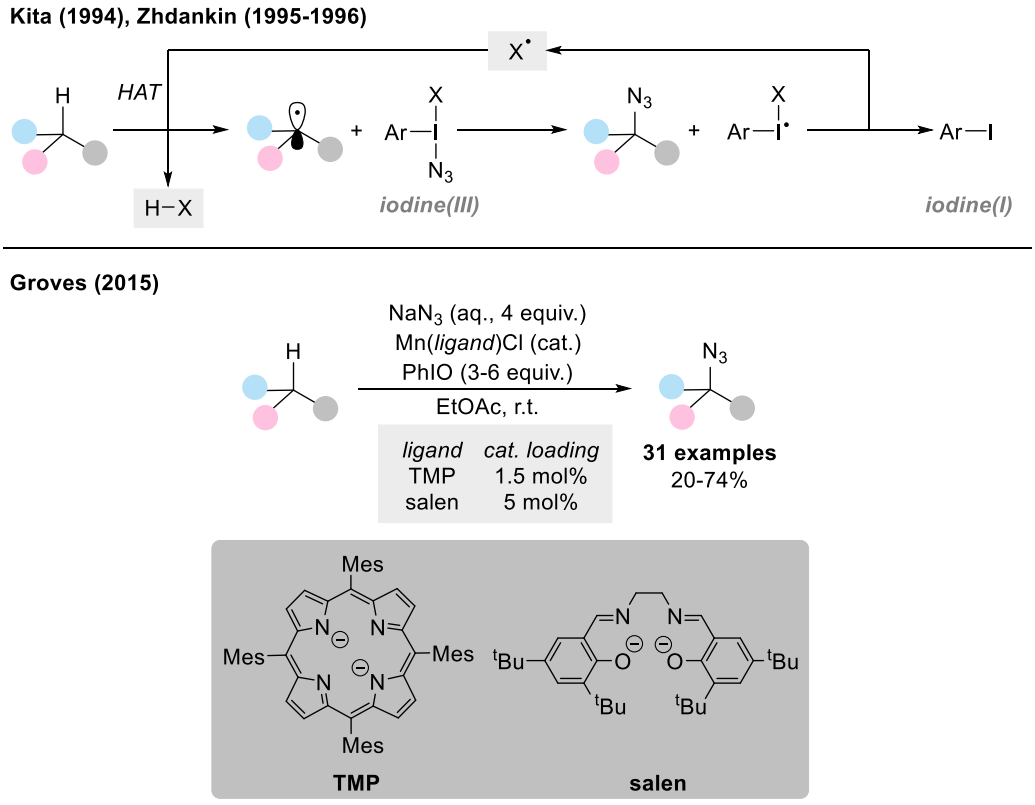
radical azidofunctionalisation reactions have been disclosed in three recent publications (all 2021), from the groups of Hongli Bao and Guosheng Liu, respectively.[144–146]



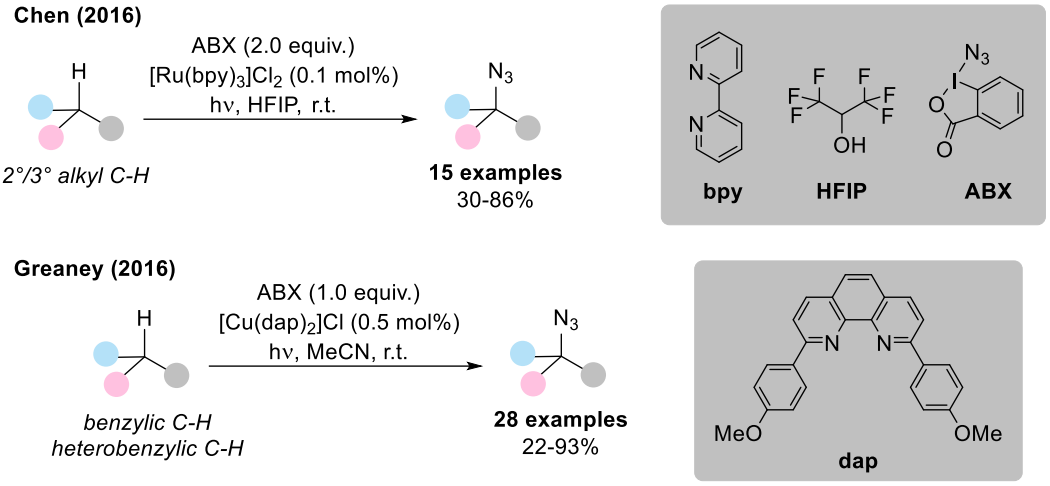

***Scheme 3.*** *Azidofunctionalisation of alkenes*

Radical 'C–H azidation',[32,36,106] *i.e.*, abstraction of H• from an organic molecule, followed by transfer of azide, has the potential to be an especially powerful paradigm within radical azidations: regioselective and perhaps stereoselective conversion of C–H to C–$N_3$ could circumvent many steps in the preparation of desired organic azides (and their derivatives) from feedstock chemicals. In general, the loss of a C–H bond (BDEs often ≥100 kcal·mol$^{-1}$ for C($sp^2$/$sp^3$)-H)[147–150] is not enthalpically compensated by the formation of a C–$N_3$ bond (BDEs typically 50-90 kcal·mol$^{-1}$).[32] In these cases, some other process must render the C–H azidation exergonic, such as strong X–H bond formation.

In early publications from Kita[121] and Zhankin,[151,152] C–H azidation was paired with both relatively strong X–H bond formation and overall reduction of organoiodine(III) compounds to give organoiodine(I) byproducts. Later work from Groves matched this thermodynamic manifold with Mn(III/IV/V) catalysis, resulting in a kinetically competent system for C–H azidation to give a wide range of benylic, heterobenzylic, and alkyl azides, in moderate to good yields.[153] Using photoredox catalysts, similar systems have since been optimised individually for benzylic C–H azidation[154] and alkyl C–H azidation,[155] by the Greaney and Chen groups, respectively. Both of these sets of conditions use ABX (the Zhdankin reagent) as an azide source, H-atom acceptor, and terminal oxidant.

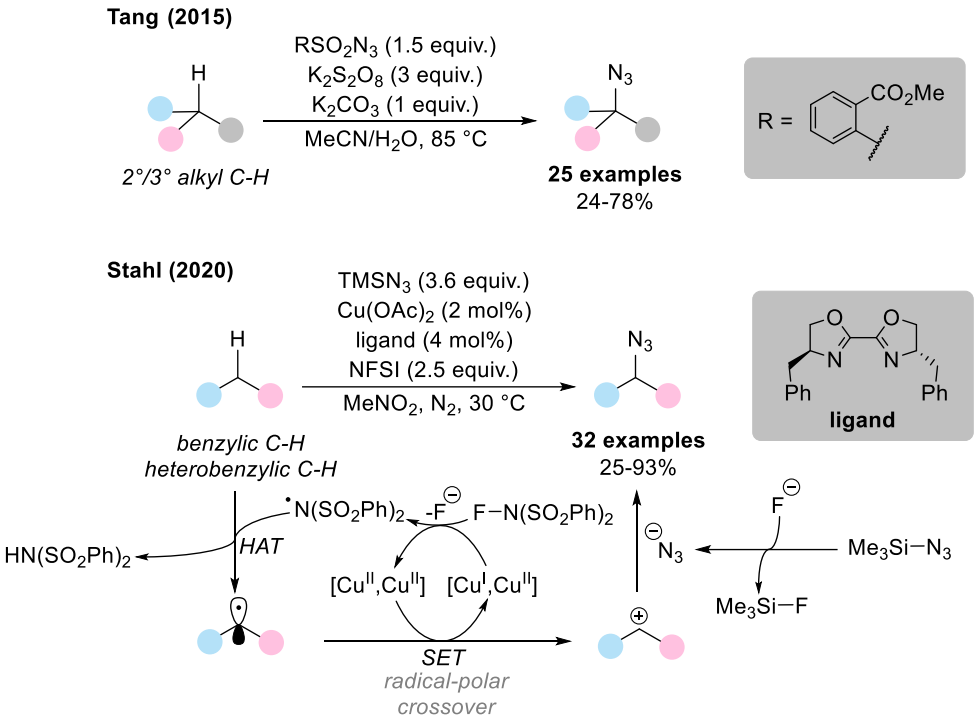



***Scheme 4.*** *C–H azidation with organoiodine(III) reagents/Mn catalysis*




***Scheme 5.*** *C–H azidation with ABX/probable photoredox catalysis*

Mechanistically distinct systems for C–H azidation include the operationally simple, metal-free alkyl azidation developed by Tang,[156] and the Cu-catalysed benzylic oxidation disclosed by the Stahl group.[157] In the Tang conditions, persulfate ($S_2O_8^{2-}$) decomposes upon heating to form $SO_4^{\bullet-}$ - a strongly electrophilic radical, which rapidly abstracts an H atom from the substrate to generate an alkyl radical. This alkyl radical then reacts with a sulfonyl azide to give the desired azide product; in this respect, these conditions bear some resemblance to the dehalogenative and decarboxylative radical azidations discussed previously. The Stahl azidation is mechanistically more complex: on the basis of stoichiometric control reactions and computational investigation, the operative pathway for this reaction is believed to involve dimeric Cu(II)/Cu(II) and Cu(I)/Cu(II) complexes as well as radical-polar crossover – strictly speaking, although the reaction proceeds *via* a radical, the putative C–N bond forming event is a nucleophilic azidation.

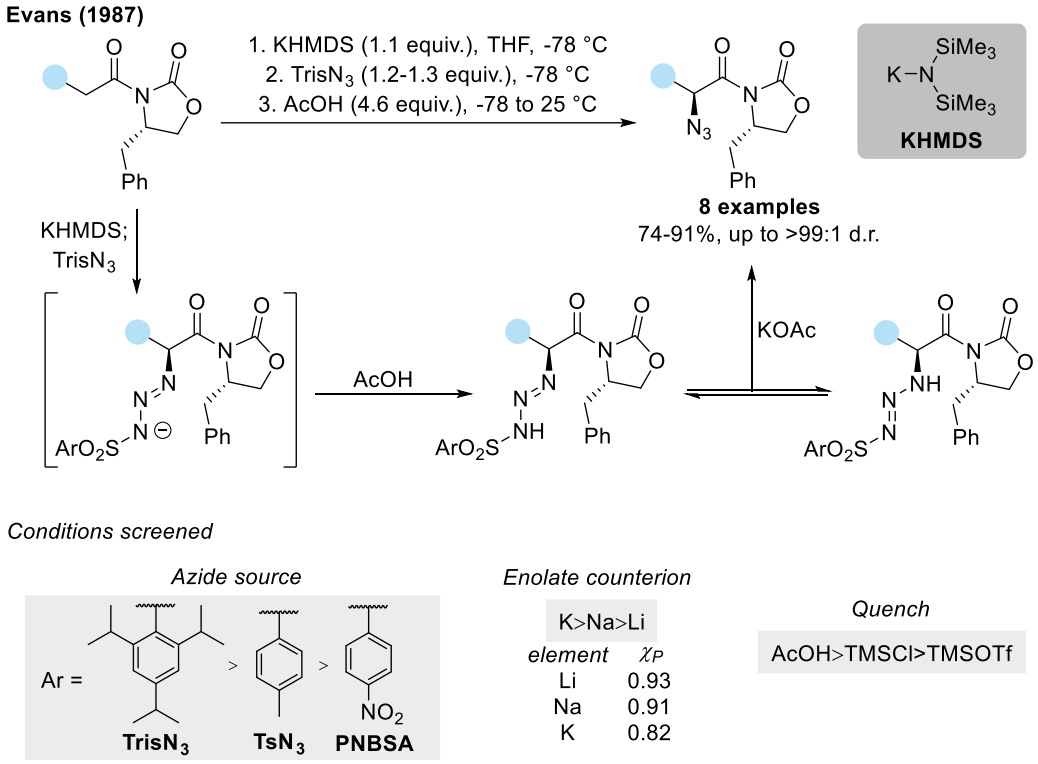



***Scheme 6.*** *Alternative redox manifolds for C–H azidation*

## 1.2.3: Electrophilic azidations

Compared to nucleophilic and radical azidation reactions, electrophilic azidations are considerably less well established. Although sulfonyl azides are electrophilic at nitrogen, transfer of the azide group is not straightforward: following addition of a carbon nucleophile, fragmentation pathways exist for both loss of sulfinate (giving the azide product) and loss of sulfonamide (giving the diazo product – see Section 1.2.4); care must be taken to avoid a mixture of these two products.[158] The Evans group were the first to optimise conditions for enolate azidation in a systematic way.[159] Among the findings of the Evans group, it was established that, for imide enolates, azidation was favoured with electron-rich, sterically bulky azides (specifically, $TrisN_3$), more electropositive enolate counterions (*i.e.*, K>Na>Li)[160], and a mild acid quench following sulfonyl azide addition.

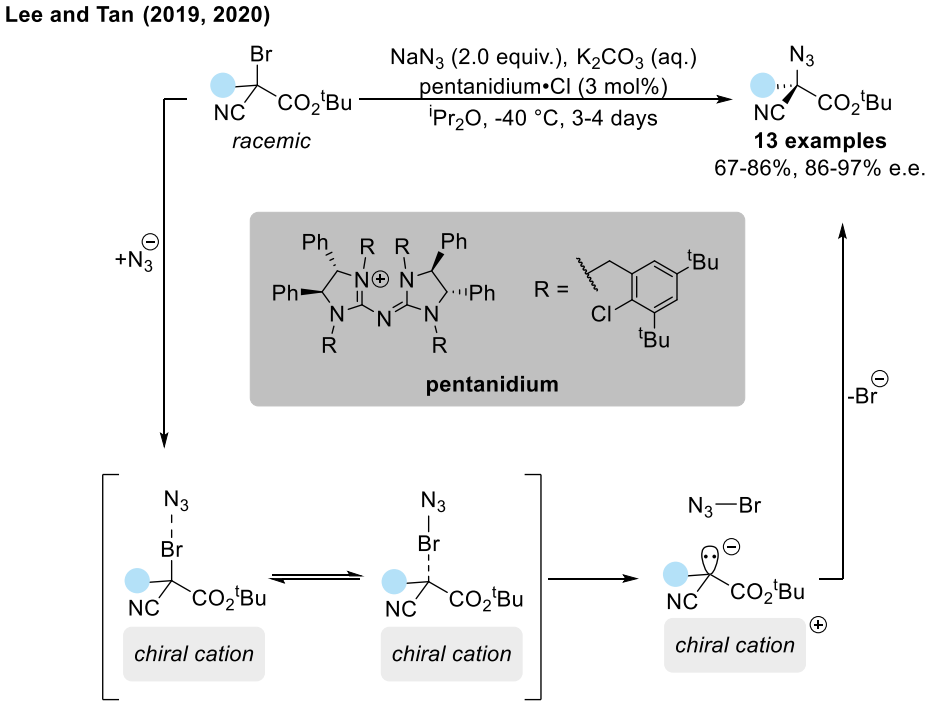
Ester enolates were also shown to undergo azidation with $TrisN_3$ and an AcOH quench; in contrast with imides, however, ester enolates displayed little sensitivity to changes in the enolate counterion. These azidation conditions were later shown to be applicable to other nucleophiles, such as organolithium reagents.[161,162]




***Scheme 7.*** *Evans-type electrophilic azidation*

Aside from the discoveries of the Evans group, two more recent approaches to electrophilic azidation merit discussion. The first approach comes from two publications by Beier, which disclose new methods for the synthesis of perfluoroalkyl azides.[163,164] Using the corresponding perfluoroalkyl Grignard reagents or trimethylsilanes (in the presence of fluoride) and strongly electrophilic sulfonyl azides, a range of perfluoroalkyl azides were prepared in good yield. The second approach is an innovative system from Lee and Tan for the preparation of certain enantiomerically enriched tertiary alkyl azides.[165,166] It was established by these groups that

tertiary alkyl bromides – when activated by two electron-withdrawing groups – could be attacked by azide anion at bromine, leading to *in situ* formation of $BrN_3$, which is then itself attacked irreversibly at nitrogen by the resulting carbanion, in an overall 'halogenophilic' nucleophilic substitution, or '$S_N2X$' process. Using a $C_2$-symmetric pentanidium species as a catalytic counterion, very good yields and enantioselectivities were obtained for this reaction.

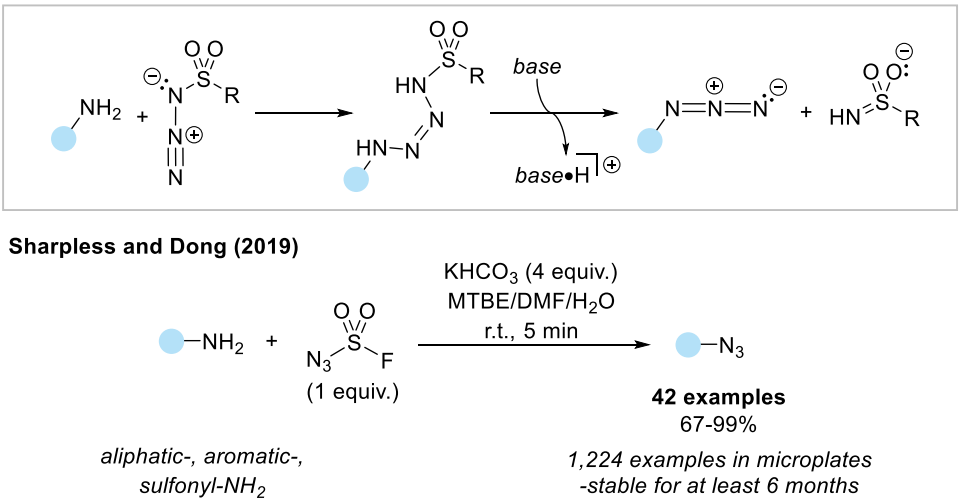



***Scheme 8.*** *Halogenophilic azidation*

## 1.2.4: Azide synthesis by diazo transfer

Sulfonyl azides are perhaps best known for their use in diazo transfer reactions, as pioneered by Regitz in the mid-1960s.[167] Classical diazo transfer to activated methylene positions ($CH_2$ to $CN_2$) proceeds under complementary conditions to those developed by Evans for enolate azidation: amine bases and sterically unencumbered, electron-deficient sulfonyl azides tend to give the diazo compound exclusively. By analogy

with the above, diazo transfer to primary amines ($NH_2$ to $N_3$) is also feasible – this provides a conceptually different approach to the preparation of azides to those described in previous sections. Typically, very electrophilic sulfonyl azides are more practical for this kind of reaction; for example, tosyl azide ($TsN_3$) will only undergo diazo transfer with fully deprotonated amines, whereas triflyl azide ($TfN_3$) reacts readily with amines in the presence of mild bases.[168–170] Recent work from Sharpless and Dong has shown that fluorosulfuryl azide is a powerful diazo transfer agent for this application – over 40 aliphatic and aromatic amines were shown to give the corresponding azides in high isolated yield, and a library of over 1,000 azides were also synthesised in microplates using this method.[171]

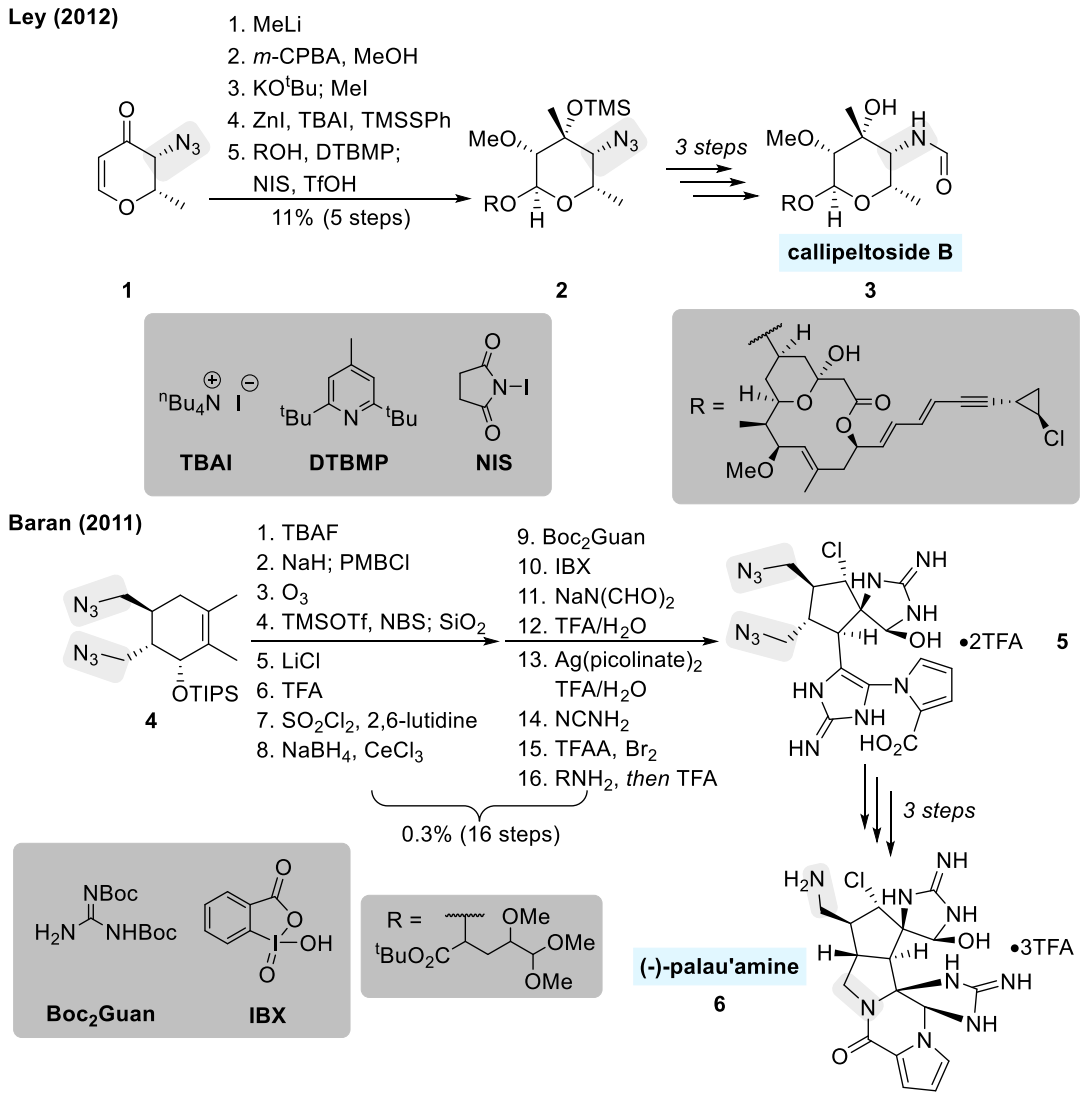



***Scheme 9.*** *Diazo transfer to amines*

## 1.3: Reactions of Organic Azides

Although organic azides can display thermal instability, alkyl and aryl azides frequently display considerable chemical stability. Indeed, the use of azides in chemical biology (see Sections 1.3.5 and 1.3.7) is frequently described as 'bioorthogonal' – that is, the azide functional group is

understood to interact with little of the biochemical composition of a cell (*e.g.*, compounds in solution, receptors, enzymes).[172–174] For chemists engaged in synthesis, this relative chemical stability has led to the use of azides as intermediates in a number of multi-step total syntheses, in which the azide group has been shown to be inert to a wide range of reactions at other positions in a molecule (see Scheme 10).[175–179] As discussed in the following sections, the azide group can be considered as a retron[180] for an amine or nitrene, two functionalities of very wide utility.




***Scheme 10.*** *Azides as intermediates in total synthesis*

### 1.3.1: Sigmatropic rearrangements

Allylic azides are unusual among organic azides, in that they are not – in general – configurationally stable at room temperature: they readily undergo [3,3]-sigmatropic rearrangements known as Winstein rearrangements.[181] The equilibrium between the two azide isomers can, however, lie significantly to one side: when one isomer has a more substituted alkene, that isomer tends to be the major component,[182] and when the alkene is conjugated with an aryl group or an electron-withdrawing group, a single isomer is often observed.[183–185] In addition, the rearrangement is stereospecifically suprafacial in the absence of metal catalysts;[73] this means that stereochemical information is preserved for sufficiently substituted allylic azides.[186]

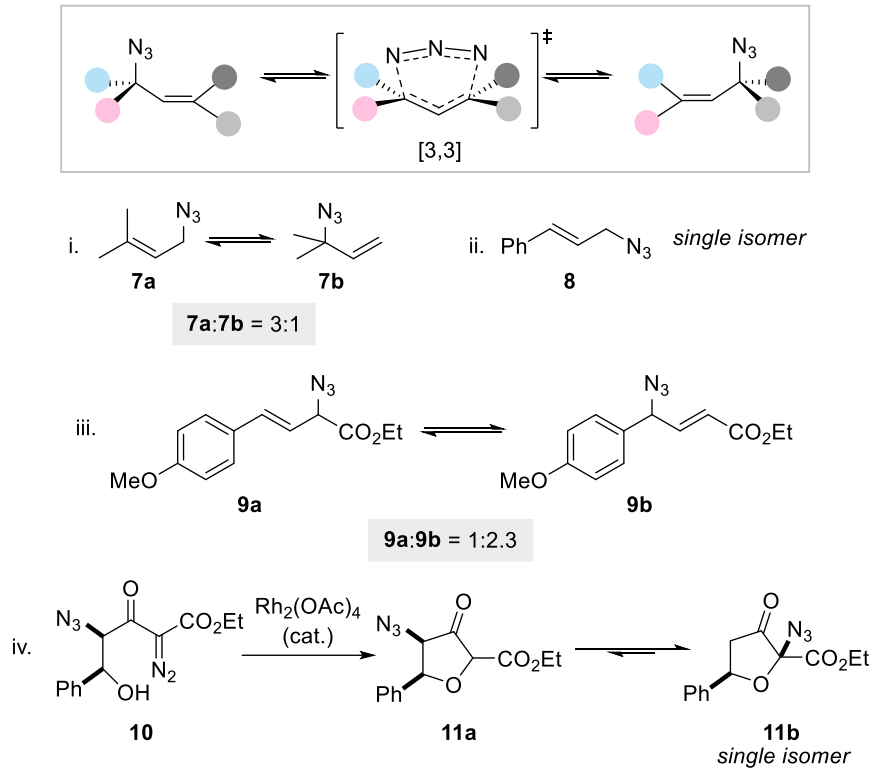
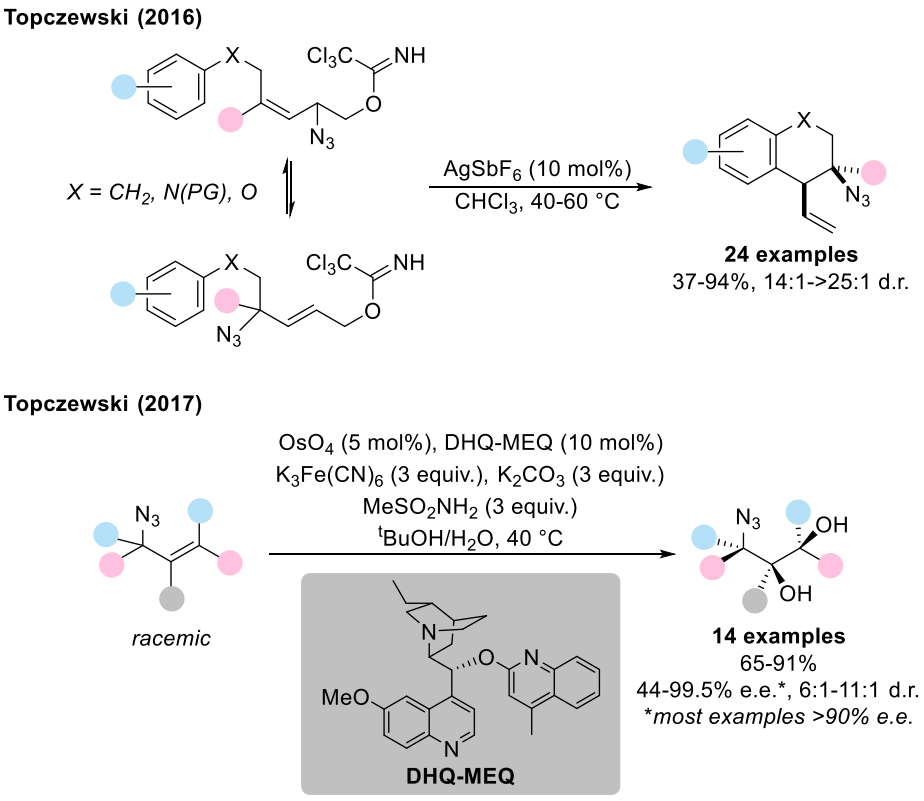



***Figure 6.*** *Winstein rearrangements (all ratios recorded at room temperature)*

Since 2016, the Topczewski group have shown that it is possible to harness the dynamic behaviour of allylic azides in reactions where one isomer

reacts specifically or with high selectivity. The group first applied this concept to differentially substituted systems: an equilibrating mixture of regioisomers can be converted to, for example, a single cyclisation product, in cases where only one regioisomer is activated for cyclisation.[187] It was then shown that symmetrically substituted systems (*i.e.*, interconverting enantiomers) can undergo dynamic kinetic resolution, where the DKR system is sufficiently enantiotopos-discriminating. The DKR system chosen was a Sharpless-type asymmetric dihydroxylation,[188] which gave good enantio- and diastereoselectivities after a small amount of optimisation.[189]




***Scheme 11.*** *Applications of the Winstein rearrangement*

Propargyl azides undergo similar [3,3]-sigmatropic rearrangements to allylic azides, but instead give allenyl azides after rearrangement, which then typically undergo rapid 6π electrocyclic reactions to generate highly electrophilic 'triazafulvene' intermediates. These triazafulvenes will

polymerise or react with solvent molecules unless an exogenous nucleophile is added; the whole process, terminated with nucleophilic trapping, is referred to as a Banert cascade.[190] As Topczewski notes, Banert cascades offer a useful, regiospecific approach to the synthesis of 1*H*-1,2,3-triazoles.[191]

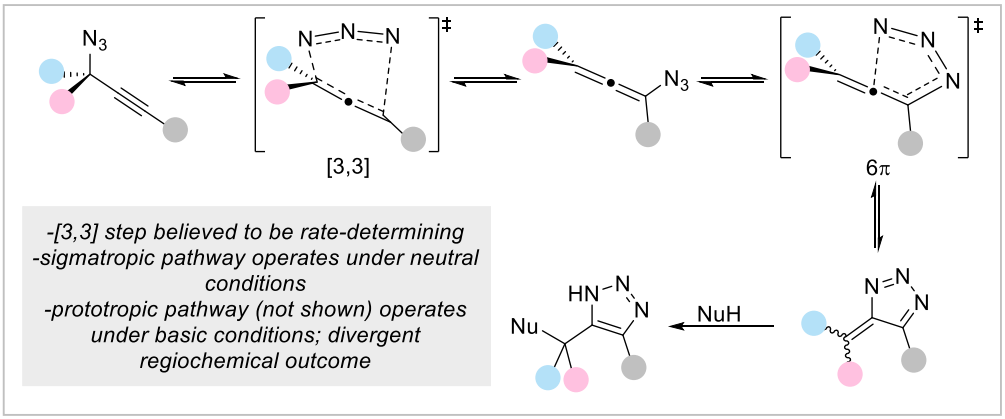



***Figure 7.*** *Banert cascades*

## 1.3.2: Curtius rearrangements

One of the first reactions of organic azides to be discovered, the Curtius rearrangement remains a popular transformation even on industrial scales.[68,192] In the Curtius rearrangement, heat, light, or acid catalysis triggers loss of dinitrogen from an acyl azide, with concomitant migration of the group attached to the carbonyl. For the thermal process, a concerted mechanism is frequently invoked, although the photochemical process appears to occur in a stepwise fashion, *via* an acyl nitrene intermediate (see Section 1.3.4).[193] The resulting isocyanate is a useful functional handle, which can be transformed into a urea, a carbamate, or the free amine, following reaction with an amine, an alcohol, or water, respectively.

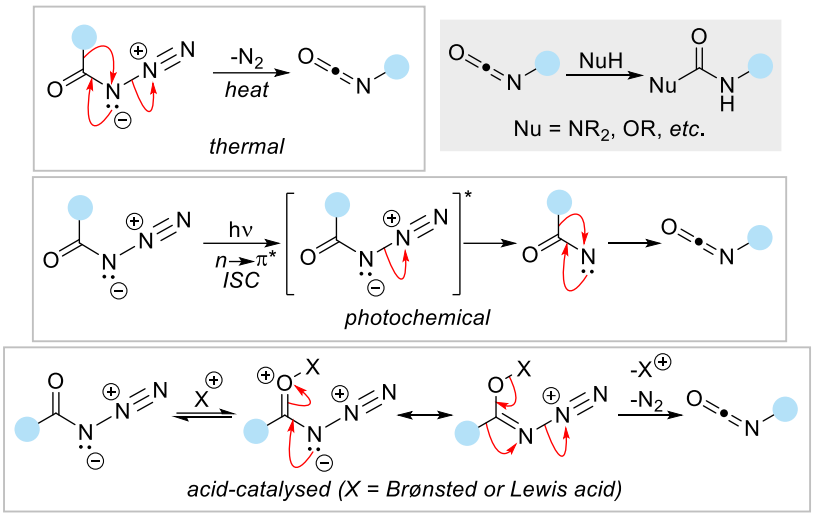



***Figure 8.*** *Curtius rearrangements*

## 1.3.3: Schmidt and related reactions

The classical Schmidt reaction[194] involves addition of hydrazoic acid to a carbonyl electrophile – typically a carboxylic acid or a ketone. This addition forms an azide intermediate that quickly decomposes under the reaction conditions, *via* loss of dinitrogen and an accompanying Curtius-like migration. For carboxylic acid electrophiles, the net result is decarboxylative amination (*cf*. Curtius rearrangement-hydrolysis), but for ketones an amide is obtained, by overall N-atom insertion (*cf*. Beckmann[195] and Baeyer-Villiger[196] chemistry). The use of hydrazoic acid in reactions of this kind renders them impractical even on small scales. However, given recent interest in so-called 'molecular editing' – a strategy in which reactive intermediates can be key to altering the connectivity of a scaffold,[197–200] a safer (*i.e.*, $HN_3$-free) Schmidt secondary amide synthesis could be a valuable transformation.

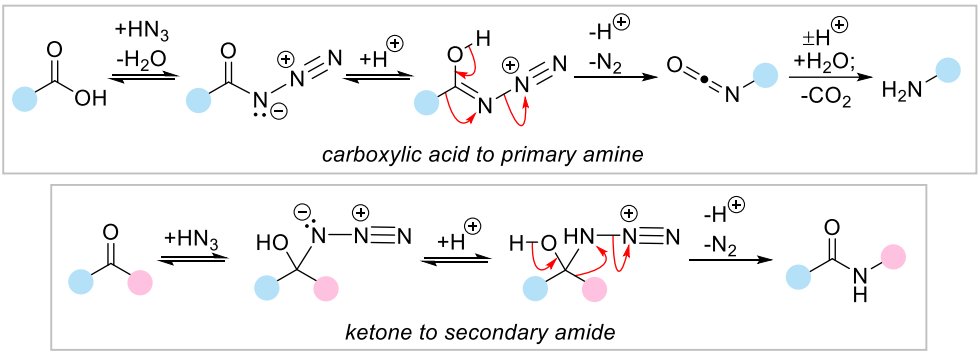
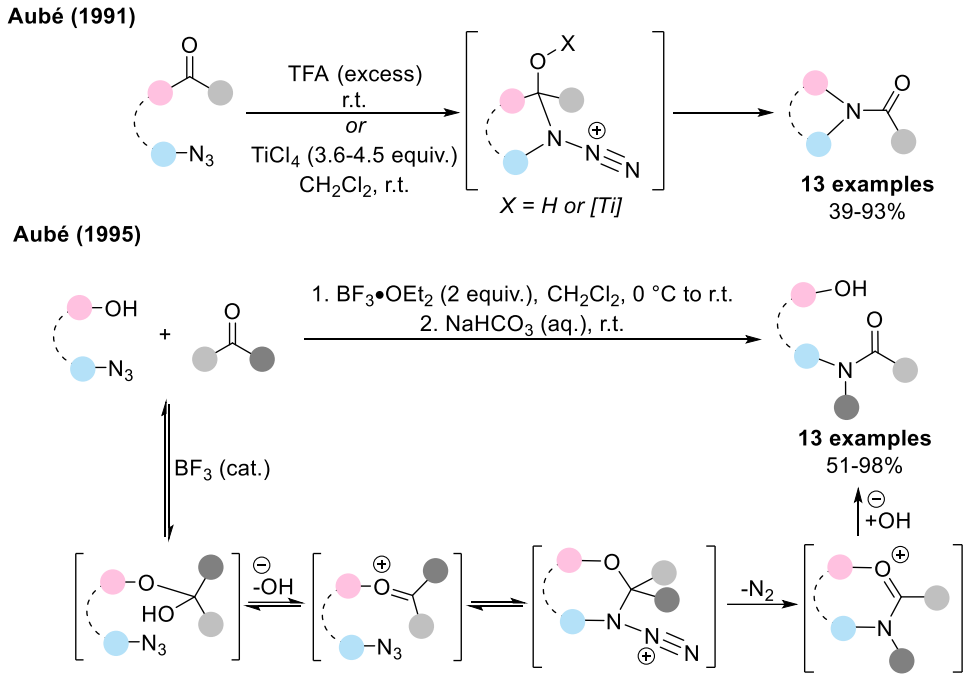



***Figure 9.*** *Schmidt reactions to give amines and secondary amides*

A more desirable version of the Schmidt reaction would be the use of a preformed organic azide as the nucleophile, and a ketone as the electrophile. Until the early 1990s, no successful examples of Schmidt reactions between ketones and organic azides had been published; the closest related work was an aldehyde amidation from Boyer.[201] In 1991, Jeffrey Aubé established that ketone-tethered azides could undergo intramolecular Schmidt reactions at ambient temperatures, under Brønsted or Lewis-acid catalysis.[202] In general, intramolecular reactions are expected to display smaller entropies of activation ($\Delta S^{\ddagger}$) than their intermolecular counterparts, which can lead to faster reactions.[203,204]

Having observed the rate enhancement effects of pre-tethering the azide and ketone components, the Aubé group applied this strategy in the development of an intermolecular azide-ketone Schmidt reaction: using an azido alcohol as the azide component, the group showed that pre-association *via* hemiketal formation led to rapid rearrangement in the presence of $BF_3$.[205] In addition, different azido alcohols can be chosen to enable 'deprotection' of the amide nitrogen under oxidative or reductive

conditions, or – in the case of chiral azido alcohols – to induce asymmetry in the rearrangement.[206]




***Scheme 12.*** *Schmidt reactions of alkyl azides and ketones*

Azides have been shown to act as nucleophiles with other strong electrophiles,[207] also proceeding *via* Schmidt-like migration/nitrogen extrusion. Typically under acid catalysis, examples of nucleophilic addition/migration/loss of dinitrogen to acid chlorides, epoxides, and benzylic cations have been documented.[208–211] A notable example from the Aggarwal laboratory is the enantiospecific synthesis of α-tertiary amines from alkyl azides and trifluoroborates, in which loss of dinitrogen and boronate migration[212] are combined to enable C–N bond formation with predictable regio- and stereochemical outcomes.[213]

### 1.3.4: Nitrene formation and reactions of vinyl azides

For non-acyl azides, thermal and photochemical decomposition pathways lead to nitrenes.[214] Like carbenes, nitrenes are very electron-deficient and react rapidly with heteroatom lone pairs, π-systems, X–H bonds, and similar sources of electron density – in the absence of external sources of electron density, nitrenes will isomerise to imines or dimerise to give azo compounds.[215] Two possible kinds of electron arrangements are possible for nitrenes: they can exist in either triplet or singlet states (again like carbenes), with the triplet state generally expected to be the lower-energy spin state.[21] Transition metals can stabilise nitrenes as metal 'imido'[216] or 'nitrenoid'[217] complexes; some transition metals are also known to catalyse azide decomposition. Research into the use of azides as metal imido/nitrenoid precursors, *e.g.*, for catalytic C–H amination, is a rapidly growing field.[218–221]

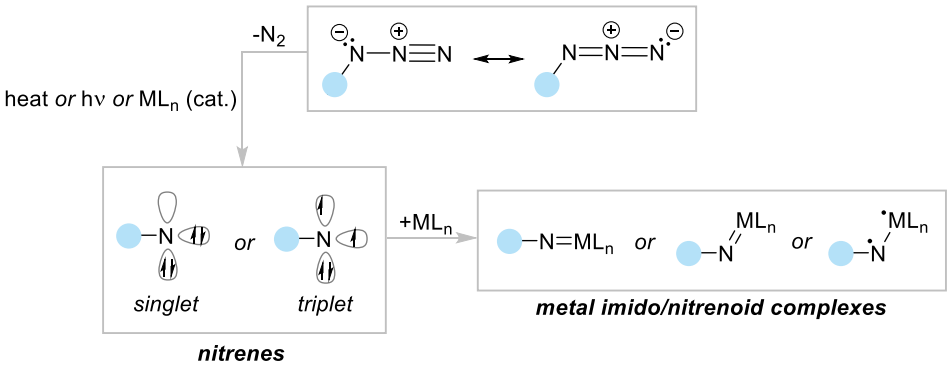



***Figure 10.*** *Nitrenes and metal imido/nitrenoid complexes*

Catalytic decomposition of azides is preferable to thermolysis or photolysis for safety reasons: lower temperatures and substoichiometric catalyst loadings allow for controlled nitrogen evolution and reduce the risk of explosion. In addition, the reactivity of metal imido and nitrenoid complexes (at nitrogen) can be 'tuned' with appropriate choices of metal

and ligand sets. For example, while Ti and Zr imido complexes will react rapidly with ketones to form imines,[222,223] and Co nitrenoid complexes will aziridinate olefins,[224] Schrock-type Mo imido carbene complexes are much less reactive at nitrogen: they first react with alkenes at carbon in olefin metathesis reactions, even in the presence of ketones.[225,226]

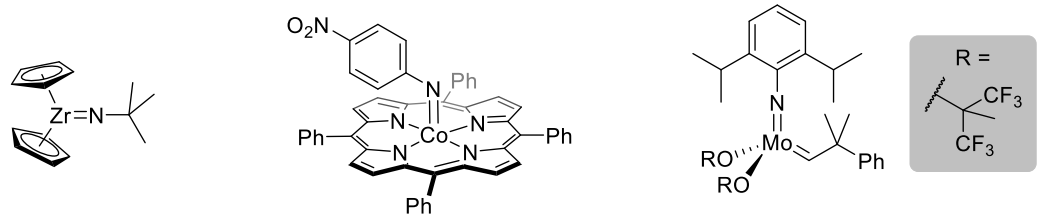



***Figure 11.*** *Metal imido/nitrenoid complexes*

Vinyl azides are a particularly interesting class of azides: they are capable of losing dinitrogen by one of three distinct pathways.[227] The first is nitrene formation, as discussed above. Upon extrusion of $N_2$, vinyl nitrenes rapidly isomerise to 2*H*-azirines, highly strained 3-membered rings that can undergo nucleophilic and electrophilic additions or regenerate the vinyl nitrene upon heating.[228] The second mode of fragmentation is electrophilic addition: vinyl azides are enamine-like nucleophiles that react with electrophiles under (Brønsted- or Lewis-) acid catalysis. Following nucleophilic addition, the resulting diazoiminium species tends to lose dinitrogen with accompanying Curtius-like migration, leading to a nitrilium ion that gives an amide upon addition of water. Finally, radical additions to vinyl azides trigger immediate loss of dinitrogen, to give very electrophilic iminyl radicals which can then undergo further reactions.

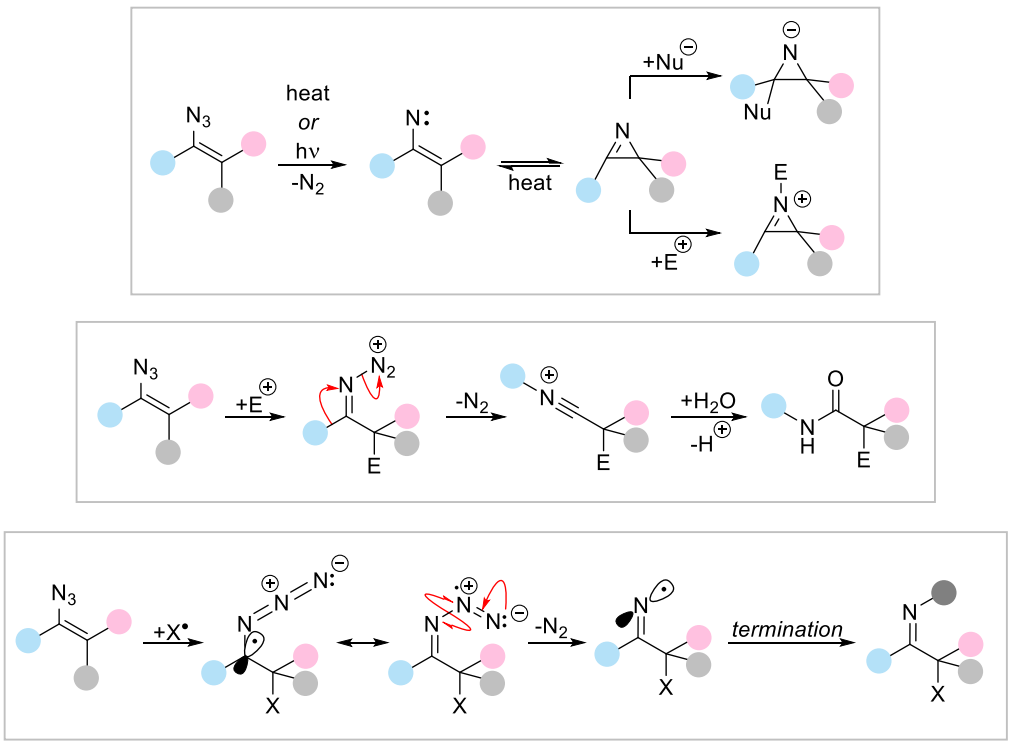



***Figure 12.*** *Vinyl azides – decomposition pathways*

## 1.3.5: [3+2] cycloadditions and click chemistry

As outlined in Section 1.1, azides are 1,3-dipoles, *i.e.*, conjugated 4π systems. Per the Woodward-Hoffmann rules, [$_{\pi}4_{s}$ + $_{\pi}2_{s}$] cycloadditions are thermally allowed, and so azides should undergo cycloadditions with 2π components.[229] Indeed, [3+2] cycloadditions between azides and a range of dipolarophiles are known. Azides are typical 'ambiphilic' dipoles: cycloadditions to azides are accelerated for both electron-rich and electron-deficient dipolarophiles, relative to simple alkenes.[17] In a seminal paper from Sustmann,[230] it was shown that – for a range of dipolarophiles – plotting the rate constants of their reactions with phenyl azide against their ionisation potentials resulted in a parabolic distribution, visually demonstrating the ambiphilic behaviour of azides. Ignoring other factors, such as strain, this remains a good first-pass analysis for predicting the

reactivity of an azide with a dipolarophile in the absence of, for example, metal catalysts.[231,232]

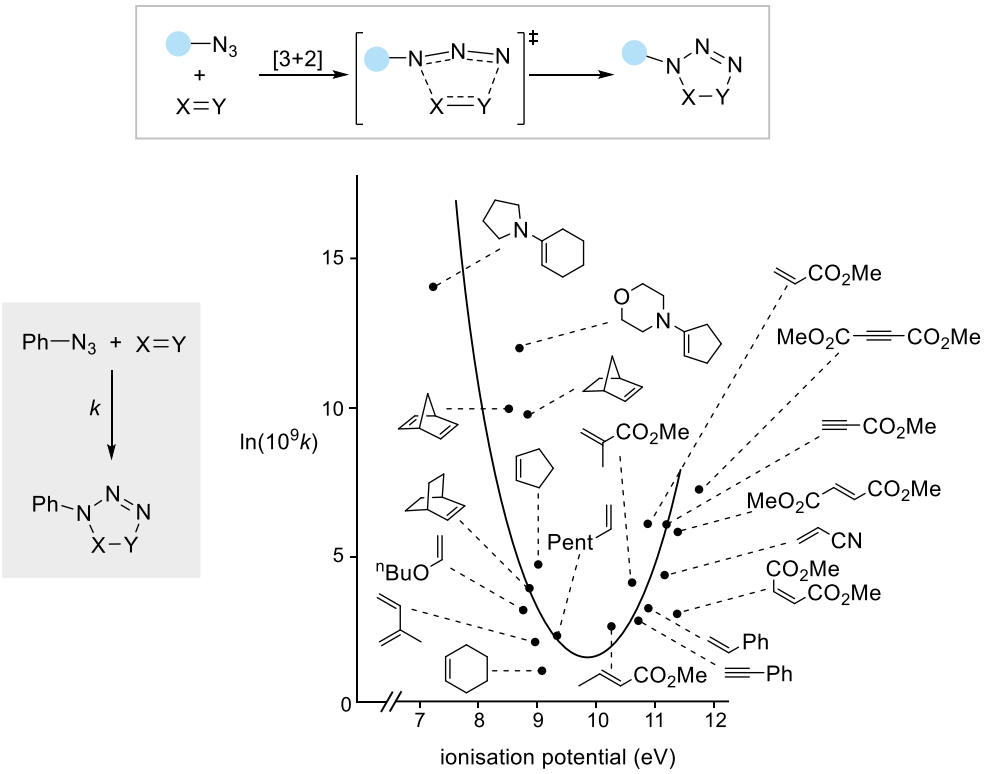
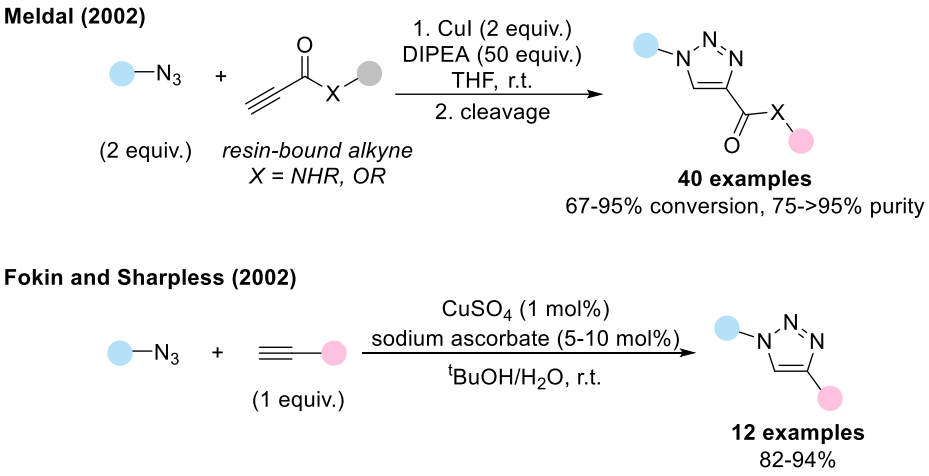



***Figure 13.*** *Azide 1,3-dipolar cycloadditions, with Sustmann's dipolarophile analysis*

The above discussion considers only the relative rates of reaction for different dipolarophiles with organic azides; when this reaction is examined in absolute terms, it is notable that these cycloadditions must generally be carried out at high temperatures, over long reaction times.[6,233] Since the early 2000s, transition metals have been used to catalyse the azide-alkyne cycloaddition such that it can be carried out rapidly, at ambient temperature.[234,235] Most notably, copper(I) catalysis greatly facilitates the reaction of terminal alkynes and azides, providing a non-concerted pathway for the reaction to proceed. Other metals, such as ruthenium(II), can be used to alter the regioselectivity of the reaction.[236]




***Scheme 13.*** *Copper(I)-catalysed azide-alkyne cycloadditions (CuAACs)*

Much of this work has been discussed within the framework of 'click chemistry', as labelled by the Sharpless group.[233] So-called 'click' reactions are understood as reactions that are 'simple' to run (with respect to accessibility of starting materials, ease of purification, etc.), modular, reliably high-yielding, and stereospecific; Sharpless included the azide-alkyne cycloaddition as an example of this kind of reaction upon introducing this framework, even before the discovery of the copper-catalysed variant, or 'CuAAC'. Since that discovery, the CuAAC has become the pre-eminent example of click chemistry, and indeed is sometimes even referred to metonymically as 'the click reaction'.[237] The applications of the CuAAC are numerous, but it is in the areas of polymer chemistry, materials chemistry, and medicinal chemistry/chemical biology that this reaction has especial prominence.[238–240]

## 1.3.6: Azide reductions

The transformation of an organic azide into an amine is one of the most important classes of reactions for these compounds. Considering azides as

dinitrogen-'protected' amines, this 'protecting group' strategy has several appealing features. The $N_3$ group is relatively easy introduce to a molecule (perhaps unlike the $NH_2$ group), by any of the many strategies discussed in Section 1.2, and it already contains the protecting group, avoiding the protection step. Dinitrogen is a very low molecular weight protecting group, and so, when carrying this functionality through a synthesis sequence, the impact of the azide group on the atom economy and process mass intensity (PMI) of the sequence can be considerably smaller than for other common protected amine functionalities.[241] Finally, upon 'deprotection' of the azide group, dinitrogen is given off as a benign byproduct, leaving no organic byproducts which would need to be removed from the desired product (unlike, *e.g.*, Fmoc, Cbz).

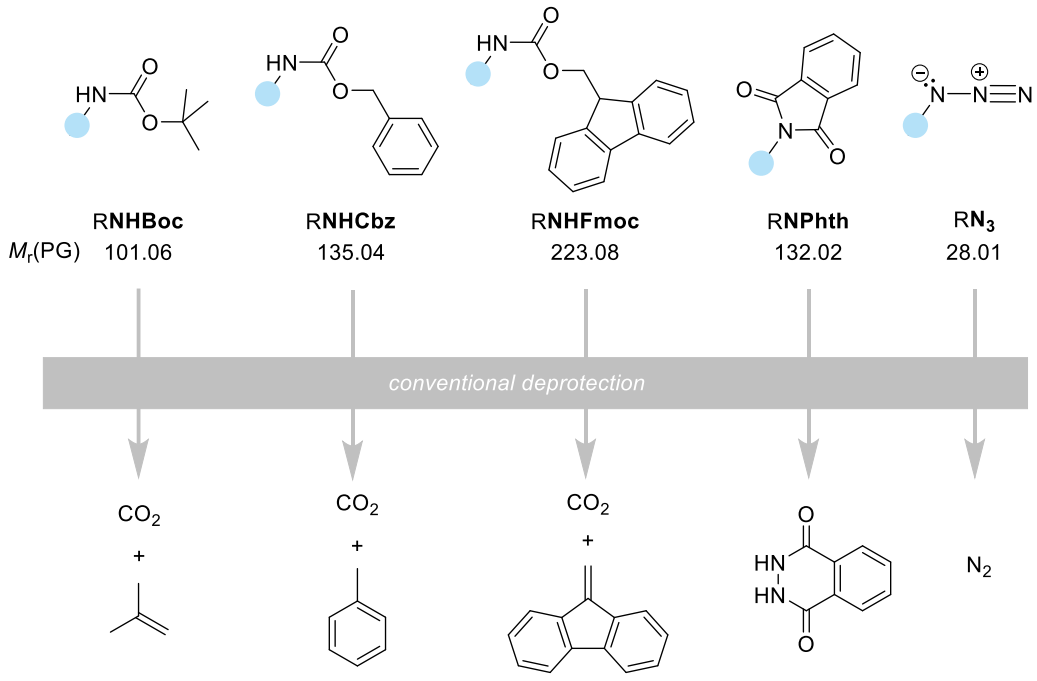



***Figure 14.*** *Comparing azide to common protected amine functionalities*

Azide-to-amine reductions can be carried out under hydrogenolytic conditions, or with strong reducing agents such as $LiAlH_4$,[242] $Zn(BH_4)_2$,[243] or $SmI_2$.[244] While these reductions are practical for simpler azides, they

display poor functional group tolerance – for example, hydrogenolysis of azides will also result in hydrogenation of alkenes and alkynes, and $LiAlH_4$ will reduce esters and nitriles in the presence of azides. For mild, chemoselective azide reduction, a Staudinger reduction is often chosen.[245] First described in 1919, the Staudinger reduction involves addition of a phosphorus(III) reagent (such as a phosphine or phosphite) to the azide of interest.[246] The immediate product of this reaction is a phosphazide, which then cyclises to form a transient 4-membered intermediate (*cf*. Wittig reactions[247]). Loss of dinitrogen from this intermediate leads to an iminophosphorane, which can then be hydrolysed to give the free amine and a phosphorus(V) by-product. This mechanism is commonly accepted on the basis of kinetics studies,[248,249] observation and isolation of phosphazides and iminophosphoranes,[249–253] and computational studies.[253,254]

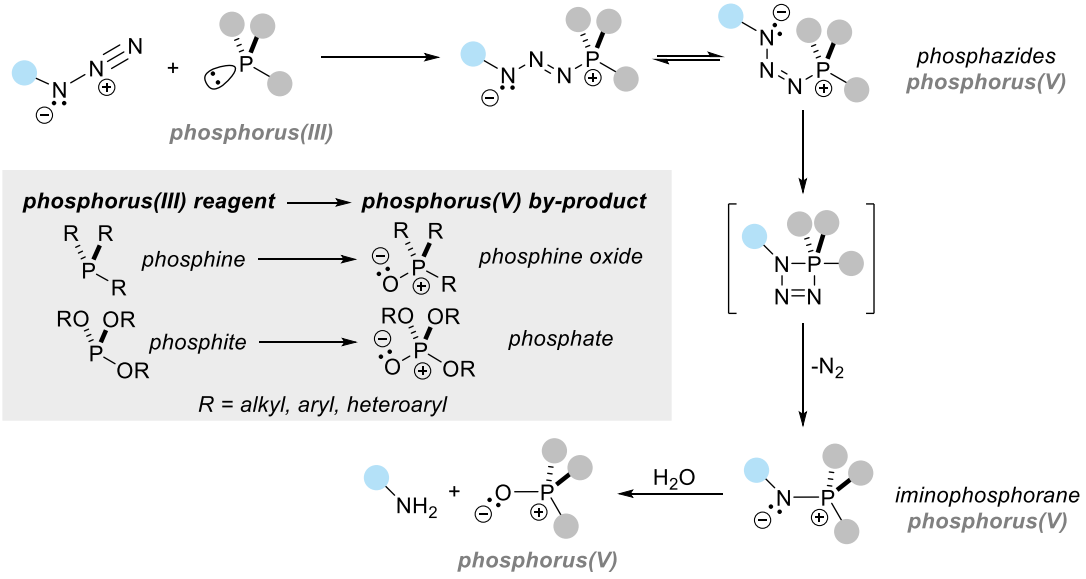
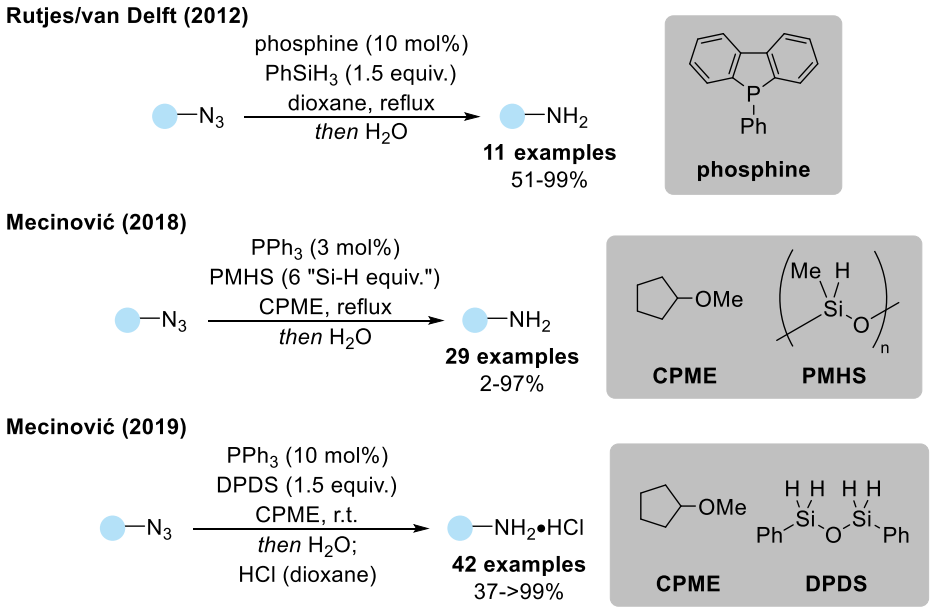



***Figure 15.*** *The Staudinger reduction - mechanism*

While the functional group compatibility of the Staudinger reduction is high compared to other azide reductions, generation of stoichiometric phosphorus(V) waste is an undesirable aspect of this reaction. Aside from

atom economy/PMI issues associated with the generation of phosphorus(V) by-products, these compounds also present practical difficulties: removal of phosphine oxides (in particular) from reaction mixtures is a non-trivial reaction engineering problem.[255,256] The first catalytic Staudinger reduction was developed by Rutjes and van Delft in 2012.[257] The Rutjes/van Delft system uses a simple triarylphosphine catalyst, with phenylsilane as terminal reductant, and displays good yields for a range of amine products. Unfortunately, the need to run this reaction in dioxane at reflux (b.p. = 101 °C) renders it undesirable, given both the potential explosiveness of azides and the possible carcinogenicity[258] of dioxane. More recently, the Mecinović group have achieved catalytic Staudinger reductions in a more benign solvent and at room temperature, using triphenylphosphine as the catalyst and a siloxane as the terminal reductant.[259,260] Although the siloxane needed for the room-temperature protocol is not commercial, this latter paper from Mecinović represents the mildest and most practical catalytic Staudinger reaction yet published.




***Scheme 14.*** *Catalytic Staudinger reductions – the state of the art*

At the time of writing, the mechanisms for the van Delft and Mecinović systems are not completely understood. As in the classical Staudinger reduction, iminophosphorane formation is observed in both cases, and then it is understood that the silicon hydride reagent reduces the iminophosphorane to give a silanamine, regenerating the phosphine catalyst. The silanamine formed from the catalytic reaction is then hydrolysed in a separate step, to give silanol/siloxane by-products and the free amine. Neither van Delft nor Mecinović provide a model to explain the reductive turnover step. This step in particular would seem to be of particular importance: understanding the processes involved could help to identify other catalyst designs or commercially available reductants, and, in the cases where heating is required, it seems likely that this step is turnover-limiting.

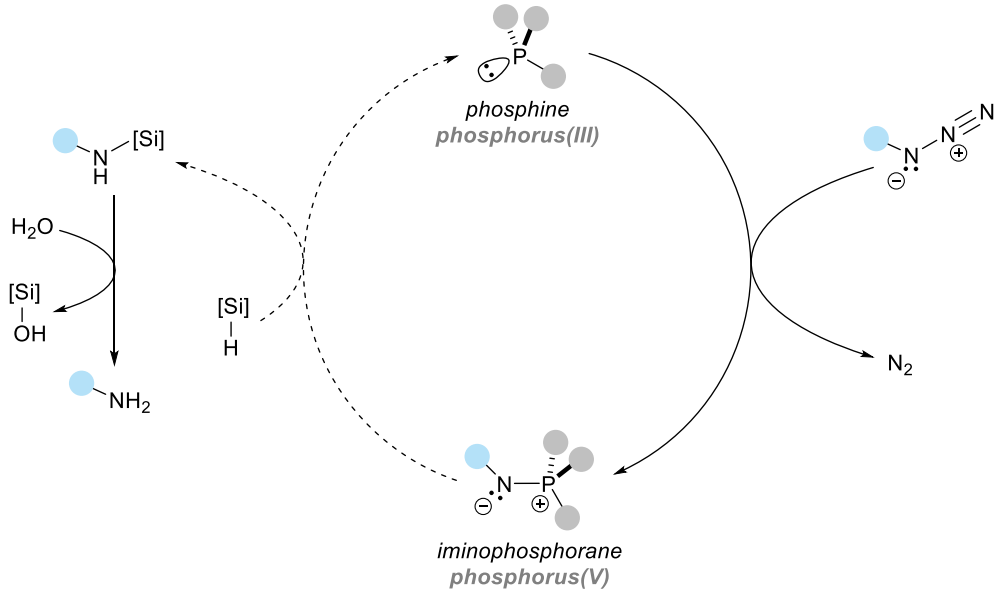
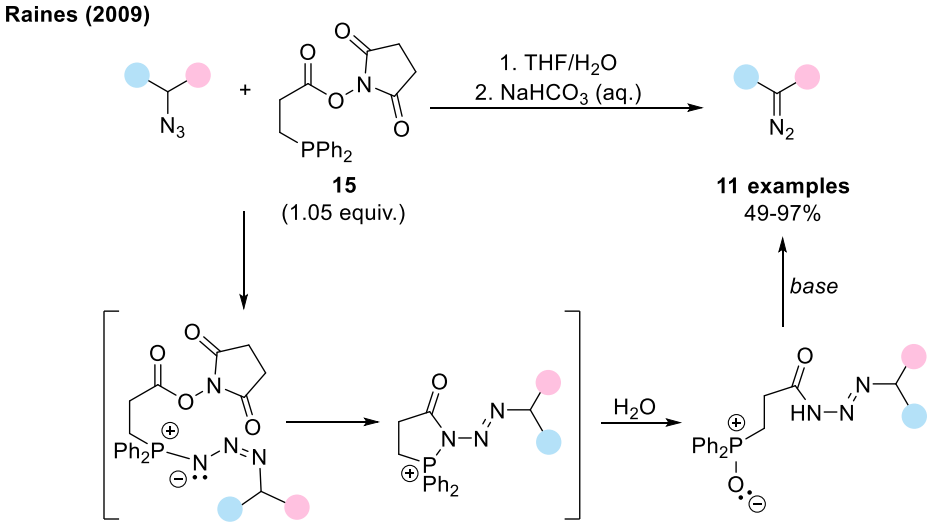



***Figure 16.*** *Proposed catalytic cycles for Staudinger reductions*

## 1.3.7: Reactions of phosphazides and iminophosphoranes

The intermediates of the Staudinger reduction – namely, phosphazides and iminophosphoranes – are interesting classes of compounds in themselves. Aside from the conventional hydrolytic work-up of the Staudinger reduction, a number of useful reactions involving these intermediates have been reported. While the short-lived nature of phosphazides typically renders them the less useful of the two kinds of intermediate, one particularly interesting application of these compounds has been described by the Raines group. Using a phosphine bearing a readily cleaved hydroxysuccinimyl ester, the Raines group showed that the trinitrogen moiety of the phosphazide intermediate can be transferred to a nearby reactive acyl group to give a stable acyltriazene compound.[261] These acyltriazenes can then undergo base-mediated fragmentation to give diazo compounds. This overall azide-to-diazo transformation represents a novel approach to diazo compounds, quite unlike diazo transfer chemistry (see Sections 1.2.3 and 1.2.4).




***Scheme 15.*** *Phosphine-mediated conversion of azides to diazo compounds*

Applications of iminophosphoranes in synthesis are numerous and diverse. Iminophosphoranes are basic (p$K_a$H = 22-26, *cf*. $Et_3N$ = 18.8, all in MeCN) and nucleophilic at nitrogen.[262] Thus, addition of carboxylic acids to iminophosphoranes leads to so-called Staudinger ligation[263] (the other major 'bioorthogonal' reaction, as described by Bertozzi[174]), addition of carbonyl compounds leads to Wittig-like imine formation known as 'aza-Wittig' chemistry,[264] and Staudinger reduction of azidohydrins leads to a stable $\sigma^5$-phosphorane intermediate, which can undergo thermal collapse to give an aziridine.[265] Formation of a phosphine oxide typically serves as sufficient driving force for these reactions; where the phosphine oxide can be reduced,[266,267] they can be rendered catalytic in phosphine – a good example of this is Ashfeld's catalytic Staudinger ligation chemistry.[268,269]

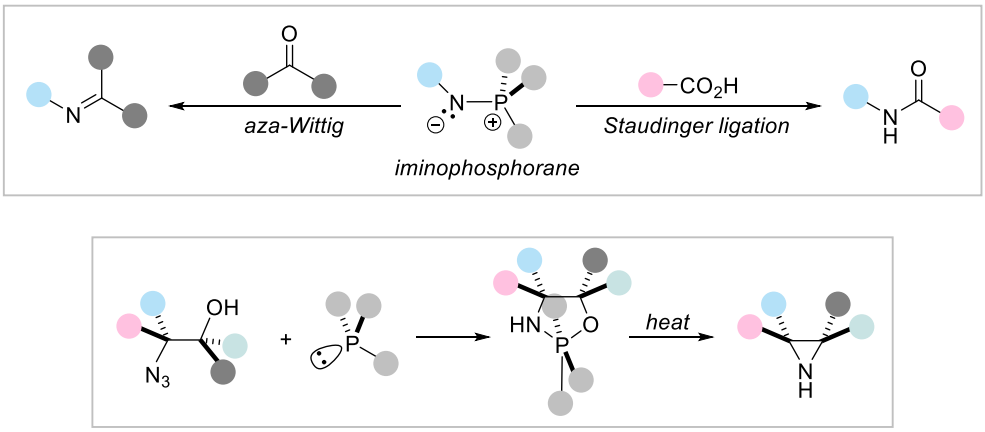
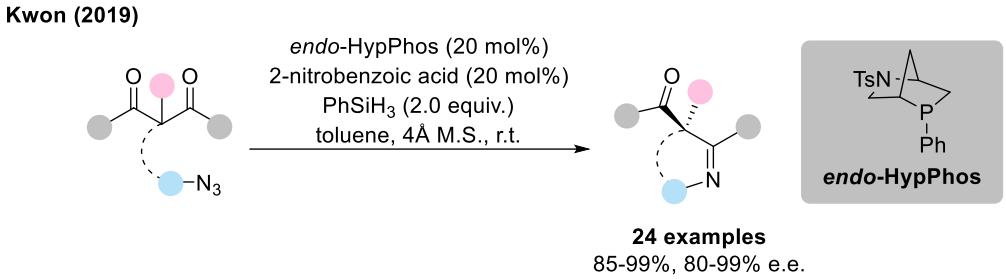



***Figure 17.*** *Reactions of iminophosphoranes*

While many more reactions of iminophosphoranes are known, one example from Ohyun Kwon is of particular note. Using one of their 'HypPhos' catalysts in combination with phenylsilane and an acid co-catalyst, the Kwon group have reported a catalytic, desymmetrising aza-Wittig reaction.[270] Despite computational contributions from the Houk group, catalyst turnover by the reductant is poorly understood. Nevertheless, high

yields and enantioselectivities were obtained for a range of substrates, and interesting synthesis applications of this chemistry were demonstrated.




***Scheme 16.*** *A catalytic, desymmetrising aza-Wittig reaction*

The success of this recent work from Kwon demonstrates the value of rationally designed, catalytic systems not only in azide chemistry, but also in modern organophosphorus chemistry as a whole. In the last 15 years, related catalytic phosphorus(III/V) manifolds[271,272] have been developed for Wittig reactions,[273,274] Cadogan cyclisations,[275] and reductive C-N cross couplings,[276–278] all enabled by rational catalyst design. Through greater understanding of fundamental organophosphorus chemistry, increasingly efficient computational investigations, and detailed mechanistic experiments, the phosphorus(III/V) redox couple has emerged as a powerful and flexible tool for the design of synthesis methods. The development and applications of one such method is described in Chapters 2 and 3 of this thesis.

# 2. Applications of a Catalytic Azide Reduction

## 2.1: Background

Following the work of Rutjes/van Delft[257] and Mecinović[259,260], previous members[ii] of the Denton group sought to develop a catalytic azide reduction that could be carried out at room temperature, using a commercially available terminal reductant. It was believed that such a system could be achieved *via* rational catalyst design: rather than using simple triarylphosphines, as in previous papers, the possibility of including additional functionality within the catalyst was explored. With the understanding that the turnover-limiting step for the previously described systems is likely to be the silane-mediated iminophosphorane-to-phosphine reduction, the central aim of the catalyst design was to include structural features that would facilitate reductive turnover. Specifically, it was envisaged that a 5-coordinate (10-P-5)[279] phosphorane intermediate might be more readily reduced than the initially-formed iminophosphorane, and that such an intermediate could be accessed by tethering a Lewis basic (XH) moiety to the phosphine (see Figure 18).

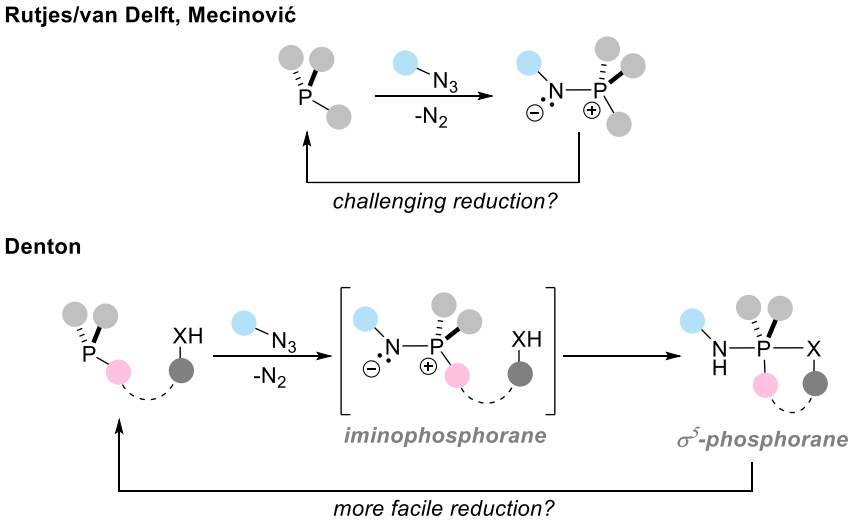
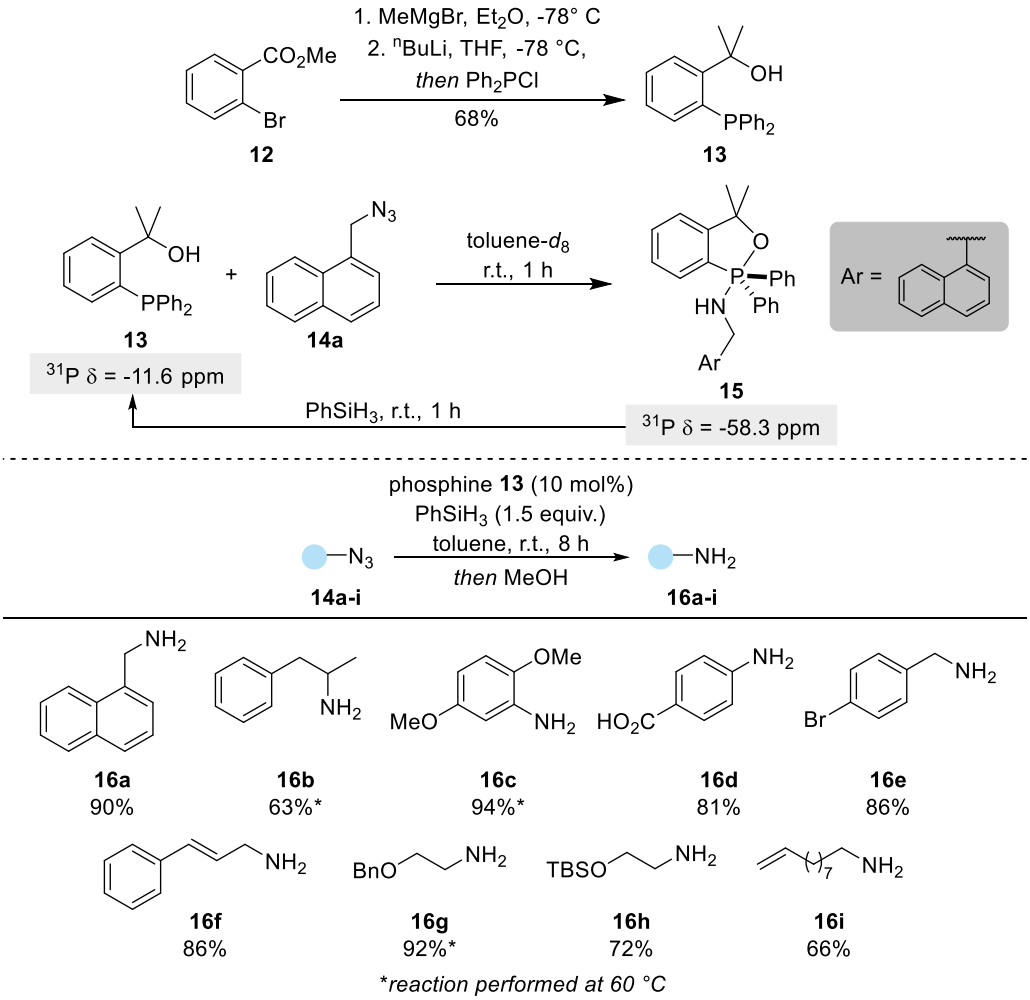



***Figure 18.*** *Catalyst design*

[ii] Dr. Jan Saska, Professor Jie An, Dr. Charlotte Chapman, and Dr. Emma Stoll

The design principles outlined above led to the synthesis of bifunctional phosphine **13** (see Scheme 17[iii]). Phosphine **13** rapidly formed $\sigma^5$-phosphorane **15** upon treatment with stoichiometric 1-(azidomethyl)naphthalene (**14a**), presumably *via* a transient iminophosphorane. Addition of phenylsilane to the $\sigma^5$-phosphorane then resulted in the regeneration of phosphine **13**, with concomitant generation of a silanamine. It was then demonstrated that phosphine **13** was catalytically competent in the reduction of azide **14a**, as well as a further 8 azide substrates, under mild conditions. Other reductants, such as sodium borohydride, were also shown to effect catalyst regeneration.




***Scheme 17.*** *Synthesis, reactivity, and catalytic properties of phosphine* ***13***

[iii] Work carried out by Dr. Jan Saska, Professor Jie An, and Dr. Charlotte Chapman

In order to account for the efficacy of catalyst **13**, it is necessary to consider fundamental differences in bonding between $\sigma^5$-phosphoranes and tetrahedral phosphorus(V) compounds such as iminophosphoranes and phosphine oxides.[280] Trigonal bipyramidal $\sigma^5$-phosphoranes are generally understood to display three-centre-four-electron (3c-4e) bonding[281,282] between phosphorus and the ligands in the axial/apical positions (see Figure 19). Within this bonding model, the phosphorus atom is considered to bear a formal positive charge, and the apical substituents are each considered to bear half of a formal negative charge; more electronegative atoms are expected to occupy apical positions whenever geometry permits.[283–285] While tetrahedral, four-coordinate phosphorus(V) compounds also bear a formal positive charge at phosphorus, a full formal negative charge is assigned to one of the atoms bonded to phosphorus (labelled X below).[286] The bonding between this atom and the central P atom is generally accepted to be strengthened by interactions between orbitals on the X atom and σ*-orbital components, such that P-X is considered to have multiple bond character – evidenced by crystallography and IR spectroscopy.[280,287–290]

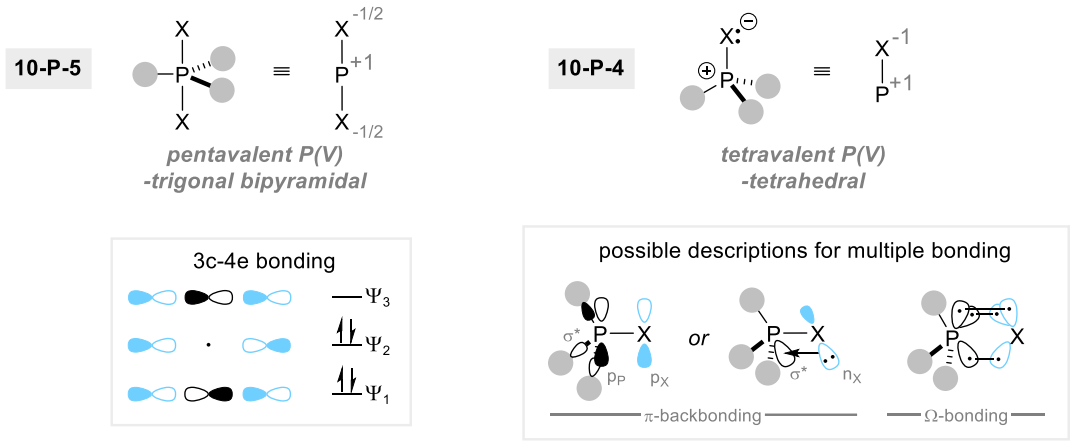
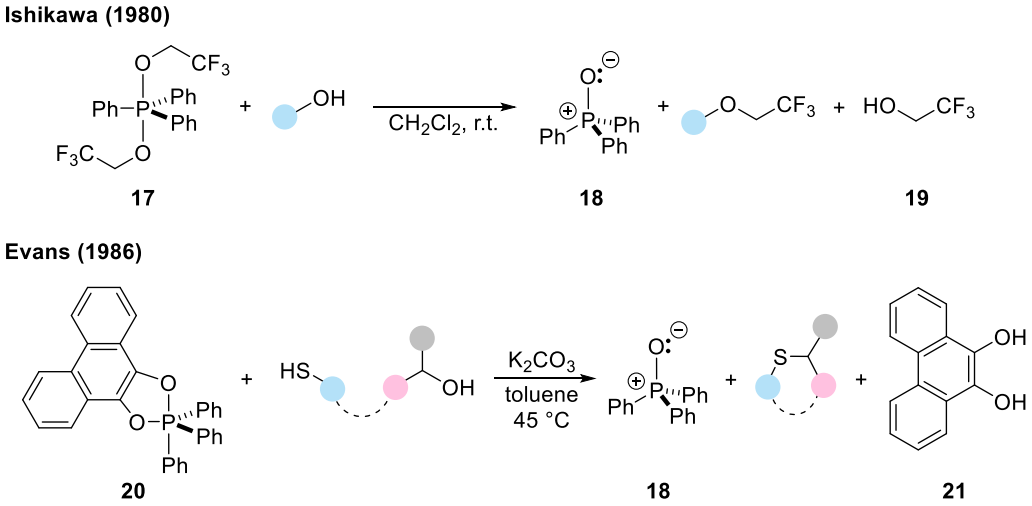


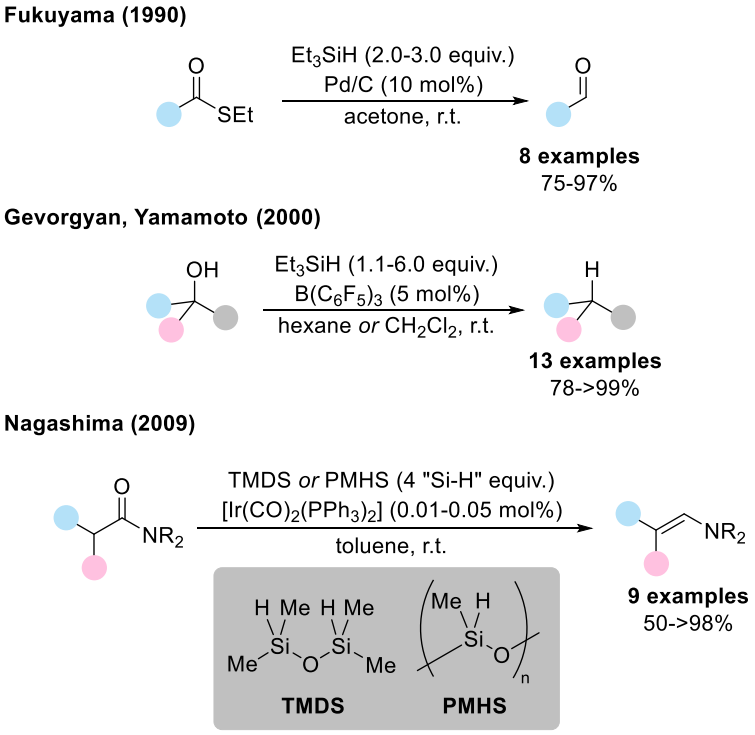

***Figure 19.*** *Geometry and bonding descriptions of phosphorus(V) compounds*

The above discussion might provide a useful framework for understanding reactivity patterns of phosphorus(V) compounds: for both 10-P-4 and 10-P-5 compounds, the central P atom bears a formal positive charge and is the location of a significant lobe of the LUMO, but there are additional bonding interactions between X and P for 10-P-4 compounds relative to 10-P-5 compounds. These interactions are stabilising, *i.e.*, they are HOMO-lowering (where the HOMO is a lone pair on X) and LUMO-raising; this stabilisation therefore reduces the electrophilicity of 10-P-4 compounds and renders substitution reactions thermodynamically unfavourable. Thus, nucleophilic addition to tetrahedral phosphorus(V) compounds is typically not observed unless they are overall positively charged (*e.g.*, halophosphonium ions).[291,292] Generally, neutral 10-P-4 compounds react with electrophiles and Brønsted/Lewis acids, either at the X atom alone[293–295] or in a concerted reaction at X and P,[247,296,297] depending on the nature of the electrophile. By contrast, $\sigma^5$-phosphoranes are moderately electrophilic (see Scheme 18) - for these compounds, nucleophilic addition can occur at phosphorus itself or at ligand β-positions (populating $\sigma^*_{P\text{-}X}$), often leading to phosphine oxide formation.




***Scheme 18.*** *Reactions of $\sigma^5$-phosphoranes with nucleophiles*[298,299]

Silanes feature as terminal reductants both in previously published catalytic Staudinger reactions and in the system developed in the Denton group. It is known that (hydro)silanes act as 'hydride' reagents, *i.e.*, σ-nucleophiles, in a variety of reduction reactions – notable examples include Fukuyama reductions,[300] alcohol deoxygenations,[301] and reductions of amides to enamines/aldehydes [302,303] (see Scheme 19). While many boron- and aluminium-based reducing agents are water-sensitive inorganic solids with (sometimes) poor chemoselectivity,[304] silanes are generally organic-miscible liquids with mild reactivity and greater robustness to moisture. For these reasons, silanes are desirable reagents on laboratory scales. It should be noted, however, that the cost of (non-polymeric) silanes can be prohibitive on larger industrial scales.




***Scheme 19.*** *Selected silane reductions*

Due to the rich and varied reactivity of organosilicon compounds, silane reductions can operate under several distinct mechanisms (see Figure 20).

Firstly, for positively charged electrophiles such as carbocations, in the absence of Lewis basic counterions, silanes can donate hydride directly; this results in the formation of a silylium ion,[305] which reacts rapidly with nucleophiles. Secondly, certain silanes have sufficiently weak Si-H bonds (BDEs = 75-95 kcal·mol$^{-1}$)[306,307] to enable reductions *via* HAT to carbon-centred radicals;[308] in this way, silanes are comparable to tin compounds such as $^{n}Bu_3SnH$, and exhibit considerably more attractive toxicological profiles. Finally, in the presence of Lewis bases, silanes can form five-coordinate, negatively charged 'ate' complexes. Silicon 'ate' complexes display 3c-4e bonding similar to $\sigma^5$-phosphoranes,[281,288,309] but with higher-lying HOMOs. Consequently, formation of a Lewis base adduct leads to enhanced reactivity in reduction reactions, rendering silanes capable of transferring hydride to electrophiles (*e.g.*, carbonyl compounds).[310–313] In the context of this work, this latter mode of silane reactivity is the most significant: it seems likely that the mildly basic conditions of the azide reduction promote 'ate' complex formation.

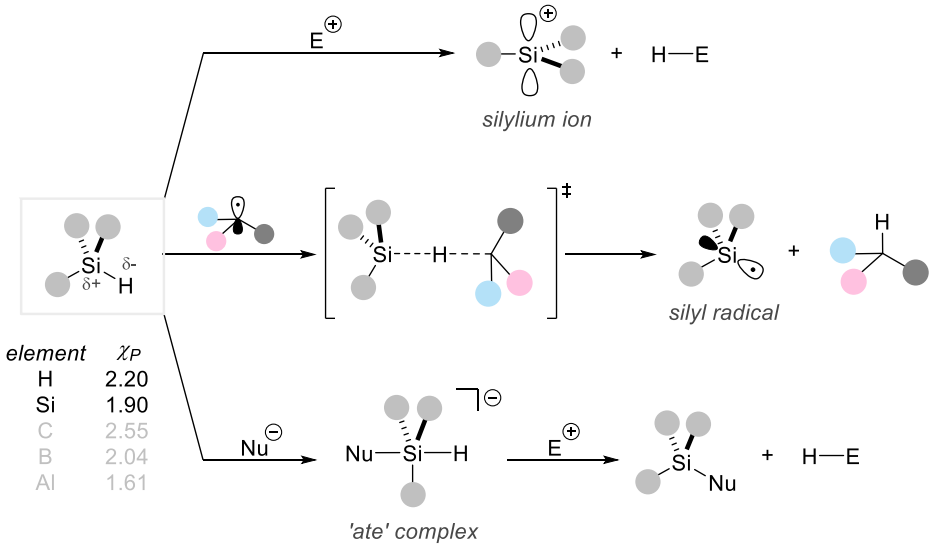



***Figure 20.*** *Silane reductions – possible mechanisms*[160]

Considering the reactivities of phosphoranes and silanes outlined above, the following catalytic cycle is proposed (see Figure 21) provides a plausible model for understanding the catalytic azide reduction developed in the Denton group. First, phosphine **13** reacts with a given azide and, as previously discussed, forms a $\sigma^5$-phosphorane. Then, probably as an 'ate' complex, phenylsilane transfers hydride to the *N*,*O*-phosphorane, with loss of the N-ligand as a silanamine. Two conceivable *H*-phosphoranes can result from this hydride transfer – the axial (**22$_{ax}$**) and equatorial (**22$_{eq}$**) isomers. Only the axial isomer is believed to have been observed ($^{31}$P δ = -61.1 ppm, $^{1}J_{P\text{-}H}$ = 261.3 Hz)[284,314,315], but it is the equatorial isomer that appears to be required for reductive elimination, which regenerates phosphine **13**. Since the barrier for interconversion between **22$_{ax}$** and **22$_{eq}$** is estimated[iv] to be prohibitively high at room temperature, the nature of the reductive turnover has yet to be fully established.

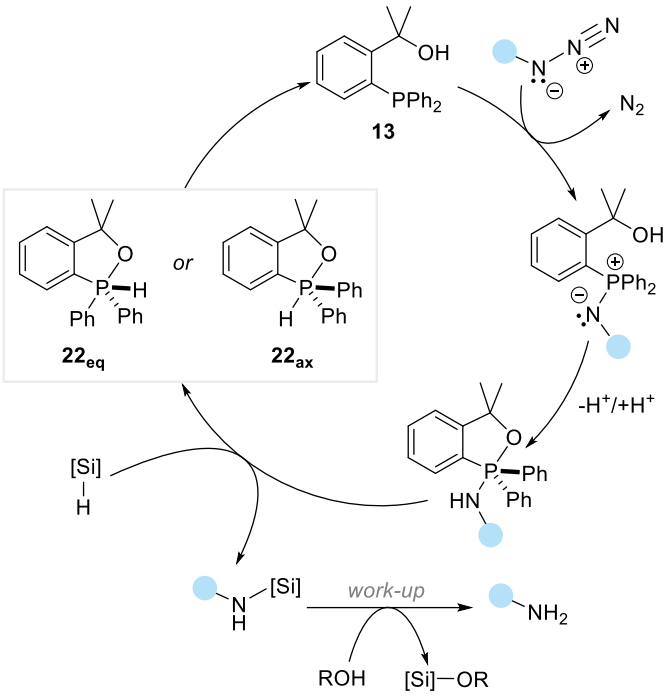



***Figure 21.*** *Proposed catalytic cycle*

[iv] Calculations carried out by Professor Ross Denton

## 2.2: Project Aims

The central aim of this project was to establish the utility of the catalytic azide reduction in a broader sense. Although the efficacy of the method had already been demonstrated for a set of 9 substrates, as discussed above, this scope was still somewhat limited. It was felt that it was important to explore the limits of the method by subjecting to the reduction conditions not only more substrates but also more complex substrates. In particular, we proposed to investigate substrates bearing greater steric bulk around the azide moiety, and/or other potentially reducible functionalities. As the starting materials and products of the method – azides and primary amines – are prominent classes of compounds within biological and medicinal research, we also hoped to investigate substrates and/or products with greater relevance to these fields of study.

In addition to extending the substrate scope, we also proposed to develop sequential 'one-pot'[316] procedures, combining the azide reduction with transformations of the resulting silanamine or amine. Ideally, these procedures would be 'telescoped', *i.e.*, they would avoid a work-up of the crude product. If efficient two-step protocols could be established involving pharmaceutically relevant reactions (*e.g.*, reductive amination, amidation, *etc.*),[317] then the potential utility of the catalytic azide reduction would be greatly increased.

## 2.3: Results and Discussion

### 2.3.1: Catalytic azide reductions

#### 2.3.1.1: Rate acceleration of the catalytic azide reduction by amine base additives

From previous work carried out in the Denton group,[v] it was known that addition of an amine base – namely triethylamine – to the catalytic azide reduction resulted in significantly faster conversion. As this effect may provide insight into the nature of the catalytic turnover, we wanted to establish whether a hindered, non-nucleophilic base could provide the same rate acceleration. The mechanism by which this effect occurs was not known, and so we were keen to establish whether the efficacy of the base additive was dependent on factors such as sterics and/or p$K_a$H.[318–320]

Two bases – DIPEA and 2,6-di-*tert*-butylpyridine (2,6-DTB) – were selected for this study, and they were each added to the reduction of a fluorine-labelled azide substrate, **14j** (see Figure 22). The reactions were each monitored by quantitative $^{19}$F NMR, which revealed a considerable difference in rate associated with the two bases. DIPEA was observed to behave much like triethylamine, leading to over 60% conversion in less than one hour for this reaction. 2,6-DTB, however, seemed to have little effect on the rate of azide reduction: the conversion curve for this reaction more or less resembled that of the base-free azide reduction, *i.e.*, apparently pseudo-zero order in azide **14j** (by visual inspection alone).

[v] Work carried out by Dr. Emma Stoll and Dr. James Cuthbertson

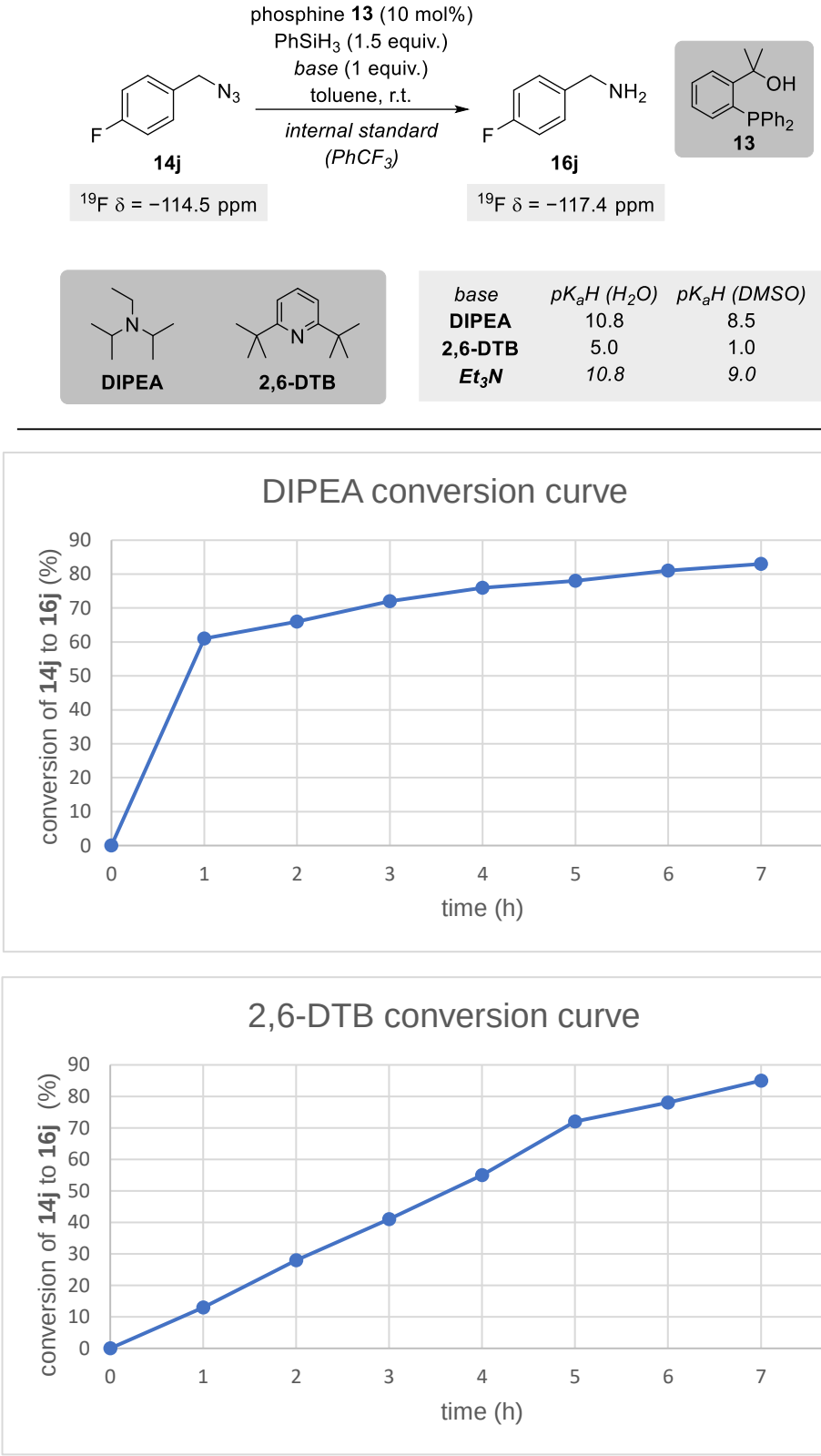


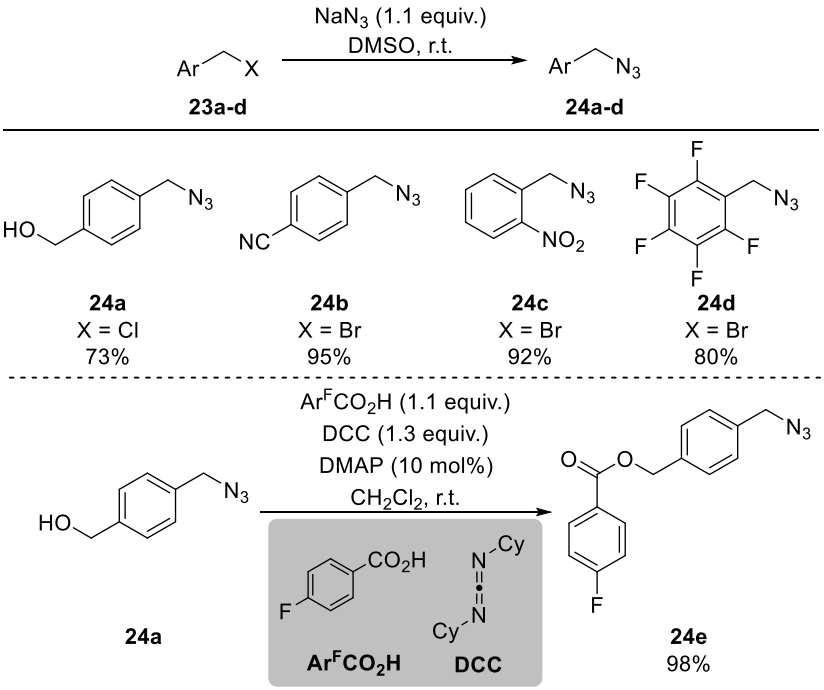

***Figure 22.*** *Rate effects of hindered base additives*

While it is difficult to draw conclusions from this study with respect to the mechanism of catalyst turnover, it is clear that the rate acceleration effect

depends on the base chosen. In practical terms, the efficacy of DIPEA is encouraging: for substrates sensitive to nucleophiles, or where tandem reactions involving the newly-formed amine are desired, rapid azide reduction should still be feasible with this base.

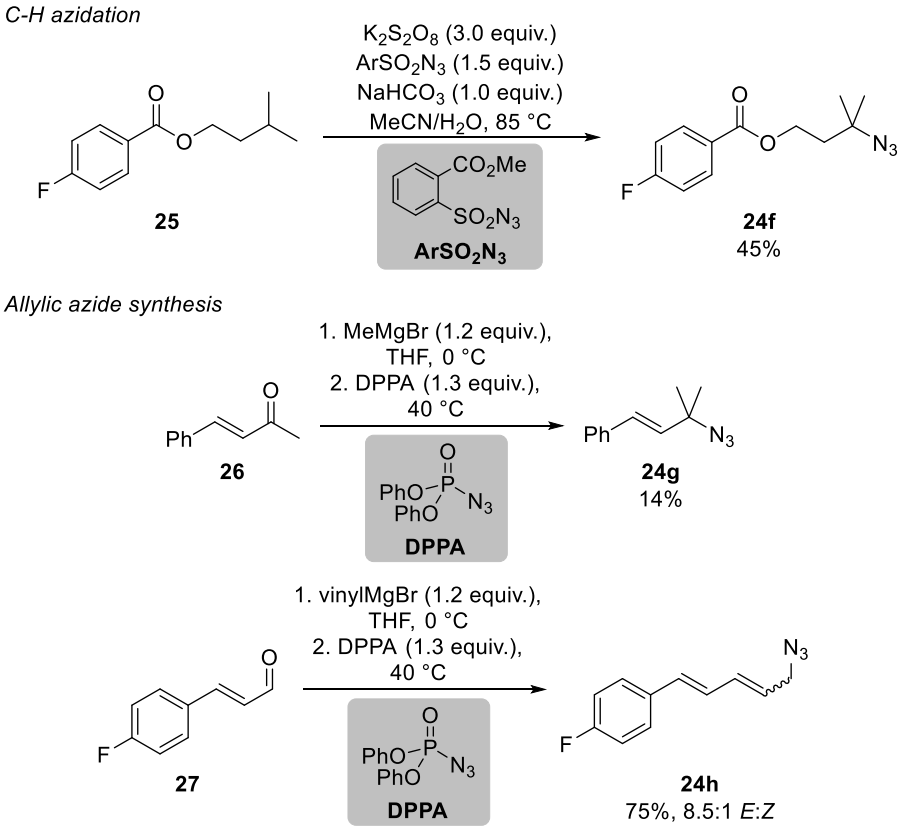
### 2.3.1.2: Extensions to the substrate scope

Among the first objectives of the project was the acquisition of a range of new potential azide substrates. Although some of the potential substrates were commercially available, most had to be synthesised by appropriate azidations. First, a series of benzyl azides (**24a-e**) was prepared, including substrates with potentially reducible functionalities (see Scheme 20). In general, these substrates were prepared by classical nucleophilic substitution from the corresponding benzyl halides and sodium azide; ester **24e** was accessed from azido alcohol **24a** by esterification under Steglich conditions.[321]



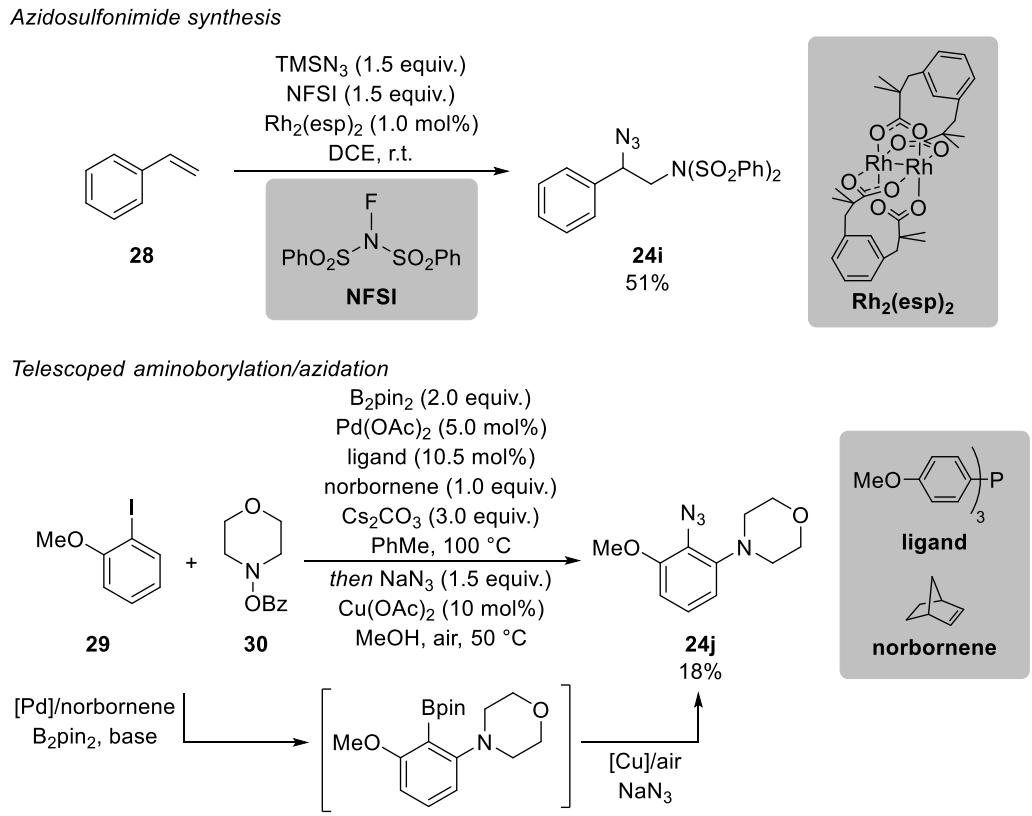

***Scheme 20.*** *Preparation of benzyl azides*

As no tertiary azides had yet been employed as substrates in the azide reduction, this class of compounds was of interest. Two methods from the literature were identified as promising approaches to tertiary azides: the C–H azidation protocol developed by Tang,[156] and the allylic/benzylic azide synthesis developed by the Topczewski group.[80] These methods in particular were chosen due to the simplicity of the functional groups required for azide installation in each case – secondary/tertiary C–H bonds, and aldehydes/ketones, respectively. As shown in Scheme 21, tertiary azide substrates **24f** and **24g** were prepared using these approaches. Having observed the utility of the Topczewski method in the synthesis of **24g**, these conditions were also used to access the novel dienyl azide **24h** from the corresponding cinnamaldehyde.



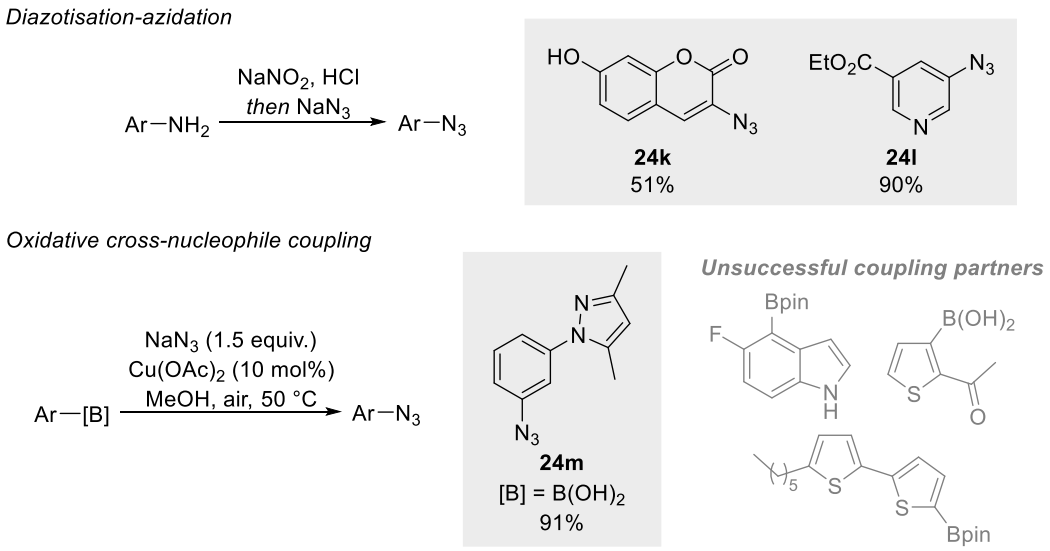

***Scheme 21.*** *Preparation of tertiary and allylic azides*

While the original set of 9 azide substrates included examples of α-azido ethers/silyl ethers and an *ortho*-methoxy aryl azide, we hoped to gain a more general understanding of the tolerance for Lewis-basic heteroatoms in the azide reduction. Metal-catalysed azidations were investigated as a means of constructing α-heteroatom substituted azides. Rh catalysis was employed in the preparation of α-azido sulfonimide **24i** from styrene (**28**), following a recent method[322] described by Wang – believed to occur *via* radical-polar crossover (*cf*. Stahl azidation chemistry[157]). A telescoped two-step Catellani[323,324] aminoborylation/azidation procedure[325] from the Ritter group was identified as an attractive method for the synthesis of a hindered di-heteroatom-substituted aryl azide (**24j**) from 2-iodoanisole (**29**) and *O*-acylhydroxylamine **30**.




***Scheme 22.*** *Metal-catalysed azidations*

Although the original azide reduction scope contained two examples of aryl azides, heteroaromatic azides had yet to be investigated. Consequently, a small number of substrates belonging to this class were prepared (see Scheme 23). Following literature procedures[326,327], azidocoumarin **24k** and azidopyridine **24l** were prepared from the corresponding heteroaryl amines by diazotisation and azidation of the resulting diazonium salts. The oxidative cross-nucleophile coupling conditions from the synthesis of **24j** (*cf*. Chan-Evans-Lam coupling[328–331]) were investigated for the preparation of other heteroaromatic azides, from other boronic acids and esters. Unfortunately, while **24m** was accessed in good yield, other electron-rich heteroaromatic azides could not be prepared in this way.




***Scheme 23.*** *Heteroaromatic azide syntheses*

The above 13 substrates, alongside 4 commercially available azides, were all subjected to the catalytic azide reduction (see Table 1). The commercially available substrates consisted of the anti-HIV medication zidovudine/AZT[332] (**24n**), a densely functionalised cyclitol (**24o**), and two crosslinkers used in biochemical research – APN azide (**24p**) and PTAD azide (**24q**). Out of the 17 azides tested, 13 gave the corresponding

amines, with yields ranging from 22->99%. For the unsuccessful substrates, few side products were observed – typically, the remaining starting material was recovered.

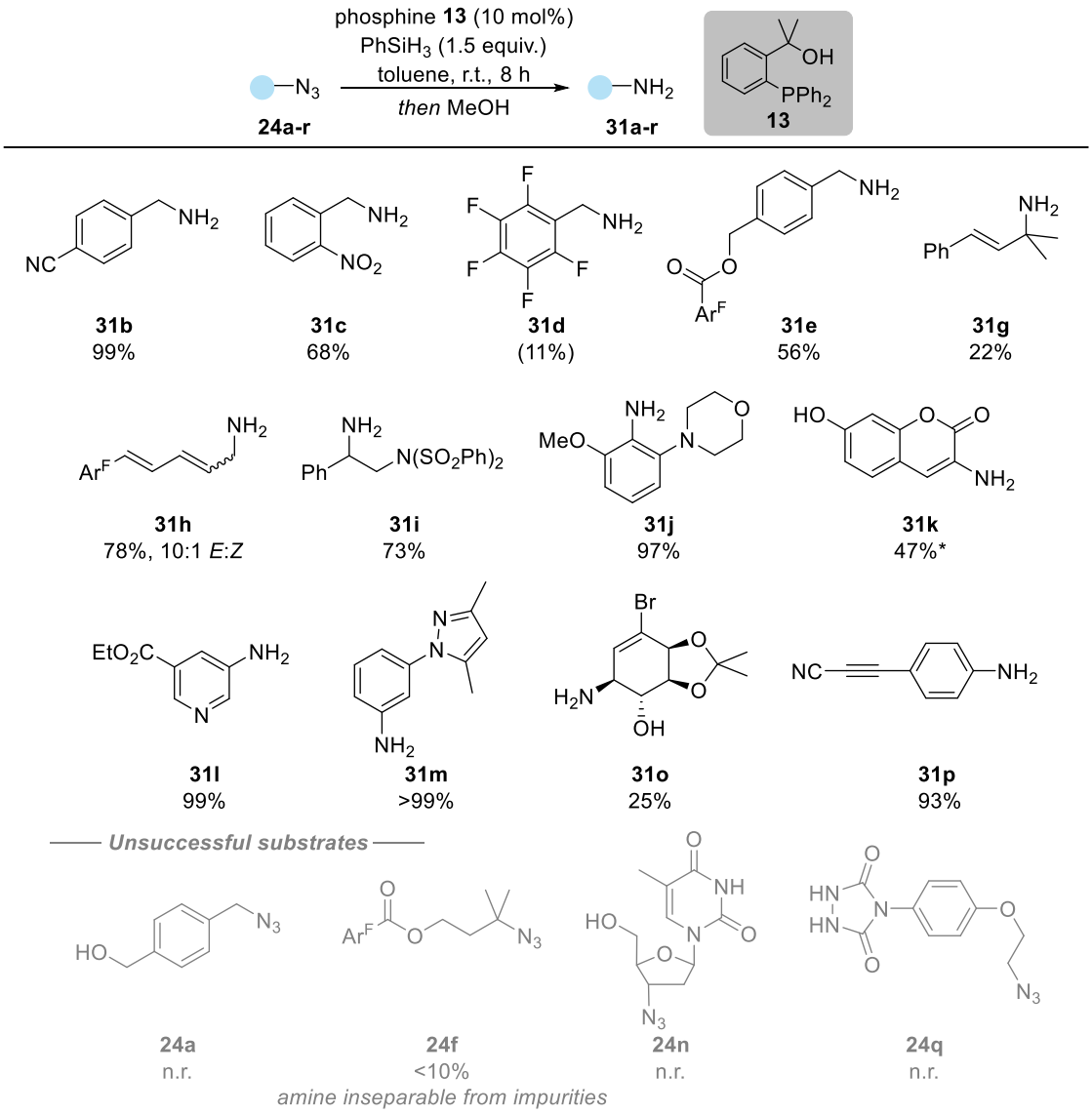



***Table 1.*** *Extensions to the substrate scope of the catalytic azide reduction. Starred yield indicates that the reaction was carried out in acetonitrile. Yield in parenthesis was obtained by $^1$H NMR spectroscopy, using dimethylsulfone as an internal standard.*

We were pleased to observe that the azide reduction conditions display reasonable chemoselectivity: potentially reducible functional groups such as esters (**24e** and **24l**), nitro groups (**24c**), and nitriles (**24b** and **24q**)

did not seem to undergo reduction. Esters (**24e** and **24l**), unprotected azido alcohols (**24a** and **24p**) and phenols (**24k**) seemed to give poorer yields than other classes of azides, possibly due to side reactions between phenylsilane and oxygen-containing functional groups in those molecules. In the case of azido alcohol **24o**, the steric bulk around the azide may also have suppressed the reactivity: the reduction of other sterically encumbered substrates (**24f**, **24g**) also appeared to be challenging.

Solubility plays a major role in the efficacy of the azide reduction. As a result of the sparing solubility of azidocoumarin **24k** in toluene, the reduction of this substrate was carried out in acetonitrile, with moderate success. Highly polar heteroaromatic substrates such as **24n** and **24q** proved to be prohibitively insoluble in the solvents investigated: attempts to reduce these azides resulted in almost quantitative recovery of the azide starting materials, even in acetonitrile and at lower concentrations.

In addition to the 17 small molecule substrates, a polymer-bound azide (**34**) was also prepared. Polymer-supported reagents, catalysts, and scavengers – collectively, resins – are valuable tools for synthesis, especially for reactions carried out in flow.[333,334] Preparation of a novel resin requires careful optimisation to achieve the desired properties (pore size, glass transition temperature, *etc*.). However, several resins are available with both well-defined properties and appropriate functionality to enable attachment of a desired group. Azide-substituted benzyl bromide **33** was prepared from **24a** by treatment with $PBr_3$, and then used as an electrophile in a Williamson ether synthesis with a commercially available Wang resin,[335] to give a new polymer, **34**. Evidence for the incorporation

of the azidobenzyl group was provided by IR spectroscopy and colorimetry.[336] When polymer-bound azide **34** was subjected to the azide reduction conditions, little change was observed: an N–H stretch could not be identified since a broad residual O-H peak also occupied that region of the spectrum, and the intensity of the azide stretch seemed to decrease only slightly (see Figure 23).

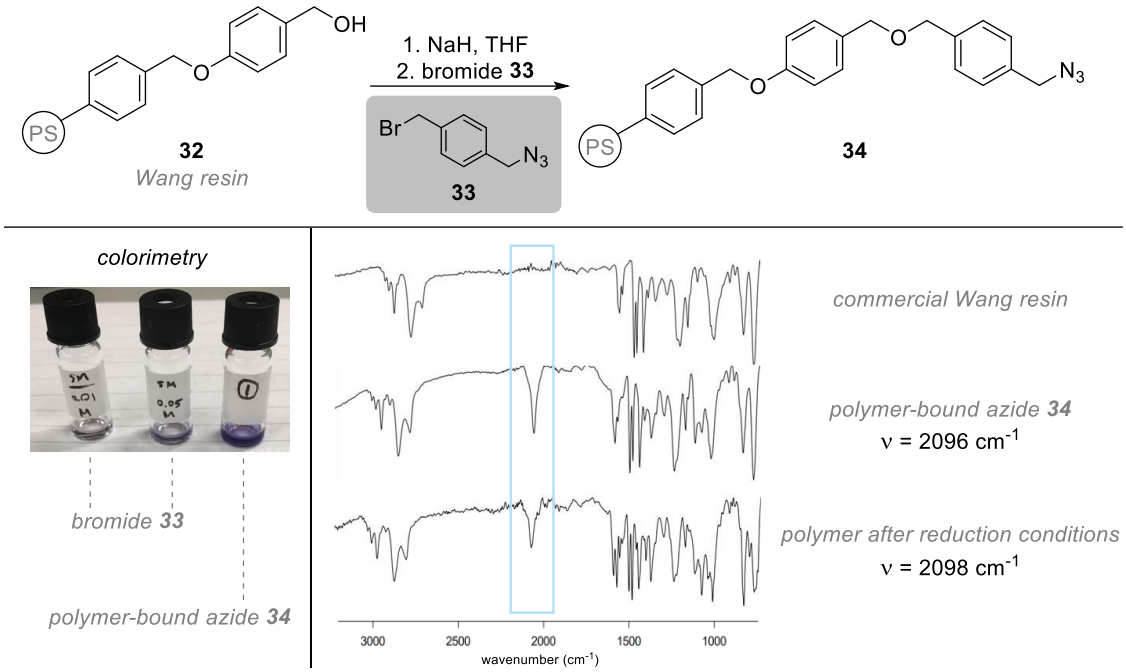
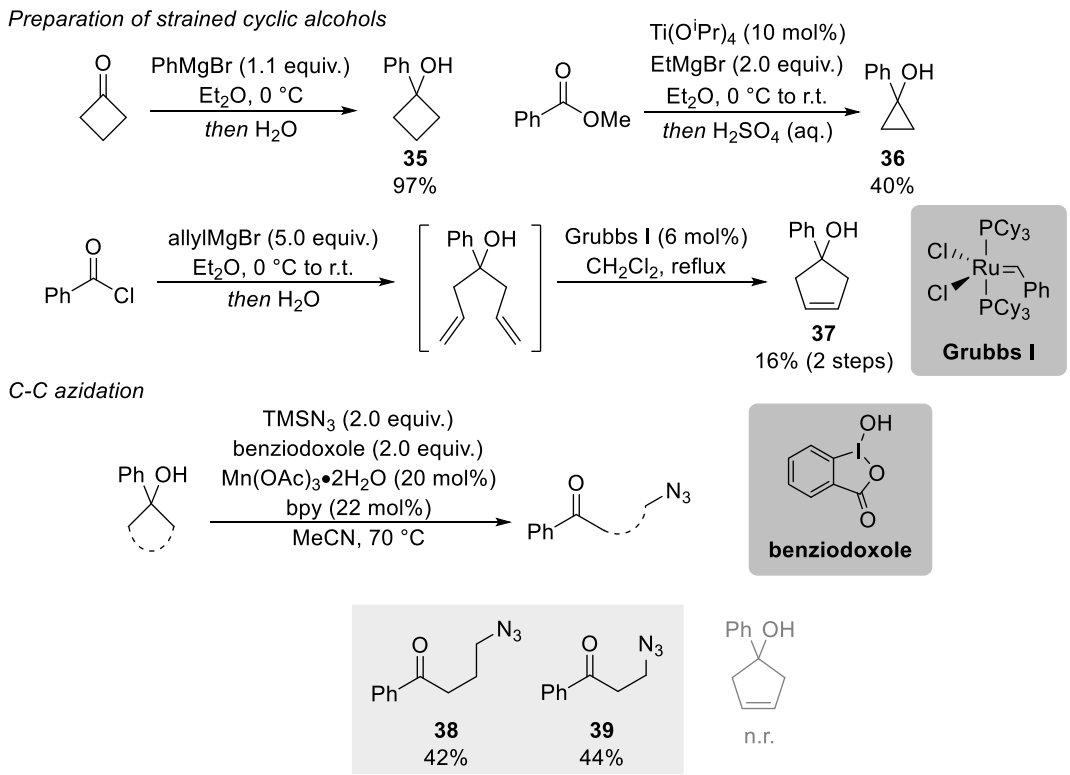



***Figure 23.*** *Preparation and attempted reduction of a polymer-bound azide*

## 2.3.1.3: Tandem azide reductions/cyclisations

Since the azide reduction acts as a kind of 'deprotection' to unveil an amine (or silanamine), we were also interested in substrates for which this 'deprotection' could trigger a secondary reaction of the nucleophilic amine/silanamine moiety. In particular, we were keen to explore the possibility of azide reduction/tandem ring formation, by tethering an electrophilic functional group to the azide in the substrate.

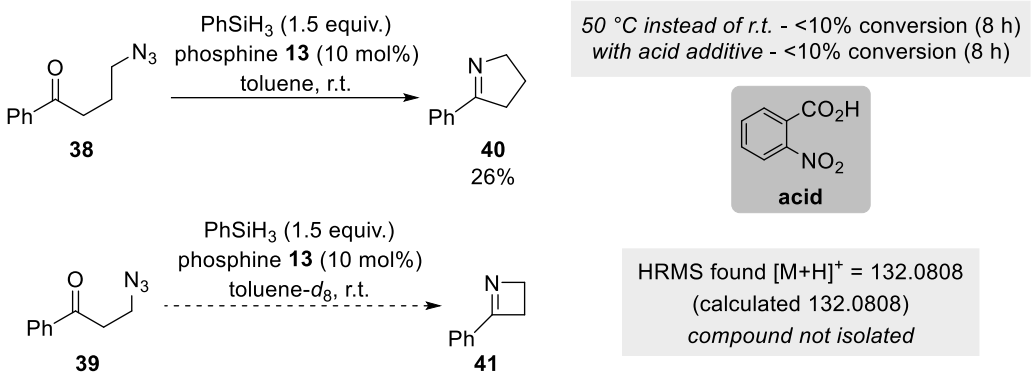
The strain-release C-C azidation developed by Zhu[131] was identified as a convenient method for the preparation of 4-azidoketones from cyclobutanols; the synthesis of ketone **38** was carried out under Zhu's conditions (see Scheme 24). Although cyclopropanol opening had not been demonstrated in the Zhu publication, it was believed that C-C azidation should also be possible for this ring size. Gratifyingly, subjection of cyclopropanol[337] **36** to the azidation conditions gave azido ketone **39** in good yield. The possibility of opening a larger ring was also investigated: cyclopentenol compound **37** was prepared by ring-closing metathesis, but was then found to be unreactive under the azidation conditions.




***Scheme 24.*** *C-C azidation of strained cyclic alcohols*

Upon subjection of azido ketone **38** to the standard azide reduction, imine **40** was obtained in 26% yield, with the rest of the starting material recovered (see Scheme 25). Although compound **40** was accessed in low

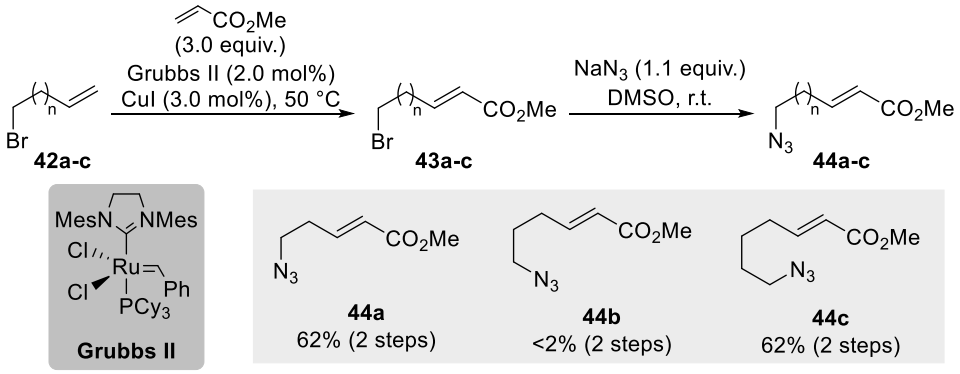
yield, this result indicated that at least some of the imine formation was occurring by a process other than a classical aza-Wittig reaction,[338] in which the phosphine would be expected to react in a stoichiometric sense to give a yield no greater than its loading, *i.e.*, ≤10%. Emboldened by this result, the reaction was repeated at higher temperature, and with an acid additive (following the aza-Wittig system[270] developed by Kwon). Unfortunately, less than 10% conversion was observed for these reactions, again with recovery of the remaining starting material. For azido ketone **39**, a peak matching the expected *m/z* of imine **41** was found in the mass spectrum for the crude reaction mixture, but $^{1}$H and $^{13}$C NMR spectra indicated that a complex mixture of compounds was present. Thin-layer chromatography of the reaction mixture led to decomposition (on silica and alumina). As there is little spectroscopic data available for imine **41**, its presence cannot be confirmed.[339]




***Scheme 25.*** *Azide reduction/intramolecular imine formation*

Following the limited success experienced while working with the azido ketone substrates, other potential cyclisations were instead investigated. Based on work from Vaultier,[340] electron-deficient alkenes (*i.e.*, Michael acceptors) were selected as a promising class of compounds – azides tethered to, *e.g.*, α,β-unsaturated esters, were expected to undergo

cyclisation immediately following reduction, and with no obvious pathway for phosphine oxide-forming side reaction(s). Accordingly, a series of ω-azido α,β-unsaturated esters (**44a**-**c**) were prepared over two steps, by cross metathesis and azidation (see Scheme 26).




***Scheme 26.*** *Preparation of ω-azido α,β-unsaturated esters*

Unfortunately, the ω-azido α,β-unsaturated ester substrates displayed significant stability issues. It is believed that these substrates are highly reactive in intramolecular [3+2] cycloadditions – a reaction that appeared to occur more rapidly when the azides were in solution, necessitating rapid purification of the azides upon consumption of the bromide starting materials. For example, the reaction of bromide **43c** with sodium azide gave organic azide **44c** in 71% yield after 16 hours, but only 17% after 3 days, and significant changes were observed after leaving a sample of concentrated **44c** at room temperature for 4 days: the previously pale yellow sample darkened, and new peaks were visible in its $^{1}$H NMR spectrum (see Figure 24). Shorter-chain azide **44b** appeared to be too unstable to be isolated in preparatively useful yields.

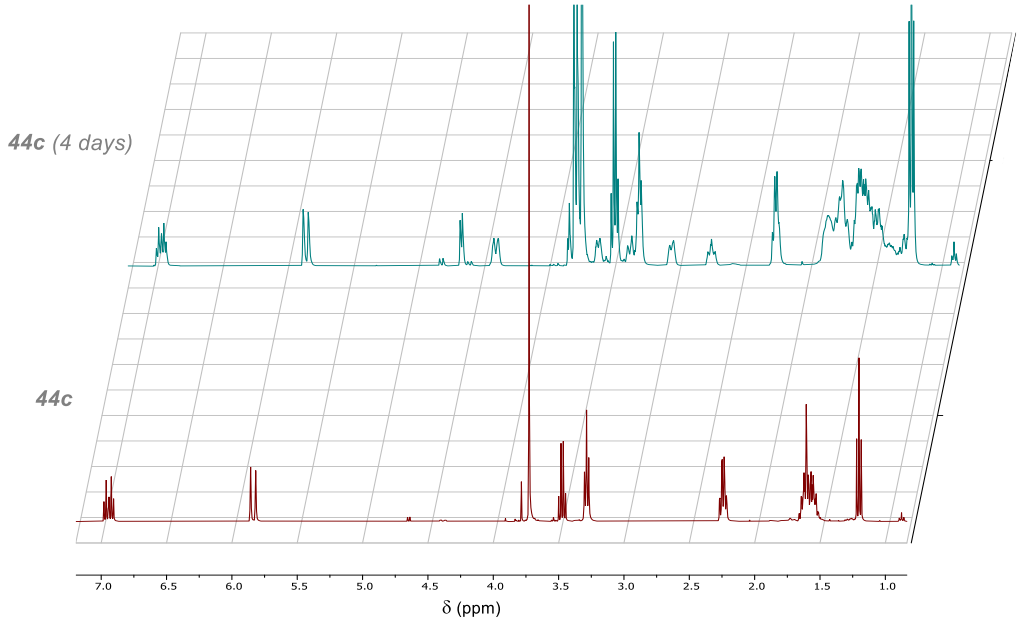
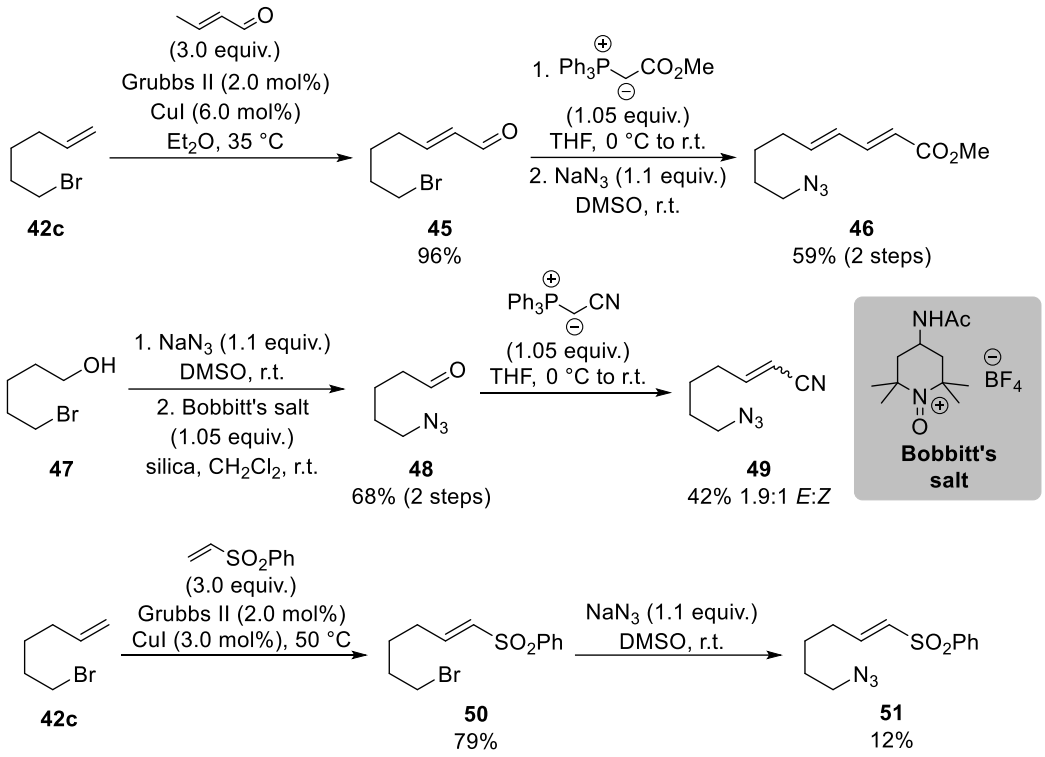



***Figure 24.*** *Degradation of azido ester* ***44c*** *as observed by* $^{1}H$ *NMR spectroscopy (400 MHz,* $CDCl_3$*)*

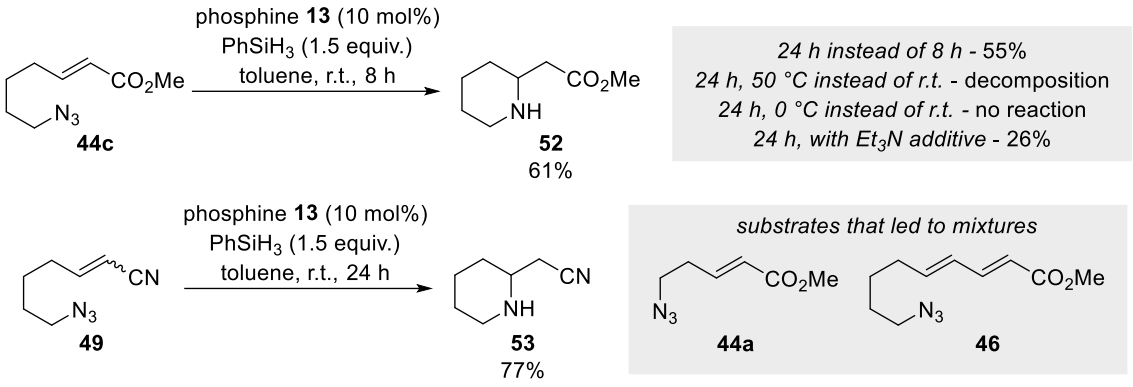
In addition to the azido α,β-unsaturated esters, other kinds of azide-tethered electron-deficient alkenes were also prepared (see Scheme 27). Using cross metathesis and Wittig chemistry, α,β,γ,δ-unsaturated ester **46** was accessed in good yield. Acrylonitrile **49** was prepared over three steps from the corresponding bromo alcohol by azidation, oxidation with Bobbitt's salt,[341] and Wittig olefination. It was found that the precursor to **49** – bromo alcohol **47** – underwent side reactions over time (believed to include intramolecular etherification and oligomer formation), which may account for the moderate yield of aldehyde **48**. Vinyl sulfone **51** was prepared by a similar route to **44a**-**c** – *i.e.*, cross metathesis followed by azidation. All of these substrates were observed to degrade within days of their preparation; the low yield of substrate **51** is attributed to especially rapid degradation.




***Scheme 27.*** *Preparation of other ω-azido Michael acceptors*

Reductive cyclisation was attempted on azide **44c** by subjection to the standard catalytic azide reduction conditions. Pleasingly, the corresponding α-substituted piperidine (**52**) was accessed in 61% yield (see Scheme 28), with the rest of the starting material largely recovered. Optimisation of this reaction was attempted, but with little success: running the reaction for longer had little effect, raising the temperature led to degradation of the starting material, lowering the temperature suppressed reactivity, and adding triethylamine to the reaction mixture (*cf.* Section 2.3.1) resulted in a lower yield. Rather than changing further reaction parameters, it was decided that other substrates should be tested under the standard conditions. Acrylonitrile **49** gave the corresponding piperidine in 77% yield. Reduction of azide **44a** gave a new alkene species – believed to be the immediate reduction product, *i.e.*, the corresponding primary amine – which was inseparable from at least one other unidentified

compound. In order to investigate the possibility that the open-chain reduction product may be interconverting with another species (*e.g.*, the closed-chain 4-ring), DOSY and VT-NMR experiments were performed. Unfortunately, the DOSY experiment did not resolve the spectra and no coalescence was observed up to 100 °C. Reduction of diene **46** appeared to give the desired cyclisation product, but as an inseparable mixture with an unknown impurity, and in less than 35% yield.




***Scheme 28.*** *Cyclisations of ω-azido, electron-deficient alkenes*

## 2.3.2: Sequential azide reductions/intermolecular amine functionalisation

As discussed in Section 2.1, the catalytic azide reduction proceeds under mild conditions and at ambient temperature, and – as demonstrated in Section 2.3.1.2 – good chemoselectivity can be achieved for the azide reduction over other conceivable reduction reactions. It is known that the products of the reaction – both the immediate silanamine products and the corresponding amines – can undergo useful reactions at nitrogen. In sum, then, the catalytic azide reduction appears to be a good candidate for telescoping with other reactions, in an overall 'deprotection'/functionalisation strategy (see Figure 25).

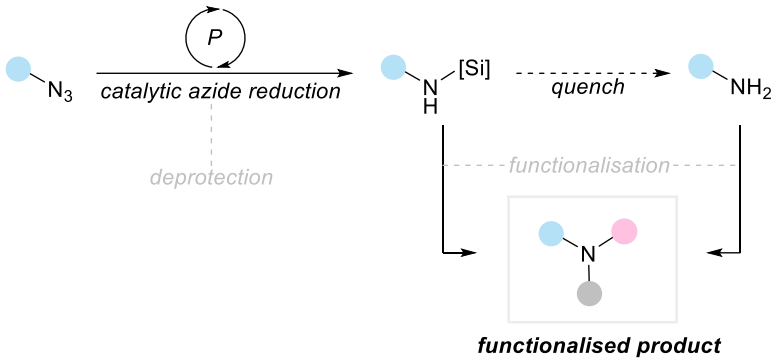



***Figure 25.*** *Tandem azide reductions/post-reduction functionalisations*

## 2.3.2.1: Intermolecular conjugate additions

Having established the feasibility of azide reduction followed by intramolecular conjugate addition, we next turned to the development of an intermolecular variant of this chemistry. After reduction of benzyl azide (**54**) to the corresponding silanamine(s), methyl acrylate was added. We were very pleased to observe that the resulting β-amino ester (**55a**) was obtained in 93% yield. Subsequently, the reaction was carried out with a selection of other Michael acceptors (see Table 2).

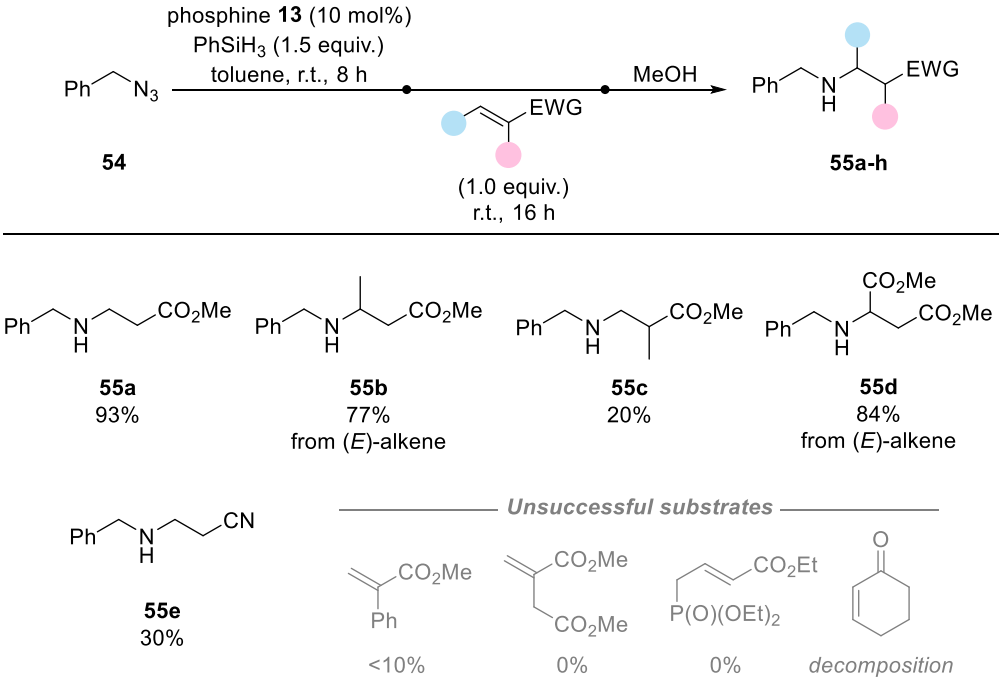
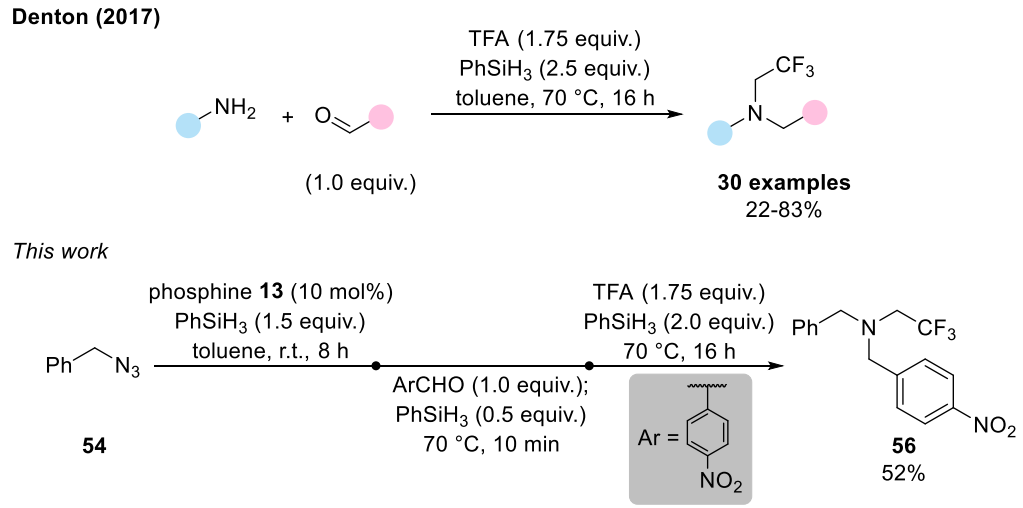



***Table 2.*** *Catalytic azide reduction/intermolecular conjugate additions*

As shown in Table 2, 6 conjugate addition products were prepared under very mild conditions. Interestingly, the reaction appears to be sensitive to steric bulk at the α-position of the electrophile. It is difficult to account for this observation on the basis of relative electrophilicities: in Mayr's reactivity studies,[342] β-substitution is shown to decrease electrophilicity more than α-substitution. For our system, the difference in yields may arise from additional stereoelectronic effects and/or interactions at silicon.

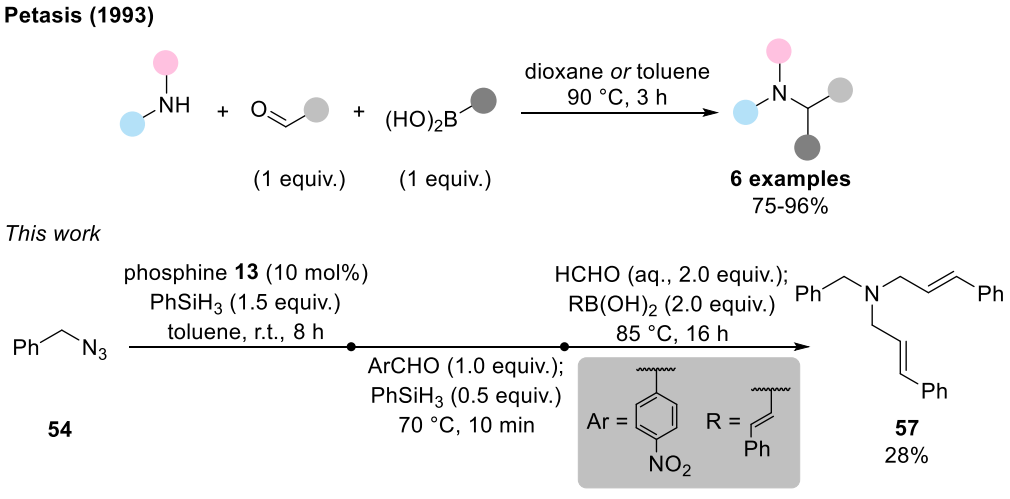
### 2.3.2.2: Reactions of imine/iminium intermediates

As imine/iminium intermediates are common in the reactions of amines, we were keen to demonstrate that a reaction of this kind could be performed after the catalytic azide reduction. Following previous work[343] in the Denton group, a three-component reductive amination/trifluoroethylation was appended to the azide reduction (see Scheme 29). In this reaction, an aldehyde was added to the post-reduction reaction mixture, followed by the addition of TFA and heating. From this reaction, trifluoroethylamine **56** was accessed cleanly in 52% yield over 2 steps.

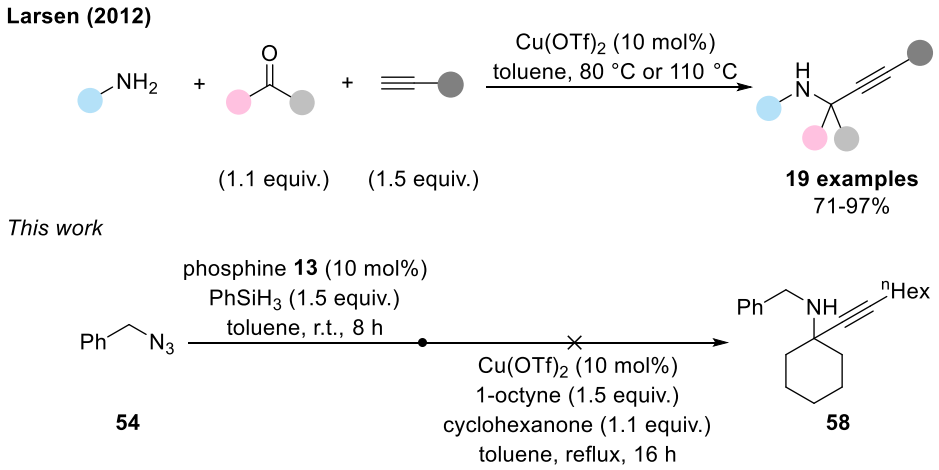



***Scheme 29.*** *Azide reduction/three-component trifluoroethylation*

The success of the three-component coupling encouraged us to look at other multi-component reactions proceeding *via* similar intermediates. Two potential reactions were selected: the Petasis borono-Mannich reaction,[344–346] and the so-called 'A$^3$ coupling' (aldehyde-alkyne-amine coupling)[347,348] (see Schemes 30 and 31). Presuming that the trifluoroethylation reaction proceeded *via* a reductive amination with the aldehyde first to give a secondary (silan)amine, this first step was repeated (*i.e.*, the same aldehyde was added to the post-reduction reaction mixture, with further phenylsilane). After this step, aqueous formaldehyde and *trans*-styrylboronic acid were added. Surprisingly, symmetrical double Petasis product **57** was accessed instead of the desired product. From this result, it appears that TFA may be required for both the reductive amination and the trifluoroethylation steps in the formation of **56**. The A$^3$ coupling conditions proved to be incompatible with the post-reduction reaction mixture – a tarry black residue resulted, with none of the desired product observed by HRMS or NMR.




***Scheme 30.*** *Attempted Petasis reaction*

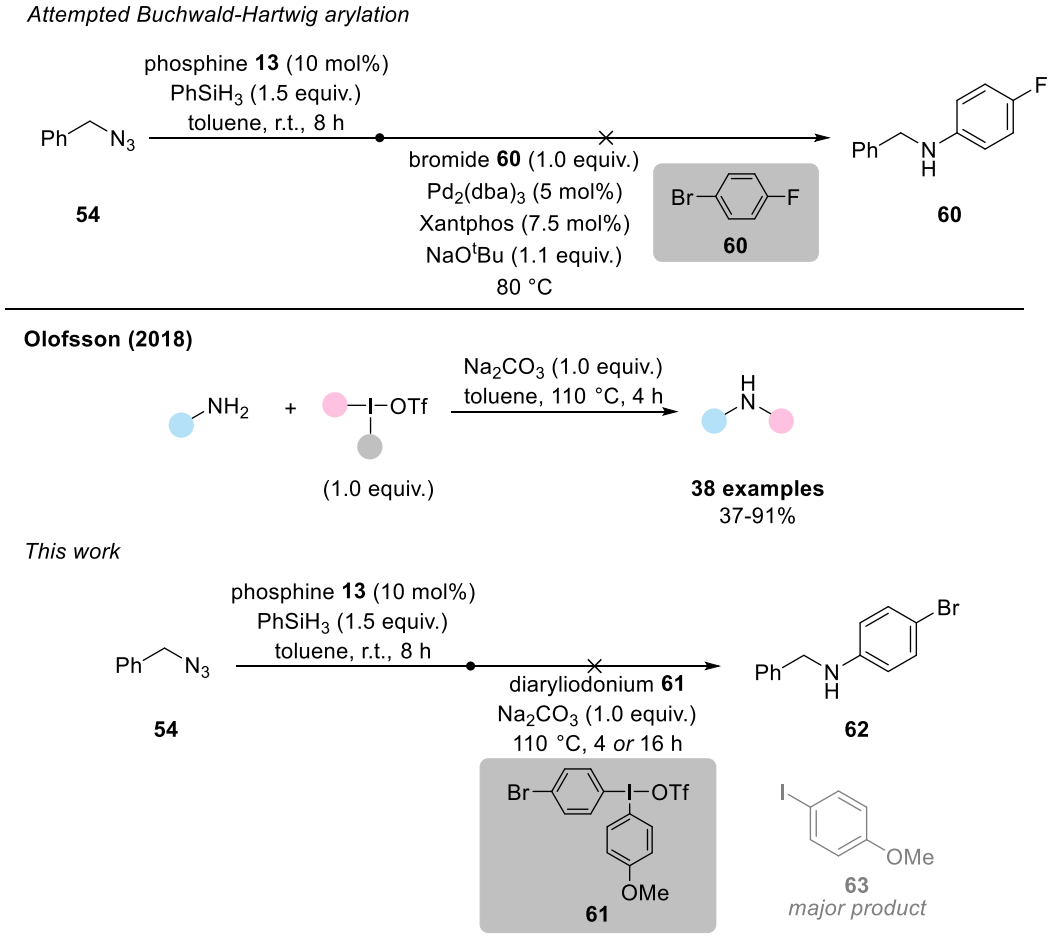



***Scheme 31.*** *Attempted A³ coupling*

## 2.3.2.3: Arylation attempts and heterocycle syntheses

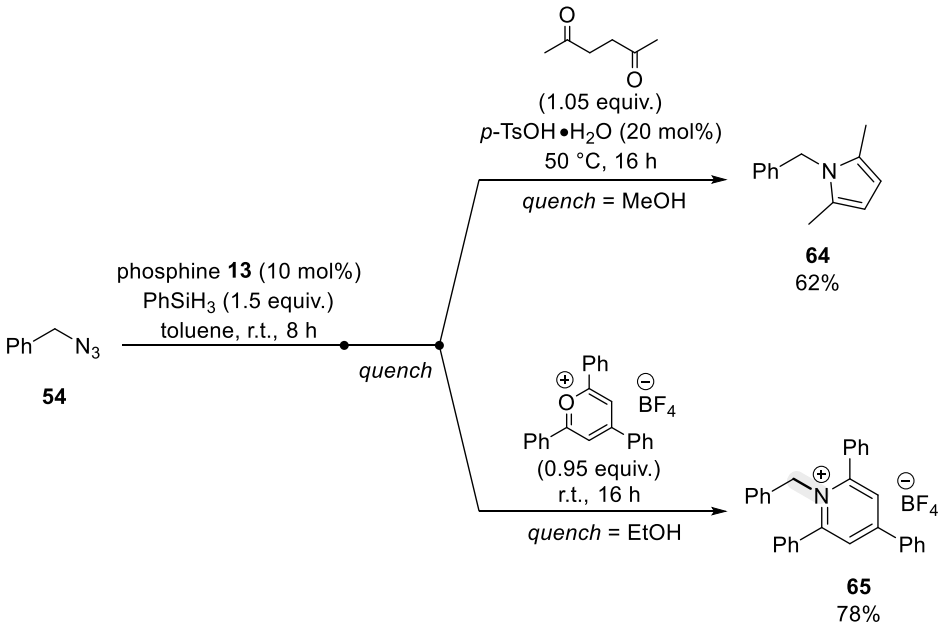
Amine arylations are increasingly common in the synthesis of industrially significant compounds.[349] The Buchwald-Hartwig coupling[350–352] is perhaps the most prominent class of these reactions, and aminations of this type are known for a wide variety of aryl and heteroaryl halides and triflates. We were – therefore – interested in the possibility of combining the azide reduction with Buchwald-Hartwig chemistry (see Scheme 32). Unfortunately, attempting to carry out a two-step procedure[353] of this kind resulted in decomposition of the benzyl silanamine(s) to give benzaldehyde (after work-up). As an alternative to this strategy, the Olofsson metal-free arylation[354] was instead investigated. This reaction also proved to be incompatible with the azide reduction: reduction of the diaryliodonium salt (**61**) was observed, but with no formation of the desired aniline. The difficulties encountered in these reactions are believed to result from chemoselectivity issues – although nitro groups, esters and electron-deficient alkenes were not reduced under the azide reduction conditions, it appears that stronger oxidants (*e.g.*, palladium(II) species, iodine(III)

compounds) can undergo side reactions with the reducing silanes/silanamines present in the post-reduction reaction mixture.




***Scheme 32.*** *Attempted Buchwald-Hartwig and metal-free arylations*

Given the prominence of nitrogen-containing heterocycles in the structures of APIs and agrochemicals,[355,356] we hoped to achieve heterocycle formation by adding a suitable electrophile to the quenched reduction reaction mixture. Gratifyingly, azide reduction/heterocycle formation proceeded in good yield for both Paal-Knorr pyrrole synthesis and pyridinium salt formation (see Scheme 33). The specific kind of pyridinium salt chosen – a Katritzky salt[357] – enables transformations of the highlighted bond in **65**, by nucleophilic or radical substitution. In other words, this transformation represents an entryway into functionalisations at carbon, beyond the reactions at nitrogen discussed in this work.

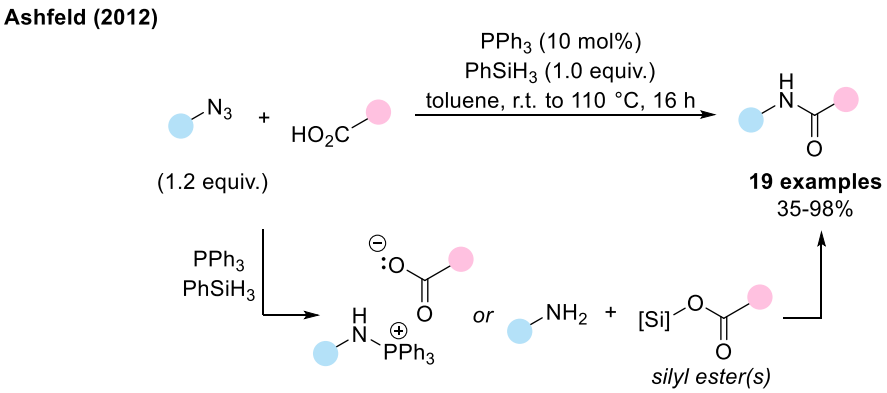



***Scheme 33.*** *Paal-Knorr pyrrole synthesis and Katritzky salt formation*

## 2.3.2.4: Amidations

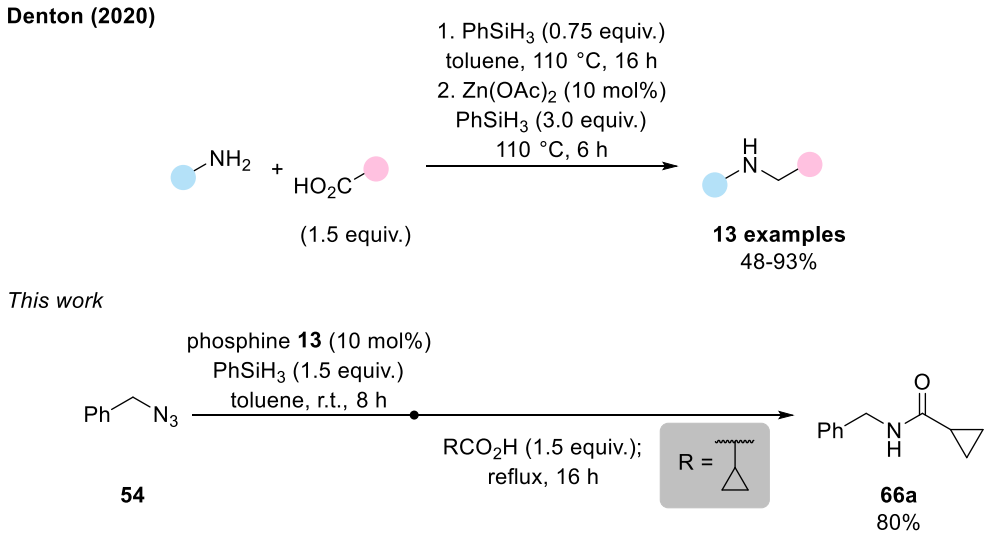
Amidations are among the most fundamental reactions of amines, and are of critical importance to the pharmaceutical and agrochemical industries.[358] In light of this importance, we hoped to develop a practical and efficient two-step azide reduction/amidation protocol. Ideally, we hoped to use carboxylic acids directly in this chemistry, since carboxylic acids are generally widely available, bench-stable, and non-hazardous.[311] Carboxylic acids typically require activation by reagents including guanidinium/uronium and phosphonium salts, carbodiimides (often alongside *N*-hydroxy compounds), CDI,[359] T3P,[360] *etc.*, to undergo amidation efficiently with free amines.[361,362] Ultimately, all amide coupling reagents represent 'wasted' mass from the perspectives of atom economy and PMI, alongside any other practical issues they may present; increasingly, catalytic amidation by, *e.g.*, boron compounds,[363] is being investigated as an alternative to stoichiometric acid activation.

As discussed in Chapter 1, the use of azides in Staudinger ligations (*i.e.*, amidations) is an established technique – albeit one that sees little use on large scales due to the safety issues associated with azides and the generation of stoichiometric phosphine oxide waste. It was demonstrated by Ashfeld (see Scheme 34) that substoichiometric amounts of phosphine can be used to effect Staudinger ligation, in concert with phenylsilane as a terminal reductant.[268,269] Ashfeld's system, however, involves heating the reaction to 110 °C – this is a serious practical limitation, given the thermal instability of organic azides. Previous members of the Denton group have shown[364] that silyl esters are key intermediates in Ashfeld's chemistry: silanes activate carboxylic acids towards amidation. Taking all of the above into account, it was our belief that we could develop an amidation protocol using the catalytic azide reduction (carried out at room temperature) as a method to generate a silanamine, which should transfer a silyl group to a carboxylic acid (BDEs: Si-N = 77 kcal·mol$^{-1}$; Si-O = 108 kcal·mol$^{-1}$)[365], to give an amine and a silyl ester – known participants in amidations. Thus, it should be possible to effect amidation under very similar conditions to the azide reduction, without the addition of an exogeneous amide coupling reagent.




***Scheme 34.*** *Ashfeld's catalytic Staudinger ligation*

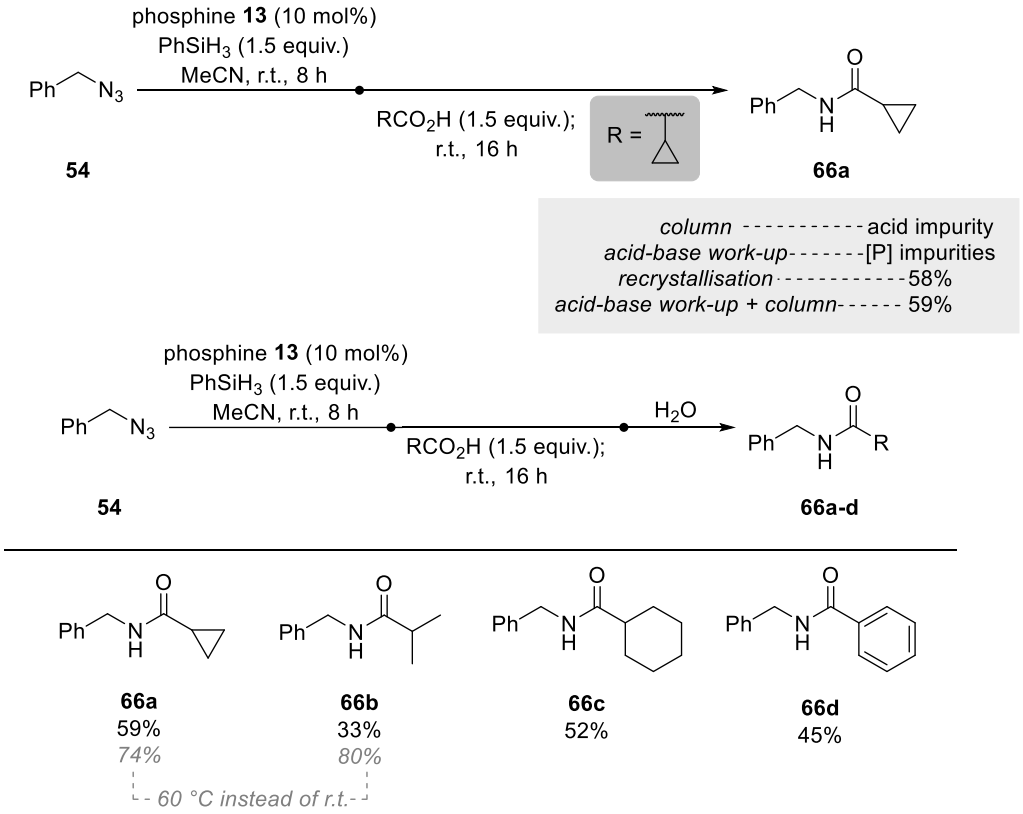
Following the Ashfeld conditions as well as reductive amination chemistry[311] previously developed in the Denton group, amidation was first attempted by simply adding a carboxylic acid to the azide reduction mixture after 8 hours (the standard duration), and then refluxing the resulting mixture for 16 hours. Encouragingly, these conditions gave the desired amide product in good yield (see Scheme 35), but with co-elution of the remaining carboxylic acid after purification by column chromatography.




***Scheme 35.*** *Azide reduction/amidation tests*

Although we were pleased to observe that amidation was feasible in refluxing toluene, we ultimately hoped to develop a room-temperature amidation protocol. As many carboxylic acids are poorly soluble in toluene at room temperature, we believed that a more polar solvent might facilitate the desired reaction. Accordingly, the two-step azide reduction/amidation reaction was carried out in acetonitrile (ε(MeCN) = 37.5; ε(PhMe) = 2.38)[366]. Initially, work-up and purification procedures were established for the formation of **66a**, as a model reaction, and the highest-yielding procedure was then applied to the amidation of three

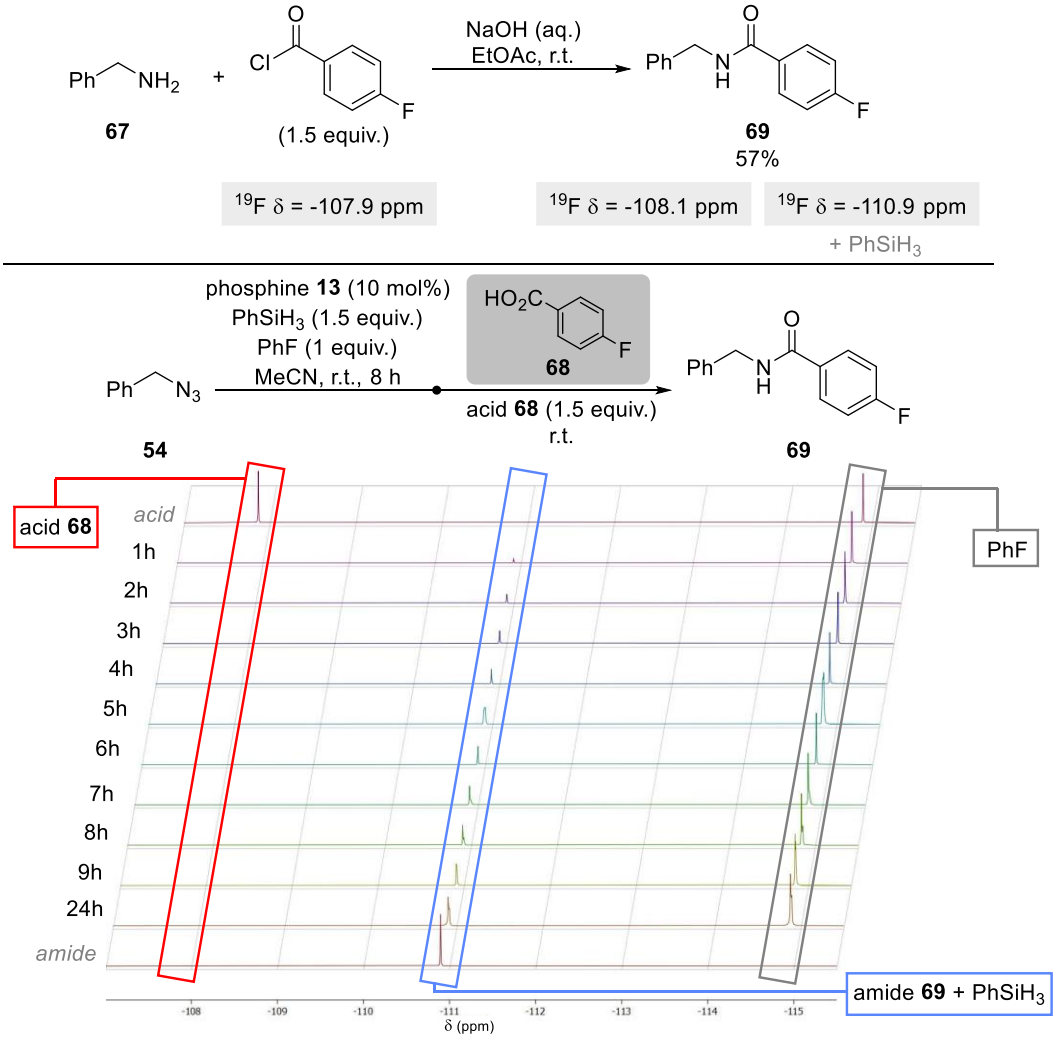
other acids (see Scheme 36). Moderate yields were observed for the two-step procedure (33-59%), which we considered to be unsatisfactory, given the importance of the reaction class and the number of existing amidation conditions. Taking the best and worst results from the small acid screen, the amidation was carried out at 60 °C instead of room temperature, which resulted in higher yields for both compounds. These conditions represented an improvement upon high-temperature amidations, but still did not fulfil our objective of developing a room-temperature azide reduction/amidation system.




***Scheme 36.*** *Development of an amidation procedure*

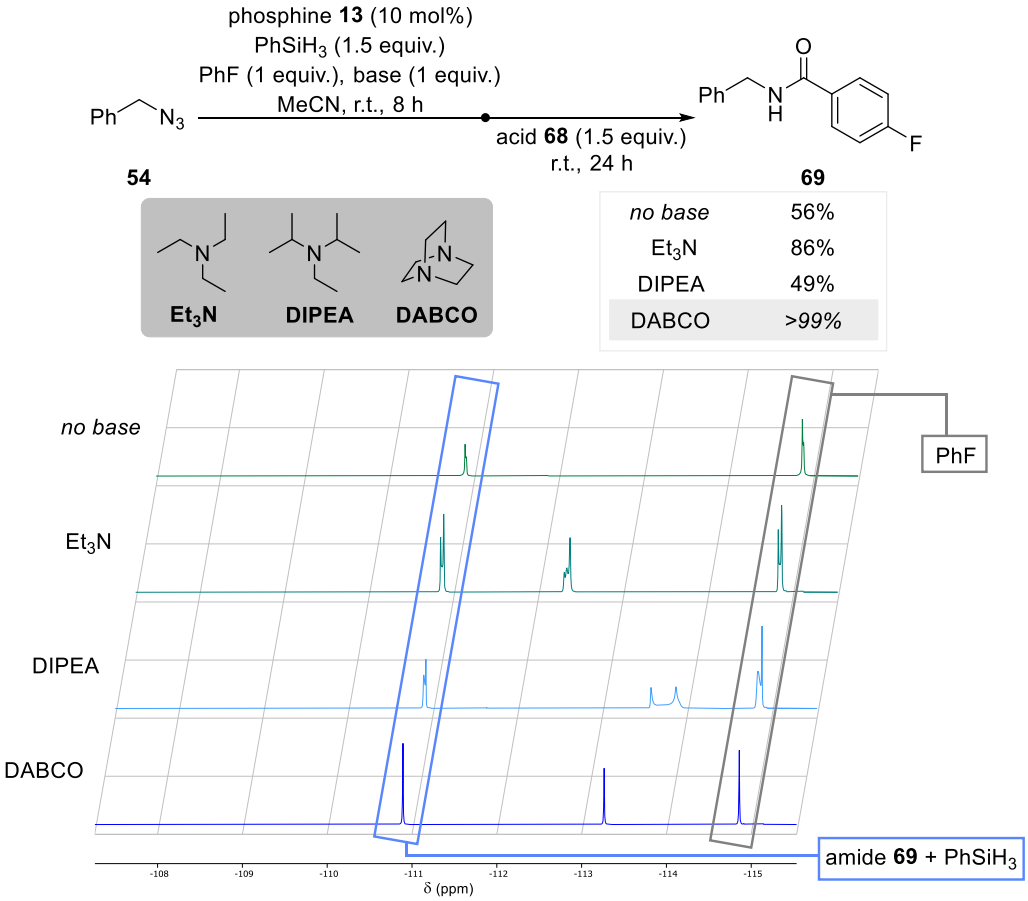
In order to investigate the progress of the reaction, a quantitative $^{19}F$ NMR study was devised (see Scheme 37): $^{19}F$ NMR spectra were obtained for 4-fluorobenzoic acid (**68**) and fluorinated amide **69**, and the conversion of the acid to the amide was then monitored for the two-step azide

reduction/amidation procedure. When the reaction mixture was sampled, no peak was detected at the $^{19}F$ chemical shift measured for pure **69**, even though this compound was visible in the $^{1}H$ NMR spectrum. It was subsequently determined that the presence of phenylsilane significantly alters the chemical shift of the $^{19}F$ signal for the amide product; fortunately, the silane-spiked amide sample displays a very similar relaxation time ($T_1$) to the pure compounds, and so the experiments remain quantitative for all species observed. From this reaction monitoring, the amidation was shown to reach around 56% conversion after 24 hours. Other $^{19}F$ peaks - in the range of -105.5 to -107.5 ppm – are observed throughout the reaction.




***Scheme 37.*** *Amidation monitoring by quantitative $^{19}F$ NMR (376 MHz, MeCN-$d_3$)*

Having determined that the room-temperature amidation reaction did not go to completion, new conditions were sought for this reaction. After the publication of Radosevich's three-component amide synthesis[367], amine bases were investigated as potential additives for the amidation (see Scheme 38). Since it was already known that amines could provide a rate enhancement effect in the catalytic azide reduction, the bases were each added at the beginning of the two-step procedure, and then the acid was added as before. Triethylamine was shown to enhance the yield of the amidation significantly, and DABCO gave apparently quantitative conversion. Interestingly, DIPEA gave a lower NMR yield – this may result from its lower nucleophilicity or from the formation of a strong ion pair.




***Scheme 38.*** *Amine bases as additives in the amidation reaction, showing $^{19}F$ NMR spectra (376 MHz, MeCN-$d_3$) taken after 24 h*

From the base screen, the use of DABCO as an additive appeared to be very promising. Consequently, several amidation reactions were set up in the presence of 1 equivalent of DABCO. Unfortunately, a new problem emerged from these conditions: the DABCO-silanamine-acid combination results in the formation of insoluble, apparently polymeric materials, the compositions of which are not known. The presence of these solids makes recovery of the amide from the reaction mixture extremely difficult: it seems that the amides are trapped in the presumed polymers, allowing little of the product to be extracted during the work-up. As a result of these difficulties, a practical base-enhanced amidation has so far proven elusive for DABCO. Hopefully, in future work for this project, the use of other additives can be investigated; triethylamine, for example, would seem to be the next best base, and other nucleophiles could be considered.

## 2.4: Conclusions

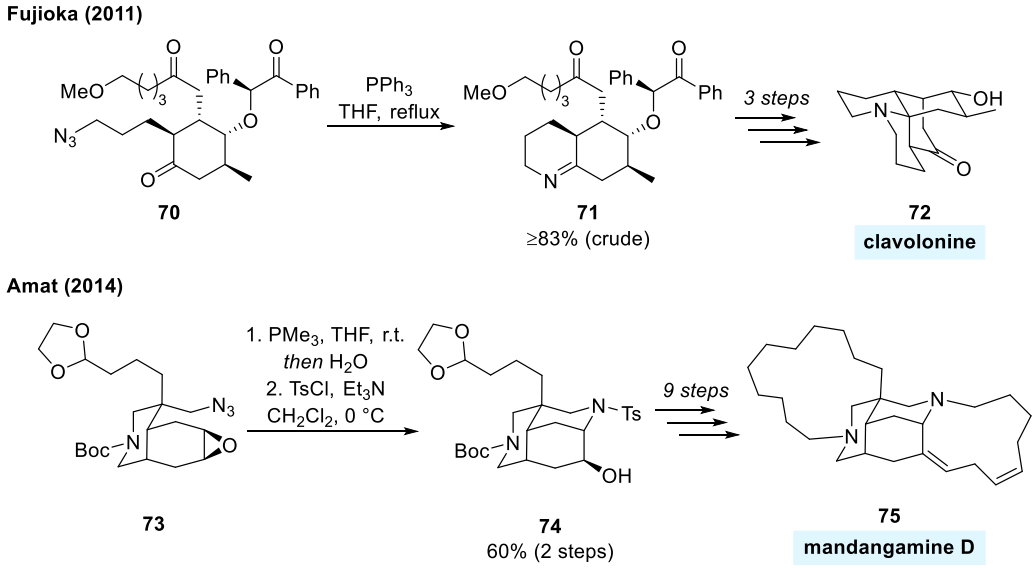
From the initial work carried out in the Denton group, it was known that a rationally designed phosphine could be used to carry out room-temperature, catalytic Staudinger reactions for a selection of simple azides. In this project, we have demonstrated that the azide reduction tolerates considerable diversity of structure and functionality among the substrates, as well as enabling the first examples of cyclisation by (non-aza-Wittig) imine formation and conjugate addition. Tandem azide reduction-functionalisation protocols were developed for several reactions, including intermolecular conjugate additions, reductive amination/trifluoroethylation, and heterocycle formation. A practical, efficient azide reduction/amidation remains under development, but

significant progress has been made in this direction: from screening reaction conditions and $^{19}F$ NMR experiments, considerable insight has been gained into this reaction, and further optimisation is anticipated.

# 3. Azides as Building Blocks for Target Synthesis

## 3.1: Background

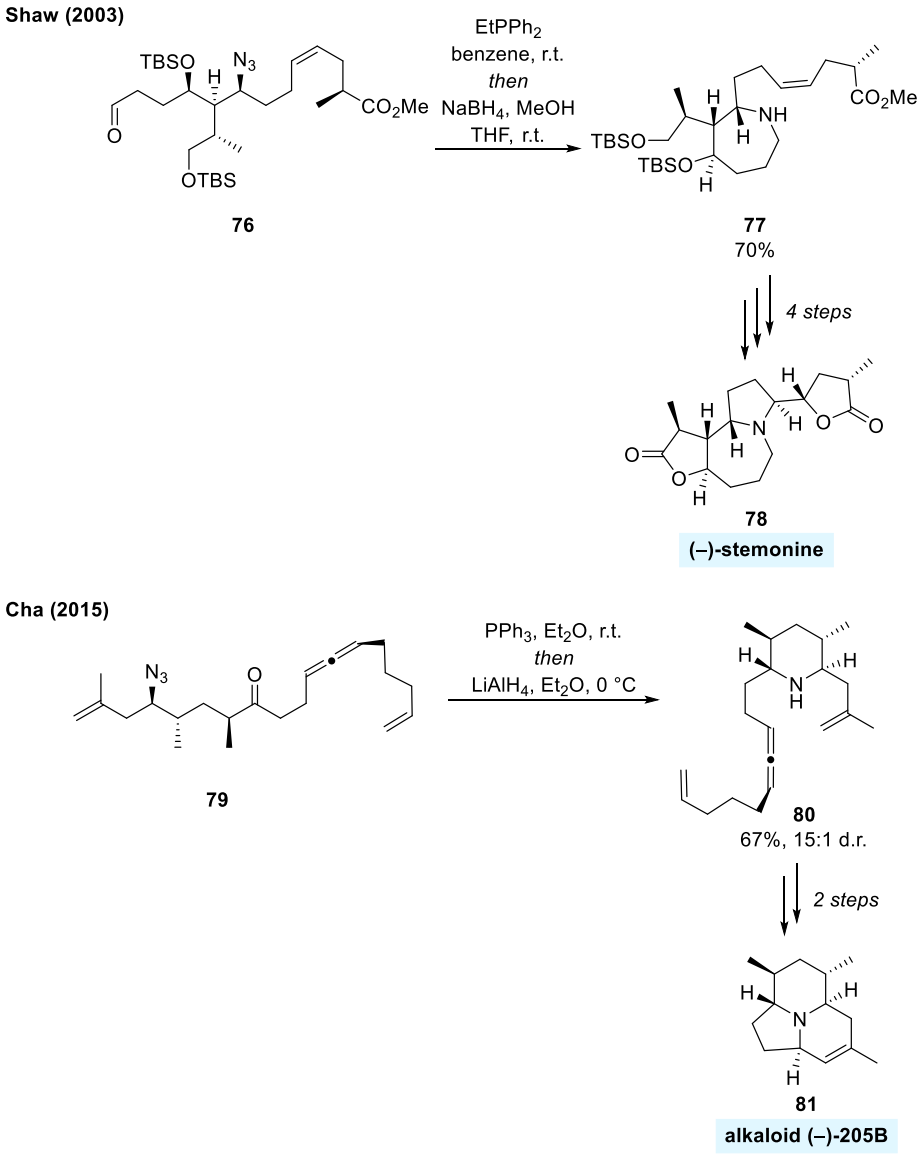
With the utility of the catalytic azide reduction established, we next hoped to apply this method to the construction of amine targets, including natural products, agrochemicals,[368] and APIs.[356] The use of azides as 'protected amines' has some precedent in total synthesis[175] – in particular, azide intermediates appear in several syntheses of indolizidine and quinolizidine alkaloids.[369] For these kinds of bi- or polycyclic targets, the azide functional group is especially useful because it can be introduced to one ring, typically by nucleophilic substitution, and then – upon reduction of the azide group – cyclisation can be effected by reaction of the newly-formed iminophosphorane or amine with a proximal ring substituent (see Scheme 39).




***Scheme 39.*** *Polycyclic alkaloid syntheses* via *reductive cyclisations of azides*[370,371]

In addition to cyclisations onto pre-formed rings, nitrogen-containing rings have also been prepared by cyclisation of linear azides (see Scheme 40). Although there are relatively fewer examples of this strategy, the relative ease of installing an azide group, and the inert nature of the azide group

to many kinds of reaction conditions (both discussed in Chapter 1) render this strategy an interesting alternative to the functionalisation of cyclic amines.




***Scheme 40.*** *Synthesis of monocyclic building blocks by reductive cyclisation of linear azides*[372,373]

Cyclisation of amine-tethered epoxides (see Figure 26, also *cf*. the Amat mandangamine D synthesis[371]) would seem to be an especially interesting approach to ring formation: epoxides tend to undergo stereospecific opening with inversion, and there exist many methods for the asymmetric

synthesis of epoxides.[94,96–98,100,102,104] With respect to the regioselectivity of intramolecular epoxide opening, it is known that – for cyclic ether syntheses – the smaller ring size (arising from the *spiro* transition state)[374] will generally be preferred, except in cases of steric hindrance, promotion of the *fused* pathway by directing groups, or solvent/substrate templating effects.[375] Therefore, catalytic azide reduction/tandem epoxide opening could represent a powerful, asymmetric approach to the construction of C2-substituted nitrogen-containing rings.

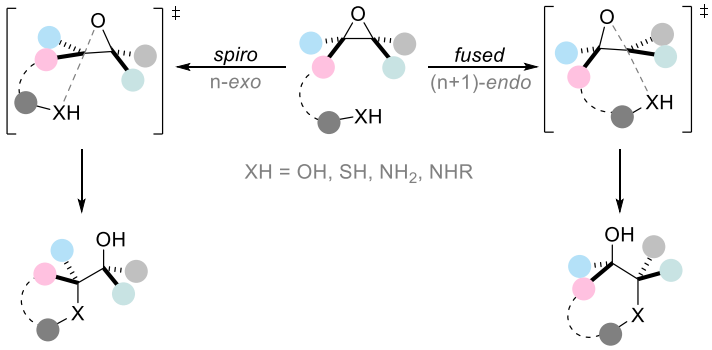



***Figure 26.*** *Ring formation by intramolecular epoxide opening*

A wide variety of alkaloids[369,376] contain stereodefined nitrogen-containing rings with substitution at the 2-position – in particular, piperidines bearing this substitution pattern are common (see Figure 27). The applications of these compounds are diverse, yet there are relatively few general strategies for their synthesis. Ring formation strategies include,[377–379] *e.g.*, ring-closing metathesis, [4+2] cycloadditions, or other amination reactions – generally these methods require additional redox steps as well as protection and deprotection of the amine. Aside from ring formation, approaches to the synthesis of chiral, enantiomerically enriched C2-substituted piperidines fall into one of three categories: addition to/reduction of pyridines and pyridinium compounds,[380–392] addition

to/reduction of cyclic imine/enamine compounds,[393–400] and asymmetric functionalisation of achiral piperidines.[401–408]

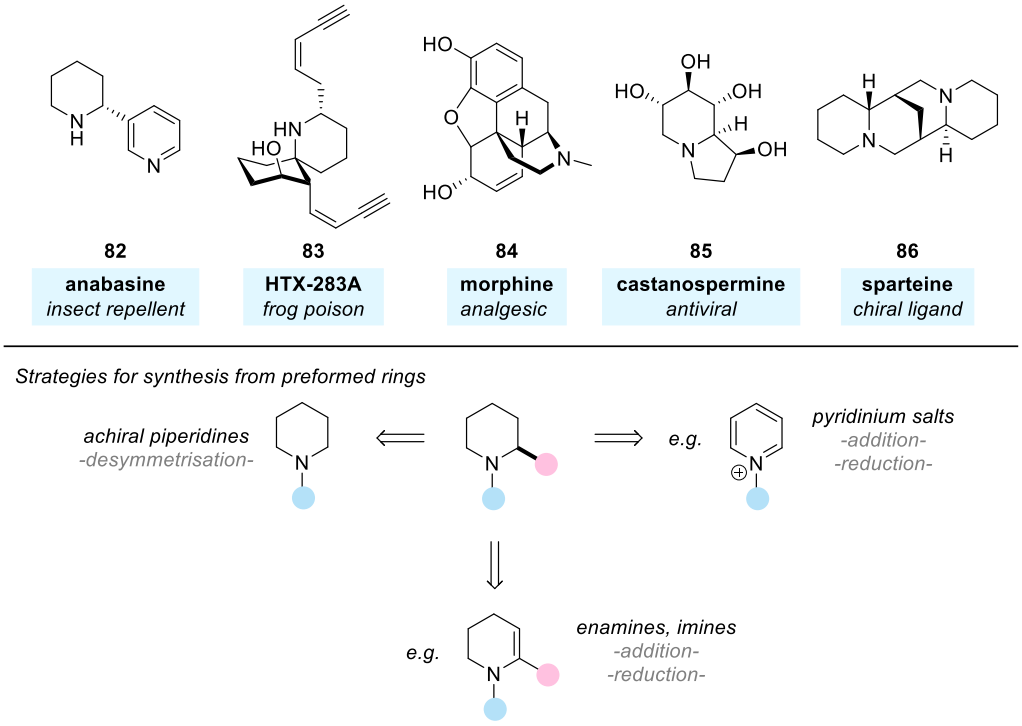



***Figure 27.*** *Stereodefined C2-substituted piperidines*

Certain chiral C2-substituted piperidines are synthesised and used as mixtures of enantiomers and/or diastereoisomers (see Figure 28). Consequently, for these kinds of compounds, stereoselective cyclisation may not be necessary. Included among these piperidines are compounds sold on very large scales, globally (**88**, **89**),[409,410] as well as life-saving medications (**87**, **89**).

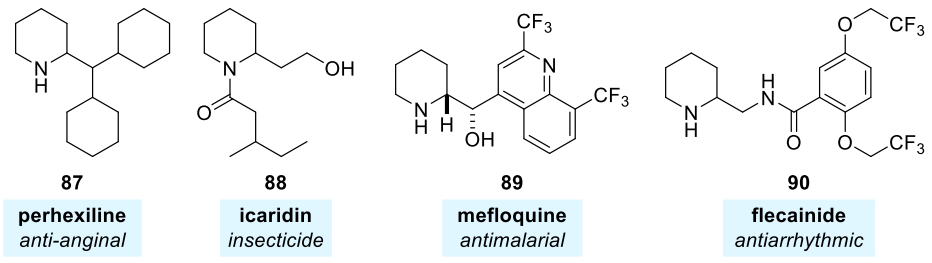



***Figure 28.*** *C2-substituted piperidines used as mixtures of stereoisomers*

The bioactivities of the compounds described above stem in no small part from the properties – physicochemical and pharmacological – of the piperidine moiety in general. Piperidines are typically basic and nucleophilic at nitrogen,[411–413] and this reactivity can be altered by *N*-substitution or substitution around the ring (see Figure 29).[414,415] The inclusion of a piperidine ring within a scaffold can improve its solubility,[355] impart stereochemical rigidity,[416] and enable the compound to 'mimic' naturally occurring ligands for certain receptors (*e.g.*, opioid receptors).[417] The development of novel methods for the preparation of piperidines, then, can be a valuable area of research for pharmaceutical applications.

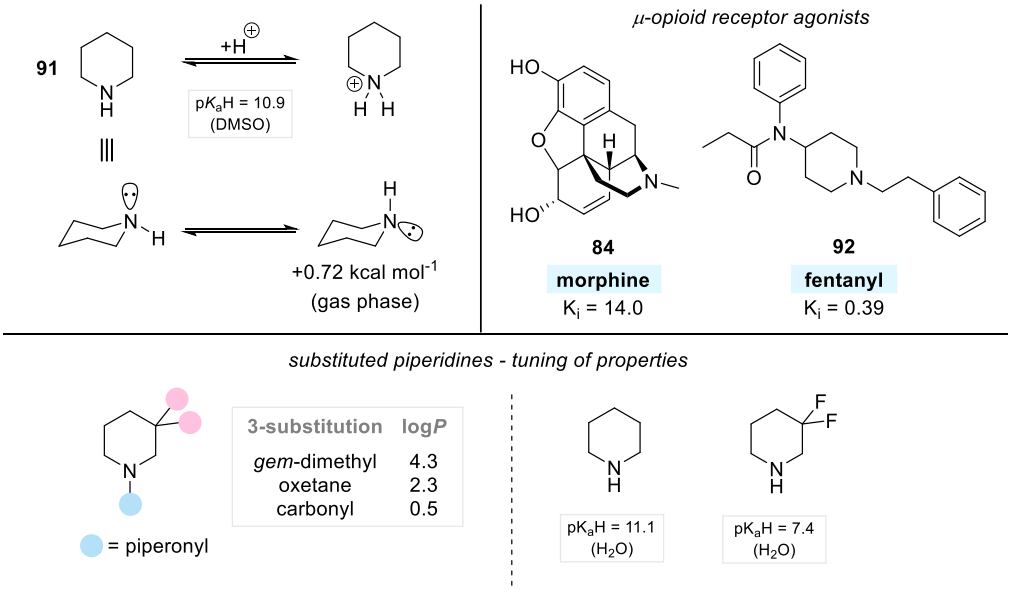



***Figure 29.*** *Piperidines: physicochemical and pharmacological properties*[414,415,418]

## 3.2: Project Aims

Building on the above discussion and the work described in Chapter 2, we hoped to prepare azides tethered to functionalities that could enable cyclisation. Once synthesised, it was our intention to employ both azide reduction/conjugate addition – as previously demonstrated – and also

azide reduction/epoxide opening in the conversion of these azides to piperidines with applications in medicine, agrochemistry, and/or organic synthesis generally. In the case of intramolecular conjugate additions, we hoped to extend previously developed chemistry to targets of interest. *Via* asymmetric, organocatalytic epoxidation strategies, we hoped to develop a 'programmable' approach to 2-hydroxyalkyl piperidines, in which the stereochemistry of the products could be set from the starting epoxides, using the aforementioned catalytic reactions.

## 3.3: Results and Discussion

### 3.3.1: Attempted synthesis of methylphenidate

Having observed that piperidine **52** could be prepared by catalytic azide reduction/intramolecular conjugate addition from precursor **44c**, an analogous retrosynthetic analysis was applied to methylphenidate (**93**) (see Figure 30). We were attracted to methylphenidate not only because of its structural similarity to compounds prepared in Chapter 2 but also because of its medical significance: methylphenidate is one of the most commonly prescribed anti-ADHD medications, worldwide.

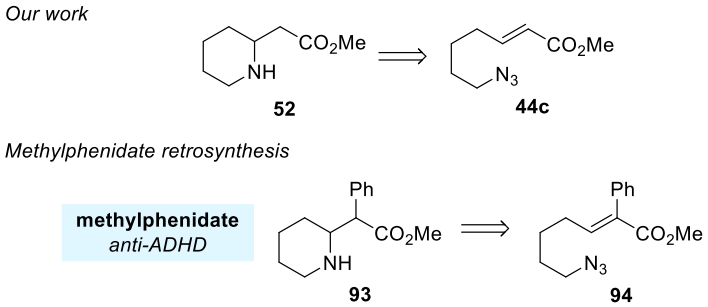
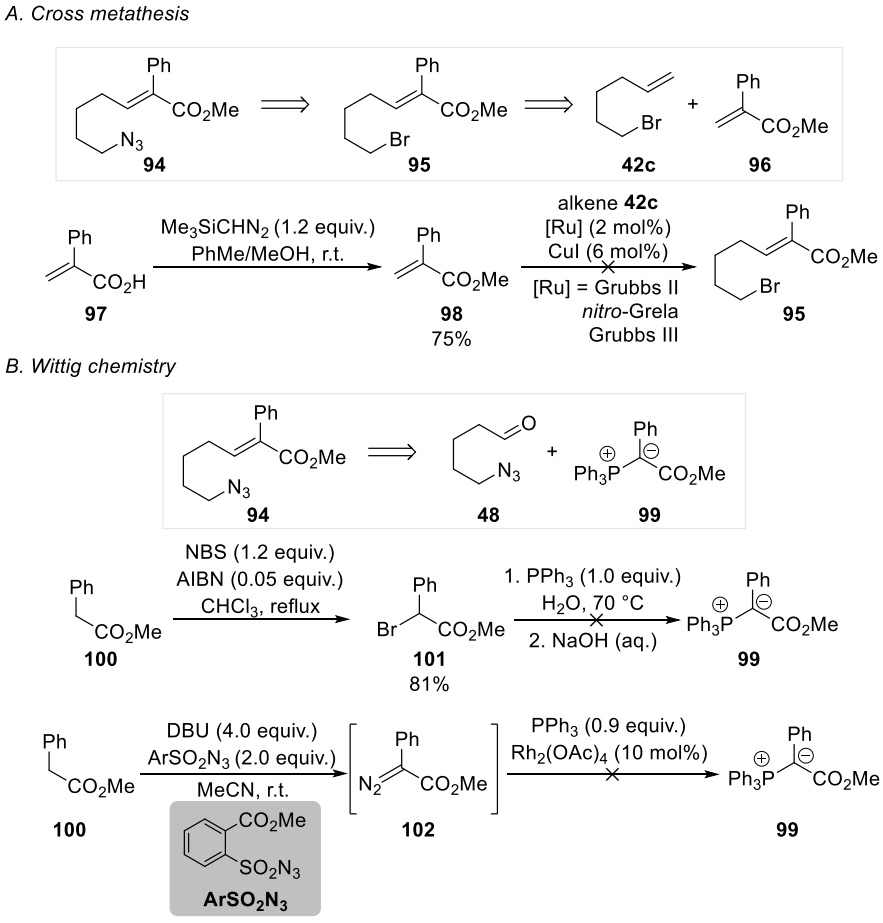


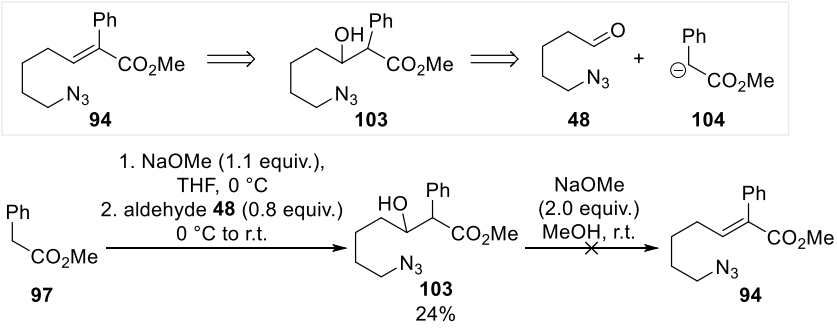

***Figure 30.*** *Retrosynthetic analysis of methylphenidate*

Initial attempts to prepare α,β-unsaturated ester **94** *via* cross metathesis were unsuccessful: acrylate **96** was unreactive towards metathesis precatalysts[419–421] (see Scheme 41). As this route seemed to be unfeasible, an alternative forward synthesis was investigated: Wittig-type olefination of aldehyde **48**. While bromide **101** could be prepared efficiently, attempts to react this bromide with triphenylphosphine resulted in near-exclusive oxidation to give triphenylphosphine oxide. Presumably, this oxidation occurred *via* attack of the phosphorus at bromine (*cf*. Corey-Fuchs[422] chemistry), due to steric hindrance at carbon, followed by hydrolysis. Preparation of **99** was also attempted by diazo transfer/Rh-catalysed ylide formation[423–425] – again, only the phosphine oxide was obtained.




***Scheme 41.*** *A. Attempted preparation of* ***94*** *by olefin metathesis. B. Attempted preparation of* ***94*** *by Wittig chemistry.*

Olefination by aldol reaction followed by elimination was next considered (see Scheme 42). Reaction of aldehyde **48** with ester enolate **104** resulted in the formation of aldol product **103** as a single diastereoisomer (stereochemistry not known), but in low yield. Treatment of β-hydroxy ester **103** with base did not trigger the desired elimination, but instead returned aldehyde **48**. In order to assess the viability of a Mukaiyama aldol reaction,[426] $TiCl_4$ was added to aldehyde **48** at 0 °C; this immediately resulted in total decomposition of the aldehyde, probably by an Aubé-Schmidt-type pathway.[202] Based on the work carried out in Chapter 2, it was anticipated that **94** – once synthesised – might be unstable, and so, having experienced considerable difficulty even accessing this precursor, methylphenidate was abandoned as a target.

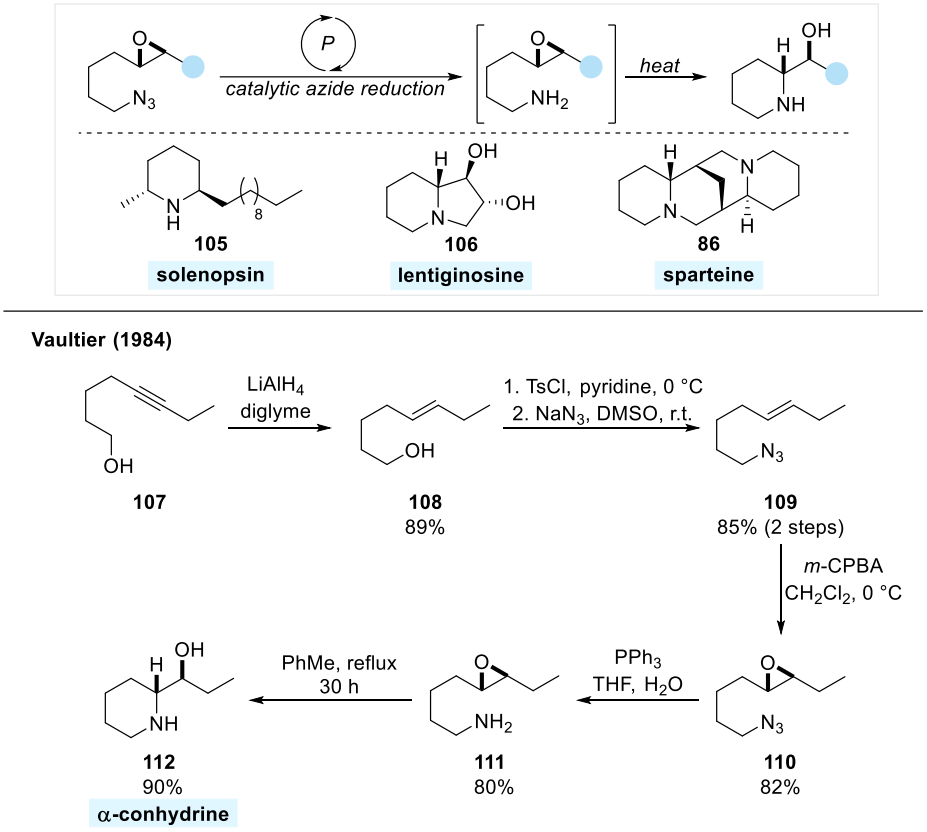



***Scheme 42.*** *Attempted synthesis of* ***94*** *by aldol chemistry*

## 3.3.2: Progress towards piperidine alkaloids

As discussed in Section 3.1, we hoped to further develop our chemistry by combining the azide reduction with intramolecular epoxide opening, as a stereospecific approach to piperidine alkaloids. The most direct precedent for this reaction we could find in the literature was a synthesis of conhydrine (**112**) by Vaultier (see Scheme 43).[427] Although the conhydrine synthesised by Vaultier was racemic, the cyclisation step was

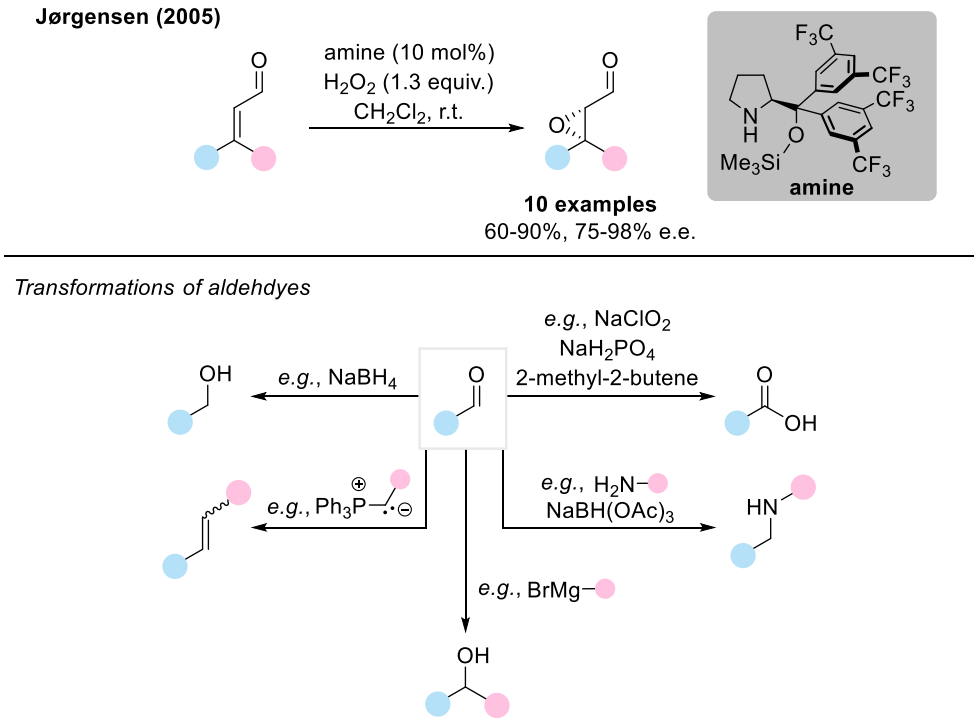
stereospecific for a single diastereoisomer (α-conhydrine). We hoped to employ asymmetric epoxidation reactions to set the absolute stereochemistry of the resulting piperidines in the same way. Using this approach, we intended to prepare enantiomerically enriched C2-substituted piperidines to be used as building blocks in the construction of natural products such as solenopsin (**105**), lentiginosine (**106**), and sparteine (**86**).




***Scheme 43.*** *Stereospecific preparation of C2-substituted piperidines*

It was envisaged that the Jørgensen epoxidation[102] (see Scheme 44) should prove useful in the preparation of cyclisation precursors: since the Jørgensen epoxidation uses 'enal' substrates, there remains in the molecule an aldehyde functional handle after installation of the epoxide group. By functional group interconversion (*e.g.*, olefination, organometallic addition, reductive amination, redox transformations, *etc.*),

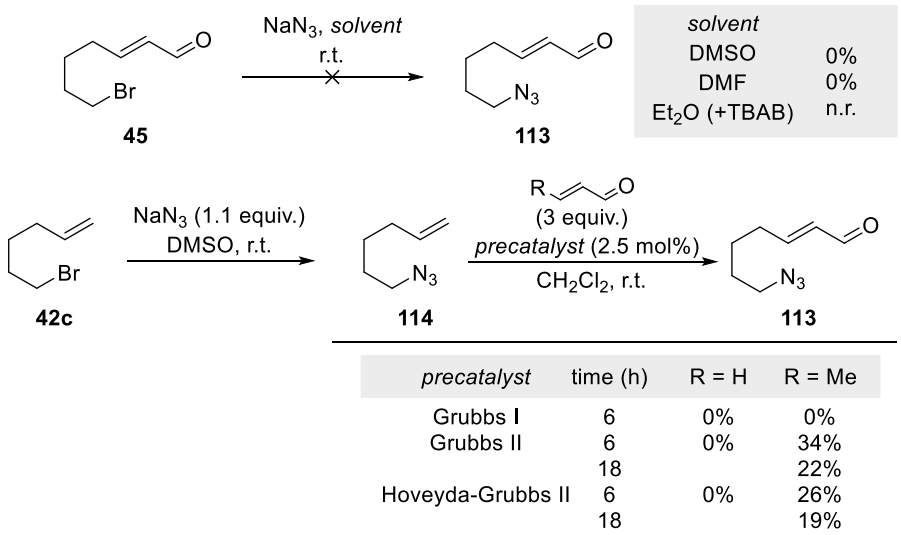
we believed that the aldehyde group would allow us to access a wide variety of functionalised epoxy azides.




***Scheme 44.*** *Jørgensen epoxidation and aldehyde transformations*

In order to investigate the use of the Jørgensen epoxidation, azidoenal substrate **113** was required (see Scheme 45). Following the preparation of similar compounds in Chapter 2, it was expected that a two-step cross metathesis/azidation procedure should furnish **113** efficiently. Unfortunately, all attempts to prepare enal **113** this way were unsuccessful: azidation of bromoenal **45** proved completely impractical due to degradation of the presumed azide in dipolar aprotic solvents. We next investigated the possibility of re-ordering the azidation and metathesis steps. This work required the preparation of azide **114** - although this compound was volatile and unstable on silica, it could be handled as a solution in pentane and purified by chromatography on alumina, with yields ≥90% even on large scales (up to 100 mmol). For the cross metathesis step, a small screen of conditions was carried out, using

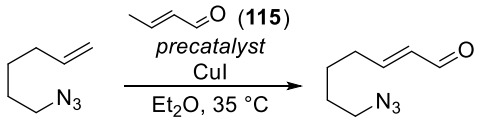
two different α,β-unsaturated aldehydes and three different metathesis precatalysts: the first- and second-generation Grubbs complexes (Grubbs I and II, respectively) and the 2nd-generation Hoveyda-Grubbs complex (Hoveyda-Grubbs II).[419,428,429] Observing from the initial results that only two combinations of precatalyst and α,β-unsaturated aldehyde gave the desired product, it was decided that these reactions should be repeated over a longer time – 18 h instead of 6 h. The longer reaction times resulted in lower yields of **113** in both cases, probably due to [3+2] cycloaddition of the product.




***Scheme 45.*** *Preparation of azidoenal* ***113***

Since the best result from all metathesis tests up this point was still a rather low yield – 34%, with recovery of large amounts of unreacted **114** – new conditions were sought. It was decided to investigate the rate enhancement effects of copper(I) iodide, as reported by Lipshutz,[430] in the hope that an increased rate would help to increase yield by out-competing catalyst deactivation. Under these conditions, enhanced yields were indeed observed: **113** was synthesised in up to 61%, with no recovery of **114**.

Although other fast-initiating metathesis precatalysts[420,421] were also tested, none gave better yields (see Table 3).

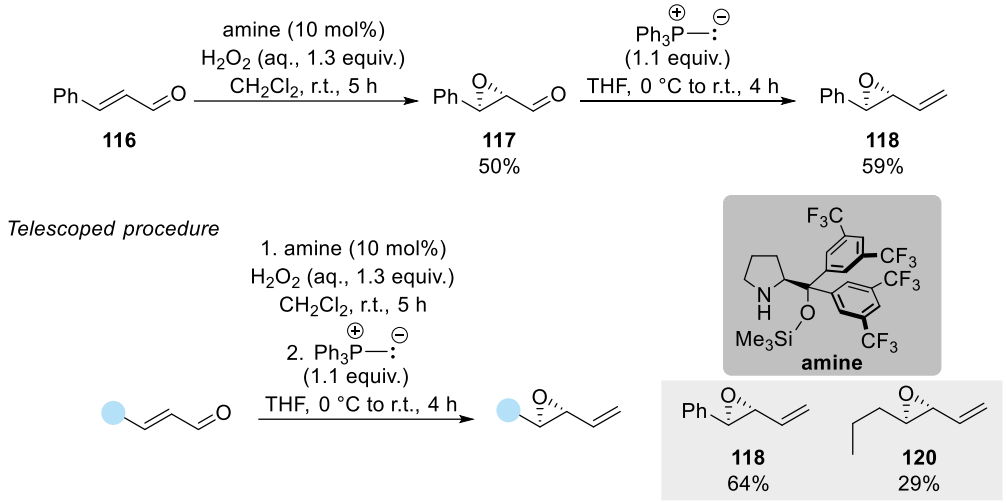



**114** **113**

| *precatalyst* | [*precatalyst*] (mol%) | [CuI] (mol%) | [**115**] (equiv.) | time (h) | yield (%) |
|---|---|---|---|---|---|
| Grubbs II | 2 | 6 | 3 | 4 | 61 |
| | 5 | 6 | 3 | 4 | 33 |
| | 2 | 0 | 3 | 4 | 32 |
| | 2 | 100 | 3 | 4 | 41 |
| | 2 | 6 | 5 | 4 | 29 |
| | 2 | 6 | 3 | 6 | 30 |
| *nitro*-Grela | 2 | 6 | 3 | 4 | 27 |
| | 2 | 0 | 3 | 4 | 30 |
| Grubbs III | 2 | 6 | 3 | 4 | 28 |
| | 2 | 0 | 3 | 4 | 43 |

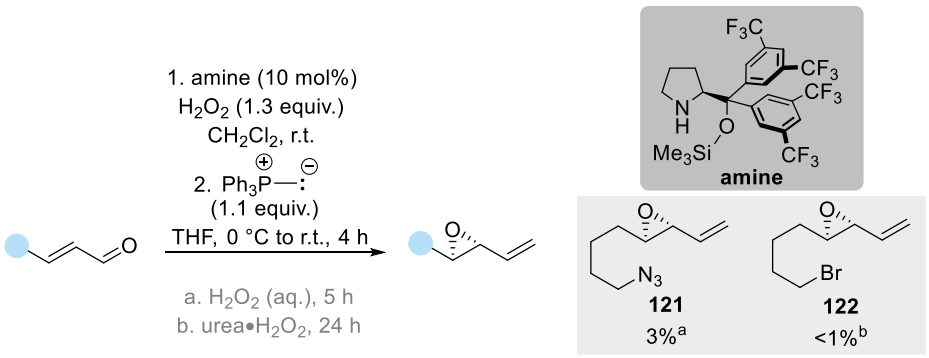
***Table 3.*** *Optimisation of cross metathesis*

With azidoenal **113** in hand, an epoxidation/aldehyde functionalisation procedure was required. For the functionalisation step, Wittig olefination was chosen – it was expected that carbon-carbon bond formation would be useful for target syntheses. A two-step epoxidation/Wittig methylenation sequence was established using cinnamaldehyde (**116**) as a test substrate: first, the steps were carried out separately, and then a telescoped procedure was implemented, delivering epoxy alkene **118** in good yield (see Scheme 46). The Jørgensen catalyst[431] (shown) proved to be key to this reactivity – substitution of the bis(bistrifluoromethyl)phenyl catalyst with the Hayashi-Jørgensen diphenyl catalyst[432] resulted in very low levels of conversion in the epoxidation step. The procedure was then validated using a model substrate that more closely resembled **113** – hex-2-enal (**119**), for which the sequence also delivered the desired product, albeit in moderate yield.



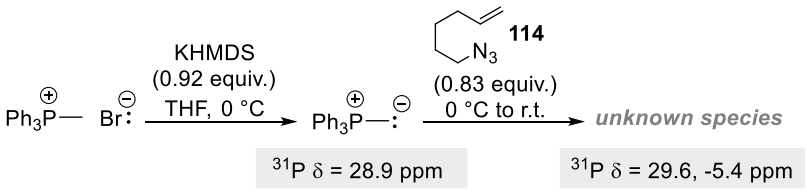

***Scheme 46.*** *Development of a telescoped epoxidation/methylenation procedure*

Having established a procedure for the epoxidation/methylenation of enals using test substrates, the procedure was then applied to enal **113**, with limited success (see Scheme 47). As the yield of **121** was only 3%, the use of bromide **45** was instead considered. While it had been observed that azidoenal **113** underwent high levels of conversion in the epoxidation step within 5 hours, bromide **45** reacted more sluggishly under the same conditions. With a longer reaction time and a different source of $H_2O_2$, >90% conversion was achieved for the epoxidation of **45**, and so a modified epoxidation/methylenation procedure was used for this substrate. Unfortunately, only trace amounts of the corresponding epoxy alkene were observed – it seems likely that the conditions of the Wittig step are too basic to tolerate the bromide group.




***Scheme 47.*** *Epoxidation/Wittig methylenation attempts*

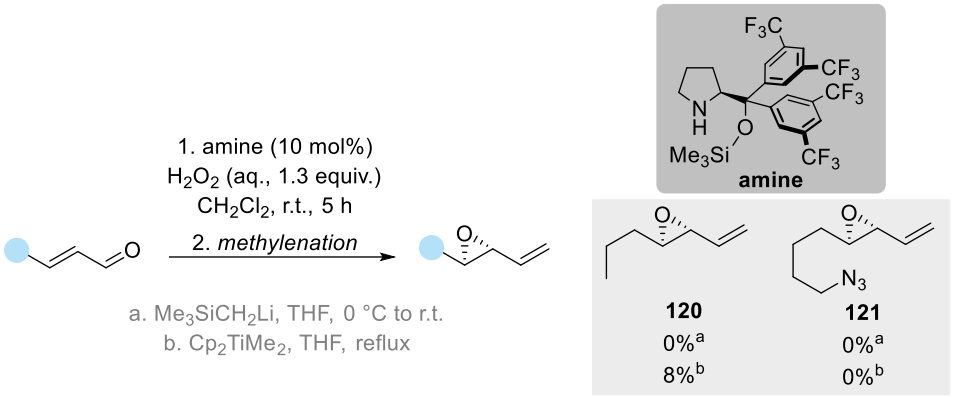
In order to investigate the poor yield of **121** from **113**, azide **114** was subjected to identical Wittig methylenation conditions. *A priori*, there is no obvious reaction that should occur between these two compounds. However, $^{31}P$ and $^{1}H$ NMR spectroscopic monitoring revealed unexpected changes. Within 20 minutes of the azide addition, two new peaks appeared in the $^{31}P$ NMR spectrum, one of which appears to be a phosphorus(III) species (δ = -5.4 ppm); this peak then disappeared over the course of the reaction (4 h). The triplet corresponding to the $CH_2$ attached to the azide (δ = 3.27 ppm) also disappeared from the $^{1}H$ NMR spectrum over the course of the reaction. If a phosphorus(III) species (*e.g.*, a phosphine) is present in the reaction mixture, then it could plausibly react with azide **114** to form an iminophosphorane, which may be visible in the $^{31}P$ NMR spectrum. While an unidentified peak was observed (δ = 29.6 ppm), this more closely resembles a phosphine oxide.




***Scheme 48.*** *Possible reactivity between azides and phosphonium ylides*

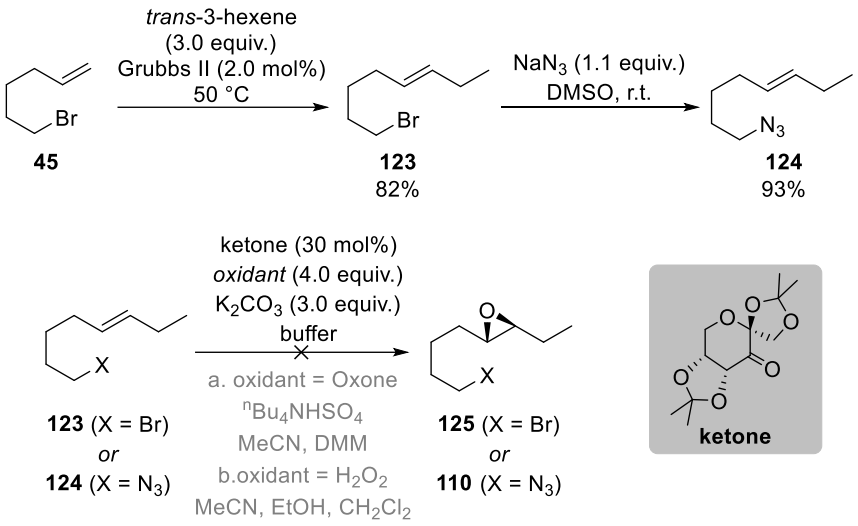
Since Wittig methylenation led to poor results, other methylenation conditions were investigated. Hex-2-enal was subjected to telescoped epoxidation/methylenation procedures using Peterson[433,434] and Petasis[435] methylenation conditions, respectively. While the Petasis reagent did give a small amount (8%) of the desired product for the test substrate, neither of these sets of conditions were successful when applied to substrate **113**.

Following the failure of the alternative methylenation conditions, the epoxidation/methylenation route was abandoned.



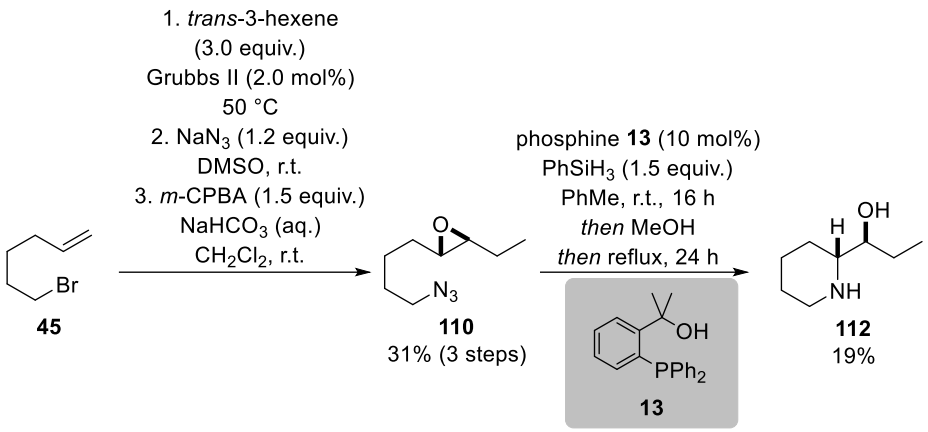

***Scheme 49.*** *Peterson and Petasis methylenation tests*

As we had experienced difficulties working with epoxy aldehyde intermediates, we looked for an alternative method for asymmetric epoxidation. The Shi epoxidation[100,101] seemed to be the most directly applicable to the synthesis of alkaloids: conhydrine (**112**) was selected as a target for this work. Effectively, we hoped to develop an asymmetric route based on the Vaultier synthesis, in which the azide reduction could be carried out catalytically and telescoped with the cyclisation step. Accordingly, alkenes **123** and **124** were prepared, and subjected to the Shi epoxidation (see Scheme 50). Unfortunately, no reaction was observed for these alkenes under the classical Shi epoxidation conditions[100] or more solubilising conditions.[436]




***Scheme 50.*** *Preparation of alkenes and attempted Shi epoxidations*

Although attempts to prepare enantiomerically enriched **110** were unsuccessful, we were still keen to attempt a synthesis of racemic α-conhydrine. Racemic epoxy azide substrate **110** was prepared by a telescoped metathesis-azidation-epoxidation procedure (using *m*-CPBA), and then subjected to the catalytic azide reduction (see Scheme 51). After quenching with methanol, the reaction mixture was heated to reflux overnight. We were pleased to observe that these conditions delivered α-conhydrine, albeit with low yield. As in previous cases, most of the remainder of epoxy azide **110** was left unreacted after the two steps. In spite of the poor yield, however, this synthesis demonstrates a more time- and pot-economical approach to the preparation of conhydrine than previous work: the shortest published syntheses[427,437,438] are each 5 or 6 steps (LLS) with no telescoping, whereas our route is a 4-step, 2-pot process. We hope that future research will enable us to optimise this route and deploy this general strategy in the synthesis of other alkaloid targets.




***Scheme 51.*** *A concise synthesis of α-conhydrine*

## 3.4: Conclusions

In this project, we have investigated several approaches to the synthesis of C2-substituted piperidines. Syntheses of methylphenidate were attempted *via* cross metathesis, Wittig, and aldol chemistry. Organocatalytic methods were examined for the preparation of piperidine building blocks. While these methods displayed little success, the methods deployed in this work enabled a highly telescoped synthesis of α-conhydrine. Through this project, the first example of a telescoped, catalytic azide reduction/intramolecular epoxide opening has been demonstrated. We hope to develop this work in the future by optimising cyclisation conditions, applying the method to other targets of interest, and investigating other phosphine catalysts for this purpose.

# 4: Experimental

## 4.1: General experimental details

Unless otherwise indicated, reagents and technical grade solvents were purchased from commercial suppliers and used without further purification. All water was deionised before use. "Brine" refers to a saturated aqueous solution of sodium chloride. "Petroleum ether" refers to the fraction of petroleum with boiling points in the range of 40-60 °C. All reactions were carried out in conventional glassware. All reactions were carried out in a nitrogen-enriched atmosphere, unless otherwise specified. Reactions under argon were carried out either under Schlenk conditions or in an argon-enriched atmosphere, which was generated by purging the flask with an argon filled rubber balloon. Reactions carried out under microwave conditions were performed using a Biotage® Initiator microwave. Analytical thin layer chromatography (TLC) was performed on silica plates and visualised under UV light or by staining with a solution of potassium permanganate. Column chromatography was carried out using Fluorochem silica gel 60A (40-63 mesh) or Acros activated neutral alumina (50-200 microns). Fourier-transform infrared spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption ($cm^{-1}$). High resolution mass spectra (HRMS) were measured on a Bruker microTOF II with electrospray ionisation (ESI). HRMS data are quoted to four decimal places (0.1 mDa). All NMR spectra were recorded on Bruker AV 400 and AV 500 spectrometers, and internally referenced to residual solvent signals ($CDCl_3$ δ 7.26 ($^1H$) and 77.16 ($^{13}C$); DMSO-$d_6$ δ

2.50 ($^{1}$H) and 39.52 ($^{13}$C)). All NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz). The $^{1}$H NMR spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons, proton position). Where appropriate, two-dimensional NMR spectroscopic experiments (COSY, HSQC, HMBC, and NOESY) were performed to aid assignment.

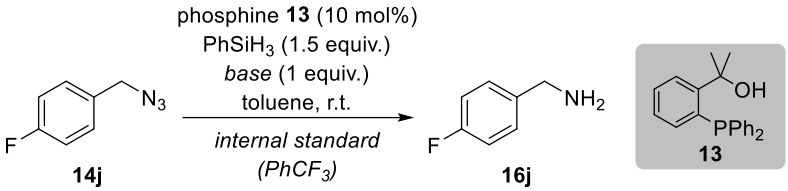
### 4.1.1: Azide safety note

As discussed in Section 1.1, both inorganic azides and organic azides can be explosive, and inorganic azides display acute toxicity. Personal protective equipment (PPE) and careful handling remain essential while carrying out work with azides. To avoid the formation of other azide salts, sodium azide should be weighed out with non-metallic implements (*e.g.*, glass pipettes or plastic spatulae). If <500 mg of sodium azide is spilled outside of a ventilated enclosure, add solid sodium hydrogen carbonate liberally, and then dispose of the mixture as toxic solid waste. If >500 mg of sodium azide is spilled outside of a ventilated enclosure, evacuate the laboratory and contact the relevant authorities.[vi] Reaction mixtures containing inorganic azides and/or low molecular weight organic azides should be placed behind a blast shield. If low molecular-weight azides are isolated, it is advised that they are first synthesised on a small scale (<1 mmol), and always handled as a solution. Azide-containing aqueous waste solutions should be quenched with sodium nitrite (1.6 equiv., relative to azide) followed by sulfuric acid (2M, aq.).[439]

[vi] Safety Manual, School of Chemistry, University of Nottingham

## 4.2: Experimental procedures and compound data

Rate effects of hindered base additives – $^{19}$F NMR study

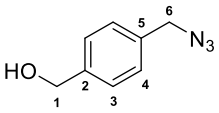



To a stirred solution of azide **14j**[vii] (76 mg, 0.50 mmol), phenylsilane (81 mg, 0.75 mmol), trifluorotoluene (71 µL, 0.50 mmol), and the relevant base (0.50 mmol) in toluene (0.50 mL) was added phosphine **13** (16 mg, 0.05 mmol). The resulting reaction mixture was stirred at room temperature and aliquots were taken hourly for analysis by $^{19}$F NMR spectroscopy (delay time set as 25 s, NMR yields referenced to internal standard).[viii]

**$^{19}$F NMR** (376 MHz, Chloroform-*d*): azide **14j** δ = -113.6; amine **16j** δ = -116.5.

Preparation of azide substrates

(4-(Azidomethyl)phenyl)methanol (**24a**)




To a stirred suspension of sodium azide (1.43 g, 22.0 mmol) in DMSO (40.0 mL) at room temperature was added (4-(chloromethyl)phenyl)methanol (3.13 g, 20.0 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (40.0 mL) was added. The reaction mixture was then extracted with diethyl ether (100 mL × 3). The combined organic extracts were washed with water (2 × 50.0 mL) and brine (50.0 mL). The aqueous extracts were re-extracted

[vii] Azide **14j** and phosphine **13**, as well as data for compounds **14j** and **16j**, were generously provided by Dr. Emma Stoll – manuscript in preparation.
[viii] NMR experiment designed by Dr. Emma Stoll and Dr. Kevin Butler (School of Chemistry, University of Nottingham).

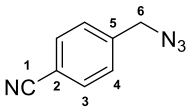
with diethyl ether (50.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and then the crude benzyl azide was purified by flash column chromatography ($SiO_2$, 40% diethyl ether/pentane, $R_f$ = 0.1) to give **24a** as a pale yellow oil (2.39 g, 14.6 mmol, 73%). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[259]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 8.0 Hz, 2H, $H^3$), 7.31 (d, *J* = 8.0 Hz, 2H, $H^4$), 4.69 (s, 2H, $H^1$), 4.33 (s, 2H, $H^6$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 141.1 (C), 134.7 (C), 128.5 (CH), 127.4 (CH), 64.9 ($CH_2$), 54.5 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3340 (br., O-H), 3027, 2930, 2875, 2090 (N=N=N), 1514, 1449, 1420, 1343, 1247, 1209, 1112, 1040. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_9N_3O$ $[M+Na]^+$= 465.0662, found 465.0659; $[M+NH_4]^+$ = 460.1108, found 460.1105.

General procedure A: benzyl azide preparation

To a stirred suspension of sodium azide (358 mg, 5.50 mmol) in DMSO (10.0 mL) at room temperature was added the appropriate benzyl bromide (5.00 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (10.0 mL) was added. The reaction mixture was then extracted with diethyl ether (25.0 mL × 3). The combined organic extracts were washed with water (2 × 10.0 mL) and brine (10.0 mL), and then dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and then the crude benzyl azide was purified by flash column chromatography.

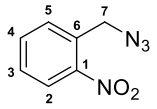
4-(Azidomethyl)benzonitrile (**24b**)




General procedure A was followed with 4-(bromomethyl)benzonitrile. Purification by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, $R_f$ = 0.3) gave **24b** as a pale yellow oil (750 mg, 4.75 mmol, 95%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR; IR.[440]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 8.3 Hz, 2H, $H^3$), 7.44 (d, *J* = 8.3 Hz, 2H, $H^4$), 4.45 (s, 2H, $H^6$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 140.8 (C), 132.7 (CH), 128.5 (CH), 118.4 (C), 112.2 (C), 54.1 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2229 (C≡N), 2093 (N=N=N), 1610, 1506, 1439, 1414, 1346, 1252, 1115, 1021, 847, 814, 751, 696, 659, 549, 493, 418. *HRMS failed to find the correct mass for this compound*.

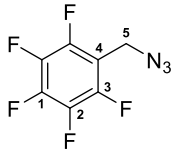
1-(Azidomethyl)-2-nitrobenzene (**24c**)




General procedure A was followed with 2-nitrobenzyl bromide. Purification by flash column chromatography ($SiO_2$, 5-10% diethyl ether/pentane, $R_f$ = 0.5 in 10% diethyl ether/pentane) gave **24c** as a yellow oil (818 mg, 4.60 mmol, 92%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[441]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 8.11 (dd, *J* = 8.1, 1.2 Hz, 1H, $H^2$), 7.70-7.65 (m, 2H, $H^4$,$H^5$), 7.54-7.49 (m, 1H, $H^3$), 4.84 (s, 2H, $H^7$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 147.7 (C), 134.0 (CH), 131.6 (C), 130.1 (CH), 129.0 (CH), 125.3 (CH), 52.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2098 (N=N=N), 1611, 1521 (O–N=O), 1445, 1345 (O–N=O), 1291, 1113, 919, 857, 787, 727, 552, 471. *HRMS failed to find the correct mass for this compound*.

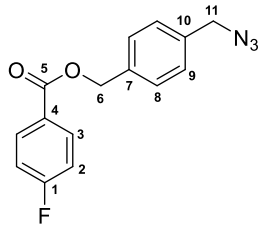
1-(Azidomethyl)-2,3,4,5,6-pentafluorobenzene (**24d**)



General procedure A was followed with pentafluorobenzyl bromide. Purification by flash column chromatography ($SiO_2$, 5% diethyl ether/pentane, $R_f$ = 0.2) gave **24d** as a yellow oil (891 mg, 4.00 mmol, 80%). Characterisation data were consistent with previous literature: $^1$H NMR.[442]

**$^1$H NMR** (400 MHz, Chloroform-*d*) 4.46 (s, 2H, $H^5$). **$^{13}$C{$^{19}$F} NMR** (126 MHz, Chloroform-*d*) δ 145.4 (C, t, *J* = 4.7 Hz), 141.6 (C, s), 137.6 (C, s), 109.3 (C, t, *J* = 4.5 Hz), 41.6 ($CH_2$, t, *J* = 147.6 Hz). **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -142.3 – -142.5 (m, $F^2$ or $F^3$), -152.3 (tt, *J* = 21.0 Hz, 2.3 Hz, $F^1$), -160.7 – -160.9 (m, $F^2$ or $F^3$). **FTIR** (neat) $\nu_{max}$ 2102 (N=N=N), 1656, 1502, 1457, 1428, 1350, 1308, 1291, 1247, 1124, 1034. *HRMS failed to find the correct mass for this compound*.

4-(Azidomethyl)benzyl 4-fluorobenzoate (**24e**)

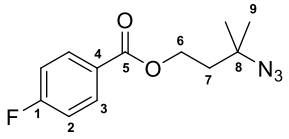


To a stirred suspension of 4-fluorobenzoic acid (154 mg, 1.10 mmol), dicyclohexylcarbodiimide (272 mg, 1.30 mmol), and *N*,*N*-dimethyl-4-aminopyridine (12 mg, 0.10 mmol) in dichloromethane (2.00 mL) under argon, at room temperature, was added azide **24a** (163 mg, 1.00 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 days, after which the precipitate was removed by filtration. The filtrate was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 30% diethyl

ether/pentane, $R_f$ = 0.6) to give **24e** as a colourless oil (280 mg, 0.97 mmol, 97%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.13 – 8.03 (m, 2H, $H^3$), 7.46 (d, *J* = 8.2 Hz, 2H, $H^8$), 7.35 (d, *J* = 8.2 Hz, 2H, $H^9$), 7.16 – 7.06 (m, 2H, $H^2$), 5.36 (s, 2H, $H^6$), 4.36 (s, 2H, $H^{11}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 165.9 (C, d, *J* = 254.1 Hz), 165.4 (C), 136.1 (C), 135.6 (C), 132.3 (CH, d, *J* = 9.4 Hz), 128.7 (CH), 128.5 (CH), 126.3 (C), 115.6 (CH, d, *J* = 22.0 Hz), 66.4 ($CH_2$), 54.5 ($CH_2$). **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -105.4. **FTIR** (neat) $\nu_{max}$ 2952, 2094 (N=N=N), 1715 (C=O), 1602, 1507, 1449, 1412, 1375, 1346, 1263, 1237, 1153, 1104, 1088, 1014, 961, 853, 801, 765, 687, 607, 569, 502, 472. **HRMS** (ESI-TOF) *m/z* calculated for $C_{15}H_{12}N_3O_2F$ $[M+Na]^+$ = 308.0806, found 308.0802; $[M+NH_4]^+$ = 303.1252, found 303.1254.

3-Azido-3-methylbutyl 4-fluorobenzoate (**24f**)



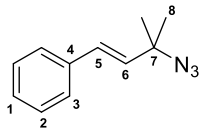

Synthesised by an adapted literature procedure.[156]

To a mixture of freshly prepared methyl 2-(azidosulfonyl)benzoate[443] (362 mg, 1.50 mmol), sodium hydrogen carbonate (84 mg, 1.00 mmol), and potassium persulfate (810 mg, 3.00 mmol) was added acetonitrile/water (4.00 mL, 3:2), followed by 3-methylbutyl 4-fluorobenzoate[156] (105 mg, 1.00 mmol). The reaction mixture was stirred under nitrogen at 85 °C for 4 hours, and then cooled to room temperature. The reaction mixture was diluted with ethyl acetate (5.00 mL) and water (5.00 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (10.0 mL × 3), and the combined organic extracts were then washed with water (10.0 mL) and brine (20.0 mL), and dried with magnesium sulfate. The crude product was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 2-7.5% diethyl

ether/pentane, $R_f$ = 0.3 in 10% diethyl ether/pentane) to give **24f** as a yellow oil (114 mg, 0.45 mmol, 45%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$, $^{19}F$ NMR; IR.[156]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 8.09 – 8.00 (m, 2H, $H^3$), 7.11 (t, *J* = 8.7 Hz, 2H, $H^2$), 4.43 (t, *J* = 6.8 Hz, 2H, $H^6$), 1.97 (t, *J* = 6.8 Hz, 2H, $H^7$), 1.37 (s, 6H, $H^9$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 165.8 (d, *J* = 254.1 Hz, C), 165.5 (C), 132.1 (d, *J* = 9.3 Hz, CH), 126.4 (C, d, *J* = 3.0 Hz), 115.6 (d, *J* = 22.0 Hz, CH), 61.4 ($CH_2$), 60.2 (C), 39.7 ($CH_2$), 26.4 ($CH_3$). **$^{19}$F{$^{1}$H} NMR** (376 MHz, Chloroform-*d*) δ -105.6. **FTIR** (neat) $\nu_{max}$ 2974, 2097 (N=N=N), 1717 (C=O), 1603, 1508, 1462, 1411, 1390, 1372, 1316, 1269, 1235, 1152, 1110, 1090, 1047, 1027, 1015, 968, 854, 823, 804, 766, 714, 688, 633, 609, 565, 504, 457. **HRMS** (ESI-TOF) *m/z* calculated for $C_{12}H_{14}N_3O_2F$ $[M+Na]^+$ = 274.0962, found 274.0966; $[M+NH_4]^+$ = 269.1408, found 269.1409.

(*E*)-(3-Azido-3-methylbut-1-en-1-yl)benzene (**24g**)



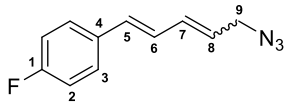

Synthesised by an adapted literature procedure.[80]

To a stirred solution of methylmagnesium bromide (1.60 mL of a 3 M solution in diethyl ether, 4.80 mmol) in anhydrous THF (2.00 mL) at 0 °C was added *trans*-4-phenylbuten-2-one (585 mg, 4.00 mmol) as a solution in THF (2.00 mL). Further THF (2.00 mL) was added. Upon completion of the addition, a grey precipitate formed rapidly from the yellow solution. The reaction mixture was left to stir for 2 minutes at 0 °C and then warmed to room temperature. After 15 minutes, the reaction mixture was cooled to 0 °C and diphenylphosphoryl azide (1.12 mL, 5.20 mmol) was added dropwise over 2 minutes, then allowed to stir for a further 8 minutes. The reaction mixture was then heated to 45 °C for 16 hours. After cooling to room temperature, water (10.0 mL) and dichloromethane

(5 mL) were added, and the reaction mixture was stirred for 5 minutes. The reaction mixture was extracted with dichloromethane (3 × 20.0 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 10% ethyl acetate/pentane, $R_f$ = 0.1) to give **24g** as a colourless oil (103 mg, 0.56 mmol, 14%). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[80]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.38 (m, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 1H), 6.59 (d, *J* = 16.1 Hz, 1H), 6.23 (d, *J* = 16.1 Hz, 1H), 1.46 (s, 6H). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 136.3 (C), 132.7 (CH), 129.0 (CH), 128.7 (CH), 127.9 (CH), 126.6 (CH), 62.0 (C), 26.7 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3028, 2976, 2932, 2867, 2472, 2094 (N=N=N), 1802, 1650, 1600, 1579, 1493, 1448, 1384, 1367, 1303, 1242, 1203, 1177, 1130, 1073, 1029, 967, 913, 861, 841, 781, 746, 692, 638, 595, 565, 520, 493, 472, 438.

1-((1*E*,3*E*)-5-Azidopenta-1,3-dien-1-yl)-4-fluorobenzene + 1-((1*E*,3*Z*)-5-azidopenta-1,3-dien-1-yl)-4-fluorobenzene (**24h**)




Synthesised by an adapted literature procedure.[80]

To a stirred solution of vinylmagnesium bromide (5.30 mL of a 0.9 M solution in THF, 4.80 mmol) in anhydrous THF (2.00 mL) at 0 °C was added 4-fluorocinnamaldehyde (601 mg, 4.00 mmol) as a solution in THF (2.00 mL). Further THF (2.00 mL) was added. The reaction mixture was left to stir for 2 minutes at 0 °C and then warmed to room temperature. After 15 minutes, the reaction mixture was cooled to 0 °C and diphenylphosphoryl azide (1.12 mL, 5.20 mmol) was added dropwise over 2 minutes, then allowed to stir for a further 8 minutes. The reaction mixture was then heated to 45 °C for 16 hours. After cooling

to room temperature, water (10.0 mL) and dichloromethane (5.00 mL) were added, and the reaction mixture was stirred for 5 minutes. The reaction mixture was extracted with dichloromethane (3 × 20.0 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 0-5% diethyl ether/pentane, $R_f$ = 0.3 in 5% diethyl ether/pentane) to give a colourless oil containing an inseparable mixture of and (1*E*,3*E*)- and (1*E*,3*Z*)-**24h** (613 mg, 3.02 mmol, 75%, (1*E*,3*E*):(1*E*,3*Z*) = 8.5:1).

1*E*,3*E*-**24h**:

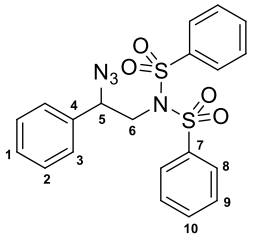
**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.41 – 7.34 (m, 2H, $H^3$), 7.06 – 6.95 (m, 2H, $H^2$), 6.70 (dd, *J* = 15.7, 10.3 Hz, 1H, $H^6$), 6.56 (d, *J* = 15.7 Hz, 1H, $H^5$), 6.43 (ddt, *J* = 15.1, 10.3, 1.4 Hz, 1H, $H^7$), 5.83 (dt, *J* = 15.1, 6.7 Hz, 1H, $H^8$), 3.87 (dd, *J* = 6.7, 1.4 Hz, 2H, $H^9$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 162.5 (d, *J* = 247.7 Hz, C), 134.7 (CH), 132.7 (CH), 128.0 (d, *J* = 8.0 Hz, CH), 127.2 (CH), 127.2 (CH), 126.1 (CH), 115.7 (d, *J* = 21.7 Hz, CH), 52.8 ($CH_2$). **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -113.6.

1*E*,3*Z*-**24h**:

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.42 – 7.38 (presumed m, 2H, $H^3$), 7.06 – 6.95 (presumed m, 2H, $H^2$), 6.92 (dd, *J* = 15.4, 11.2 Hz, 1H, $H^6$), 6.62 (d, *J* = 15.4 Hz, 1H, $H^5$), 6.43 (presumed dt, 1H, $H^7$), 5.60 (dt, *J* = 10.9, 7.5 Hz, 1H, $H^8$), 4.04 (d, *J* = 7.5 Hz, 1H, $H^9$). *$^{13}$C{$^1$H} NMR signals indistinguishable from baseline.* **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -113.2.

**FTIR** (neat) $\nu_{max}$ 3035, 2927, 2870, 2092 (N=N=N), 1887, 1644, 1599, 1506, 1442, 1415, 1351, 1299, 1224, 1157, 1116, 1095, 1012, 985, 864, 827, 797, 775, 708, 664, 572, 557, 516, 432. *HRMS failed to find the correct mass for this compound*.

*N*-(2-Azido-2-phenylethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**24i**)

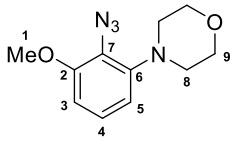


Synthesised by an adapted literature procedure.[322]

To a mixture of $Rh_2(esp)_2$ (15 mg, 0.02 mmol) and *N*-fluorobenzenesulfonimide (946 mg, 3.00 mmol) under argon, was added 1,2-dichloroethane (10.0 mL), which resulted in the formation of a deep red solution. To the reaction mixture was added styrene (208 mg, 2.00 mmol), at which point the reaction mixture became dark green. To the reaction mixture was added azidotrimethysilane (0.40 mL, 3.00 mmol), which resulted in the formation of a blue-green solution. The reaction mixture was then stirred at room temperature under argon for 2 hours. To the resulting brown solution was added water (10.0 mL), and the reaction mixture was extracted with dichloromethane (3 × 10.0 mL). The combined organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography, ($SiO_2$, 5-10% ethyl acetate/pentane, $R_f$ = 0.2 in 10% ethyl acetate/pentane) to give **24i** as a colourless oil (480 mg, 1.08 mmol, 54%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[322]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.10 – 8.00 (m, 4H, $H^8$), 7.70 – 7.61 (m, 2H, $H^{10}$), 7.55 (dd, *J* = 8.6, 7.1 Hz, 4H, $H^9$), 7.43 – 7.33 (m, 5H, $H^1$, $H^2$, $H^3$), 5.01 (dd, *J* = 9.6, 4.2 Hz, 1H, $H^5$), 4.06 (dd, *J* = 15.6, 9.6 Hz, 1H, $H^{6a}$), 3.72 (dd, *J* = 15.6, 4.2 Hz, 1H, $H^{6b}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) 139.3 (C), 136.5 (C), 134.1 (CH), 129.2 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.3 (CH), 65.6 (CH), 53.2 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2984, 2256, 2106 (N=N=N), 1731, 1586, 1479, 1449, 1375, 1316, 1245, 1168, 1085, 1046, 1000, 906, 825, 781, 726, 702, 685, 649, 613, 581, 549, 460.

4-(2-Azido-3-methoxyphenyl)morpholine (**24j**)



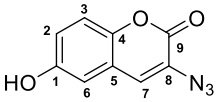

Synthesised by an adapted literature procedure.[325]

To a mixture of palladium(II) acetate (28 mg, 0.125 mmol), tris(4-methoxyphenyl)phosphine (93 mg, 0.263 mmol), and caesium carbonate (2.21 g, 6.25 mmol) was added degassed toluene (25.0 mL), and the reaction mixture was stirred at room temperature for 15 minutes. To the reaction mixture was added a solution of 2-iodoanisole (0.325 mL, 2.50 mmol), freshly prepared morpholino benzoate[444] (518 mg, 2.63 mmol), norbornene (235 mg, 2.50 mmol), and bis(pinacolato)diboron (637 mg, 2.50 mmol) in degassed toluene (25.0 mL), after which the reaction mixture was heated at 100 °C for 16 hours. The reaction mixture was allowed to cool to room temperature, filtered through Celite, and concentrated under reduced pressure to give a dark brown residue. The residue was dissolved in methanol (30.0 mL), and to the reaction mixture was added copper(II) acetate (45 mg, 0.25 mmol) and sodium azide (244 mg, 3.75 mmol). The reaction mixture was heated to 50 °C for 24 hours, and then allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.4) to give **24j** as a dark brown oil (104 mg, 0.44 mmol, 18%).

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.05 (dd, *J* = 8.2, 8.1 Hz, 1H, $H^4$), 6.64 – 6.63 (m, 1H, $H^5$), 3.89 – 3.87 (m, 4H, $H^9$), 3.87 (s, 3H, $H^1$), 3.04 – 3.01 (m, 4H, $H^8$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) 154.0 (C), 146.0 (C), 125.4 (CH), 121.3 (C), 112.1 (CH), 107.1 (CH), 66.9 ($CH_2$), 56.2 ($CH_3$), 51.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2957, 2855, 2120, 2092 (N=N=N), 1736, 1592, 1473, 1447, 1374, 1292, 1263, 1237, 1178, 1115, 1100, 1069, 1043, 970, 922, 867, 835, 777, 726,

666, 595, 521, 462. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{14}N_4O_2$ $[M+H]^+$ = 235.1190, found 235.1185; $[M+Na]^+$ = 257.1009, found 257.1005.

3-Azido-7-hydroxy-2*H*-chromen-2-one (**24k**)

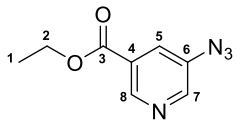



Synthesised by an adapted literature procedure.[326]

To a stirred solution of freshly prepared 3-amino-7-hydroxy-2*H*-chromen-2-one hydrochloride[326] (2.13 g, 10.0 mmol) in ice water (20.0 mL) was added sodium nitrite (1.38 g, 20.0 mmol). The resulting suspension was stirred for 10 minutes, after which sodium azide (1.95 g, 30.0 mmol) was added portionwise. The reaction mixture was stirred at 0 °C for 30 minutes, and then filtered to give **24k** as a brown solid (1.04 g, 5.12 mmol, 51%), which was used without further purification. Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[326]

**$^1$H NMR** (400 MHz, DMSO-$d_6$) δ 10.53 (s, 1H, OH), 7.60 (s, 1H, $H^7$), 7.48 (d, *J* = 8.5 Hz, 1H, $H^3$), 6.81 (dd, *J* = 8.5, 2.3 Hz, 1H, $H^2$), 6.76 (d, *J* = 2.3 Hz, 1H, $H^6$). **$^{13}$C{$^1$H} NMR** (101 MHz, DMSO-$d_6$) δ 160.8 (C), 157.8 (C), 153.3 (C), 129.6 (CH), 128.3 (CH), 121.6 (C), 114.3 (CH), 111.8 (C), 102.5 (CH). **FTIR** (neat) $\nu_{max}$ 3288, 3051, 2385, 2115 (N=N=N), 1679 (C=O), 1616, 1513, 1454, 1373, 1342, 1316, 1258, 1221, 1156, 1120, 1067, 981, 953, 925, 894, 837, 815, 757, 743, 721, 625, 584, 533, 477, 458, 412. **m.p.** *ca.* 200 °C (decomp.)

Ethyl 5-azidonicotinate (**24l**)

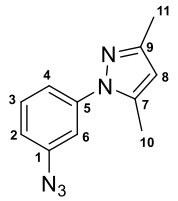



Synthesised by an adapted literature procedure.[327]

To a stirred solution of freshly prepared ethyl 5-aminonicotinate hydrochloride[327] (367 mg, 2.45 mmol) in hydrochloric acid (12.5 mL of a concentrated aqueous solution) at 0 °C was added sodium nitrite (187 mg, 2.71 mmol, in 1.5 mL of water) dropwise over 10 minutes. The resulting yellow reaction mixture was allowed to stir at 0 °C for 20 minutes, after which it was added to a stirred slurry of sodium azide (240 mg, 3.67 mmol) and sodium acetate (530 mg, 6.45 mmol) in ice-water (1.00 mL, ~20% ice v/v). The reaction mixture was allowed to stir at 0 °C for 1 hour, after which it was allowed to warm to room temperature. To the reaction mixture was added ammonium hydroxide, followed by sodium hydroxide, until a pH of 10 was reached. The reaction mixture was extracted with ethyl acetate (10.0 mL × 3). The combined organic layers were washed with brine (20.0 mL), dried with sodium sulfate, and concentrated under reduced pressure to give **24l** as an orange oil, which was used without further purification (423 mg, 2.20 mmol, 90%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 9.03 – 8.92 (m, 1H, $H^8$), 8.49 (d, *J* = 2.7 Hz, 1H, $H^7$), 7.95 (dd, *J* = 2.7, 1.7 Hz, 1H, $H^5$), 4.43 (q, *J* = 7.1 Hz, 2H, $H^2$), 1.42 (t, *J* = 7.1 Hz, 3H, $H^1$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 164.6 (C), 144.8 (C), 146.7 (CH), 144.7 (CH), 137.4 (C), 126.5 (CH), 61.6 ($CH_2$), 14.4 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3438, 3325, 3187, 2986, 2114 (N=N=N), 1705 (C=O), 1652, 1599, 1573, 1478, 1441, 1395, 1371, 1337, 1301, 1278, 1248, 1171, 1109, 1018, 958, 901, 864, 815, 768, 699, 680, 560, 505, 448. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_8N_4O_2$ $[M+H]^+$ = 193.0720, found 193.0718; $[M+Na]^+$ = 215.0539, found 215.0546.

1-(3-Azidophenyl)-3,5-dimethyl-1*H*-pyrazole (**24m**)




Synthesised by an adapted literature procedure.[325]

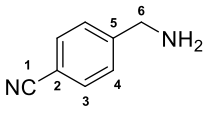
To a stirred solution of copper(II) acetate (55 mg, 0.30 mmol) and (3-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl)boronic acid (648 mg, 3.00 mmol) in methanol (6 mL) at room temperature was added sodium azide (292 mg, 4.50 mmol) portionwise. The resulting reaction mixture was exposed to the air and stirred at 50 °C for 16 hours, after which time the previously dark brown reaction mixture had become green. The reaction mixture was concentrated under reduced pressure and then purified by flash column chromatography ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.3) to give **24m** as an orange oil (584 mg, 2.74 mmol, 91%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.41 (dd, *J* = 8.1, 8.1 Hz, 1H, $H^3$), 7.20 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H, $H^2$ or $H^4$), 7.15 (dd, *J* = 2.2, 2.0 Hz, 1H, $H^6$), 7.00 (ddd, *J* = 8.1, 2.2, 1.0 Hz, 1H, $H^2$ or $H^4$), 6.00 (s, 1H, $H^8$), 2.32 (s, 3H, $H^{10}$ or $H^{11}$), 2.29 (s, 3H, $H^{10}$ or $H^{11}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 149.4 (C), 141.3 (C), 141.1 (C), 139.5 (C), 130.1 (CH), 120.8 9 (CH), 117.6 (CH), 115.4 (CH), 107.5 (CH), 13.5 ($CH_3$), 12.5 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 2981, 2926, 2405, 2101 (N=N=N), 1736, 1605, 1592, 1558, 1494, 1468, 1447, 1417, 1378, 1363, 1295, 1262, 1238, 1166, 1135, 1116, 1089, 1044, 1023, 1000, 974, 938, 872, 858, 782, 715, 686, 661, 634, 607, 586, 533, 509, 452, 416. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{11}N_5$ $[M+H]^+$ = 214.1087, found 214.1087; $[M+Na]^+$ = 236.0907, found 236.0906.

General procedure B: catalytic azide reduction

To a stirred solution of the appropriate azide (0.50 mmol) in toluene (0.5 mL) at room temperature was added phenylsilane (81 mg, 0.75 mmol) followed by phosphine **13** (16 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 8 hours, after which methanol (0.25 mL) was added. The crude product was concentrated under reduced pressure and then purified by flash column chromatography, eluting with either ethyl acetate/pentane or ammoniacal methanol/dichloromethane.

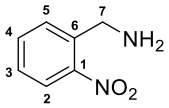
4-(Aminomethyl)benzonitrile (**31b**)




General procedure B was followed with azide **24b**. Purification by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (7M))/dichloromethane, $R_f$ = 0.3) gave **31b** as a yellow oil (65 mg, 0.49 mmol, 99%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[445]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.2 Hz, 2H, $H^3$), 7.43 (d, *J* = 8.2 Hz, 2H, $H^4$), 3.94 (s, 2H, $H^6$). **$^{13}$C{$^{1}$H} NMR** (126 MHz, Chloroform-*d*) δ 148.5 (C), 132.3 (CH), 127.7 (CH), 119.0 (C), 110.5 (C), 46.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3392, 2930, 2207, 1609, 1577, 1516, 1444, 1340, 1165, 1123, 1052, 955, 855, 787, 726, 701, 663, 592, 475. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_8N_2$ $[M+H]^+$ = 153.0659, found 153.0654; $[M+Na]^+$ = 175.0478, found 175.0471.

(2-Nitrophenyl)methanamine (**31c**)

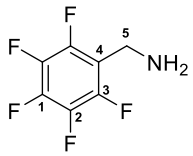



General procedure B was followed with azide **24c**. Purification by flash column chromatography ($SiO_2$, 1-2% (ammonia/methanol (7M))/dichloromethane, $R_f$ = 0.1 in 2% (ammonia/methanol (7M))/dichloromethane) gave **31c** as a yellow oil

(52 mg, 0.34 mmol, 68%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[446]

**$^{1}H$ NMR** (500 MHz, Chloroform-*d*) δ 7.98 (dd, *J* = 7.8, 1.7 Hz, $H^{2}$), 7.62 – 7.57 (m, 2H, $H^{4}$, $H^{5}$), 7.41 (ddd, *J* = 8.5, 5.1, 2.2 Hz, 1H, $H^{3}$), 4.09 (d, *J* = 1.7 Hz, 2H, $H^{7}$). **$^{13}C\{^{1}H\}$ NMR** (126 MHz, Chloroform-*d*) δ 148.5 (C), 138.5 (C), 133.7 (CH), 130.6 (CH), 127.9 (CH), 124.9 (CH), 44.1 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3379, 2855, 2226, 1607, 1504, 1414, 1269, 1175, 1054, 1019, 809, 733, 701, 680, 548, 508, 425. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_8N_2O_2$ $[M+H]^+$ = 133.0760, found 133.0761.

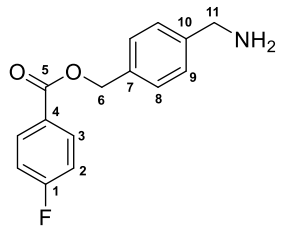
2,3,4,5,6-Pentafluorobenzylamine (**31d**)




To a stirred solution of the azide **24d** (112 mg, 0.50 mmol) in toluene (0.5 mL) at room temperature was added phenylsilane (81 mg, 0.75 mmol) followed by phosphine **13** (16 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 8 hours, after which methanol (0.25 mL) was added, followed by dimethylsulfone (23.8 mg, 0.25 mmol). An aliquot was taken of the crude reaction mixture, and the NMR yield (5.3 mg, 0.027 mmol, 11%) was obtained by comparison of the integrals for the $H^{5}$ peak ($^{1}H$ δ = 3.96 ppm) and the sulfone methyl peak ($^{1}H$ δ = 3.00 ppm). Characterisation data were consistent with previous literature: $^{1}H$, $^{19}F$ NMR.[447]

**$^{1}H$ NMR** (400 MHz, Chloroform-*d*) δ 3.96 ppm (s, 2H, $H^{5}$). **$^{19}F\{^{1}H\}$ NMR** (376 MHz, Chloroform-*d*) δ -145.4, -156.0, -162.0.

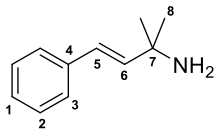
4-(Aminomethyl)benzyl 4-fluorobenzoate (**31e**)



General procedure B was followed with azide **24e**. Purification by flash column chromatography ($SiO_2$, 10% ammonia/methanol (7M))/dichloromethane, $R_f$ = 0.5) gave **31e** as a yellow oil (72 mg, 0.28 mmol, 56%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.13 – 8.03 (m, 2H, $H^3$), 7.43 (d, *J* = 8.2 Hz, 2H, $H^8$), 7.36 (d, *J* = 8.2 Hz, 2H, $H^9$), 7.16 – 7.06 (m, 2H, $H^2$), 3.90 (s, 2H, $H^6$), 3.52 – 3.42 (m, 2H, $H^{11}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 167.1 (C), 165.8 (C, d, *J* = 254.1 Hz), 143.4 (C), 134.5 (C), 132.3 (CH, d, *J* = 9.3 Hz), 128.6 (CH), 127.4 (CH), 126.4 (C, d, *J* = 3.0 Hz), 115.5 (CH, d, *J* = 22.0 Hz), 66.7 ($CH_2$), 46.2 ($CH_2$). **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -105.5. **FTIR** (neat) $\nu_{max}$ 2932, 1713, 1602, 1507, 1455, 1412, 1375, 1266, 1237, 1153, 1106, 1088, 1014, 937, 853, 801, 765, 686, 632, 607, 568, 502, 472. **HRMS** (ESI-TOF) *m/z* calculated for $C_{15}H_{14}NO_2F$ $[M+H]^+$ = 260.1081, found 260.1078; $[M+Na]^+$ = 282.0901, found 282.0900.

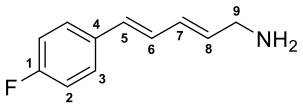
(*E*)-2-Methyl-4-phenylbut-3-en-2-amine (**31g**)[448]



General procedure B was followed with azide **24g**. Purification by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (0-10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.2 in 10% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane) gave **31g** as a brown oil (17 mg, 0.11 mmol 22%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[448]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.38 – 7.35 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.19 (m, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 6.33 (d, *J* = 16.2 Hz, 1H), 1.44 (s, 6H). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 136.5 (CH), 128.6 (CH), 128.3 (C), 127.7 (CH), 126.6 (CH), 126.6 (CH), 53.1 (C), 28.4 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 2923, 1642, 1599, 1505, 1414, 1297, 1222, 1156, 1094, 986, 826, 774, 516. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{15}N$ $[M+Na]^+$ = 200.0846, found 200.0859.

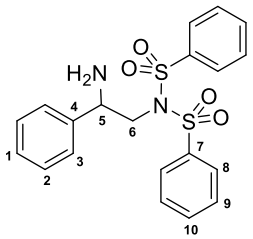
(2*E*,4*E*)-5-(4-Fluorophenyl)penta-2,4-dien-1-amine (**31h**)




General procedure B was followed on a 1.00 mmol scale with azide **24h**. Purification by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (0-10% $NH_4OH$ in MeOH))/dichloromethane $R_f$ = 0.3 in 10% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane) gave **31h** as an air-sensitive orange oil (138 mg, 0.78 mmol, 78%).

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.51 – 7.46 (m, 2H, $H^3$), 7.17 – 7.11 (m, 2H, $H^2$), 6.84 (dd, *J* = 15.7, 10.5 Hz, 1H, $H^6$), 6.51 (d, *J* = 15.7 Hz, 1H, $H^5$), 6.29 (ddd, *J* = 15.3, 10.5, 1.8 Hz, 1H, $H^7$), 5.93 (dt, *J* = 15.3, 5.7 Hz, 1H, $H^8$), 3.24 (dd, *J* = 5.7, 1.8 Hz, 2H, $H^9$). **$^{13}$C{$^1$H} NMR** (126 MHz, DMSO-$d_6$) δ 161.9 (C, d, *J* = 244.6 Hz), 138.0 (CH), 137.9 (CH), 134.3 (C, d, *J* = 3.3 Hz), 129.6 (CH), 129.2 (CH), 128.4 (CH, d, *J* = 7.9 Hz), 116.0 (CH, d, *J* = 21.5 Hz), 43.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2923, 1642, 1599, 1505, 1414, 1297, 1222, 1156, 1094, 986, 826, 774, 516. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{12}NF$ $[M+Na]^+$ = 200.0846, found 200.0859.

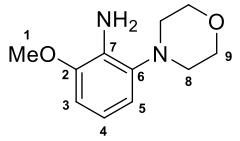
*N*-(2-Amino-2-phenylethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (**31i**)



General procedure B was followed with azide **24i**. Purification by flash column chromatography ($SiO_2$, 1% (ammonia/methanol (7M))/dichloromethane, $R_f$ = 0.4) gave **31i** as a yellow oil (153 mg, 0.37 mmol, 73%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.07 – 8.01 (m, 4H, $H^8$), 7.69 – 7.61 (m, 2H, $H^{10}$), 7.54 (dd, *J* = 8.5, 7.1 Hz, 4H, $H^9$), 7.41 – 7.27 (m, 5H, $H^1$, $H^2$, $H^3$), 4.42 (dd, *J* = 9.7, 4.1 Hz, 1H, $H^5$), 3.88 (dd, *J* = 15.1, 4.1 Hz, 1H, $H^{6a}$), 3.75 (dd, *J* = 15.1, 9.7 Hz, 1H, $H^{6b}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) 142.4 (C), 139.6 (C), 134.0 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 127.8 (CH), 126.6 (CH), 56.1 ($CH_2$), 55.0 (CH). **FTIR** (neat) $\nu_{max}$ 3063, 1584, 1479, 1448, 1368, 1291, 1162, 1083, 1054, 1024, 999, 899, 803, 752, 737, 719, 701, 683, 624, 579, 545, 463. **HRMS** (ESI-TOF) *m/z* calculated for $C_{20}H_{20}N_2O_4S_2$ $[M+H]^+$ = 417.0937, found 417.0932; $[M+Na]^+$ = 439.0757, found 439.0754.

2-Methoxy-6-morpholinoaniline (**31j**)

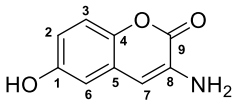


General procedure B was followed with azide **24j**. Purification by flash column chromatography ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.7) gave **31j** as an off-white solid (101 mg, 0.49 mmol, 97%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.75 – 6.69 (m, 2H, $H^4$, $H^5$), 6.65 (dd, *J* = 7.0, 2.4 Hz, 1H, $H^3$), 3.89 – 3.76 (m, 7H, $H^1$, $H^9$), 2.99 – 2.90 (m, 4H, $H^8$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) 147.6 (C), 139.0 (C), 131.1 (C), 117.3 (CH), 112.3 (CH), 106.7 (CH), 67.7 ($CH_2$), 55.7 ($CH_3$), 51.4 ($CH_2$). **FTIR** (neat)

$\nu_{max}$ 3452, 3407, 3360 (N–H), 3321, 3003, 2956, 2921, 2862, 2836, 2754, 2683, 2100, 1901, 1834, 1744, 1607, 1595, 1566, 1478, 1453, 1441, 1394, 1373, 1362, 1332, 1297, 1271, 1251, 1237, 1206, 1191, 1173, 1161, 1132, 1109, 1087, 1066, 1042, 950, 917, 853, 804, 782, 738, 711, 630, 608, 574, 553, 535, 506, 489, 417. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{16}N_2O_2$ $[M+H]^+$ = 209.1285, found 209.1285. **m.p.** 115-117 °C.

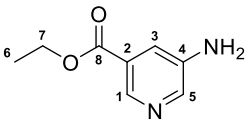
3-Amino-7-hydroxy-2*H*-chromen-2-one (**31k**)




General procedure B was followed with azide **24k**. Purification by flash column chromatography ($SiO_2$, 50% ethyl acetate/pentane, $R_f$ = 0.4) gave **31k** as an orange solid (42 mg, 0.24 mmol, 47%). Characterisation data were consistent with previous literature: m.p.; $^1$H, $^{13}$C NMR.[326]

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 9.80 (s, 1H, OH), 7.23 (d, *J* = 8.4 Hz, 1H, $H^3$), 6.69 (s, 1H, $H^7$), 6.68 – 6.67 (m, 1H, $H^2$), 6.65 (d, *J* = 2.3 Hz, 1H, $H^6$), 5.23 (s, 2H, $NH_2$). **$^{13}$C{$^1$H} NMR** (126 MHz, DMSO-$d_6$) δ 159.5 (C), 156.6 (C), 149.8 (C), 130.7 (C), 126.2 (CH), 114.0 (CH), 113.4 (C), 110.3 (CH), 102.3 (CH). **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_7NO_3$ $[M+H]^+$ = 178.0499, found 178.0506; $[M+Na]^+$ = 200.0318, found 200.0327. **m.p.** 214-216 °C.

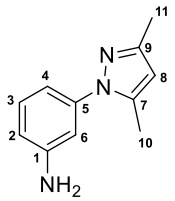
Ethyl 5-aminonicotinate (**31l**)




General procedure B was followed with azide **24l**. Purification by flash column chromatography ($SiO_2$, 60% ethyl acetate/pentane, $R_f$ = 0.2) gave **31l** as an off-white solid (82 mg, 0.49 mmol, 99%). Characterisation data were consistent with previous literature: m.p.[327]

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 1.8 Hz, 1H, $H^{1}$), 8.23 (d, *J* = 2.8 Hz, 1H, $H^{5}$), 7.56 (dd, *J* = 2.8, 1.8 Hz, 1H, $H^{3}$), 4.38 (q, *J* = 7.1 Hz, 2H, $H^{7}$), 1.39 (t, *J* = 7.1 Hz, 3H, $H^{6}$). **$^{13}$C{$^{1}$H} NMR** (126 MHz, Chloroform-*d*) δ 165.7 (C), 142.2 (C), 141.0 (CH), 140.90 (CH), 126.5 (C), 121.8 (CH), 61.3 ($CH_2$), 14.3 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3438, 3325, 3187, 2986, 1705 (C=O), 1651, 1599, 1573, 1478, 1441, 1395, 1371, 1337, 1301, 1278, 1248, 1171, 1108, 1018, 958, 901, 864, 815, 768, 699, 680, 560, 504, 448. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_{10}N_2O_2$ $[M+H]^+$ = 167.0815, found 167.0816. **m.p.** 93-95 °C.

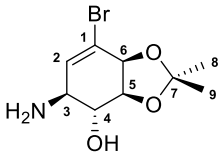
3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)aniline (**31m**)




General procedure B was followed with azide **24m**. Purification by flash column chromatography ($SiO_2$, 20-50% ethyl acetate/pentane, $R_f$ = 0.3) gave **31m** as a yellow oil (93 mg, 0.50 mmol, >99%).

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.18 (dd, *J* = 8.0, 7.9 Hz, 1H, $H^{3}$), 6.77 (dd, *J* = 2.3, 2.0 Hz, 1H, $H^{6}$), 6.76 – 6.73 (m, 1H, $H^{2}$ or $H^{4}$), 6.64 (ddd, *J* = 8.0, 2.3, 0.9 Hz, 1H, $H^{2}$ or $H^{4}$), 5.96 (s, 1H, $H^{8}$), 2.29 (s, 3H, $H^{11}$), 2.28 (s, 3H, $H^{10}$). **$^{13}$C{$^{1}$H} NMR** (126 MHz, Chloroform-*d*) δ 148.7 (C), 147.3 (C), 140.9 (C), 139.4 (C), 129.6 (CH), 114.6 (CH), 114.0 (CH), 111.5 (CH), 106.7 (CH), 13.5 ($CH_3$), 12.5 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3334, 3218, 2923, 2860, 2366, 2136, 1918, 1729, 1607, 1553, 1499, 1469, 1419, 1379, 1367, 1312, 1283, 1239, 1163, 1131, 1044, 1022, 996, 978, 885, 857, 778, 692, 676, 662, 642, 609, 587, 530, 506, 455, 424. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{13}N_3$ $[M+H]^+$ = 188.1182, found 188.1177; $[M+Na]^+$ = 210.1002; found 210.0995.

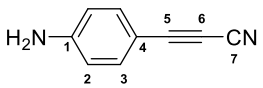
(3a*S*,4*R*,5*S*,7a*S*)-5-Amino-7-bromo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (**31o**)




General procedure B was followed with (1*R*,2*S*,5*S*,6*S*)-2-azido-4-bromo-5,6-isopropylidenedioxycyclohexa-3-ene-1-ol. Purification by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (0-10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.1) gave **31o** as a light brown solid (33 mg, 0.13 mmol, 25%). Methyl peaks were assigned using NOESY ($H^8$-$H^6$ interaction). Characterisation data were consistent with previous literature: m.p.[449]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.15 (d, *J* = 1.1 Hz, 1H, $H^2$), 4.68 (dd, *J* = 6.3, 1.1 Hz, 1H, $H^6$), 4.13 (dd, *J* = 8.6, 6.3 Hz, 1H, $H^5$), 3.44 (dd, *J* = 8.6, 8.3 Hz, 1H, $H^4$), 3.26 (d, *J* = 8.3 Hz, 1H, $H^3$), 1.55 (s, 3H, $H^9$), 1.42 (s, 3H, $H^8$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) 136.5 (CH), 118.4 (C), 110.7 (C), 78.4 (CH), 77.3 (CH), 74.6 (CH), 53.9 (CH), 28.2 ($CH_3$), 26.0 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3323, 3266, 3183, 2987, 2920, 2871, 1640, 1611, 1453, 1380, 1274, 1243, 1216, 1160, 1138, 1092, 1067, 1007, 975, 954, 914, 869, 825, 794, 733, 655, 601, 582, 534, 506, 451. **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_{14}NO_3Br$ $[M+H]^+$ = 264.0230, found 264.0232; $[M+Na]^+$ = 286.0049, found 286.0055. **m.p.** 86-88 °C

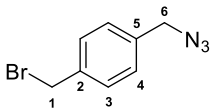
3-(4-Aminophenyl)propiolonitrile (**31p**)




General procedure B was followed with 3-(4-azidophenyl)propiolonitrile. Purification by flash column chromatography ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.1) gave **31p** as an orange solid (66 mg, 0.46 mmol, 93%). Characterisation data were consistent with previous literature: m.p.; $^1$H, $^{13}$C NMR.[450]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.42 – 7.36 (m, 2H, $H^3$), 6.65 – 6.56 (m, 2H, $H^2$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 149.8 (C), 135.5 (CH), 114.5 (CH), 106.3 (C), 105.6 (C), 85.1 (C), 62.0 (C). **FTIR** (neat) $\nu_{max}$ 3430, 3328, 2256 (C≡N), 2133, 1632, 1597, 1510, 1302, 1178, 826, 526, 496, 452. **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_6N_2$ $[M+H]^+$ = 143.0604, found 143.0599; $[M+Na]^+$ = 165.0423, found 165.0420; $[M+NH_4]^+$ = 160.0869, found 160.0866. **m.p.** 136-138 °C.

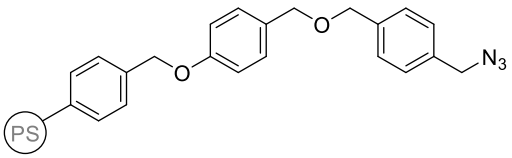
1-Azidomethyl-4-bromomethylbenzene (**33**)




To a stirred solution of alcohol **24a** (815 mg, 5.00 mmol) in dichloromethane (10.0 mL) at 0 °C was added phosphorus tribromide (0.47 mL, 5.00 mmol) dropwise over 5 minutes. The resulting reaction mixture was stirred at room temperature for 1 hour, and then poured into ice/water (20.0 mL, ~20% ice v/v). The mixture was allowed to warm to room temperature and then the organic layer was separated, washed with water (12.5 mL), and dried over sodium sulfate. The crude product was concentrated under reduced pressure. The resulting brown oil was then passed through a silica plug with dichloromethane (~2.00 mL), and concentrated again under reduced pressure to give **33** as a yellow oil (872 mg, 3.88 mmol, 78%), which was used without further purification. Characterisation data were consistent with previous literature: $^{1}$H, $^{13}$C NMR.[451]

**$^{1}$H NMR** (500 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 8.2 Hz, 2H, $H^3$), 7.30 (d, *J* = 8.2 Hz, 2H, $H^4$), 4.50 (s, 2H, $H^1$), 4.34 (s, 2H, $H^6$). **$^{13}$C{$^{1}$H} NMR** (126 MHz, Chloroform-*d*) δ 137.9 (C), 135.7 (C), 129.6 (CH), 128.6 (CH), 54.4 ($CH_2$), 32.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3030, 2930, 2091 (N=N=N), 1913, 1614, 1514, 1439, 1419, 1344, 1247, 1227, 1201, 1099, 1021, 968, 876, 817, 764, 736, 715, 667, 603, 556, 492, 456. *HRMS failed to find the correct mass for this compound*.

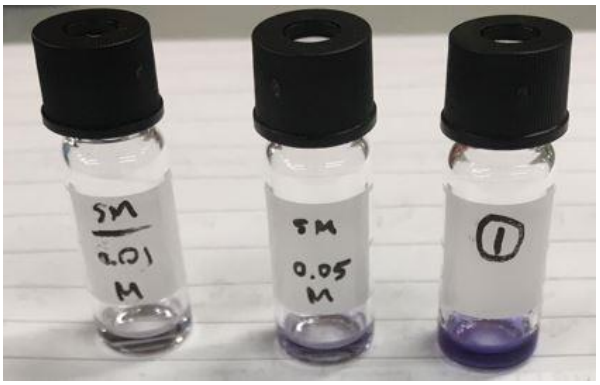
Polymer-bound azide **34**




To a stirred suspension of Wang resin (455 mg, 1.10 mmol/g loading, 0.50 mmol) in anhydrous THF (3.00 mL) at room temperature, sodium hydride (36 mg of a 60wt% suspension in mineral oil, 1.50 mmol) was added. The reaction mixture was cooled to 0 °C, and bromide **33** (225 mg, 1.00 mmol) was added dropwise. The resulting reaction mixture was stirred for 3 days and allowed to warm to room temperature. The suspension was filtered and washed with diethyl ether to give polymer **34** as an off-white solid. The presence of the azide functional group was confirmed by IR spectroscopy. Colorimetric tests were performed as described in the literature[336] (heating each solution to 85 °C for 10 minutes), and compared against soluble azide **33** (see below).

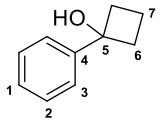
**FTIR** (neat) $\nu_{max}$ 3418, 3025, 2922, 2851, 2096 (N=N=N), 1601, 1510, 1492, 1451, 1380, 1301, 1239, 1171, 1112, 1016, 820, 757, 697, 538.

Colorimetric tests




Positive result (blue stain) observed for <1 mg of polymer product (right). Soluble azide **33** gave negative result at 0.01 M (left) and faint positive result at 0.05 M (centre).

1-Phenylcyclobutan-1-ol (**35**)

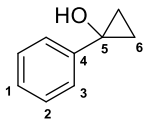



Synthesised by an adapted literature procedure.[452]

To a stirred solution of cyclobutanone (350 mg, 5.00 mmol) in anhydrous diethyl ether (10.0 mL) at 0 °C was added phenylmagnesium bromide (2.00 mL of a 2.8 M solution in diethyl ether, 5.60 mmol) dropwise over five minutes. The reaction mixture was allowed to stir at 0 °C for three hours, with sonication after one hour to break up the precipitate. Water (5.00 mL) was added portionwise at 0 °C, and then the reaction mixture was allowed to warm to room temperature. Diethyl ether (10.0 mL) was added, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with water (10.0 mL) and brine (10.0 mL), and then the combined aqueous layer was re-extracted with diethyl ether (5.00 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.2) to give **35** as a yellow oil (715 mg, 4.82 mmol, 97%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[131,452]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.53 – 7.48 (m, 2H, $H^2$), 7.38 (t, *J* = 7.6 Hz, 2H, $H^3$), 7.31 – 7.27 (m, 1H, $H^1$), 2.62 – 2.53 (m, 2H, $H^{6a}$), 2.43 – 2.33 (m, 2H, $H^{6b}$), 2.09 – 1.96 (m, 1H, $H^{7a}$) 1.76 – 1.64 (m, 1H, $H^{7b}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 146.2 (C), 128.5 (CH), 127.3 (CH), 125.0 (CH), 77.1 (C), 36.8 ($CH_2$), 13.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3333 (br., O-H), 3059, 3027, 2984, 2940, 2872, 1959, 1723, 1595, 1494, 1474, 1446, 1422, 1373, 1278, 1244, 1183, 1131, 1071, 1043, 1025, 956, 910, 890, 826, 756, 696, 541, 513, 441.

1-Phenylcyclopropan-1-ol (**36**)

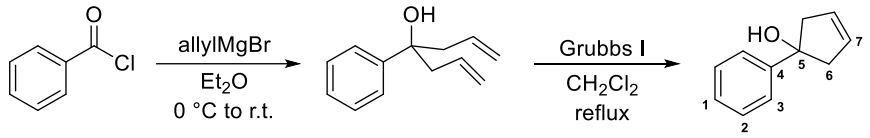



Synthesised by an adapted literature procedure.[337]

To a stirred solution of methyl benzoate (1.26 mL, 10.0 mmol) and freshly distilled titanium(IV) isopropoxide (0.3 mL, 1.00 mmol) in anhydrous diethyl ether (35 mL) at 0 °C was added ethylmagnesium bromide dropwise (6.70 mL of a 3.0 M solution in diethyl ether, 20.0 mmol) over 1 hour. The reaction mixture was stirred for three hours, during which time it was allowed to warm to room temperature. The reaction mixture was then poured into cooled sulfuric acid (100 mL, 2M aq., stirred in ice), after which all solids dissolved. The reaction mixture was extracted with diethyl ether (3 × 30.0 mL), and the combined organic extracts were washed with sodium hydrogen carbonate (10.0 mL, sat. aq.), potassium carbonate (2 × 10.0 mL, sat. aq.), water (20.0 mL), and brine (20.0 mL). The crude product was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was then purified by flash column chromatography ($SiO_2$, 15-20% ethyl acetate/petrol, $R_f$ = 0.3) to give **36** as a colourless oil (539 mg, 4.02 mmol, 40%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[453]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 4H, $H^2$, $H^3$), 7.23 (m, 1H, $H^1$), 1.30 – 1.24 (m, 2H, $H^{6a}$), 1.07 – 1.03 (m, 2H, $H^{6b}$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 144.3 (C), 128.4 (CH), 126.4 (CH), 124.4 (CH), 56.7 (C), 17.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3312 (br., O-H), 3088, 3061, 3027, 3007, 2969, 1677, 1603, 1497, 1454, 1375, 1301, 1233, 1099, 1077, 1045, 1014, 969, 919, 865, 754, 694, 556, 491.

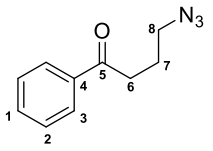
1-Phenylcyclopent-3-en-1-ol (**37**)




To a stirred solution of allylmagnesium bromide (12.5 mL of a 1 M solution in diethyl ether, 12.5 mmol) in diethyl ether (4.00 mL) at 0 °C was added benzoyl chloride (0.30 mL, 2.50 mmol) dropwise over 3 minutes. The reaction mixture was stirred at 0 °C for 2 hours, then allowed to warm to room temperature and stirred for a further 4 hours. The reaction mixture was cooled to 0 °C and water (10.0 mL) was added portionwise, followed by ammonium chloride (20.0 mL, sat. aq.). The reaction mixture was extracted with diethyl ether (2 × 10.0 mL), then ethyl acetate (10.0 mL). The combined organic extracts were washed with water (20.0 mL), brine (20.0 mL), and $Na_2$(EDTA) (20.0 mL, $4 \cdot 10^{-4}$ M). The organic extracts were then dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude intermediate was purified by flash column chromatography ($SiO_2$, 40% diethyl ether/pentane, $R_f$ = 0.6) and concentrated to give a colourless oil which was then dissolved in degassed dichloromethane (10.0 mL). The first-generation Grubbs complex was added (128 mg, 0.15 mmol), and the reaction mixture was heated at reflux for 4 hours. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, Rf = 0.1) to give **37** as a viscous brown oil (63 mg, 0.39 mmol, 16% over 2 steps). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[454]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.54 – 7.50 (m, 2H, $H^2$), 7.39 – 7.34 (m, 2H, $H^3$), 7.28 – 7.25 (m, 1H, $H^1$), 5.84 (s, 2H, $H^7$), 3.00 – 2.92 (m, 2H, $H^{6a}$), 2.80 – 2.73 (m, 2H, $H^{6b}$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 147.0 (C), 128.5 (CH), 128.2 (CH), 126.8 (CH), 125.0 (CH), 82.2 (C), 50.3 ($CH_2$). **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{12}O$ $[M+H]^+$ = 183.0780, found 183.0779.

4-Azido-1-phenylbutan-1-one (**38**)

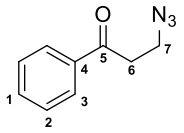



Synthesised by an adapted literature procedure.[131]

To a mixture of manganese(III) acetate dihydrate (54 mg, 0.20 mmol), 2,2'-bipyridyl (34 mg, 0.22 mmol), freshly prepared 1-hydroxy-1λ$^3$-benzo[*d*][1,2]iodaoxol-3(1*H*)-one[455] (528 mg, 2.00 mmol), and **35** (148 mg, 1.00 mmol) was added acetonitrile (7.50 mL), and the reaction mixture was stirred at room temperature for 5 minutes. Azidotrimethylsilane (262 µL, 2.00 mmol) was added, and the reaction mixture was heated to 75 °C for 8 hours. The reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 10% ethyl acetate/pentane, $R_f$ = 0.5 in 20% ethyl acetate/pentane) to give **38** as an orange oil (79 mg, 0.42 mmol, 42%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[131]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 8.3, 1.4 Hz, 2H, H$^3$), 7.60 – 7.55 (m, 1H, H$^1$), 7.51 – 7.44 (m, 2H, H$^2$), 3.43 (t, *J* = 6.6 Hz, 1H, H$^8$), 3.09 (t, *J* = 7.0 Hz, 1H, H$^6$), 2.10 – 2.02 (m, 2H, H$^7$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 199.0 (C), 136.7 (C), 133.3 (CH), 128.7 (CH), 128.0 (CH), 50.9 ($CH_2$), 35.2 ($CH_2$), 23.3 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3350, 3062, 2935, 2092 (N=N=N), 1736, 1682 (C=O), 1597, 1580, 1448, 1411, 1355, 1264, 1228, 1201, 1180, 1076, 1000, 988, 916, 889, 755, 739, 689, 656, 596, 565, 498, 459. **HRMS** (ESI-TOF) *m/z* calculated for $C_{10}H_{11}N_3O$ $[M+H]^+$ = 190.0975, found 190.0973; $[M+Na]^+$ = 212.0794, found 212.0796.

3-Azido-1-phenylpropan-1-one (**39**)

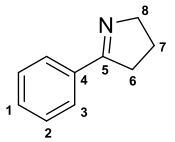



Synthesised by an adapted literature procedure.[131]

To a mixture of manganese(III) acetate dihydrate (54 mg, 0.20 mmol), 2,2'-bipyridyl (34 mg, 0.22 mmol), freshly prepared 1-hydroxy-1λ$^3$-benzo[*d*][1,2]iodaoxol-3(1*H*)-one[455] (528 mg, 2.00 mmol), and **36** (134 mg, 1.00 mmol) was added acetonitrile (7.50 mL), and the reaction mixture was stirred at room temperature for 5 minutes. Azidotrimethylsilane (262 µL, 2.00 mmol) was added, and the reaction mixture was heated to 75 °C for 8 hours. The reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (3 × 10.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 10% ethyl acetate/pentane, $R_f$ = 0.4 in 20% ethyl acetate/pentane) to give **39** as an orange oil (38 mg, 0.22 mmol, 44%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[113]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 8.2, 1.5 Hz, 2H, H$^3$), 7.60 – 7.53 (m, 1H, H$^1$), 7.50 – 7.43 (m, 2H, H$^2$), 3.06 – 2.99 (m, 2H, H$^6$), 1.26 – 1.23 (m, 2H, H$^7$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 200.8 (C), 136.9 (C), 132.9 (CH), 128.6 (CH), 128.0 (CH), 31.8 ($CH_2$), 29.7 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3063, 2938, 2100 (N=N=N), 1734, 1682 (C=O), 1597, 1580, 1448, 1399, 1368, 1299, 1238, 1210, 1180, 1101, 1046, 1001, 979, 923, 836, 747, 688, 656, 632, 566, 486, 422. **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_9N_3O$ $[M+H]^+$ = 176.0818, found 176.0816; $[M+Na]^+$ = 198.0638, found 198.0635; $[M+NH_4]^+$ = 193.1084, found 193.1089.

5-Phenyl-3,4-dihydro-2*H*-pyrrole (**40**)




To a stirred solution of azide **38** (79 mg, 0.42 mmol) in toluene (0.4 mL) at room temperature was added phenylsilane (68 mg, 0.63 mmol) followed by phosphine **13** (13 mg, 0.04 mmol). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was concentrated under reduced pressure and then purified by flash column chromatography ($SiO_2$, 40% ethyl acetate/pentane, $R_f$ = 0.3) to give **40** as a yellow oil (16 mg, 0.11 mmol, 26%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[456]

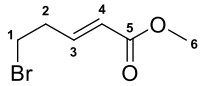
**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 7.5, 2.2 Hz, 2H, $H^3$), 7.44 – 7.38 (m, 3H, $H^1$, $H^2$), 4.07 (tt, *J* = 7.3, 2.1 Hz, 2H, $H^8$), 2.95 (tt, *J* = 8.0, 2.1 Hz, 2H, $H^6$), 2.04 (tt, *J* = 8.0, 7.3 Hz, 2H, $H^7$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 173.3 (C), 134.6 (C), 130.3 (CH), 128.4 (CH), 127.6 (CH), 61.5 ($CH_2$), 35.0 ($CH_2$), 22.7 ($CH_2$). **HRMS** (ESI-TOF) *m/z* calculated for $C_{10}H_{11}N$ $[M+H]^+$ = 146.0964, found 146.0959; $[M+H]^+$ = 168.0784; found 168.0784.

General procedure C: preparation of ω-bromo esters by cross metathesis

Adapted from literature procedure.[430]

To a mixture of the second-generation Grubbs complex (68 mg, 0.08 mmol) and copper(I) iodide (23 mg, 0.12 mmol) was added the appropriate bromoalkene (4.00 mmol), followed by methyl acrylate (1.1 mL, 12.0 mmol). The resulting reaction mixture was heated to 50 °C for 16 hours, after which the reaction mixture was concentrated and purified by flash column chromatography, eluting with diethyl ether/pentane.

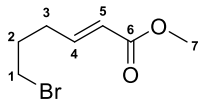
Methyl (*E*)-5-bromopent-2-enoate (**43a**)




General procedure C was followed with 4-bromo-1-butene. Purification by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.4) gave **43a** as a pale yellow oil (512 mg, 2.67 mmol, 67%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[457]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.90 (dt, *J* = 15.8, 6.8 Hz, 1H, $H^3$), 5.92 (dt, *J* = 15.8, 1.6 Hz, 1H, $H^4$), 3.73 (s, 3H, $H^6$), 3.44 (t, *J* = 6.8 Hz, 2H, $H^1$), 2.77 (dtd, *J* = 6.8, 6.8, 1.6 Hz, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 166.5 (C), 144.8 (CH), 123.4 (CH), 51.6 ($CH_3$), 35.1 ($CH_2$), 29.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2951, 2179, 2111, 2065, 2008, 1720 (C=O), 1659, 1436, 1344, 1313, 1281, 1269, 1203, 1180, 1143, 1041, 982, 917, 852, 720, 638, 616, 601, 566, 504, 486, 446, 429, 417, 406. **HRMS** (ESI-TOF) *m/z* calculated for $C_6H_9O_2Br$ $[M+Na]^+$ = 214.9678, found 214.9672.

Methyl (*E*)-6-bromohex-2-enoate (**43b**)

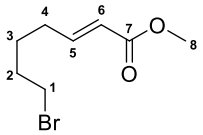



General procedure C was followed with 5-bromo-1-pentene. Purification by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, $R_f$ = 0.2) gave **43b** as a colourless oil (758 mg, 3.68 mmol, 92%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.91 (dt, *J* = 15.6, 7.0 Hz, 1H, $H^4$), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H, $H^5$), 3.72 (s, 3H, $H^7$), 3.40 (t, *J* = 6.5 Hz, 2H, $H^1$), 2.37 (dtd, *J* = 7.2, 7.0, 1.6 Hz, 2H, $H^3$), 2.06 – 1.95 (tt, *J* = 7.0, 6.5 Hz, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 166.8 (C), 147.1 (CH), 122.2 (CH), 51.5 ($CH_3$), 32.5 ($CH_2$), 30.8 ($CH_2$), 30.4 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2950, 2844, 1722 (C=O), 1659, 1436, 1311, 1272, 1203, 1176, 1154, 1138, 1038, 976, 912, 855, 719,

648, 567, 489, 444. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_{11}O_2Br$ $[M+H]^+$ = 207.0015, found 207.0026; $[M+Na]^+$ = 228.9835, found 228.9836.

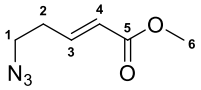
Methyl (*E*)-7-bromohept-2-enoate (**43c**)




General procedure C was followed with 6-bromo-1-hexene. Purification by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, $R_f$ = 0.2) gave **43c** as a colourless oil (773 mg, 3.51 mmol, 88%).

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 6.93 (dt, *J* = 15.7, 7.0 Hz, 1H, $H^5$), 5.83 (dt, *J* = 15.7, 1.6 Hz, 1H, $H^6$), 3.71 (s, 3H, $H^8$), 3.39 (t, *J* = 6.8 Hz, 2H, $H^1$), 2.23 (dtd, *J* = 7.3, 7.0 1.6 Hz, 2H, $H^4$), 1.91 – 1.82 (m, 2H, $H^3$), 1.65 – 1.57 (m, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 166.9 (C), 148.5 (CH), 121.5 (CH), 51.5 ($CH_3$), 33.2 ($CH_2$), 32.0 ($CH_2$), 31.2 ($CH_2$), 26.5 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2947, 2862, 1719 (C=O), 1657, 1435, 1314, 1271, 1250, 1196, 1175, 1135, 1076, 1039, 976, 912, 882, 846, 804, 718, 643, 562, 453. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_{13}O_2Br$ $[M+H]^+$ = 221.0172, found 221.0181; $[M+Na]^+$ = 242.9991, found 242.9988.

Methyl (*E*)-5-azidopent-2-enoate (**44a**)

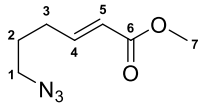



To a stirred suspension of sodium azide (184 mg, 2.83 mmol) in DMSO (5.00 mL) at room temperature was added bromide **43a** (494 mg, 2.57 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (5.00 mL) was added, followed by diethyl ether (5.00 mL). The reaction mixture was then extracted with diethyl ether (15.0 mL × 3). The combined organic extracts were washed with water (2 × 10.0 mL) and brine (20.0 mL). The aqueous extracts were re-extracted with diethyl ether (5.0 mL), and then the combined

organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, $R_f$ = 0.2) to give **44a** as a pale yellow oil (370 mg, 2.39 mmol, 93%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.91 (dt, *J* = 15.7, 7.0 Hz, 1H, $H^3$), 5.93 (dt, *J* = 15.7, 1.6 Hz, 2H, $H^4$), 3.42 (t, *J* = 6.8 Hz, 2H, $H^1$), 2.52 – 2.45 (m, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 166.5 (C), 144.3 (CH), 123.5 (CH), 51.6 ($CH_3$), 49.6 ($CH_2$), 31.6 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3460, 3400, 3321, 2955, 2872, 2691, 2091 (N=N=N), 1720 (C=O), 1688, 1565, 1485, 1437, 1354, 1247, 1211, 1169, 1125, 1085, 1021, 985, 943, 900, 867, 852, 823, 786, 755, 726, 660, 561, 539, 506, 475, 429, 412. **HRMS** (ESI-TOF) *m/z* calculated for $C_6H_9N_3O_2$ $[M+Na]^+$ = 178.0587, found 178.0585.

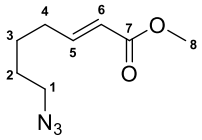
Methyl (*E*)-6-azidohex-2-enoate (**44b**)




To a stirred suspension of sodium azide (257 mg, 4.0 mmol) in DMSO (5 mL) at room temperature was added bromide **43b** (758 mg, 3.6 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (5.0 mL) was added, followed by diethyl ether (5.0 mL). The reaction mixture was then extracted with diethyl ether (15.0 mL × 3). The combined organic extracts were washed with water (2 × 10.0 mL) and brine (20.0 mL). The aqueous extracts were re-extracted with diethyl ether (5.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 10% diethyl ether/pentane, $R_f$ = 0.2) to give a colourless oil believed to contain impure **44b** (15 mg, <0.09 mmol, <2%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.93 (dt, *J* = 15.6, 7.1 Hz, 1H, $H^4$), 5.86 (dt, *J* = 15.6, 1.6 Hz, 1H, $H^5$), 3.73 (s, 3H, $H^7$), 3.31 (t, *J* = 6.7 Hz, 2H, $H^1$), 2.33-2.25 (m, 2H, $H^3$), 1.80-1.71 (m, 2H, $H^1$). *$^{13}$C NMR peaks were indistinguishable from impurities*. *HRMS failed to find the correct mass for this compound*.

Methyl (*E*)-7-azidohept-2-enoate (**44c**)

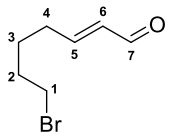



To a stirred suspension of sodium azide (236 mg, 3.7 mmol) in DMSO (6.6 mL) at room temperature was added bromide **43c** (718 mg, 3.3 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (10.0 mL) was added, followed by diethyl ether (10.0 mL). The reaction mixture was then extracted with diethyl ether (20.0 mL × 3). The combined organic extracts were washed with water (2 × 20.0 mL) and brine (40.0 mL). The aqueous extracts were re-extracted with diethyl ether (10.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.2) to give **44c** as a colourless oil (429 mg, 2.34 mmol, 71%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 6.96 (dt, *J* = 15.7, 6.9 Hz, 1H, $H^5$), 5.85 (dt, *J* = 15.7, 1.6 Hz, 1H, $H^6$), 3.74 (s, 3H, $H^8$), 3.30 (t, *J* = 6.6 Hz, 2H, $H^1$), 2.26 (dtd, *J* = 7.1, 7.0, 1.6 Hz, 2H, $H^4$), 1.68 – 1.53 (m, 4H, $H^2$ and $H^3$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 167.0 (C), 148.5 (CH), 121.5 (CH), 51.5 ($CH_3$), 51.2 ($CH_2$), 31.6 ($CH_2$), 28.3 ($CH_2$), 25.2 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3423, 3385, 2944, 2929, 2857, 2769, 2088 (N=N=N), 1725 (C=O), 1695, 1605, 1492, 1438, 1374, 1347, 1309, 1280, 1232, 1202, 1188, 1164, 1115, 1083, 1073, 1056, 1036, 1014, 998, 976, 952, 929, 888, 859, 844, 830, 815, 797, 768, 759, 690, 653, 595, 546, 483,

448, 428. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_{13}N_3O_2$ $[M+H]^+$ = 184.1081, found 184.1081; $[M+Na]^+$ = 206.0900, found 206.0898.

(*E*)-7-Bromohept-2-enal (**45**)

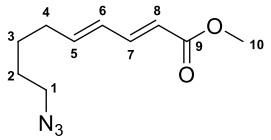



Synthesised by an adapted literature procedure.[430]

To a mixture of the second-generation Grubbs complex (68 mg, 0.08 mmol) and copper(I) iodide (46 mg, 0.24 mmol) was added diethyl ether (8.00 mL). To the reaction mixture was added 6-bromo-1-hexene (652 mg, 4.00 mmol), followed by crotonaldehyde (0.72 mL, 12.0 mmol). The resulting reaction mixture was heated to 35 °C for 16 hours, after which the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 20-30% diethyl ether/pentane, $R_f$ = 0.3 in 30% diethyl ether/pentane) to give **45** as a colourless oil (726 mg, 3.82 mmol, 96%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 9.52 (d, *J* = 7.9 Hz, 1H, $H^7$), 6.83 (dt, *J* = 15.7, 6.8 Hz, 1H, $H^5$), 6.14 (ddt, *J* = 15.7, 7.9, 1.5 Hz, 1H, $H^6$), 3.43 (t, *J* = 6.6 Hz, 2H, $H^1$), 2.38 (dtd, *J* = 8.2, 6.8, 1.5 Hz, 2H, $H^4$), 1.98-1.82 (m, 2H, $H^3$), 1.76-1.60 (m, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloforom-*d*) δ 193.9 (CH), 157.5 (CH), 133.4 (CH), 33.1 ($CH_2$), 32.0 ($CH_2$), 31.8 ($CH_2$), 26.3 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2937, 1683 (C=O), 1637, 1433, 1247, 1156, 1110, 972, 811, 737, 644, 557. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_{11}OBr$ $[M+Na]^+$ = 212.9885, found 212.9882.

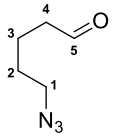
Methyl (2*E*,4*E*)-9-azidonona-2,4-dienoate (**46**)




To a stirred solution of aldehyde **45** (601 mg, 3.16 mmol) in THF (12.0 mL) at 0 °C was added methyl (triphenylphosphoranylidene)acetate (1.23 g, 3.67 mmol). The resulting reaction mixture was stirred for 16 hours, during which it was allowed to warm to room temperature. Saturated ammonium chloride solution (aq., 10.0 mL) was added, and the reaction mixture was stirred for 30 minutes at room temperature. Water (10.0 mL) was added, followed by ethyl acetate (4.00 mL). The reaction mixture was extracted with ethyl acetate (20.0 mL × 3). The combined organic extracts were washed with water (20.0 mL) and brine (40.0 mL), and then the combined aqueous extracts were re-extracted with ethyl acetate (40.0 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.5) to give a bromo α,β,γ,δ-unsaturated ester intermediate as a pale yellow oil. To a stirred solution of the bromo α,β,γ,δ-unsaturated ester intermediate (493 mg, 2.00 mmol) in DMSO (4.00 mL) at room temperature was added sodium azide (143 mg, 2.20 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (1.00 mL) was added, followed by diethyl ether (10.0 mL). The reaction mixture was then extracted with diethyl ether (20.0 mL × 3). The combined organic extracts were washed with water (2 × 20.0 mL) and brine (40.0 mL). The aqueous extracts were re-extracted with diethyl ether (10.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.2) to give **46** as a pale yellow oil (356 mg, 1.70 mmol, 59% over 2 steps).

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.25 (dd, *J* = 15.4, 10.3 Hz, 1H, $H^{7}$), 6.22 – 6.05 (m, 2H, $H^{5}$, $H^{6}$), 5.80 (d, *J* = 15.4 Hz, 1H, $H^{8}$), 3.73 (s, 3H, $H^{10}$), 3.28 (t, *J* = 6.6 Hz, 2H, $H^{1}$), 2.24 – 2.18 (m, 2H, $H^{4}$), 1.67-1.55 (m, 2H, $H^{2}$), 1.58 – 1.46 (m, 2H, $H^{3}$). **$^{13}$C{$^{1}$H}NMR** (101 MHz, Chloroform-*d*) δ 167.6 (C), 145.0 (CH), 143.5 (CH), 128.9 (CH), 119.2 (CH), 51.5 ($CH_3$), 51.2 ($CH_2$), 32.4 ($CH_2$), 28.4 ($CH_2$), 25.8 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2944, 2861, 2092 (N=N=N), 1715 (C=O), 1643, 1616, 1434, 1334, 1303, 1244, 1196, 1156, 1136, 1038, 999, 908, 871, 722, 635, 555, 454. **HRMS** (ESI-TOF) *m/z* calculated for $C_{10}H_{15}N_3O_2$ $[M+H]^+$ = 210.1237, found 210.1233; $[M+Na]^+$ = 232.1056, found 232.1051.

5-Azidopentanal (**48**)




**CAUTION** – Low molecular weight azide. Handle with care (see Section 4.1.1).

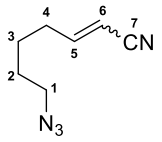
Synthesised by an adapted literature procedure.[341]

To a stirred suspension of sodium azide (1.18 g, 18.2 mmol) in DMSO (20 mL) at room temperature, behind a blast shield, was added 5-bromopentan-1-ol (2.75 g, 16.5 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room temperature for 16 hours, after which it was cooled to 0 °C and water (20.0 mL) was added, followed by diethyl ether (20.0 mL). The reaction mixture was then extracted with diethyl ether (15.0 mL × 3). The combined organic extracts were washed with water (2 × 30.0 mL) and brine (60.0 mL). The aqueous extracts were re-extracted with diethyl ether (15.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 50% diethyl ether/pentane, $R_f$ = 0.4) to give 5-azidopentan-1-ol as a colourless oil (1.70 g, 13.2 mmol). To a stirred solution of 5-azidopentan-1-ol (1.46 g, 11.3 mmol) in dichloromethane

(110 mL) at room temperature, behind a blast shield, was added a mixture of ground Bobbitt's salt (3.56 g, 11.9 mmol) and silica gel (3.50 g). The resulting suspension was stirred at room temperature for 3 days, then filtered through a plug of silica gel. The product was concentrated under reduced pressure to give **48** as a yellow oil, which was used without further purification (1.22 g, 9.61 mmol, 68% over 2 steps).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 9.78 (t, *J* = 1.5 Hz, 1H, $H^5$), 3.31 (t, *J* = 6.6 Hz, 2H, $H^1$), 2.49 (td, *J* = 7.1, 1.5 Hz, 2H, $H^4$), 1.76–1.68 (m, 2H, $H^3$), 1.67–1.58 (m, 2H, $H^2$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 201.7 (CH), 51.1 ($CH_2$), 43.2 ($CH_2$), 28.3 ($CH_2$), 19.2 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2932, 2724, 2092 (N=N=N), 1814, 1722 (C=O), 1677, 1455, 1431, 1363, 1244, 1164, 1134, 1104, 993, 840, 815, 706, 659, 555. *HRMS failed to find the correct mass for this compound*.

7-Azidohept-2-enenitrile (**49**)




To a solution of aldehyde **48** (254 mg, 2.00 mmol) in THF (4.0 0 mL) at 0 °C was added (triphenylphosphoranylidene)acetonitrile (633 mg, 2.10 mmol). The resulting reaction mixture was stirred at 0 °C for for 90 minutes. The reaction mixture was allowed to warm to room temperature and stirred for a further 3 hours. To the reaction mixture was added ammonium chloride (10.0 mL). The reaction mixture was extracted with diethyl ether (3 × 20.0 mL). The combined organic extracts were washed with water (20.0 mL) and brine (20.0 mL). The organic extracts were dried with sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.2) to give **49** as a yellow oil (126 mg, 0.84 mmol, 42%, *E*:*Z* = 1.9:1).

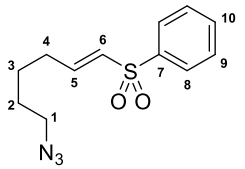
(*E*)-**49**:

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 6.70 (dt, *J* = 16.3, 6.9 Hz, 1H, $H^5$), 5.37-5.31 (m, 1H, $H^6$), 3.30 (t, *J* = 6.6 Hz, 2H, $H^1$), 2.29-2.23 (m, 2H, $H^4$), 1.66-1.50 (m, 4H, $H^2$, $H^3$). *$^{13}$C NMR peaks were indistinguishable from minor isomer*. **FTIR** (neat) $\nu_{max}$ 2942, 2864, 2222 (C≡N), 2091 (N=N=N), 1633, 1445, 1351, 1252, 1122, 1079, 969, 739, 636, 557, 489. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_{10}N_4$ $[M+H]^+$ = 151.097, found 151.086; $[M+Na]^+$ = 173.0798, found 173.0802; $[M+NH_4]^+$ = 168.1244, found 168.1239.

(*Z*)-**49**:

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 6.47 (dt, *J* = 10.9, 7.7 Hz, 1H, $H^5$), 5.36 – 5.33 (m, 1H, $H^6$), 3.31 (t, *J* = 6.6 Hz, 2H, $H^1$) 2.49 – 2.42 (m, 2H, $H^4$), 1.66-1.50 (m, 4H, $H^2$, $H^3$).

(*E*)-((6-Azidohex-1-en-1-yl)sulfonyl)benzene (**51**)



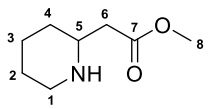

Synthesised by an adapted literature procedure.[430]

To a mixture of the second-generation Grubbs complex (31 mg, 0.04 mmol) and copper(I) iodide (10 mg, 0.05 mmol) was added 6-bromo-1-hexene (887 mg, 5.44 mmol), followed by phenyl vinyl sulfone (305 mg, 1.81 mmol). The resulting reaction mixture was heated to 50 °C for 16 hours, after which the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 20-30% diethyl ether/pentane, $R_f$ = 0.2) to give a bromo sulfone intermediate as a brown oil. To a stirred solution of the bromo sulfone intermediate (430 mg, 1.42 mmol) in DMSO (3.00 mL) at room temperature was added sodium azide (102 mg, 2.84 mmol). The headspace was purged with argon and then the reaction mixture was allowed to stir at room

temperature for 16 hours, after which it was cooled to 0 °C and water (1.00 mL) was added, followed by diethyl ether (10.0 mL). The reaction mixture was then extracted with diethyl ether (20.0 mL × 3). The combined organic extracts were washed with water (2 × 20.0 mL) and brine (40.0 mL). The aqueous extracts were re-extracted with diethyl ether (10.0 mL), and then the combined organic extracts were dried with sodium sulfate. The resulting solution was concentrated under reduced pressure and the crude product was purified by flash column chromatography ($SiO_2$, 20% ethyl acetate/pentane, $R_f$ = 0.4) to give **51** as a pale yellow oil (45 mg, 0.17 mmol, 9% over 2 steps).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.89 – 7.85 (m, 2H, $H^8$), 7.63 – 7.58 (m, 1H, $H^{10}$), 7.56 – 7.49 (m, 2H, $H^9$), 6.97 (dt, *J* = 15.1, 6.7 Hz, 1H, $H^5$), 6.34 (dt, *J* = 15.1, 1.6 Hz, 1H, $H^6$), 3.27 (t, *J* = 6.1 Hz, 2H, $H^1$), 2.31 – 2.24 (m, 2H, $H^4$), 1.64 – 1.53 (m, 2H, $H^3$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 146.0 (CH), 140.6 (C), 133.4 (CH), 131.0 (CH), 129.3 (CH), 127.6 (CH), 51.0 ($CH_2$), 30.9 ($CH_2$), 28.3 ($CH_2$), 24.8 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3062, 2941, 2864, 2097 (N=N=N), 1713, 1642, 1584, 1553, 1478, 1446, 1307 (O=S=O), 1236, 1145, 1122, 1082, 1033, 1016, 996, 944, 917, 895, 835, 811, 755, 723, 687, 656, 610, 598, 578, 560, 530, 504, 435. **HRMS** (ESI-TOF) *m/z* calculated for $C_{12}H_{15}N_3O_2S$ $[M+H]^+$ = 266.0958, found 266.0960; $[M+Na]^+$ = 288.0777, found 288.0780; $[M+NH_4]^+$ = 283.1223, found 283.1225.

Methyl 2-(piperidin-2-yl)acetate (**52**)

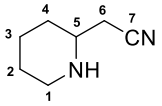



To a stirred solution of azide **44b** (183 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol), followed by phosphine **13** (32 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for 8 hours, after which methanol (0.50 mL) was added. The crude product was concentrated under reduced pressure and then purified by flash

column chromatography ($SiO_2$, 10% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.3) to give **52** as a yellow oil (96 mg, 0.61 mmol, 61%). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[458]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 3.67 (s, 3H, $H^8$), 3.10 – 3.02 (m, 1H, $H^{1a}$) 3.00 (dddd, *J* = 10.6, 7.8, 5.3, 2.7 Hz, $H^5$), 2.73 – 2.65 (m, 1H, $H^{1b}$), 2.51 (dd, *J* = 16.1, 7.8 Hz, 1H, $H^{6a}$), 2.44 (dd, *J* = 16.1, 5.3 Hz, 1H, $H^{6b}$), 1.82 – 1.73 (m, 1H, $H^{3a}$), 1.70 – 1.58 (m, 2H, $H^{2a}$, $H^{3b}$), 1.54-1.34 (m, 1H, $H^{2b}$), 1.25 – 1.11 (m, 1H, $H^{4b}$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) 172.5 (C), 53.3 (CH), 51.7 ($CH_3$), 46.3 ($CH_2$), 41.1 ($CH_2$), 31.7 ($CH_2$), 25.2 ($CH_2$), 24.1 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 2931, 2852, 2729, 1732 (C=O), 1437, 1357, 1331, 1292, 1246, 1203, 1171, 1146, 1120, 1054, 1011, 913, 880, 827, 770, 729, 642, 557, 466, 447. **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_{15}NO_2$ $[M+H]^+$ = 151.0978, found 151.0986; $[M+Na]^+$ = 173.0798, found 173.0802; $[M+NH_4]^+$ = 168.1244, found 168.1239.

2-(Piperidin-2-yl)acetonitrile (**53**)




To a stirred solution of azide **49** (75 mg, 0.50 mmol) in toluene (0.50 mL) at room temperature was added phenylsilane (81 mg, 0.75 mmol), followed by phosphine **13** (16 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 24 hours, after which methanol (0.50 mL) was added. The crude product was concentrated under reduced pressure and then purified by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.3) to give **53** as a pale yellow oil (48 mg, 0.39 mmol, 77 %).

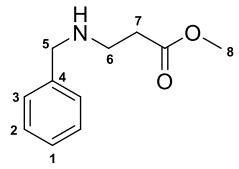
**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 3.11 – 3.05 (m, 1H, $H^{1a}$), 2.88 – 2.80 (m, 1H, $H^5$), 2.69 – 2.61 (m, 1H, $H^{1b}$), 2.46 – 2.35 (m, 2H, $H^{6a}$, $H^{6b}$), 1.84 – 1.80 (m,

1H, $H^{3a}$), 1.78 – 1.73 (m, 1H, $H^{4a}$), 1.63 – 1.59 (m, 1H, $H^{2a}$), 1.42 – 1.33 (m, 2H, $H^{2b}$, $H^{3b}$), 1.26 – 1.17 (m, 1H, $H^{4b}$). **$^{13}C\{^{1}H\}$ NMR** (101 MHz, Chloroform-*d*) δ 117.9 (C), 53.1 (CH), 46.7 ($CH_2$), 32.0 ($CH_2$), 25.5 ($CH_2$), 25.2 ($CH_2$), 24.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3305, 2931, 2855, 2746, 2248 (C≡N), 2177, 2071, 1914, 1657, 1530, 1442, 1420, 1383, 1350, 1334, 1315, 1269, 1219, 1197, 1152, 1126, 1113, 1054, 988, 947, 885, 836, 757, 700, 591, 543, 501, 450. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_{12}N_2$ $[M+H]^+$ = 151.0978, found 151.0986; $[M+Na]^+$ = 173.0798, found 173.0802; $[M+NH_4]^+$ = 168.1244, found 168.1239.

General procedure D: azide reduction/intermolecular conjugate addition

To a stirred solution of azide **54** (67 mg, 0.50 mmol) in toluene (0.50 mL) at room temperature was added phenylsilane (81 mg, 0.75 mmol) followed by phosphine **13** (16 mg, 0.05 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours, after which the appropriate electron-deficient alkene (0.50 mmol) was added. The resulting reaction mixture was stirred at room temperature for 16 hours, after which methanol (0.50 mL) was added.

Methyl 3-(benzylamino)propanoate (**55a**)

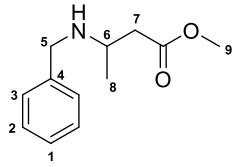



General procedure D was followed on a 1.00 mmol scale with methyl acrylate. Purification by flash column chromatography ($SiO_2$, 10% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.5) gave **55a** as a colourless oil (180 mg, 0.93 mmol, 93%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[459]

**$^{1}H$ NMR** (400 MHz, Chloroform-*d*) δ 7.33 – 7.30 (m, 4H, $H^2$, $H^3$), 7.27 – 7.21 (m, 1H, $H^1$), 3.80 (s, 2H, $H^5$) 3.67 (s, 3H), 2.90 (t, *J* = 6.5 Hz, 2H, $H^6$), 2.54 (t, *J* = 6.5 Hz, 2H, $H^7$). **$^{13}C\{^{1}H\}$ NMR** (101 MHz, Chloroform-*d*) δ 173.2 (C), 140.0 (C),

128.4 (CH), 128.1 (CH), 127.0 (CH), 51.6 ($CH_3$), 44.4 ($CH_2$), 34.5 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3027, 2951, 2842, 1732 (C=O), 1603, 1495, 1453, 1436, 1360, 1169, 1119, 1071, 1027, 983, 885, 840, 736, 698, 593, 539, 497, 421. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{15}NO_2$ $[M+H]^+$ = 194.1176, found 194.1176; $[M+Na]^+$ = 216.0995, found 216.0993.

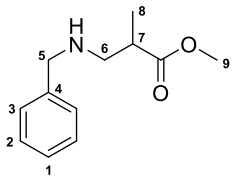
Methyl 3-(benzylamino)butanoate (**55b**)




General procedure D was followed with *trans*-methyl crotonate. Purification by flash column chromatography ($SiO_2$, 1-5% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.3 in 5% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane) gave **55b** as a brown oil (80 mg, 0.39 mmol, 77%). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[460]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.33 – 7.30 (m, 4H, $H^2$, $H^3$), 7.25 – 7.21 (m, 1H, $H^1$), 3.83 (d, *J* = 13.0 Hz, 1H, $H^{5a}$), 3.76 (d, *J* = 13.0 Hz, 1H, $H^{5b}$), 3.67 (s, 3H, $H^9$), 3.21 – 3.07 (m, 1H, $H^6$), 2.51 (dd, *J* = 15.3, 6.8 Hz, 1H, $H^{7a}$), 2.39 (dd, *J* = 15.3, 5.9 Hz, 1H, $H^{7b}$), 1.16 (d, *J* = 6.4 Hz, 3H, $H^8$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 172.8 (C), 140.3 (C), 128.4 (CH), 128.1 (CH), 127.0 (CH), 51.5 ($CH_3$), 51.2 ($CH_2$), 49.7 (CH), 41.4 ($CH_2$), 20.5 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3326, 3028, 2952, 2842, 2053, 1731 (C=O), 1603, 1494, 1453, 1436, 1376, 1294, 1252, 1192, 1172, 1118, 1091, 1027, 1007, 905, 869, 839, 734, 696, 594, 540, 521, 460. **HRMS** (ESI-TOF) *m/z* calculated for $C_{12}H_{17}NO_2$ $[M+H]^+$ = 208.1332, found 208.1330; $[M+Na]^+$ = 230.1151, found 230.1151.

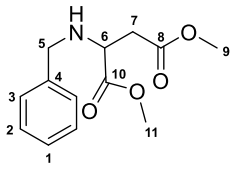
Methyl 3-(benzylamino)-2-methylpropanoate (**55c**)



General procedure D was followed with methyl methacrylate. Purification by flash column chromatography ($SiO_2$, 2% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.4) gave **55c** as a brown oil (21 mg, 0.10 mmol, 20%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[461]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 4H, $H^2$, $H^3$), 7.29 – 7.23 (m, 1H, $H^1$), 3.83 (d, *J* = 2.5 Hz, 2H, $H^5$), 3.71 (s, 3H, $H^9$), 2.95 – 2.87 (m, 1H, $H^{6a}$), 2.77 – 2.62 (m, 2H, $H^{6b}$, $H^7$), 1.20 (d, *J* = 6.9 Hz, 2H, $H^9$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 176.3 (C), 140.1 (C), 128.4 (CH), 128.1 (CH), 127.0 (CH), 53.7 ($CH_2$), 52.1 ($CH_2$), 51.7 ($CH_3$), 40.0 (CH), 15.3 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3274, 3060, 3027, 2974, 2845, 1731 (C=O), 1589, 1495, 1454, 1436, 1361, 1230, 1170, 1116, 1028, 998, 957, 901, 835, 742, 720, 696, 580, 540, 495. **HRMS** (ESI-TOF) *m/z* calculated for $C_{12}H_{17}NO_2$ $[M+H]^+$ = 208.1332, found 208.1335.

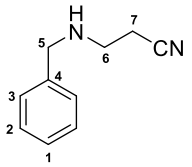
Dimethyl benzylaspartate (**55d**)



General procedure D was followed with dimethyl fumarate. Purification by flash column chromatography ($SiO_2$, 0.5-1% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.2 in 1% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane) gave **55d** as an orange oil (106 mg, 0.42 mmol, 84%). Characterisation data were consistent with previous literature: $^{13}C$ NMR.[462]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.33 – 7.30 (m, 4H, $H^{2}$, $H^{3}$), 7.27 – 7.21 (m, 1H, $H^{1}$), 3.88 (d, *J* = 13.1 Hz, 1H, $H^{5a}$), 3.76 – 3.69 (m, 4H, $H^{5b}$, $H^{11}$), 3.71 – 3.64 (m, 4H, $H^{6}$, $H^{9}$), 2.76 (dd, *J* = 15.9, 5.9 Hz, 1H, $H^{7a}$), 2.69 (dd, *J* = 15.9, 6.9 Hz, 1H, $H^{7b}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 174.0 (C), 171.3 (C), 139.4 (C), 128.4 (CH), 128.3 (CH), 127.2 (CH), 56.9 (CH), 52.2 ($CH_3$), 52.0 ($CH_3$), 51.9 ($CH_2$), 37.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3334, 3029, 2952, 2847, 2102, 1732 (C=O), 1604, 1495, 1453, 1436, 1363, 1200, 1164, 1046, 1027, 997, 849, 735, 698, 615, 584, 497, 472, 416. **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{17}NO_4$ $[M+H]^+$ = 252.1230, found 252.1232; $[M+Na]^+$ = 274.1050, found 274.1052.

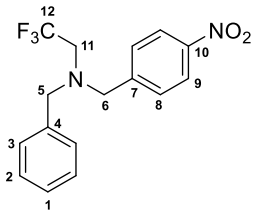
3-(Benzylamino)propanenitrile (**55e**)




General procedure D was followed with acrylonitrile. Purification by flash column chromatography ($SiO_2$, 5% (ammonia/methanol (10% $NH_4OH$ in MeOH))/dichloromethane, $R_f$ = 0.6) gave **55e** as an orange oil (24 mg, 0.15 mmol, 30%). Characterisation data were consistent with previous literature: $^{1}$H, $^{13}$C NMR.[463]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 4H, $H^{2}$, $H^{3}$), 7.29 – 7.24 (m, 1H, $H^{1}$), 2.93 (t, *J* = 6.6 Hz, 2H, $H^{7}$), 2.52 (t, *J* = 6.6 Hz, 2H, $H^{6}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 139.4 (C), 128.6 (CH), 128.1 (CH), 127.3 (CH), 118.7 (C), 53.2 ($CH_2$), 44.3 ($CH_2$), 18.8 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3261, 3060, 3028, 2928, 2849, 2247 (C≡N), 2098, 1726, 1682, 1590, 1494, 1454, 1436, 1362, 1311, 1232, 1167, 1116, 1072, 1028, 998, 969, 860, 742, 719, 696, 580, 540, 446. **HRMS** (ESI-TOF) *m/z* calculated for $C_{10}H_{12}N_2$ $[M+H]^+$ = 161.1073, found 161.1068.

*N*-Benzyl-3,3,3-trifluoro-*N*-(4-nitrobenzyl)propan-1-amine (**56**)

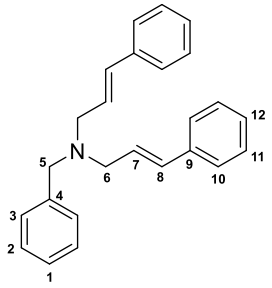



Synthesised by an adapted literature procedure.[343]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added 4-nitrobenzaldehyde (151 mg, 1.00 mmol), followed by phenylsilane (54 mg, 0.50 mmol). The resulting reaction mixture was heated at 70 °C for 10 minutes. To the reaction mixture was added trifluoroacetic acid (200 mg, 1.75 mmol), followed by phenylsilane (216 mg, 2.00 mmol). The resulting reaction mixture was heated at 70 °C for 16 hours. The reaction mixture was allowed to cool to room temperature and silica gel (100 mg) was added. The crude reaction mixture was purified by flash column chromatography ($SiO_2$, 5% diethyl ether/petroleum ether, $R_f$ = 0.3) to give **56** as a yellow oil (170 mg, 0.52 mmol, 52%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.37 – 7.27 (m, 2H), 3.90 (s, 1H), 3.81 (s, 1H), 3.13 (q, *J* = 9.4 Hz, 1H). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 147.4 (C), 146.3 (C), 137.5 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 125.9 (q, *J* = 282.3 Hz, C), 123.7 (CH), 58.6 ($CH_2$) 57.6 ($CH_2$), 53.4 (q, *J* = 30.4 Hz, $CH_2$). **$^{19}$F{$^1$H} NMR** (376 MHz, Chloroform-*d*) δ -68.0. **FTIR** (neat) $\nu_{max}$ 2849, 1602, 1519, 1495, 1454, 1374, 1343, 1267, 1177, 1136, 1109, 1069, 1029, 1015, 980, 931, 846, 739, 697, 671, 613, 549, 488, 452. **HRMS** (ESI-TOF) *m/z* calculated for $C_{16}H_{15}N_2O_2F_3$ $[M+H]^+$ = 325.1158, found 325.1150; $[M+Na]^+$ = 347.0978, found 347.0971.

(*E*)-*N*-Benzyl-*N*-cinnamyl-3-phenylprop-2-en-1-amine (**57**)




Synthesised by an adapted literature procedure.[344]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added 4-nitrobenzaldehyde (151 mg, 1.00 mmol), followed by phenylsilane (54 mg, 0.50 mmol). The resulting reaction mixture was heated at 70 °C for 10 minutes. To the reaction mixture was added formaldehyde (162 mg of a 37 wt% aqueous solution, 2.00 mmol), followed by water (0.30 mL), and the reaction mixture was allowed to stir at 70 °C for 10 minutes. To the reaction mixture was added (*E*)-styrylboronic acid (296 mg, 2.00 mmol), and the resulting reaction mixture was heated to 80 °C for 16 hours. The reaction mixture was allowed to cool to room temperature, and diethyl ether (10.0 mL) was added. The crude reaction mixture was dried with magnesium sulfate, and filtered, with dichloromethane washings (~5.00 mL). The crude reaction mixture was purified by flash column chromatography ($SiO_2$, 5-10% diethyl ether/pentane, $R_f$ = 0.3 in 10% diethyl ether/pentane) to give **57** as a yellow oil (95 mg, 0.28 mmol, 28%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.41 – 7.37 (m, 6H, $H^3$, $H^{11}$), 7.36 – 7.29 (m, 6H, $H^2$, $H^{10}$), 7.28 – 7.21 (m, 3H, $H^1$, $H^{12}$), 6.55 (d, *J* = 15.9 Hz, 2H, $H^8$), 6.32 (dt, *J* = 15.9, 6.6 Hz, 2H, $H^7$), 3.69 (s, 2H, $H^5$), 3.31 (dd, *J* = 6.6, 1.4 Hz, 4H, $H^6$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 139.4 (C), 137.2 (C), 132.6 (CH), 129.0 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 126.3 (CH),

58.0 ($CH_2$), 56.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3081, 3059, 3025, 2917, 2793, 1946, 1875, 1677, 1626, 1598, 1577, 1494, 1448, 1361, 1232, 1204, 1120, 1070, 1028, 963, 908, 841, 804, 730, 690, 649, 607, 581, 558, 492, 468, 427. **HRMS** (ESI-TOF) *m/z* calculated for $C_{25}H_{25}N$ $[M+H]^+$ = 340.2060, found 340.2057.

Attempted $A^3$ coupling

Adapted from a literature procedure.[464]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added copper(II) trifluoromethanesulfonate (37 mg, 0.10 mmol), after which the reaction atmosphere was purged with argon for 10 minutes. To the reaction mixture was added cyclohexanone (108 mg, 1.10 mmol) and 1-octyne (165 mg, 1.50 mmol). The reaction mixture was heated at 110 °C for 16 hours. TLC and $^1$H NMR spectroscopic analysis of the crude reaction mixture showed no evidence of the desired product.

Attempted Buchwald-Hartwig arylation

Adapted from a literature procedure.[353]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in degassed toluene (1.0 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was sparged with argon, and then added to a mixture of sodium *tert*-butoxide (106 mg, 1.10 mmol) and Xantphos (43 mg, 0.08 mmol) under argon. To the reaction mixture was added tris(dibenzylideneacetone)dipalladium(0) (16 mg, 0.05 mmol). The resulting

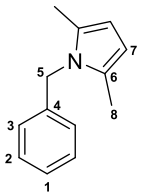
reaction mixture was heated at 80 °C for 24 hours. TLC and $^1$H NMR spectroscopic analysis of the crude reaction mixture showed no evidence of the desired product.

Attempted metal-free arylation

Adapted from a literature procedure.[354]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added sodium carbonate (106 mg, 1.00 mmol), freshly prepared (4-bromophenyl)(4-methoxyphenyl)iodonium trifluoromethanesulfonate[465] (539 mg, 1.00 mmol), and further toluene (4.00 mL). The resulting reaction mixture was sparged with argon and then heated to reflux for 16 hours. TLC and $^1$H NMR spectroscopic analysis of the crude reaction mixture showed no evidence of the desired product.

1-Benzyl-2,5-dimethyl-1H-pyrrole (**64**)

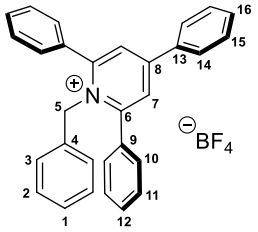



To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added methanol (0.50 mL); the resulting reaction mixture was stirred at room temperature for 20 minutes. To the reaction mixture was added 2,5-hexanedione (120 mg, 1.05 mmol); the resulting reaction mixture was stirred at room temperature for 5 minutes. To the reaction mixture was added *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol). The resulting reaction mixture was heated to 50 °C for 16

hours. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 2-5% diethyl ether/pentane, $R_f$ = 0.4 in 5% diethyl ether/pentane) to give **64** as a pale brown solid (114 mg, 0.62 mmol, 62%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[466]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.32 – 7.28 (m, 2H, $H^2$), 7.25 – 7.21 (m, 1H, $H^1$), 6.89 (d, *J* = 7.5 Hz, 2H, $H^3$), 5.79 (br s, 2H, $H^7$), 5.01 (s, 2H, $H^5$), 2.15 (s, 6H, $H^8$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 138.6 (C), 128.7 (CH), 128.0 (C), 127.0 (CH), 125.7 (CH), 105.4 (CH), 46.7 ($CH_2$), 12.5 ($CH_3$). **HRMS** (ESI-TOF) *m/z* calculated for $C_{13}H_{15}N$ $[M+H]^+$ = 186.1277, found 186.1274.

1-Benzyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate (**65**)




Synthesised by an adapted literature procedure.[357]

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in toluene (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 8 hours. To the reaction mixture was added ethanol (0.50 mL); the resulting reaction mixture was stirred at room temperature for 10 minutes. To the reaction mixture was added 2,4,6-triphenylpyrylium tetrafluoroborate (376 mg, 0.95 mmol), followed by further ethanol (0.50 mL). The resulting reaction mixture was allowed to stir at room temperature for 16 hours. To the reaction mixture was added diethyl ether (5.00 mL). The resulting precipitate was collected by filtration, and washed with diethyl ether to give **65** as

a yellow solid (361 mg, 0.78 mmol, 78%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[467]

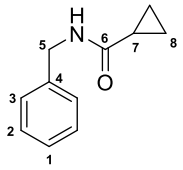
**$^{1}H$ NMR** (400 MHz, Chloroform-*d*) δ 7.97 (s, 2H, $H^{7}$), 7.86 – 7.80 (m, 2H, $H^{14}$), 7.67 – 7.63 (d, *J* = 6.5 Hz, 4H, $H^{10}$), 7.60 – 7.54 (m, 3H, $H^{15}$, $H^{16}$), 7.52 – 7.44 (m, 6H, $H^{11}$, $H^{12}$), 7.20 – 7.14 (m, 1H, $H^{1}$), 7.13 – 7.06 (m, 2H, $H^{2}$), 6.47 (d, *J* = 7.3 Hz, 2H, $H^{3}$), 5.78 (s, 2H, $H^{5}$). **$^{13}C\{^{1}H\}$ NMR** (101 MHz, Chloroform-*d*) δ 157.6 (C), 156.3 (C), 134.3 (C), 133.9 (C), 132.8 (C), 132.4 (C), 131.0 (CH) (CH), 129.8 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.2 (C), 128.2 (CH), 126.6 (CH), 126.2 (CH), 58.3 ($CH_2$). **$^{19}F$ NMR** (376 MHz, Chloroform-*d*) δ -153.2. **FTIR** (neat) $\nu_{max}$ 3064, 2119, 1814, 1620, 1597, 1581, 1562, 1496, 1453, 1414, 1367, 1348, 1326, 1284, 1265, 12412, 1187, 1160, 1046, 1033, 1000, 962, 929 895, 886, 857, 793, 771, 757, 731, 702, 692, 640, 610, 596, 579, 523, 479, 461. **HRMS** (ESI-TOF) *m/z* calculated for $C_{30}H_{24}N^{+}BF_4^{-}$ $[M\text{-}BF_4]^{+}$ = 398.1903, found 398.1903.

General procedure E: azide reduction/amidation

To a stirred solution of azide **54** (67 mg, 0.50 mmol) in acetonitrile (0.50 mL) at room temperature was added phenylsilane (81 mg, 0.75 mmol), followed by phosphine **13** (16 mg, 0.05 mmol). The resulting reaction mixture was allowed to stir at room temperature for 8 hours, after which the appropriate carboxylic acid (0.50 mmol) was added, with further acetonitrile (0.50 mL). The resulting reaction mixture was allowed to stir at room temperature for 16 hours, after which water (1.00 mL) was added; after the resulting effervescence had ceased, further water (4.00 mL) was added. The reaction mixture was extracted with ethyl acetate (10.0 mL × 3). The combined organic extracts were then washed with ammonium chloride (2 × 5.00 mL), then sodium bicarbonate (2 × 5.00 mL), and then brine (10.0 mL). The organic extracts were dried with magnesium sulfate, filtered, and

concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with ethyl acetate/pentane.

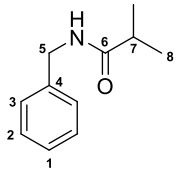
*N*-Benzylcyclopropanecarboxamide (**66a**)



General procedure E was followed with cyclopropanecarboxylic acid. Purification by flash column chromatography ($SiO_2$, 20-40% ethyl acetate/pentane, $R_f$ = 0.2 in 40% ethyl acetate/pentane) gave **66a** as a white solid (52 mg, 0.30 mmol, 59%). Characterisation data were consistent with previous literature: $^{1}H$, $^{13}C$ NMR.[468]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.33 (m, 2H, $H^3$), 7.31 – 7.28 (m, 3H, $H^1$, $H^2$), 5.87 (br. s, 1H, NH), 4.46 (d, *J* = 5.6 Hz, 2H, $H^5$), 1.35 (tt, *J* = 7.9, 4.6 Hz, 1H, $H^7$), 1.04 – 0.99 (m, 2H, $H^{8a}$), 0.78 – 0.72 (m, 2H, $H^{8b}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 173.4 (C), 138.5 (C), 128.7 (CH), 127.9 (CH), 127.5 (CH), 43.9 ($CH_2$), 14.8 (CH) 7.22 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3289 (N–H), 3068, 3030, 3004, 2925, 2120, 1697, 1631 (C=O), 1540, 1493, 1452, 1401, 1347, 1236, 1218, 1154, 1106, 1077, 1055, 1029, 986, 932, 912, 870, 824, 790, 748, 695, 573, 518, 423. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{13}NO$ $[M+H]^+$ = 176.1070, found 176.1073; $[M+Na]^+$ = 198.0889, found 198.0892.

*N*-Benzylisobutyramide (**66b**)

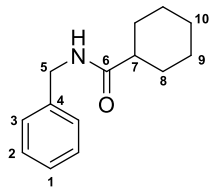


General procedure E was followed with isobutyric acid. Purification by flash column chromatography ($SiO_2$, 20-40% ethyl acetate/pentane, $R_f$ = 0.1 in 40% ethyl acetate/pentane) gave **66b** as a white solid (29 mg, 0.16 mmol, 33%).

Characterisation data were consistent with previous literature: m.p.; $^{1}$H, $^{13}$C NMR.[469,470]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H, $H^{3}$), 7.32 – 7.25 (m, 3H, $H^{1}$, $H^{2}$), 5.72 (s, 1H), 4.44 (d, *J* = 5.7 Hz, 2H), 2.39 (hept, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 176.8 (C), 138.5 (C), 128.7 (CH), 127.8 (CH), 127.5 (CH), 43.5 ($CH_2$), 35.7 (CH), 19.7 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3284 (N–H), 3067, 3033, 2971, 2873, 2778, 2066, 1636 (C=O), 1538, 1497, 1455, 1385, 1371, 1349, 1309, 1240, 1225, 1172, 1157, 1102, 1078, 1062, 1029, 996, 922, 863, 801, 776, 744, 692, 579, 530, 504, 454, 408. **HRMS** (ESI-TOF) *m/z* calculated for $C_{11}H_{15}NO$ $[M+H]^+$ = 178.2226, found 178.2222; $[M+Na]^+$ = 200.1046, found 200.1043. **m.p.** 94-96 °C.

*N*-Benzylcyclohexanecarboxamide (**66c**)[471]

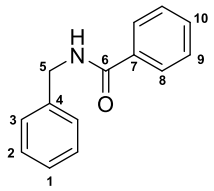



General procedure E was followed with cyclohexanecarboxylic acid. Purification by flash column chromatography ($SiO_2$, 20-40% ethyl acetate/pentane, $R_f$ = 0.1 in 40% ethyl acetate/pentane) gave **66c** as a white solid (57 mg, 0.26 mmol, 52%). Characterisation data were consistent with previous literature: m.p.; $^{13}$C NMR.[472]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.29 – 7.22 (m, 3H), 5.71 (s, 1H, NH), 4.44 (d, *J* = 5.7 Hz, 2H, $H^{5}$), 2.11 (tt, *J* = 11.7, 3.5 Hz, 1H, $H^{7}$), 1.89 (m, 2H, $H^{8a}$), 1.83 – 1.76 (m, 2H, $H^{8b}$), 1.69 – 1.63 (m, 1H, $H^{10a}$), 1.52 – 1.39 (m, 2H, $H^{9a}$), 1.32 – 1.17 (m, 3H, $H^{9b}$, $H^{10}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 175.9 (C), 138.6 (C), 128.7 (CH), 127.8 (CH), 127.5 (CH), 45.6 (CH), 43.4 ($CH_2$), 29.8 ($CH_2$), 25.8 ($CH_2$), 25.8 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3279 (N–H), 3086, 3031, 2924, 2850, 2119, 1640 (C=O), 1547, 1494, 1449, 1389, 1351, 1335, 1257, 1238, 1217, 1179, 1135, 1080, 1046, 1028, 989, 910, 897, 841,

821, 767, 742, 694, 622, 602, 525, 508, 457, 410. **HRMS** (ESI-TOF) *m/z* calculated for $C_{14}H_{19}NO$ $[M+H]^+$ = 218.2539, found 218.1540; $[M+Na]^+$ = 240.1359, found 240.1360. **m.p.** 113-114 °C

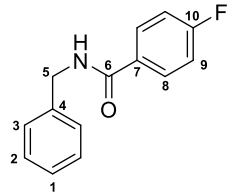
*N*-Benzylbenzamide (**66d**)



General procedure E was followed with benzoic acid. Purification by flash column chromatography (20% ethyl acetate/pentane, $R_f$ = 0.3) gave **66d** as an off-white solid (47 mg, 0.22 mmol, 45%). Characterisation data were consistent with previous literature: m.p.; $^1H$, $^{13}C$ NMR.[472]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.83 – 7.77 (m, 2H, $H^8$), 7.52 – 7.47 (m, 1H, $H^{10}$), 7.45 – 7.40 (m, 2H, $H^9$), 7.37 – 7.34 (m, 4H, $H^2$, $H^3$), 7.32 – 7.27 (m, 1H, $H^1$), 6.51 (s, 1H, NH), 4.67 – 4.61 (m, 2H, $H^5$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) 167.4 (C), 138.2 (C), 134.4 (C), 131.6 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 44.2 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3287 (N–H), 3059, 3029, 2926, 2128, 1814, 1638 (C=O), 1601, 1576, 1542, 1488, 1451, 1430, 1417, 1362, 1313, 1230, 1259, 1131, 1075, 1027, 1000, 987, 928, 805, 794, 726, 692, 599, 492, 462, 441, 414. **HRMS** (ESI-TOF) *m/z* calculated for $C_{14}H_{13}NO$ $[M+H]^+$ = 212.1070, found 212.1069; $[M+Na]^+$ = 234.0889, found 234.0888. **m.p.** 104-106 °C

*N*-Benzyl-4-fluorobenzamide (**69**)



To a stirred solution of benzylamine (0.55 mL, 5.00 mmol) in ethyl acetate (10.0 mL) at 0 °C was added sodium hydroxide (3.00 mL of a 10 wt% aqueous solution), followed by 4-fluorobenzoyl chloride (0.9 mL, 7.50 mmol), dropwise. The resulting

reaction mixture was stirred for 16 hours and allowed to warm to room temperature. The reaction mixture was extracted with ethyl acetate (3 × 40.0 mL). The organic extracts were washed with sodium hydroxide (100 mL of a 15 wt% aqueous solution), water (100 mL), and brine (100 mL). The aqueous extracts were combined and re-extracted with ethyl acetate (80.0 mL). The combined organic extracts were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was re-crystallised from diethyl ether to give **69** as white needle-like crystals (649 mg, 2.83 mmol, 57%). Characterisation data were consistent with previous literature: m.p.; $^{1}$H, $^{13}$C NMR.[471,473]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 7.83 – 7.76 (m, 2H, $H^{8}$), 7.40 – 7.28 (m, 5H, $H^{1}$, $H^{2}$, $H^{3}$), 7.14 – 7.04 (m, 2H, $H^{9}$), 6.34 (s, 1H, NH), 4.64 (d, *J* = 5.6 Hz, 1H, $H^{5}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) 166.0 (C), 164.9 (d, *J* = 274.2 Hz, C), 146.3 (C), 138.0 (C) 129.3 (d, *J* = 8.9 Hz, CH), 128.9 (CH), 128.0 (CH), 127.7 (CH), 115.7 (d, *J* = 21.9 Hz, CH), 44.3 ($CH_2$). **$^{19}$F NMR** (376 MHz, Chloroform-*d*) δ -108.1. **FTIR** (neat) $\nu_{max}$ 3323, 3067, 3031, 2932, 2068, 1954, 1874, 1814, 1642 (C=O), 1597, 1551, 1496, 1451, 1421, 1361, 1320, 1290, 1257, 1226, 1160, 1100, 1078, 1053, 1029, 1011, 987, 904, 853, 790, 766, 724, 711, 696, 664, 631, 607, 588, 527, 493, 459, 421. **m.p.** 146-148 °C

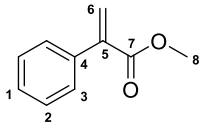
Amidation – $^{19}$F NMR studies

To a stirred solution of azide **54** (133 mg, 1.00 mmol) in acetonitrile (1.00 mL) at room temperature was added phenylsilane (162 mg, 1.50 mmol) and fluorobenzene (96 mg, 1.00 mmol), followed by phosphine **13** (32 mg, 0.10 mmol). The resulting reaction mixture was allowed to stir at room temperature for 16 hours. To the reaction mixture was added 4-fluorobenzoic acid (**68**) (162 mg, 1.50 mmol), with further acetonitrile (1.00 mL). The reaction mixture was allowed to stir at room temperature. The reaction was monitored hourly by

removal of 0.10 mL aliquots, which were diluted with MeCN-$d_3$ (0.40 mL), and analysed by quantitative $^{19}$F NMR spectroscopy (delay time = 25 s, offset = -108.0 ppm), by comparison of the integrated $^{19}$F signals for the amide and fluorobenzene. Phenylsilane-spiked amide sample prepared by addition of 1.5 equiv. of phenylsilane to a sample of pure amide **69** at room temperature.

**$^{19}$F NMR** (376 MHz, MeCN-$d_3$) 4-fluorobenzoic acid (**68**) (δ = -107.9, $T_1$ = 4.9 s); amide **69** (δ = -108.1, $T_1$ = 4.9 s); phenylsilane-spiked amide **69** (δ = -111.0, $T_1$ = 4.7 s).

Methyl 2-phenylacrylate (**98**)




To a stirred solution of 2-phenylacrylic acid (1.48 g, 10.0 mmol) in toluene/methanol (100 mL, 3:2) at room temperature was added trimethylsilyldiazomethane (6.00 mL of a 2M solution in diethyl ether, 12.0 mmol) dropwise over 10 minutes until a yellow colour persisted. The resulting reaction mixture was stirred at room temperature for 30 minutes, after which acetic acid (0.50 mL, glacial) was added. The reaction mixture was stirred at room temperature for 5 minutes, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 5-10% ethyl acetate/pentane, $R_f$ = 0.6 in 10% ethyl acetate/pentane) to give **98** as a pale yellow oil (1.22 g, 7.52 mmol, 75%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[474]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 7.43 – 7.40 (m, 2H, $H^3$), 7.38 – 7.31 (m, 3H, $H^1$, $H^2$), 6.37 (d, *J* = 1.2 Hz, 1H, $H^{6a}$), 5.89 (d, *J* = 1.2 Hz, 1H, $H^{6b}$), 3.83 (s, 3H, $H^8$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 167.3 (C), 141.3 (C), 136.7 (C), 128.3 (CH), 128.2 (CH) 128.1 (CH), 127.0 ($CH_2$), 52.2 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 2952, 1720 (C=O), 1615, 1575, 1495, 1435, 1401, 1373, 1333, 1308, 1239,

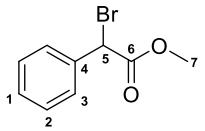
1199, 1177, 1094, 1075, 1045, 1029, 990, 948, 918, 867, 846, 813, 775, 699, 645, 592, 497, 460. *HRMS failed to find the correct mass for this compound.*

Attempted preparation of α,β-unsaturated ester **94** by cross metathesis

Adapted from a literature procedure.[430]

To a mixture of the appropriate metathesis precatalyst (0.016 mmol) and copper(I) iodide (9 mg, 0.048 mmol) was added 6-bromo-1-hexene (0.32 mL, 2.40 mmol) and methyl 2-phenylacrylate (130 mg, 0.80 mmol). The resulting reaction mixture was stirred and heated to 50 °C for 24 hours.

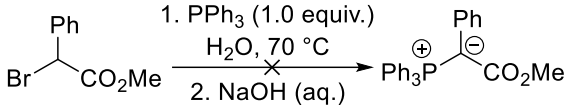
Methyl 2-bromo-2-phenylacetate (**101**)




To a stirred solution of methyl phenylacetate (1.40 mL, 10.0 mmol) in chloroform (50.0 mL) at room temperature was added *N*-bromosuccinimide (2.14 g, 12.0 mmol) and azobisisobutyronitrile (82 mg, 0.50 mmol). The resulting reaction mixture was heated to reflux for 48 h, after which it was allowed to cool to room temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography ($SiO_2$, 5% diethyl ether/pentane, $R_f$ = 0.2) to give **101** as a pale yellow oil (1.85 g, 8.11 mmol, 81%). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[475]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.57 – 7.51 (m, 2H, $H^2$), 7.40 – 7.34 (m, 3H, $H^1$, $H^3$), 5.36 (s, 1H, $H^5$), 3.79 (s, 3H, $H^7$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 168.8 (C), 135.8 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 53.4 ($CH_3$), 46.5 (CH). **HRMS** (ESI-TOF) *m/z* calculated for $C_9H_9O_2Br$ $[M+NH_4]^+$ = 246.0124, found 246.0138.

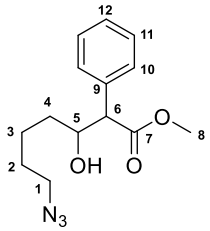
Attempted preparation of ylide **99** by alkylation/deprotonation




Adapted from a literature procedure.[476]

To a suspension of triphenylphosphine (2.58 g, 9.85 mmol) in water (20.0 mL) was added bromide **101** (2.25g, 9.85 mmol). The resulting reaction mixture was stirred and heated to 70 °C for 16 hours. The reaction mixture was cooled to 0 °C and sodium hydroxide (4.00 mL of a 10 wt% aqueous solution) was added dropwise. To the reaction mixture was added dichloromethane (20.0 mL), and the aqueous layer was extracted with dichloromethane (30.0 mL × 2). The combined organic layers were washed with brine (30.0 mL) and dried with sodium sulfate. The reaction mixture was concentrated under reduced pressure and pentane (~10.0 mL) was added. The resulting precipitate (2.20 g) was collected by filtration. $^{31}P$ and $^{1}H$ NMR spectroscopic analysis indicated that the majority of this precipitate was triphenylphosphine oxide.

Methyl 7-azido-3-hydroxy-2-phenylheptanoate (**103**)

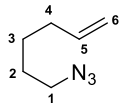



To a suspension of sodium methoxide (30 mg, 0.55 mmol) in THF (1.00 mL) at room temperature was added methyl phenylacetate (90 mg, 0.60 mmol). The reaction mixture was stirred at room temperature for 10 minutes, and then cooled to 0 °C. To the reaction mixture was added aldehyde **48** (64 mg, 0.50 mmol, in 0.50 mL THF) dropwise over 2 minutes. The reaction mixture was stirred for 16 hours and allowed to warm to room temperature. Water (5.00 mL) was added to the reaction mixture, followed by diethyl ether (5.00 mL). The aqueous layer was extracted with diethyl ether (5.00 mL × 2), and the organic layers were washed with water (10.0 mL), and brine (10.0 mL). The aqueous layers were re-extracted

with diethyl ether (10.0 mL) and dried with magnesium sulfate. The crude product was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 10-20% ethyl acetate/pentane, $R_f$ = 0.2 in 20% ethyl acetate/pentane) to give **103** as a yellow oil (34 mg, 0.12 mmol, 24%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.36 – 7.29 (m, 3H, $H^{11}$, $H^{12}$), 7.27 – 7.22 (m, 2H, $H^{10}$), 4.15 (ddd, *J* = 9.1, 7.2, 4.2 Hz, 1H, $H^5$), 3.68 (s, 3H, $H^8$), 3.57 (d, *J* = 9.1 Hz, 1H, $H^6$), 3.18 (t, *J* = 6.6 Hz, 2H, $H^1$), 1.69 – 1.42 (m, 4H, $H^2$, $H^3$), 1.32 – 1.23 (m, 2H, $H^4$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 174.1 (C), 136.0 (C), 129.0 (CH), 128.3 (CH), 127.8 (CH), 73.0 (CH), 58.6 (CH), 52.2 ($CH_3$), 51.3 ($CH_2$), 33.2 ($CH_2$), 28.6 ($CH_2$), 22.6 ($CH_2$). **HRMS** (ESI-TOF) *m/z* calculated for $C_{14}H_{19}N_3O_3$ $[M+H]^+$ = 278.1499, found 278.1500; $[M+Na]^+$ = 300.1319, found 300.1315; $[M+NH_4]^+$ = 295.1765, found 295.1768.

6-Azido-1-hexene (**114**)

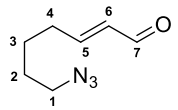



**CAUTION** – Low molecular weight azide. Handle with care (see Section 4.1.1).

To a solution of sodium azide (7.15 g, 110 mmol) in DMSO (100 mL), behind a blast shield, was added 6-bromo-1-hexene (13.4 mL, 100 mmol) over two minutes. The reaction was stirred at room temperature under argon for 24 h and monitored by TLC. The reaction was quenched with water (200 mL). The reaction mixture was allowed to cool to room temperature and then extracted with diethyl ether (100 mL × 3). The combined organic extracts were dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography (neutral $Al_2O_3$, 100% pentane, $R_f$ = 0.7) to give **114** as a colourless oil – handled as a ~50 wt% solution in pentane (11.6 g, 93.0 mmol, 93%). Characterisation data were consistent with previous literature: $^1$H, $^{13}$C NMR.[477]

**$^{1}$H NMR** (400 MHz, Chloroform-*d*) δ 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, $H^{5}$), 5.11 – 4.88 (m, 2H, $H^{6a}$, $H^{6b}$), 3.27 (t, *J* = 6.9 Hz, 2H, $H^{1}$), 2.13 – 2.02 (m, 2H, $H^{4}$), 1.67 – 1.56 (m, 2H, $H^{2}$), 1.53 – 1.43 (m, 2H, $H^{3}$). **$^{13}$C{$^{1}$H} NMR** (101 MHz, Chloroform-*d*) δ 138.2 (CH), 115.0 ($CH_2$), 51.3 ($CH_2$), 33.2 ($CH_2$), 28.3 ($CH_2$), 25.9 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3079, 2936, 2862, 2089 (N=N=N), 1641, 1455, 1350, 1247, 993, 910, 739, 633, 557. **HRMS** (ESI-TOF) *m/z* calculated for $C_6H_{11}N_3$ $[M+H]^+$ = 126.1026, found 126.1034.

7-Azidohept-2-enal (**113**)




Initial metathesis screening conditions

Adapted from a literature procedure.[478]

To a stirred solution of azide **114** (100 mg, 0.8 mmol) and the appropriate metathesis catalyst (0.02 mmol) in dichloromethane (1.00 mL) under argon was added crotonaldehyde (0.72 mL, 2.4 mmol) dropwise. The reaction was allowed to stir at room temperature for 6 h. The reaction mixture was then purified by flash column chromatography ($SiO_2$, 40% diethyl ether/petroleum ether) to give **113** as an orange oil.

Metathesis optimisation procedure

Adapted from a literature procedure.[430]

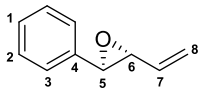
To a mixture of the appropriate metathesis catalyst and copper(I) iodide was added diethyl ether (1.60 mL), azide **114** (100 mg, 0.8 mmol) and crotonaldehyde. The resulting reaction mixture was stirred and heated to 50 °C for the appropriate length of time, after which it was allowed to cool to room temperature. The crude product was concentrated under reduced pressure and purified by flash column chromatography on silica gel ($SiO_2$, 40% diethyl ether/pentane) to give **113** as an orange oil.

Scaled-up procedure

To a mixture of the second-generation Grubbs complex (64 mg, 0.08 mmol) and copper(I) iodide (48 mg, 0.25 mmol) was added azide **114** (500 mg, 4.00 mmol) and crotonaldehyde (1.00 mL, 12.0 mmol). The resulting reaction mixture was stirred and heated to 50 °C for 4 hours, after which it was allowed to cool to room temperature. The crude product was concentrated under reduced pressure and purified by flash column chromatography ($SiO_2$, 40% diethyl ether/pentane, $R_f$ = 0.4) to give **113** as an orange oil (275 mg, 1.80 mmol, 45%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 9.52 (d, *J* = 7.8 Hz, 1H, $H^7$), 6.83 (dt, *J* = 15.7, 6.7 Hz, 1H, $H^5$), 6.14 (ddt, *J* = 15.7, 7.8, 1.5 Hz, 1H, $H^6$), 3.32 (t, *J* = 6.1 Hz, 2H, $H^1$), 2.49 – 2.22 (m, 2H, $H^4$), 1.84 – 1.49 (m, 4H, $H^2$ and $H^3$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 193.9 (C), 157.5 (CH), 133.4 (CH), 51.1 ($CH_2$), 32.1 ($CH_2$), 28.4 ($CH_2$), 25.0 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3369, 2935, 2865, 2735, 2091 (N=N=N), 1687 (C=O), 1637, 1455, 1350, 1256, 1167, 1132, 1094, 1010, 975, 739, 636, 556, 452, 421, 412. **HRMS** (ESI-TOF) *m/z* calculated for $C_7H_{11}N_3O$ $[M+H]^+$ = 154.0975, found 154.0970.

(2*R**,3*R**)-2-Phenyl-3-vinyloxirane (**118**)




To a stirred solution of (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (120 mg, 0.20 mmol) in dichloromethane (4.00 mL) was added the cinnamaldehyde (0.25 mL, 2.00 mmol) at room temperature. The resulting reaction mixture was left to stir for 10 minutes, after which time hydrogen peroxide solution (252 mg, 35 wt%, 2.60 mmol) was added. The reaction mixture was left to stir for 5 hours at room temperature. During the reaction time, a phosphonium ylide solution was prepared as follows: to methyltriphenylphosphonium bromide (857 mg, 2.40 mmol) was added tetrahydrofuran (1.0 mL); the resulting suspension was stirred and cooled to 0

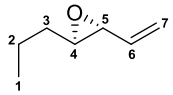
°C. After stirring for 15 minutes, potassium bis(trimethylsilyl)amide solution (2.20 mL, 1 M in THF, 2.20 mmol) was added dropwise over 5 minutes. The resulting solution was allowed to stir at 0 °C for 1 hour. After the epoxidation reaction mixture had stirred for 5 hours, water (~4.00 mL) and sodium thiosulfate (2.00 mL) were added. The resulting biphasic mixture was extracted with dichloromethane (20.0 mL × 3), and the organic extracts were washed with brine (3 × 10.0 mL), before drying with sodium sulfate. The crude epoxide product was concentrated under reduced pressure, and then dissolved in tetrahydrofuran (3.00 mL). The epoxide solution was then added dropwise to the ylide solution at 0 °C over the course of 5 minutes. The reaction mixture was stirred and allowed to warm to room temperature over the course of 1 hour, after which time ammonium chloride solution (10.0 mL of a 1M aqueous solution) was added to the reaction mixture, and the crude product was extracted into diethyl ether (20.0 mL × 3). The extracts were washed with water (20.0 mL) and brine (20.0 mL), and then dried with sodium sulfate. The crude product was purified by flash column chromatography ($SiO_2$, 0-10% diethyl ether/pentane, $R_f$ = 0.3 in 10% diethyl ether/pentane) to give **118** as a pale yellow oil (188 mg, 1.29 mmol, 64%). Characterisation data were consistent with previous literature: $^1$H NMR.[479]

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H, $H^1$, $H^2$, $H^3$) 5.74 (ddd, *J* = 17.3, 10.4, 7.4 Hz, 1H, $H^7$), 5.53 (ddd, *J* = 17.3, 1.3, 0.6 Hz, 1H, $H^8$-*cis*) 5.35 (dd, *J* = 10.4, 1.3 Hz, 1H, $H^8$-*trans*), 3.78 (d, *J* = 1.8 Hz, 1H, $H^5$), 3.37 (dd, *J* = 7.4, 1.8 Hz, 1H, $H^6$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 137.0 (CH), 135.1 (C), 128.5 (CH), 128.2 (CH), 125.5 (CH), 119.6 ($CH_2$), 63.0 (CH), 60.2 (CH). **FTIR** (neat) $\nu_{max}$ 3123, 3077, 3052, 3006, 2027, 1660, 1528, 1475, 1448, 1417, 1301, 1245, 1165, 1010, 964, 898, 853, 816, 773, 714, 680, 628, 548. *HRMS failed to find the correct mass for this compound.*

General procedure F: Telescoped Jorgensen epoxidation/Wittig methylenation

To a stirred solution of (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (60 mg, 0.10 mmol) in dichloromethane (2.00 mL) was added the appropriate enal substrate (1.00 mmol) at room temperature. The resulting reaction mixture was left to stir for 10 minutes, after which time hydrogen peroxide solution (126 mg, 35 wt%, 1.30 mmol) was added. The reaction mixture was left to stir for 5 hours at room temperature. During the reaction time, a phosphonium ylide solution was prepared as follows: to methyltriphenylphosphonium bromide (429 mg, 1.20 mmol) was added tetrahydrofuran (0.5 mL); the resulting suspension was stirred and cooled to 0 °C. After stirring for 15 minutes, potassium bis(trimethylsilyl)amide solution (1.10 mL, 1 M in THF, 1.10 mmol) was added dropwise over 5 minutes. The resulting solution was allowed to stir at 0 °C for 1 hour. After the epoxidation reaction mixture had stirred for 5 hours, water (~2.00 mL) and sodium thiosulfate (1.00 mL) were added. The resulting biphasic mixture was extracted with dichloromethane (10.0 mL × 3), and the organic extracts were washed with water (10.0 mL) and sodium thiosulfate (2 × 5.0 mL), before drying with sodium sulfate. The crude epoxide product was concentrated under reduced pressure, and then dissolved in tetrahydrofuran (1.50 mL). The epoxide solution was then added dropwise to the ylide solution at 0 °C over the course of 5 minutes. The reaction mixture was stirred and allowed to warm to room temperature over the course of 1 hour, after which time ammonium chloride solution (5.00 mL of a 1M aqueous solution) was added to the reaction mixture, and the crude product was extracted into diethyl ether (10.0 mL × 3). The extracts were washed with water (10.0 mL) and brine (10.0 mL). The aqueous layers were re-extracted with diethyl ether (10.0 mL) and then concentrated to give the crude product as an oil. The crude product was purified by flash column chromatography, eluting with pure pentane or pentane/diethyl ether to give the epoxy alkene product.

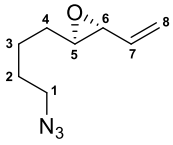
(2*R**,3*R**)-2-Propyl-3-vinyloxirane (**120**)



General procedure F was followed with *trans*-hex-2-enal. Purification by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.6) gave **118** as a yellow oil (32 mg, 0.29 mmol, 29%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 5.63 – 5.53 (m, 1H, $H^6$), 5.45 (dd, *J* = 17.2, 1.6 Hz, 1H, $H^7$-*trans*), 5.25 (dd, *J* = 10.2, 1.6 Hz, 1H, $H^7$-*cis*), 3.09 (dd, *J* = 7.6, 2.1 Hz, 1H, $H^5$), 2.86 – 2.78 (m, 1H, $H^4$), 1.60 – 1.42 (m, 2H, $H^5$), 1.23 – 1.14 (m, 2H, $H^6$), 0.96 (t, J = 7.1 Hz, 3H, $H^1$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 136.0 (CH), 118.9 ($CH_2$), 60.3 (CH), 58.7 (CH), 34.0 ($CH_2$), 19.2 ($CH_2$), 13.9 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3359, 2961, 2918, 2850, 1595, 1500, 1472, 1371, 1277, 1173, 1133, 1070, 1025, 1000, 901, 844, 811, 753, 711, 691, 682, 530, 508, 446. *HRMS failed to find the correct mass for this compound.*

(2*R**, 3*R**)-2-(4-Azidobutyl)-3-vinyloxirane (**121**)



General procedure F was followed with enal **113**. Purification by flash column chromatography ($SiO_2$, 20% diethyl ether/pentane, $R_f$ = 0.4) gave **121** as a colourless oil (5 mg, 0.03 mmol, 3%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 5.60 (ddd, *J* = 17.4, 10.1, 7.4 Hz, 1H, $H^7$), 5.48 (dd, *J* = 17.4, 1.7 Hz, 1H, $H^8$-*cis*), 5.32 – 5.26 (m, 1H, $H^8$-*trans*), 3.30 (t, *J* = 6.6 Hz, 2H, $H^1$) 3.13 (dd, *J* = 7.4, 2.2 Hz, 1H, $H^6$), 2.85 (ddd, *J* = 5.8, 4.5, 2.2 Hz, 1H, $H^5$), 1.70 – 1.50 (m, 6H, $H^2$, $H^3$, $H^4$). **$^{13}$C{$^1$H} NMR** (101 MHz, Chloroform-*d*) δ 135.6 ($CH_2$), 119.2 (CH), 60.0 (CH), 58.6 (CH), 51.3 ($CH_2$), 31.5 ($CH_2$), 28.6 ($CH_2$), 23.2 ($CH_2$). **FTIR** (neat) $\nu_{max}$ 3438, 3075, 3016, 2962, 2932, 2856, 2649, 2544, 2093 (N=N=N), 1988, 1963, 1907, 1694, 1597, 1573, 1460, 1413, 1336, 1290, 1258, 1136, 1102, 1087, 1073, 967, 934, 897, 849, 807, 762, 747, 718,

667, 652, 549, 501, 456, 418*. HRMS failed to find the correct mass for this compound.*

Peterson and Petasis methylenations

To a stirred solution of (*S*)-α,α-Bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (30 mg, 0.05 mmol) in dichloromethane (1.00 mL) was added the appropriate enal substrate (0.50 mmol) at room temperature. The resulting reaction mixture was left to stir for 10 minutes, after which time hydrogen peroxide solution (63 mg, 35 wt%, 0.65 mmol) was added. The reaction mixture was left to stir for 5 hours at room temperature. After the epoxidation reaction mixture had stirred for 5 hours, water (~1.00 mL) and sodium thiosulfate (0.50 mL) were added. The resulting biphasic mixture was extracted with dichloromethane (5.00 mL × 3), and the organic extracts were washed with water (5.00 mL) and sodium thiosulfate (2 × 5.00 mL), before drying with sodium sulfate. The crude intermediate was then subjected to one of two sets of methylenation conditions (a. or b., as below). Following the methylenation step(s), the crude reaction mixtures were analysed by TLC and $^{1}$H NMR spectroscopy.

Methylenation conditions:

a. To the crude intermediate was added tetrahydrofuran (0.50 mL), and the resulting solution was concentrated under reduced pressure. The solution was then added dropwise to a solution of (trimethylsilyl)methyllithium (0.80 mL, 0.7 M in hexanes, 0.55 mmol) in tetrahydrofuran (0.30 mL) at 0 °C. The reaction mixture was stirred and allowed to warm to room temperature over 2 hours, after which point ammonium chloride solution (10.0 mL, 1 M) was added. The reaction mixture was extracted with diethyl ether (10.0 mL × 3), and the organic extracts were washed with brine (10.0 mL). The combined

aqueous extracts were re-extracted with diethyl ether (10.0 mL), and the combined organic extracts were dried over sodium sulfate.

b. To the crude intermediate was added tetrahydrofuran (0.50 mL), and the resulting solution was concentrated under reduced pressure. The solution was then added to a freshly-prepared solution of dimethyltitanocene in tetrahydrofuran[435] (1.16 g, 13.5 wt%, 1 mmol) at room temperature. The reaction mixture was heated at reflux for 16 hours, and then reaction mixture was allowed to cool to room temperature. To the cooled reaction mixture was added cold petrol, upon which addition a yellow-orange precipitate formed, which was removed by filtration. The filtrate was concentrated under reduced pressure.

Shi epoxidation

Adapted from literature procedures.[101,436]

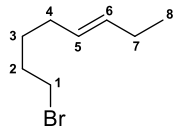
a. To a solution of the appropriate alkene (1.00 mmol) in acetonitrile/dimethoxymethane (15 mL, 1:2) at room temperature was added freshly prepared buffer solution* (10.0 mL), tetra-*n*-butylammonium hydrogen sulfate (15 mg, 0.05 mmol), and the Shi diketal catalyst (77 mg, 0.15 mmol), with stirring. The reaction mixture was cooled to -10 °C and stirred vigorously. To the reaction mixture were added Oxone™ (0.85 g in 6.50 mL of a $4{\cdot}10^{-4}$ M aqueous solution of disodium(EDTA)) and potassium carbonate (0.80 g in 6.5 mL of water) simultaneously, dropwise over 2 hours. The reaction mixture was then allowed to stir for 16 hours at 0 °C. To the reaction mixture was added pentane (30.0 mL) and water (30.0 mL). The reaction mixture was extracted with pentane (3 × 30.0 mL). The combined organic layers were washed with brine (50.0 mL), dried with sodium sulfate, and concentrated under reduced pressure. TLC and $^1$H NMR spectroscopic analysis of the

crude reaction mixture showed no evidence of the desired product in all cases.

*buffer solution prepared by dissolution of 1.907 g of $Na_2B_2O_7 \bullet 10H_2O$ in 100 mL of a $4 \cdot 10^{-4}$ M aqueous solution of disodium(EDTA).

b. To a solution of the appropriate alkene (0.50 mmol) in acetonitrile/ethanol/dichloromethane (1.00 mL, 1:1:2) at room temperature was added potassium carbonate (829 mg in 3 mL of a $4 \cdot 10^{-4}$ M aqueous solution of disodium(EDTA)), and the Shi diketal catalyst (77 mg, 0.15 mmol), with stirring. The reaction mixture was cooled to 0 °C and stirred vigorously. To the reaction mixture was added hydrogen peroxide (either 188 mg of urea•hydrogen peroxide or 194 mg of a 35 wt% aqueous solution, 2.00 mmol). The resulting reaction mixture was stirred at 0 °C. TLC and $^1$H NMR spectroscopic analysis of the crude reaction mixture showed no evidence of the desired product in all cases.

(*E*)-8-Bromooct-3-ene (**123**)

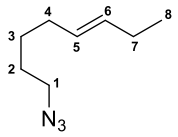



To a mixture of 6-bromo-1-hexene (650 mg, 4.0 mmol) and *trans*-3-hexene (1.01 g, 12.0 mmol) at room temperature under argon was added the second-generation Grubbs precatalyst (65 mg, 0.08 mmol). The resulting reaction mixture was heated to 50 °C for 16 hours, after which it was allowed to cool to room temperature. The crude product was purified by flash column chromatography ($SiO_2$, 100% pentane, $R_f$ = 0.3) to give **123** as a colourless oil (623 mg, 3.28 mmol, 82%).

**$^1$H NMR** (400 MHz, Chloroform-*d*) δ 5.55 – 5.26 (m, 2H, $H^5$, $H^6$), 3.41 (t, *J* = 6.9 Hz, 2H, $H^1$), 2.14 – 1.94 (m, 4H, $H^4$, $H^7$), 1.90-1.81 (m, 2H, $H^2$), 1.54-1.44 (m,

2H, $H^3$), 0.97 (t, *J* = 7.5 Hz, 3H, $H^8$). **$^{13}C\{^1H\}$ NMR** (101 MHz, Chloroform-*d*) δ 132.8 (CH), 128.3 (CH), 33.9 ($CH_2$), 32.3 ($CH_2$), 31.6 ($CH_2$), 28.1 ($CH_2$), 25.6 ($CH_2$), 13.9 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 2957, 2929, 2856, 2063, 1990, 1965, 1669, 1620, 1596, 1500, 1454, 1437, 1377, 1351, 1283, 1249, 1200, 1082, 1026, 967, 864, 807, 735, 645, 561, 492, 432, 409. *HRMS failed to find the correct mass of this compound.*

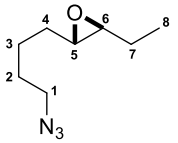
(*E*)-8-Azidooct-3-ene **124**[427]




To a stirred solution of bromide **123** (457 mg, 2.40 mmol) in DMSO (5.00 mL) at room temperature was added sodium azide (234 mg, 2.64 mmol). The resulting reaction mixture was stirred at room temperature for 48 hours, and then passed through a silica plug with pentane and diethyl ether washings. The filtrate was concentrated to give **124** as a colourless oil (342 mg, 2.23 mmol, 93%).

**$^1H$ NMR** (400 MHz, Chloroform-*d*) δ 5.51 – 5.27 (m, 2H, $H^5$, $H^6$), 3.26 (t, *J* = 6.9 Hz, 2H, $H^1$), 2.12 – 1.93 (m, 4H, $H^4$, $H^7$), 1.68 – 1.56 (m, 2H, $H^2$), 1.48 – 1.39 (m, 2H, $H^3$), 0.97 (t, *J* = 7.4 Hz, 3H, $H^8$). **$^{13}C\{^1H\}$ NMR** (101 MHz, Chloroform-*d*) δ 132.8 (CH), 128.4 (CH), 51.4 ($CH_2$), 32.0 ($CH_2$), 28.3 ($CH_2$), 26.6 ($CH_2$), 22.3 ($CH_2$), 13.9 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 2930, 2858, 2087 (N=N=N), 1669, 1455, 1350, 1261, 1139, 1051, 968, 890, 810, 739, 659, 637, 557, 452. *HRMS failed to find the correct mass for this compound.*

(2*S**, 3*S**)-2-(4-Azidobutyl)-3-ethyloxirane (**110**)[427]




To a mixture of 6-bromo-1-hexene (652 mg, 4.00 mmol) and *trans*-3-hexene (1.01 g, 12.0 mmol) at room temperature under argon was added the second-generation Grubbs precatalyst (65 mg, 0.08 mmol). The resulting reaction mixture

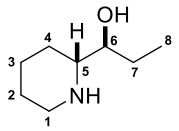
was heated to 50 °C for 16 hours, after which it was allowed to cool to room temperature. The crude product was purified by flash column chromatography on silica gel as above, to give **123** as a solution in pentane. To a stirred solution of bromide **123** in DMSO (8 mL) at room temperature was added sodium azide (312 mg, 5.00 mmol). The resulting reaction mixture was stirred at room temperature for 24 hours, after which water (10.0 mL) and diethyl ether (5.00 mL) were added. The reaction mixture was extracted with diethyl ether (3 × 20.0 mL), and the combined organic layers were washed with water (30.0 mL) and brine (10.0 mL). The organic layers were dried with sodium sulfate, filtered through a silica plug, and concentrated under reduced pressure to give **124** as a solution in diethyl ether. To a stirred solution of azide **124** in dichloromethane (8.00 mL) at room temperature was added sodium hydrogen carbonate (4.00 mL of an aqueous solution made from 2.00 mL of a saturated aqueous solution and 2.00 mL of water). The resulting reaction mixture was cooled to 0 °C, and to the reaction mixture was added 3-chloroperbenzoic acid (1.48 g, calculated as 70% pure, 6.00 mmol). The resulting reaction mixture was allowed to stir at room temperature for 16 hours. The organic layer was concentrated under reduced pressure and purified by flash column chromatography (buffered* $SiO_2$, 2% diethyl ether/petroleum ether, $R_f$ = 0.2) to give **110** as a yellow oil (210 mg, 1.24 mmol, 31% over 3 steps).

*silica gel pre-treated with 3% triethylamine/petroleum ether solution, then flushed with pure petroleum ether.

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 3.29 (t, *J* = 6.8 Hz, 2H, $H^1$), 2.72 – 2.61 (m, 2H, $H^5$, $H^6$), 1.68 – 1.62 (m, 2H, $H^4$), 1.58 – 1.47 (m, 6H, $H^2$, $H^3$, $H^7$), 0.99 (t, *J* = 7.5 Hz, 3H, $H^8$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 59.84 (CH), 58.18 (CH), 51.3 ($CH_2$), 31.6 ($CH_2$), 28.7 ($CH_2$), 25.1 ($CH_2$), 23.4 ($CH_2$), 11.6 ($CH_3$). **FTIR** (neat) $\nu_{max}$ 3438, 3075, 3016, 2962, 2932, 2857, 2649, 2544, 2093 (N=N=N), 1988, 1963, 1907, 1694, 1597, 1573, 1460, 1413, 1336, 1290, 1258,

1136, 1102, 1087, 1073, 967, 934, 897, 849, 807, 7612, 747, 718, 667, 652, 549, 501, 456, 418. *HRMS failed to find the correct mass for this compound*.

Conhydrine (**112**)




To a stirred solution of azide **110** (95 mg, 0.56 mmol) in toluene (0.60 mL) at room temperature was added phenylsilane (91 mg, 0.84 mmol), followed by phosphine **13** (18 mg, 0.06 mmol). The resulting reaction mixture was stirred at room temperature for 16 hours, after which methanol (0.60 mL) was added. The resulting reaction mixture was heated at reflux for 24 hours, and then allowed to cool to room temperature. The reaction mixture was concentrated and then purified by flash column chromatography ($SiO_2$, 5-10% (ammonia/methanol (7M))/dichloromethane, $R_f$ = 0.1) to give **112** as an off-white solid which was observed (by $^1H$ NMR) to contain a small amount of an unknown impurity ($^1H$ δ include 3.58 (m) and 0.93 (t, *J* = 7.2 Hz) ppm, as well as peaks overlapping with those of **112**). To the impure sample was added dimethyl sulfone (21.9 mg, 0.23 mmol), and an NMR yield (22 mg, 0.15 mmol, 19%) was obtained by comparison of the integrals for the $H^6$ peak ($^1H$ δ = 3.41 ppm) and the sulfone methyl peak ($^1H$ δ = 3.00 ppm). Characterisation data were consistent with previous literature: $^1H$, $^{13}C$ NMR.[480]

**$^1$H NMR** (500 MHz, Chloroform-*d*) δ 3.41 (ddd, *J* = 8.2, 4.8, 3.3 Hz, 1H, $H^6$), 3.20 – 3.10 (m, 1H, $H^{1a}$), 2.75 – 2.66 (m, 1H, $H^{1b}$), 2.65 – 2.58 (m, 1H, $H^5$), 2.05 (br. s, 2H, NH, OH) 1.86 – 1.83 (m, 1H, $H^{7a}$), 1.64 – 1.23 (m, 7H, $H^{2a}$, $H^{2b}$, $H^{3a}$, $H^{3b}$, $H^{4a}$, $H^{4b}$, $H^{7b}$), 0.97 (t, *J* = 7.4 Hz, 3H, $H^8$). **$^{13}$C{$^1$H} NMR** (126 MHz, Chloroform-*d*) δ 75.3 (CH), 60.2 (CH), 46.8 ($CH_2$), 25.9 ($CH_2$), 25.4 ($CH_2$), 24.6 ($CH_2$), 24.1 ($CH_2$), 10.6 ($CH_3$). **HRMS** (ESI-TOF) *m/z* calculated for $C_8H_{17}NO$ $[M+H]^+$ = 144.1383, found 144.1378; $[M+Na]^+$ = 166.1202, found 166.1200.

## 5: References

1 P. G. Urben, *Bretherick's Handbook of Reactive Chemical Hazards, Eighth Edition*, 2017.

2 D. Mendez, A. Gaulton, A. P. Bento, J. Chambers, M. De Veij, E. Felix, M. P. Magariños, J. F. Mosquera, P. Mutowo, M. Nowotka, F. Gordillo-Marañón, María Hunter, L. Junco, G. Mugumbate, M. Rodriguez-Lopez, F. Atkinson, N. Bosc, C. J. Radoux, A. Segura-Cabrera, A. Hersey and A. R. Leach, *Nucleic Acids Res.*, 2019, **47**, D930–D940.

3 ChEMBL, https://www.ebi.ac.uk/chembl/, (accessed 20 September 2021).

4 Web of Science, https://www.webofscience.com/wos/woscc/basic-search, (accessed 20 September 2021).

5 L. Pauling and L. O. Brockway, *J. Am. Chem. Soc.*, 1937, **59**, 13–20.

6 S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem. Int. Ed.*, 2005, **44**, 5188–5240.

7 G. V Gurskaya, E. N. Tsapkina, N. V Skaptsova, A. A. Kraevskii, S. V Lindemann and Y. T. Struchkov, *Proc. USSR Acad. Sci.*, 1986, **291**, 854–859.

8 L. Mahe, A. Izuoka and T. Sugawara, *J. Am. Chem. Soc.*, 1992, **114**, 7904–7906.

9 L. Párkányi and G. Besenyei, *J. Mol. Struct.*, 2004, **691**, 97–106.

10 J. Bae, G. Zhang, H. Park, W. S. Warren and Q. Wang, *Chem. Sci.*, 2021, **12**, 14309–14315.

11 G. Pieffet and P. A. Petukhov, *J. Mol. Model.*, 2009, **15**, 1291–1297.

12 M. T. Nguyen, D. Sengupta and T. K. Ha, *J. Phys. Chem.*, 1996, **100**, 6499–6503.

13 K. Fukui, *Science*, 1982, **218**, 747–754.

14 G. Klopman, *J. Am. Chem. Soc.*, 1968, **90**, 223–234.

15 L. Salem, *J. Am. Chem. Soc.*, 1968, **90**, 543–552.

16 K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier and K. George, *J. Am. Chem. Soc.*, 1973, **95**, 7287–7301.

17 R. Huisgen, *Angew. Chem. Int. Ed.*, 1963, **2**, 565–632.

18 L. E. Sutton, *Nature*, 1931, **128**, 639.

19 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.

20 K. Maegawa, H. Tanimoto, S. Onishi, T. Tomohiro, T. Morimoto and K. Kakiuchi, *Org. Chem. Front.*, 2021, **8**, 5793–5803.

21 G. L'Abbé, *Chem. Rev.*, 1969, **69**, 345–363.

22 J. P. Agrawal and R. D. Hodgson, *Organic Chemistry of Explosives*, John Wiley and Sons, 2006.

23 W. C. Lothrop and G. R. Handrick, *Chem. Rev.*, 1949, **44**, 419–445.

24 N. Hooper, L. J. Beeching, J. M. Dyke, A. Morris, J. S. Ogden, A. A. Dias, M. L. Costa, M. T. Barros, M. H. Cabral and A. M. C. Moutinho, *J. Phys. Chem. A*, 2002, **106**, 9968–9975.

25 S. Bräse, M. Mende, H. H. Jobelius and H.-D. Scharf, in *Ullmann's Encyclopedia of Industrial Chemistry*, 2015.

26 M. H. Keshavarz, A. Mousaviazar and M. Hayaty, *J. Therm. Anal. Calorim.*, 2017, **129**, 1659–1665.

27 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.

28 G. Fayet, P. Rotureau, L. Joubert and C. Adamo, *J. Mol. Model.*, 2010, **16**, 805–812.

29 I. Maule, G. Razzetti, A. Restelli, A. Palmieri, C. Colombo and R. Ballini, *Org. Process Res. Dev.*, 2021, **25**, 781–788.

30 C. Schotten, S. K. Leprevost, L. M. Yong, C. E. Hughes, K. D. M. Harris and D. L. Browne, *Org. Process Res. Dev.*, 2020, **24**, 2336–2341.

31 E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 297–368.

32 P. Sivaguru, Y. Ning and X. Bi, *Chem. Rev.*, 2021, **121**, 4253–4307.

33 A. S. Carlson and J. J. Topczewski, *Org. Biomol. Chem.*, 2019, **17**, 4406–4429.

34 M. Goswami and B. de Bruin, *Eur. J. Org. Chem.*, 2017, 1152–1176.

35 P.-G. Ding, X.-S. Hu, F. Zhou and J. Zhou, *Org. Chem. Front.*, 2018, **5**, 1542–1559.

36 Y. Liu, A. G. Ebadi, L. Youseftabar-Miri, A. Hassanpour and E. Vessally, *RSC Adv.*, 2019, **9**, 25199–25215.

37 L. Ge, M.-F. Chiou, Y. Li and H. Bao, *Green Synth. Catal.*, 2020, **1**, 86–120.

38 J. P. Griess, *Proc. R. Soc. London*, 1864, **13**, 375–384.

39 P. K. Dutt, H. R. Whitehead and A. Wormall, *J. Chem. Soc. Trans.*, 1921, **119**, 2088–2094.

40 O. Dimroth, *Berichte der Dtsch. Chem. Gesellschaft*, 1902, **35**, 1029–1038.

41 R. O. Lindsay, C. F. H. Allen, R. L. Shriner and J. C. Lawler, *Org. Synth.*, 1942, **22**, 96.

42 F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456–463.

43 W. P. Fehlhammer and W. Beck, *J. Inorg. Gen. Chem.*, 2013, **639**, 1053.

44 S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem. Asian J.*, 2011, **6**, 2618–2634.

45 R. West and J. S. Thayer, *J. Am. Chem. Soc.*, 1962, **84**, 1763–1764.

46 L. Birkofer, A. Ritter and P. Richter, *Angew. Chem. Int. Ed.*, 1962, **1**, 267.

47 T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203–6205.

48 Y. Lu and R. T. Taylor, *Tetrahedron Lett.*, 2003, **44**, 9267–9269.

49 V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, M. S. Formaneck and J. T. Bolz, *Tetrahedron Lett.*, 1994, **35**, 9677–9680.

50 S. Alazet, J. Preindl, R. Simonet-Davin, S. Nicolai, A. Nanchen, T. Meyer and J. Waser, *J. Org. Chem.*, 2018, **83**, 12334−12356.

51 W. Wislicenus, *Berichte der Dtsch. Chem. Gesellschaft*, 1892, **25**, 2084–2087.

52 T. B. Phan and H. Mayr, *J. Phys. Org. Chem.*, 2006, **19**, 706–713.

53 T. Curtius, *Berichte der Dtsch. Chem. Gesellschaft*, 1890, **23**, 3023–3033.

54 G. Righi, C. D. Achille and C. Bonini, *Tetrahedron Lett.*, 2003, **44**, 6999–7002.

55 A. Breuning, R. Vicik and T. Schirmeister, *Tetrahedron: Asymmetry*, 2003, **14**, 3301–3312.

56 G. Kumaraswamy and K. Ankamma, *J. Org. Chem.*, 2007, **72**, 9822–9825.

57 X. E. Hu, *Tetrahedron*, 2004, **60**, 2701–2743.

58 T. Tanaka, H. Nagai, M. Noguchi, A. Kobayashi and S. Shoda, *Chem. Commun.*, 2009, 3378–3379.

59 A. R. Bassindale, P. A. Kyle, M.-C. Soobramanien and P. G. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1173–1180.

60 Y. Zhang, S. Wu, H. Shi and J. Yan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2016, **191**, 1324–1328.

61 J. C. Kauer and R. A. Carboni, *J. Am. Chem. Soc.*, 1967, **89**, 2633–2637.

62 T. Keumi, T. Umeda, Y. Inoue and H. Kitajima, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 89–95.

63 R. N. Butler, A. Fox, S. Collier and L. A. Burke, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2243–2248.

64 K. A. H. Chehade and H. P. Spielmann, *J. Org. Chem.*, 2000, **65**,

4949–4953.

65 D. R. Miller, D. C. Swenson and E. G. Gillan, *J. Am. Chem. Soc.*, 2004, **126**, 5372–5373.

66 I. Adamo, F. Benedetti, F. Berti and P. Campaner, *Org. Lett.*, 2006, **8**, 51–54.

67 E. A. Couladouros, Z. F. Plyta, S. A. Haroutounian and V. P. Papageorgiou, *J. Org. Chem.*, 1997, **62**, 6–10.

68 A. K. Ghosh, A. Sarkar and M. Brindisi, *Org. Biomol. Chem.*, 2018, **16**, 2006–2027.

69 S.-I. Murahashi, Y. Tanigawa, Y. Imada and Y. Taniguchi, *Tetrahedron Lett.*, 1986, **27**, 227–230.

70 B. M. Trost and S. R. Pulley, *J. Am. Chem. Soc.*, 1995, **117**, 10143–10144.

71 V. Atlan, S. Racouchot, M. Rubin, C. Bremer, J. Ollivier, A. de Mejiere and J. Salaün, *Tetrahedron: Asymmetry*, 1998, **9**, 1131–1135.

72 C. Hurtado-Rodrigo, S. Hoehne and M. P. Muñoz, *Chem. Commun.*, 2014, **50**, 1494–1496.

73 D. A. Khrakovsky, C. Tao, M. W. Johnson, R. T. Thornbury, S. L. Shevick and F. D. Toste, *Angew. Chem. Int. Ed.*, 2016, **55**, 6079–6083.

74 R. Barnhat, M. D. Ironside and P. F. Vogt, *Org. Process Res. Dev.*, 2010, **14**, 1480–1484.

75 M. Kitamura, T. Koga and T. Okauchi, *Synlett*, 2012, **23**, 1335–1338.

76 O. Mitsunobu, *Synthesis*, 1981, **1**, 1–28.

77 M. C. Viaud and P. Rollin, *Synthesis*, 1990, **2**, 130–132.

78 L. He, M. Wanunu, H. Byun and R. Bittman, *J. Org. Chem.*, 1999, **64**, 6049–6055.

79 B. Lal, B. N. Pramanik, M. S. Manhas and A. K. Bose, *Tetrahedron Lett.*, 1977, **18**, 1977–1980.

80 P. P. Goswami, V. P. Suding, A. S. Carlson and J. J. Topczewski, *Eur. J. Org. Chem.*, 2016, 4805–4809.

81 T. A. Hamlin, M. Swart and F. M. Bickelhaupt, *ChemPhysChem*, 2018, **19**, 1315–1330.

82 B. P. Thanh, C. Nolte, S. Kobayashi, A. R. Ofial and H. Mayr, *J. Am. Chem. Soc.*, 2009, **131**, 11392–11401.

83 H. R. Hudson, *Synthesis*, 1969, 112–119.

84 R. Appel, *Angew. Chem. Int. Ed.*, 1975, **14**, 801–811.

85 R. O. Hutchins, D. Masilamani and C. A. Maryanoff, *J. Org. Chem.*, 1976, **41**, 1071–1073.

86 G. W. Kabalka, M. Varma and R. S. Varma, *J. Org. Chem.*, 1986, **51**, 2386–2388.

87 T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 1957, 4069–4079.

88 H.-U. Blaser, *Chem. Rev.*, 1992, **92**, 935–952.

89 Z. G. Brill, M. L. Condakes, C. P. Ting and T. J. Maimone, *Chem. Rev.*, 2017, **117**, 11753–11795.

90 R. Noyori, *Angew. Chem. Int. Ed.*, 2013, **52**, 79–92.

91 N. B. Johnson, I. C. Lennon, P. H. Moran and J. A. Ramsden, *Acc. Chem. Res.*, 2007, **40**, 1291–1299.

92 Y. Ni and J.-H. Xu, *Biotechnol. Adv.*, 2011, **30**, 1279–1288.

93 Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu and K.-X. Su, *Chem. Rev.*, 2005, **105**, 1603–1662.

94 Y. Zhu, Q. Wang, R. G. Cornwall and Y. Shi, *Chem. Rev.*, 2014, **114**, 8199–8256.

95 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976.

96 Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780.

97 W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1990, **112**, 2801–2803.

98 E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063–7064.

99 R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron: Asymmetry*, 1991, **2**, 481–494.

100 Y. Tu, Z.-X. Wang and Y. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 9806–9807.

101 Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11224–11235.

102 M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang and K. A. Jørgensen,

*J. Am. Chem. Soc.*, 2005, **127**, 6964–6965.

103 E. J. Corey and J. O. Link, *J. Am. Chem. Soc.*, 1992, **114**, 1906–1908.

104 J. F. Larrow, S. E. Schaus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420–7421.

105 L. E. Martinez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897–5898.

106 X. Huang and J. T. Groves, *ACS Catal.*, 2016, **6**, 751–759.

107 E. A. Mader, E. R. Davidson and J. M. Mayer, *J. Am. Chem. Soc.*, 2007, **129**, 5153–5166.

108 J. D. Bell and J. A. Murphy, *Chem. Soc. Rev.*, 2021, **50**, 9540–9685.

109 M. S. Alnajjar, X.-M. Zhang, G. J. Gleicher, S. V. Truksa and J. A. Franz, *J. Org. Chem.*, 2002, **67**, 9016–9022.

110 A. S. H. Ryder, W. B. Cunningham, G. Ballantyne, T. Mules, A. G. Kinsella, J. Turner-Dore, C. M. Alder, L. J. Edwards, B. S. J. McKay, M. N. Grayson and A. J. Cresswell, *Angew. Chem. Int. Ed.*, 2020, **59**, 14986–14991.

111 Y. Wang, X. Hu, C. A. Morales-Rivera, G. X. Li, X. Huang, G. He, P. Liu and G. Chen, *J. Am. Chem. Soc.*, 2018, **140**, 9678–9684.

112 H. Li, S. Shen, C. Zhu and H. Xu, *J. Am. Chem. Soc.*, 2019, **141**, 9415–9421.

113 R. P. Shirke and S. S. V. Ramasastry, *Org. Lett.*, 2017, **19**, 5482–5485.

114 D. S. Rao, T. R. Reddy, A. Gurawa, M. Kumar and S. Kashyap, *Org. Lett.*, 2019, **21**, 9990–9994.

115 J. M. Lear, J. Q. Buquoi, X. Gu, K. Pan, D. N. Mustafa and D. A. Nagib, *Chem. Commun.*, 2019, **55**, 8820–8823.

116 S. Yang, S. Zhu, D. Lu and Y. Gong, *Org. Lett.*, 2019, **21**, 8464–8468.

117 Z. Wu, R. Ren and C. Zhu, *Angew. Chem. Int. Ed.*, 2016, **55**, 10821–10824.

118 P. Wang, Y. Luo, S. Zhu, D. Lu and Y. Gong, *Adv. Synth. Catal.*, 2019, **361**, 5565–5575.

119 Z. B. Alfassi, A. Harriman, R. E. Huie, S. Mosseri and P. Neta, *J. Phys. Chem.*, 1987, **91**, 2120–2122.

120 E. Hayon and M. Simic, *J. Am. Chem. Soc.*, 1970, **92**, 7486–7487.

121 Y. Kita, H. Tohma, T. Takada, S. Mitoh, S. Fujita and M. Gyoten, *Synlett*, 1994, **1994**, 427–428.

122 J. C. Siu, J. B. Parry and S. Lin, *J. Am. Chem. Soc.*, 2019, **141**, 2825–2831.

123 P. Magnus and J. Lacour, *J. Am. Chem. Soc.*, 1992, **114**, 767–769.

124 K. Weidner and P. Renaud, *Aust. J. Chem.*, 2013, **66**, 341–345.

125 Y. Zhu, X. Li, X. Wang, X. Huang, T. Shen, Y. Zhang, X. Sun, M. Zou, S. Song and N. Jiao, *Org. Lett.*, 2015, **17**, 4702–4705.

126 R. A. Abramovitch and W. D. Holcomb, *J. Chem. Soc. D Chem. Commun.*, 1969, 1298–1299.

127 D. S. Breslow, M. F. Sloan, N. R. Newburg and W. B. Renfrow, *J. Am. Chem. Soc.*, 1969, **91**, 2273–2279.

128 C. Ollivier and P. Renaud, *J. Am. Chem. Soc.*, 2000, **122**, 6496–6497.

129 C. Ollivier and P. Renaud, *J. Am. Chem. Soc.*, 2001, **123**, 4717–4727.

130 A. Kapat, A. König, F. Montermini and P. Renaud, *J. Am. Chem. Soc.*, 2011, **133**, 13890–13893.

131 R. Ren, H. Zhao, L. Huan and C. Zhu, *Angew. Chem. Int. Ed.*, 2015, **54**, 12692–12696.

132 D. S. Masterson and N. A. Porter, *Org. Lett.*, 2002, **4**, 4253–4256.

133 Y. Xia and A. Studer, *Angew. Chem. Int. Ed.*, 2019, **58**, 9836–9840.

134 C. Liu, X. Wang, Z. Li, L. Cui and C. Li, *J. Am. Chem. Soc.*, 2015, **137**, 9820–9823.

135 D. C. Marcote, R. Street-Jeakings, E. Dauncey, J. J. Douglas, A. Ruffoni and D. Leonori, *Org. Biomol. Chem.*, 2019, **17**, 1839–1842.

136 R. Wei, H. Xiong, C. Ye, Y. Li and H. Bao, *Org. Lett.*, 2020, **22**, 3195–3199.

137 W.-Y. Li, C.-S. Wu, Z. Wang and Y. Luo, *Chem. Commun.*, 2018, **54**, 11013–11016.

138 F. Wang, X. Qi, Z. Liang, P. Chen and G. Liu, *Angew. Chem. Int. Ed.*, 2014, **53**, 1881–1886.

139 L. Zhang, S. Liu, Z. Zhao, H. Su, J. Hao and Y. Wang, *Chem. Sci.*,

2018, **9**, 6085–6090.

140 J. Xu, X. Li, Y. Gao, L. Zhang, W. Chen, H. Fang, G. Tang and Y. Zhao, *Chem. Commun.*, 2015, **51**, 11240–11243.

141 Y. Xiong, Y. Sun and G. Zhang, *Org. Lett.*, 2018, **20**, 6250–6254.

142 Y. A. Yuan, D. F. Lu, Y. R. Chen and H. Xu, *Angew. Chem. Int. Ed.*, 2016, **55**, 534–538.

143 H. Su, W. Li, Z. Xuan and W. Yu, *Adv. Synth. Catal.*, 2015, **357**, 64–70.

144 L. Ge, H. Zhou, M. F. Chiou, H. Jiang, W. Jian, C. Ye, X. Li, X. Zhu, H. Xiong, Y. Li, L. Song, X. Zhang and H. Bao, *Nat. Catal.*, 2021, **4**, 28–35.

145 D. Lv, Q. Sun, H. Zhou, L. Ge, Y. Qu, T. Li, X. Ma, Y. Li and H. Bao, *Angew. Chem. Int. Ed.*, 2021, **60**, 12455–12460.

146 L. Wu, Z. Zhang, D. Wu, F. Wang, P. Chen, Z. Lin and G. Liu, *Angew. Chem. Int. Ed.*, 2021, **60**, 6997–7001.

147 J. A. Kerr, *Chem. Rev.*, 1966, **66**, 465–500.

148 M. L. Poutsma, *J. Org. Chem.*, 2008, **73**, 8921–8928.

149 A. A. Zavitsas, D. W. Rogers and N. Matsunaga, *J. Org. Chem.*, 2010, **75**, 5697–5700.

150 M. D. Wodrich, W. C. Mckee and P. von Ragué Schleyer, *J. Org. Chem.*, 2011, **76**, 2439–2447.

151 A. P. Krasutsky, C. J. Kuehl and V. V. Zhdankin, *Synlett*, 1995, **1995**, 1081–1082.

152 V. V Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash and J. T. Bolz, *J. Am. Chem. Soc.*, 1996, **118**, 5192–5197.

153 X. Huang, T. M. Bergsten and J. T. Groves, *J. Am. Chem. Soc.*, 2015, **137**, 5300–5303.

154 P. T. G. Rabet, G. Fumagalli, S. Boyd and M. F. Greaney, *Org. Lett.*, 2016, **18**, 1646–1649.

155 Y. Wang, G. X. Li, G. Yang, G. He and G. Chen, *Chem. Sci.*, 2016, **7**, 2679–2683.

156 X. Zhang, H. Yang and P. Tang, *Org. Lett.*, 2015, **17**, 5828–5831.

157 S. Suh, S. Chen, M. Mandal, I. A. Guzei, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2020, **142**, 11388–11393.

158 L. Benati, D. Nanni and P. Spagnolo, *J. Org. Chem.*, 1999, **64**, 5132–5138.

159 D. A. Evans and T. C. Britton, *J. Am. Chem. Soc.*, 1987, **109**, 6881–6883.

160 H. O. Pritchard and H. A. Skinner, *Chem. Rev.*, 1955, **55**, 745–786.

161 J. Das, P. B. Koswatta, J. D. Jones, M. Yousufuddin and C. J. Lovely, *Org. Lett.*, 2012, **14**, 6210–6213.

162 T. Nishimura, A. K. Unni, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2013, **135**, 3243–3247.

163 Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová and P. Beier, *Angew. Chem. Int. Ed.*, 2017, **56**, 346–

349.

164 S. Voltrová, M. Muselli, J. Filgas, V. Matoušek, B. Klepetářová and P. Beier, *Org. Biomol. Chem.*, 2017, **15**, 4962–4965.

165 X. Zhang, J. Ren, S. M. Tan, D. Tan, R. Lee and C. H. Tan, *Science*, 2019, **363**, 400–404.

166 J. Ren, X. Ban, X. Zhang, S. M. Tan, R. Lee and C. H. Tan, *Angew. Chem. Int. Ed.*, 2020, **59**, 9055–9058.

167 M. Regitz, *Angew. Chem. Int. Ed. English*, 1967, **6**, 733–749.

168 W. Fischer and J. P. Anselme, *J. Am. Chem. Soc.*, 1967, **89**, 5284–5285.

169 P. A. S. Smith, C. D. Rowe and L. B. Bruner, *J. Org. Chem.*, 1969, **34**, 3430–3433.

170 C. J. Cavender and V. J. Shiner Jr., *J. Org. Chem.*, 1972, **37**, 3567–3569.

171 G. Meng, T. Guo, T. Ma, J. Zhang, Y. Shen, K. B. Sharpless and J. Dong, *Nature*, 2019, **574**, 86–89.

172 N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo and C. R. Bertozzi, *ACS Chem. Biol.*, 2006, **1**, 644–648.

173 E. M. Sletten and C. R. Bertozzi, *Angew. Chem. Int. Ed.*, 2009, **48**, 6974–6998.

174 E. M. Sletten and C. R. Bertozzi, *Acc. Chem. Res.*, 2011, **44**, 666–676.

175 H. Tanimoto and K. Kakiuchi, *Nat. Prod. Commun.*, 2013, **8**, 1021–

1034.

176 A. Ma, Y. Tu, J. Peng, Q. Dou, S. Hou, F. Zhang and S. Wang, *Org. Lett.*, 2012, **14**, 3604–3607.

177 J. R. Frost, C. M. Pearson, T. N. Snaddon, R. A. Booth and S. V. Ley, *Angew. Chem. Int. Ed.*, 2012, **51**, 9366–9371.

178 I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi and P. S. Baran, *Angew. Chem. Int. Ed.*, 2010, **49**, 1095–1098.

179 I. B. Seiple, S. Su, I. S. Young, A. Nakamura, J. Yamaguchi, L. Jørgensen, R. A. Rodriguez, D. P. O. Malley, T. Gaich, K. Matthias and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 14710–14726.

180 E. J. Corey, *Acc. Chem. Res.*, 1988, **17**, 111–133.

181 A. Gagneux, S. Winstein and W. Young, *J. Am. Chem. Soc.*, 1960, **82**, 5956–5957.

182 B. Braida, V. Prana and P. C. Hiberty, *Angew. Chem. Int. Ed.*, 2009, **48**, 5724–5728.

183 A. A. Ott and J. J. Topczewski, *Arkivoc*, 2019, 1–17.

184 A. Hassner, R. Fibiger and D. Andisik, *J. Org. Chem.*, 1984, **49**, 4237–4244.

185 A. A. Ott, M. H. Packard, M. A. Ortuno, A. Johnson, V. P. Suding, C. J. Cramer and J. J. Topczewski, *J. Org. Chem.*, 2018, **83**, 8214–8224.

186 A. Padwa and M. M. Sá, *Tetrahedron Lett.*, 1997, **38**, 5087–5090.

187 M. R. Porter, R. M. Shaker, C. Calcanas and J. J. Topczewski, *J. Am.*

*Chem. Soc.*, 2018, **140**, 1211–1214.

188 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.

189 A. A. Ott, C. S. Goshey and J. J. Topczewski, *J. Am. Chem. Soc.*, 2017, **139**, 7737–7740.

190 K. Banert, *Chem. Ber.*, 1989, **122**, 911–918.

191 J. R. Alexander, M. H. Packard, A. M. Hildebrandt, A. A. Ott and J. J. Topczewski, *J. Org. Chem.*, 2020, **85**, 3174–3181.

192 T. Curtius, *J. für Prakt. Chemie*, 1894, **50**, 275–294.

193 C. Wentrup and H. Bornemann, *Eur. J. Org. Chem.*, 2005, 4521–4524.

194 K. F. Schmidt, *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.)*, 1924, **57**, 704–706.

195 R. E. Gawley, *Org. React.*, 1988, **35**, 14–24.

196 M. Renz and B. Meunier, *Eur. J. Org. Chem.*, 1999, 737–750.

197 A. M. Szpilman and E. M. Carreira, *Angew. Chem. Int. Ed.*, 2010, **49**, 9592–9628.

198 Y. Hu, D. Stumpfe and J. Bajorath, *J. Med. Chem.*, 2017, **60**, 1238–1246.

199 S. H. Kennedy, B. D. Dherange, K. J. Berger and M. D. Levin, *Nature*, 2021, **593**, 223–227.

200 H. Qin, W. Cai, S. Wang, T. Guo, G. Li and H. Lu, *Angew. Chem. Int.*

*Ed.*, 2021, **60**, 20678–20683.

201 J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, 1955, **77**, 951–954.

202 J. Aubé and G. L. Milligan, *J. Am. Chem. Soc.*, 1991, **113**, 8965–8966.

203 H. Eyring, *J. Chem. Phys.*, 1935, **3**, 107–115.

204 M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1935, **31**, 875–894.

205 V. Gracias, G. L. Milligan and J. Aubé, *J. Am. Chem. Soc.*, 1995, **117**, 8047–8048.

206 K. Sahasrabudhe, V. Gracias, K. Furness, B. T. Smith, C. E. Katz, D. S. Reddy and J. Aubé, *J. Am. Chem. Soc.*, 2003, **125**, 7914–7922.

207 H. Mayr and M. Patz, *Angew. Chem. Int. Ed.*, 1994, **33**, 938–957.

208 X. J. Li, J. B. Qiao, J. Sun, X. Q. Li and P. Gu, *Org. Lett.*, 2014, **16**, 2865–2867.

209 P. G. Reddy, B. Varghese and S. Baskaran, *Org. Lett.*, 2003, **5**, 583–585.

210 A. Murali, M. Puppala, B. Varghese and S. Baskaran, *Eur. J. Org. Chem.*, 2011, 5297–5302.

211 S. Lang and J. A. Murphy, *Chem. Soc. Rev.*, 2006, **35**, 146–156.

212 H. Wang, C. Jing, A. Noble and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2020, **59**, 16859–16872.

213 V. Bagutski, T. G. Elford and V. K. Aggarwal, *Angew. Chem. Int. Ed.*,

2011, **50**, 1080–1083.

214 L. Horner and A. Christmann, *Angew. Chem. Int. Ed.*, 1963, **2**, 599–608.

215 D. H. R. Barton and L. R. Morgan Jr., *J. Chem. Soc.*, 1962, 622–631.

216 T. R. Cundari, *J. Am. Chem. Soc.*, 1992, **114**, 7879–7888.

217 T. Shimbayashi, K. Sasakura, A. Eguchi, K. Okamoto and K. Ohe, *Chem. Eur. J.*, 2019, **25**, 3156–3180.

218 Q. Nguyen, K. Sun and T. G. Driver, *J. Am. Chem. Soc.*, 2012, **134**, 7262–7265.

219 A. Das, Y. Chen, J. H. Reibenspies and D. C. Powers, *J. Am. Chem. Soc.*, 2019, **141**, 16232–16236.

220 Y. Baek, A. Das, S. Zheng, J. H. Reibenspies, D. C. Powers and T. A. Betley, *J. Am. Chem. Soc.*, 2020, **142**, 11232–11243.

221 A. Das, C. Wang, G. P. Van Van Trieste III, C. Sun, Y. Chen, J. H. Reibenspies and D. C. Powers, *J. Am. Chem. Soc.*, 2020, **142**, 19862–19867.

222 P. J. Walsh, F. J. Hollander and R. G. Bergman, *Organometallics*, 1993, **12**, 3705–3723.

223 A. E. Guiducci, C. L. Boyd and P. Mountford, *Organometallics*, 2006, **25**, 1167–1187.

224 A. Caselli, E. Gallo, S. Fantauzzi, S. Morlacchi, F. Ragaini and S. Cenini, *Eur. J. Inorg. Chem.*, 2008, 3009–3019.

225 T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29.

226 G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **5**, 3800–3801.

227 H. Hayashi, A. Kaga and S. Chiba, *J. Org. Chem.*, 2017, **82**, 11981–11989.

228 F. Palacios, A. Retana, E. Marigorta and J. Santos, *Eur. J. Org. Chem.*, 2001, 2401–2414.

229 R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. English*, 1969, **8**, 781–853.

230 A. Lopusinski and R. Sustmann, *Angew. Chem. Int. Ed.*, 1972, **11**, 838–840.

231 R. Sustmann, *Pure Appl. Chem.*, 1974, **40**, 569–593.

232 P. Chen, X. He, D. Svatunek, F. Liu and K. N. Houk, *J. Org. Chem.*, 2021, **86**, 5792–5804.

233 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2001, **40**, 2004–2021.

234 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.

235 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2596–2599.

236 J. R. Johansson, T. Beke-Somfai, A. Said Stålsmeden and N. Kann, *Chem. Rev.*, 2016, **116**, 14726–14768.

237 V. K. Tiwari, B. B. Mishra, K. B. Mishra, N. Mishra, A. S. Singh and X. Chen, *Chem. Rev.*, 2016, **116**, 3086–3240.

238 W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, 2008,

**29**, 952–981.

239 W. Xi, T. F. Scott, C. J. Kloxin and C. N. Bowman, *Adv. Funct. Mater.*, 2014, **24**, 2572–2590.

240 P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905–4979.

241 C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

242 H. Boyer, *J. Am. Chem. Soc.*, 1951, **73**, 5865–5866.

243 B. C. Ranu, A. Sarkar and R. Chakraborty, *J. Org. Chem.*, 1994, **59**, 4114–4116.

244 L. Benati, P. C. Montevecchi, D. Nanni, P. Spagnolo, M. Volta, C. Organica, U. Bologna and V. Risorgimento, *Tetrahedron Lett.*, 1995, **36**, 7313–7314.

245 Y. G. Gololobov, I. N. Zhmurova and L. F. Kasukhin, *Tetrahedron*, 1981, **37**, 437–472.

246 H. Staudinger and J. Meyer, *Helv. Chim. Acta*, 1919, **2**, 635–646.

247 P. A. Byrne and D. G. Gilheany, *Chem. Soc. Rev.*, 2013, **42**, 6670–6696.

248 J. E. Leffler and R. D. Temple, *J. Am. Chem. Soc.*, 1967, **89**, 5235–5246.

249 H. Goldwhite, P. Gysegem, S. Schow and C. Swyke, *J. Chem. Soc. Dalt. Trans.*, 1975, 16–18.

250 C. G. Chidester, J. Szmuszkovicz, D. J. Duchamp and L. G. Laurian,

*Acta Crystallogr.*, 1988, **C44**, 1080–1083.

251 D. E. Shalev, S. M. Chiacchiera, A. E. Radkowsky and E. M. Kosower, *J. Org. Chem.*, 1996, **61**, 1689–1701.

252 M. Alajarin, P. Molina, A. Lopez-Lazaro and C. Foces-Foces, *Angew. Chem. Int. Ed.*, 1997, **36**, 67–70.

253 C. Widauer, H. Grützmacher, I. Shevchenko and V. Gramlich, *Eur. J. Inorg. Chem.*, 1999, 1659–1664.

254 W. Q. Tian and Y. A. Wang, *J. Org. Chem.*, 2004, **68**, 4299–4308.

255 D. C. Batesky, M. J. Goldfogel and D. J. Weix, *J. Org. Chem.*, 2017, **82**, 9931–9936.

256 Y. Tamboli, B. B. Kashid, R. P. Yadav, M. Rafeeq, R. Yeole and A. Y. Merwade, *ACS Omega*, 2021, **6**, 13940–13945.

257 H. A. Van Kalkeren, J. J. Bruins, F. P. J. T. Rutjes and F. L. Van Delft, *Adv. Synth. Catal.*, 2012, **354**, 1417–1421.

258 (US) Environmental Protection Agency, https://www.epa.gov/sites/default/files/2014-03/documents/ffrro_factsheet_contaminant_14-dioxane_january2014_final.pdf, (accessed 1 February 2022).

259 D. C. Lenstra, P. E. Lenting and J. Mecinović, *Green Chem.*, 2018, **20**, 4418–4422.

260 D. C. Lenstra, J. J. Wolf and J. Mecinović, *J. Org. Chem.*, 2019, **84**, 6536–6545.

261 E. L. Myers and R. T. Raines, *Angew. Chem. Int. Ed.*, 2009, **48**,

2359–2363.

262 M. Formica, D. Rozsar, G. Su, A. J. M. Farley and D. J. Dixon, *Acc. Chem. Res.*, 2020, **53**, 2235–2247.

263 C. Bednarek, I. Wehl, N. Jung, U. Schepers and S. Bra, *Chem. Rev.*, 2020, **120**, 4301–4354.

264 F. Palacios, D. Aparicio and G. Rubiales, *Tetrahedron*, 2007, **63**, 523–575.

265 Y. Ittah, Y. Sasson, I. Shahak, S. Tsaroom and J. Blum, *J. Org. Chem.*, 1978, **43**, 4271–4273.

266 A. Voituriez and N. Saleh, *Tetrahedron Lett.*, 2016, **57**, 4443–4451.

267 A. M. Kirk, C. J. O'Brien and E. H. Krenske, *Chem. Commun.*, 2020, **56**, 1227–1230.

268 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem. Int. Ed.*, 2012, **51**, 12036–12040.

269 P. B. White, S. J. Rijpkema, R. P. Bunschoten and J. Mecinovic, *Org. Lett.*, 2019, **21**, 1011–1014.

270 L. Cai, K. Zhang, S. Chen, R. J. Lepage, K. N. Houk, E. H. Krenske and O. Kwon, *J. Am. Chem. Soc.*, 2019, **141**, 9537–9542.

271 J. M. Lipshultz, G. Li and A. T. Radosevich, *J. Am. Chem. Soc.*, 2021, **143**, 1699–1721.

272 C. Xie, A. J. Smaligo, X. R. Song and O. Kwon, *ACS Cent. Sci.*, 2021, **7**, 536–558.

273 C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R.

Kunkel, K. C. Przeworski and G. A. Chass, *Angew. Chem. Int. Ed.*, 2009, **48**, 6836–6839.

274 E. E. Coyle, B. J. Doonan, A. J. Holohan, K. A. Walsh, F. Lavigne, E. H. Krenske and C. J. O'Brien, *Angew. Chem. Int. Ed.*, 2014, **53**, 12907–12911.

275 T. V. Nykaza, A. Ramirez, T. S. Harrison, M. R. Luzung and A. T. Radosevich, *J. Am. Chem. Soc.*, 2018, **140**, 3103–3113.

276 T. V. Nykaza, J. C. Cooper, G. Li, N. Mahieu, A. Ramirez, M. R. Luzung and A. T. Radosevich, *J. Am. Chem. Soc.*, 2018, **140**, 15200–15205.

277 G. Li, T. V. Nykaza, J. C. Cooper, A. Ramirez, M. R. Luzung and A. T. Radosevich, *J. Am. Chem. Soc.*, 2020, **142**, 6786–6799.

278 G. Li, Z. Qin and A. T. Radosevich, *J. Am. Chem. Soc.*, 2020, **142**, 16205–16210.

279 C. W. Perkins, J. C. Martin, A. J. Arduengo, W. Lau, A. Alegría and J. K. Kochi, *J. Am. Chem. Soc.*, 1980, **102**, 7753–7759.

280 D. G. Gilheany, *Chem. Rev.*, 1994, **94**, 1339–1374.

281 R. E. Rundle, *J. Am. Chem. Soc.*, 1963, **85**, 112–113.

282 R. Hoffmann, J. M. Howell and E. L. Muetterties, *J. Am. Chem. Soc.*, 1972, **94**, 3047–3058.

283 S. Trippett, *Phosphorous Sulfur Relat. Elem.*, 1976, **1**, 89–98.

284 M. Nakamoto, S. Kojima, S. Matsukawa, Y. Yamamoto and K. Y. Akiba, *J. Organometalic Chem.*, 2002, **643**–**644**, 441–452.

285 I. Ugi, D. Marquarding, H. Klusacek, P. Gillespie and F. Ramirez, *Acc.*

*Chem. Res.*, 1971, **4**, 288–296.

286 H. Wallmeier and W. Kutzelnigg, *J. Am. Chem. Soc.*, 1979, **101**, 2804–2814.

287 E. Magnusson, *J. Am. Chem. Soc.*, 1990, **112**, 7940–7951.

288 A. E. Reed and P. Von Ragué Schleyer, *J. Am. Chem. Soc.*, 1990, **112**, 1434–1445.

289 M. F. Guest, I. H. Hillier and V. R. Saunders, *J. Chem. Soc. Faraday Trans. 2 Mol. Chem. Phys.*, 1972, **68**, 867–873.

290 M. W. Schmidt, S. Yabushita and M. S. Gordon, *J. Phys. Chem.*, 1984, **88**, 382–389.

291 E. V. Jennings, K. Nikitin, Y. Ortin and D. G. Gilheany, *J. Am. Chem. Soc.*, 2014, **136**, 16217–16226.

292 K. Nikitin, E. V. Jennings, S. Al Sulaimi, Y. Ortin and D. G. Gilheany, *Angew. Chem. Int. Ed.*, 2018, **57**, 1480–1484.

293 R. M. Moriarty, I. Prakash, O. Prakash and W. A. Freeman, *J. Am. Chem. Soc.*, 1984, **106**, 6082–6084.

294 N. Britto, V. G. Gore, R. S. Mali and A. C. Ranade, *Synth. Commun.*, 1989, **19**, 1899–1910.

295 M. Wada, S. I. Miyake, S. Hayashi, H. Ohba, S. I. Nobuki, S. Hayase and T. Erabi, *J. Organomet. Chem.*, 1996, **507**, 53–63.

296 F. P. Cossío, C. Alonso, B. Lecea, M. Ayerbe, G. Rubiales and F. Palacios, *J. Org. Chem.*, 2006, **71**, 2839–2847.

297 P. A. Byrne and D. G. Gilheany, *Chem. Eur. J.*, 2016, **22**, 9140–9154.

298 T. Kubota, S. Miyashita, T. Kitazume and N. Ishikawa, *J. Org. Chem.*, 1980, **45**, 5052–5057.

299 J. W. Kelly, P. L. Robinson, S. A. Evans, T. William, R. Kenan, L. Chemistry, C. Hill and N. Carolina, *J. Org. Chem.*, 1986, **51**, 4473–4475.

300 T. Fukuyama, S.-C. Lin and L. Li, *J. Am. Chem. Soc.*, 1990, **112**, 7050–7051.

301 V. Gevorgyan, M. Rubin, S. Benson, J. X. Liu and Y. Yamamoto, *J. Org. Chem.*, 2000, **65**, 6179–6186.

302 Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto and H. Nagashima, *Chem. Commun.*, 2009, 1574–1576.

303 D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almehmadi, K. Yamazaki and D. J. Dixon, *ACS Catal.*, 2020, **10**, 8880–8897.

304 H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567–607.

305 H. F. T. Klare and M. Oestreich, *Dalt. Trans.*, 2010, **39**, 9176–9184.

306 C. Chatgilialoglu, D. Griller and M. Lesage, *J. Org. Chem.*, 1988, **53**, 3641–3642.

307 C. Chatgilialoglu, *Chem. Rev.*, 1995, **95**, 1229–1251.

308 C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188–194.

309 M. E. Mowery and P. DeShong, *J. Org. Chem.*, 1999, **64**, 1684–1688.

310 J. Pesti and G. L. Larson, *Org. Process Res. Dev.*, 2016, **20**, 1164–1181.

311 E. L. Stoll, T. Tongue, K. G. Andrews, D. Valette, D. J. Hirst and R. M. Denton, *Chem. Sci.*, 2020, **11**, 9494–9500.

312 L. Benati, G. Bencivenni, R. Leardini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, G. Zanardi, C. Organica, V. Uni, R. V April, W. New, Y. Ph and X. B. Ge, *J. Org. Chem.*, 2006, **71**, 5822–5825.

313 R. Apodaca and W. Xiao, *Org. Lett.*, 2001, **3**, 1745–1748.

314 M. R. Ross and J. C. Martin, *J. Am. Chem. Soc.*, 1981, **103**, 1234–1235.

315 S. Kojima, K. Kajiyama, M. Nakamoto and K. Akiba, *J. Am. Chem. Soc.*, 1996, **118**, 12866–12867.

316 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880.

317 M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082–5103.

318 A. Streitwieser and Y. J. Kim, *J. Am. Chem. Soc.*, 2000, **122**, 11783–11786.

319 S. D. Lepore, A. Khoram, D. C. Bromfield, P. Cohn, V. Jairaj and M. A. Silvestri, *J. Org. Chem.*, 2005, **70**, 7443–7446.

320 R. L. Benoit, M. Fréchette and D. Lefebvre, *Can. J. Chem.*, 1988, **66**, 1159–1162.

321 B. Neises and W. Steglich, *Angew. Chem. Int. Ed. English*, 1978, **17**, 522–524.

322 Z. Fan, Z. Wang, R. Shi and Y. Wang, *Org. Chem. Front.*, 2021, **8**, 5098–5104.

323 M. Catellani, F. Frignani and A. Rangoni, *Angew. Chem. Int. Ed.*, 1997, **36**, 119–122.

324 M. Catellani, E. Motti and N. Della Ca, *Acc. Chem. Res.*, 2008, **41**, 1512–1522.

325 H. Shi, D. J. Babinski and T. Ritter, *J. Am. Chem. Soc.*, 2015, **137**, 3775–3778.

326 K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill and Q. Wang, *Org. Lett.*, 2004, **6**, 4603–4606.

327 P. Jain, J. T. Slama, L. A. Perez-Haddock and T. F. Walseth, *J. Med. Chem.*, 2010, **53**, 7599–7612.

328 D. M. T. Chan, K. L. Monaco, R. P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933–2936.

329 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941–2944.

330 D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937–2940.

331 J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779.

332 H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St Clair, S. N. Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry and S. Broder, *Proc. Natl. Acad. Sci. U. S. A.*, 1985, **82**, 7096–7100.

333 S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer and S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3815–4195.

334 N. Cankařová, E. Schütznerová and V. Krchňák, *Chem. Rev.*, 2019, **119**, 12089–12207.

335 A. R. Vaino and K. D. Janda, *J. Comb. Chem.*, 2000, **2**, 579–596.

336 S. Punna and M. G. Finn, *Synlett*, 2004, 99–100.

337 O. G. Kulinkovich, S. V. Sviridov and D. A. Vasilevski, *Synthesis*, 1991, **1991**, 234.

338 P. H. Lambert, M. Vaultier and R. Carrie, *J. Chem. Soc. Chem. Commun.*, 1982, 1224–1225.

339 G. Szeimies, U. Siefken and R. Rinck, *Angew. Chem. Int. Ed. English*, 1973, **12**, 161–162.

340 N. Knouzi, M. Vaultier, L. Toupet and R. Carrie, *Tetrahedron Lett.*, 1987, **28**, 1757–1760.

341 M. A. Mercadante, C. B. Kelly, J. M. Bobbitt, L. J. Tilley and N. E. Leadbeater, *Nat. Protoc.*, 2013, **8**, 666–676.

342 D. S. Allgäuer, H. Jangra, H. Asahara, Z. Li, Q. Chen, H. Zipse, A. R. Ofial and H. Mayr, *J. Am. Chem. Soc.*, 2017, **139**, 13318–13329.

343 K. G. Andrews, R. Faizova and R. M. Denton, *Nat. Commun.*, 2017, **8**, 1–6.

344 N. A. Petasis and I. Akritopolou, *Tetrahedron Lett.*, 1993, **34**, 583–586.

345 N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1997, **119**, 445–446.

346 N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1998, **120**, 11798–11799.

347 C. Wei and C. J. Li, *J. Am. Chem. Soc.*, 2002, **124**, 5638–5639.

348 B. V. Rokade, J. Barker and P. J. Guiry, *Chem. Soc. Rev.*, 2019, **48**, 4766–4790.

349 P. A. Forero-Cortés and A. M. Haydl, *Org. Process Res. Dev.*, 2019, **23**, 1478–1483.

350 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217–7218.

351 J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216.

352 J. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1997, **62**, 1268–1273.

353 S. B. Larsen, B. Bang-Andersen, T. N. Johansen and M. Jørgensen, *Tetrahedron*, 2008, **64**, 2938–2950.

354 N. Purkait, G. Kervefors, E. Linde and B. Olofsson, *Angew. Chem. Int. Ed.*, 2018, **57**, 11427–11431.

355 M. M. Heravi and V. Zadsirjan, *RSC Adv.*, 2020, **10**, 44247–44311.

356 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.

357 A. R. Katritzky and S. S. Thind, *J. Chem. Soc., Perkin Trans. 1*, 1980,

1895–1900.

358 E. Massolo, M. Pirola and M. Benaglia, *Eur. J. Org. Chem.*, 2020, **2020**, 4641–4651.

359 R. Paul, G. W. Anderson and G. W. Anderson, *J. Am. Chem. Soc.*, 1960, **82**, 4596–4600.

360 J. R. Dunetz, Y. Xiang, A. Baldwin and J. Ringling, *Org. Lett.*, 2011, **13**, 5048–5051.

361 E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606–631.

362 J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140–177.

363 S. Arkhipenko, M. T. Sabatini, A. S. Batsanov, V. Karaluka, T. D. Sheppard, H. S. Rzepa and A. Whiting, *Chem. Sci.*, 2018, **9**, 1058–1072.

364 K. G. Andrews and R. M. Denton, *Chem. Commun.*, 2017, **53**, 7982–7985.

365 E. Blokker, X. Sun, J. Poater, J. M. van der Schuur, T. A. Hamlin and F. M. Bickelhaupt, *Chem. Eur. J.*, 2021, **27**, 15616–15622.

366 L. J. Diorazio, D. R. J. Hose and N. K. Adlington, *Org. Process Res. Dev.*, 2016, **20**, 760–773.

367 J. M. Lipshultz and A. T. Radosevich, *J. Am. Chem. Soc.*, 2021, **143**, 14487–14494.

368 S. O. Duke, C. L. Cantrell, K. M. Meepagala, D. E. Wedge, N. Tabanca and K. K. Schrader, *Toxins (Basel).*, 2010, **2**, 1943–1962.

369 J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139–165.

370 K. Nakahara, K. Hirano, R. Maehata, Y. Kita and H. Fujioka, *Org. Lett.*, 2011, **13**, 2015–2017.

371 R. Ballette, M. Pérez, S. Proto, M. Amat and J. Bosch, *Angew. Chem. Int. Ed.*, 2014, **53**, 6202–6205.

372 D. R. Williams, K. Shamim, J. P. Reddy, G. S. Amato and S. M. Shaw, *Org. Lett.*, 2003, **5**, 3361–3364.

373 N. N. Rao and J. K. Cha, *J. Am. Chem. Soc.*, 2015, **137**, 2243–2246.

374 S. Danishefsky, J. Dynak, E. Hatch and M. Yamamoto, *J. Am. Chem. Soc.*, 1974, **96**, 1256–1259.

375 I. Vilotijevic and T. F. Jamison, *Angew. Chem. Int. Ed.*, 2009, **48**, 5250–5281.

376 A. R. Pinder, *Nat. Prod. Rep.*, 1990, **7**, 447–455.

377 M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701–1729.

378 J. Cossy, *Chem. Rec.*, 2005, **5**, 70–80.

379 M. S. M. Pearson, M. Mathé-Allainmat, V. Fargeas and J. Lebreton, *Eur. J. Org. Chem.*, 2005, 2159–2191.

380 D. L. Comins, S. P. Joseph and R. R. Goehring, *J. Am. Chem. Soc.*, 1994, **116**, 4719–4728.

381 A. B. Charette, M. Grenon, A. Lemire, M. Pourashraf and J. Martel, *J. Am. Chem. Soc.*, 2001, **123**, 11829–11830.

382 M. Hussain, T. S. L. Banchelin, H. Andersson, R. Olsson and F.

Almqvist, *Org. Lett.*, 2013, **15**, 54–57.

383 Z. Sun, S. Yu, Z. Ding and D. Ma, *J. Am. Chem. Soc.*, 2007, **129**, 9300–9301.

384 D. A. Black, R. E. Beveridge and B. A. Arndtsen, *J. Org. Chem.*, 2008, **73**, 1906–1910.

385 N. Christian, S. Aly and K. Belyk, *J. Am. Chem. Soc.*, 2011, **133**, 2878–2880.

386 J. P. Lutz, S. T. Chau and A. G. Doyle, *Chem. Sci.*, 2016, **7**, 4105–4109.

387 B. Qu, H. P. R. Mangunuru, X. Wei, K. R. Fandrick, J. N. Desrosiers, J. D. Sieber, D. Kurouski, N. Haddad, L. P. Samankumara, H. Lee, J. Savoie, S. Ma, N. Grinberg, M. Sarvestani, N. K. Yee, J. J. Song and C. H. Senanayake, *Org. Lett.*, 2016, **18**, 4920–4923.

388 Z. S. Ye, M. W. Chen, Q. A. Chen, L. Shi, Y. Duan and Y. G. Zhou, *Angew. Chem. Int. Ed.*, 2012, **51**, 10181–10184.

389 C. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2003, **125**, 6360–6361.

390 C. Y. Legault and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 8966–8967.

391 M. Rueping and A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2007, **46**, 4562–4565.

392 F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehmann, *Angew. Chem. Int. Ed.*, 2004, **43**, 2850–2852.

393 J. H. Xie, S. F. Zhu and Q. L. Zhou, *Chem. Rev.*, 2011, **111**, 1713–1760.

394 Z. Zhang, N. A. Butt and W. Zhang, *Chem. Rev.*, 2016, **116**, 14769–14821.

395 R. Kuwano, D. Karube and Y. Ito, *Tetrahedron Lett.*, 1999, **40**, 9045–9049.

396 T. J. Wilkinson, N. W. Stehle and P. Beak, *Org. Lett.*, 2000, **2**, 155–158.

397 C. Pousset, R. Callens, A. Marinetti and M. Larchevêque, *Synlett*, 2004, 2766–2770.

398 J. J. Verendel, J. Q. Li, X. Quan, B. Peters, T. Zhou, O. R. Gautun, T. Govender and P. G. Andersson, *Chem. Eur. J.*, 2012, **18**, 6507–6513.

399 M. T. Reding and S. L. Buchwald, *J. Org. Chem.*, 1998, **63**, 6344–6347.

400 S. Hussain, F. Leipold, H. Man, E. Wells, S. P. France, K. R. Mulholland, G. Grogan and N. J. Turner, *ChemCatChem*, 2015, **7**, 579–583.

401 W. F. Bailey, P. Beak, S. T. Kerrick, S. Ma and K. B. Wiberg, *J. Am. Chem. Soc.*, 2002, **124**, 1889–1896.

402 K. B. Wiberg and W. F. Bailey, *Angew. Chem. Int. Ed.*, 2000, **39**, 2127–2129.

403 K. B. Wiberg and W. F. Bailey, *Tetrahedron Lett.*, 2000, **41**, 9365–9368.

404 M. J. McGrath, J. L. Bilke and P. O'Brien, *Chem. Commun.*, 2006, 2607–2609.

405 P. Beak, D. R. Anderson, M. D. Curtis, J. M. Laumer, D. J. Pippel and G. A. Weisenburger, *Acc. Chem. Res.*, 2000, **33**, 715–727.

406 I. Coldham, S. Raimbault, P. T. Chovatia, J. J. Patel, D. Leonori, N. S. Sheikh and D. T. E. Whittaker, *Chem. Commun.*, 2008, 4174–4176.

407 D. Stead, G. Carbone, P. O'Brien, K. R. Campos, I. Coldham and A. Sanderson, *J. Am. Chem. Soc.*, 2010, **132**, 7260–7261.

408 T. K. Beng and R. E. Gawley, *J. Am. Chem. Soc.*, 2010, **132**, 12216–12217.

409 G. Paluch, L. Bartholomay and J. Coats, *Pest Manag. Sci.*, 2010, **66**, 925–935.

410 M. Mishra, V. K. Mishra, V. Kashaw, A. K. Iyer and S. K. Kashaw, *Eur. J. Med. Chem.*, 2017, **125**, 1300–1320.

411 H. K. Hall, *J. Am. Chem. Soc.*, 1964, **86**, 5709.

412 M. R. Crampton and I. A. Robotham, *J. Chem. Res. - Part S*, 1997, 22–23.

413 S. Minegishi and H. Mayr, *J. Am. Chem. Soc.*, 2003, **125**, 286–295.

414 P. Schnider, C. Dolente, H. Stalder, R. E. Martin, V. Reinmüller, R. Marty, C. Wyss Gramberg, B. Wagner, H. Fischer, A. M. Alker and K. Müller, *ChemBioChem*, 2020, **21**, 212–234.

415 G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F.

Schuler, M. Rogers-Evans and K. Müller, *J. Med. Chem.*, 2010, **53**, 3227–3246.

416 A. D. G. Lawson, M. Maccoss and J. P. Heer, *J. Med. Chem.*, 2018, **61**, 4383–4389.

417 A. Janecka, J. Fichna and T. Janecki, *Curr. Top. Med. Chem.*, 2004, **4**, 1–17.

418 L. Carballeira and I. Pérez-Juste, *J. Comput. Chem.*, 1998, **19**, 961–976.

419 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.

420 K. Grela, S. Harutyunyan and A. Michrowska, *Angew. Chem. Int. Ed.*, 2002, **41**, 4038–4040.

421 J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 2002, **41**, 4035–4037.

422 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, **36**, 3769–3772.

423 L. Zhou and M. P. Doyle, *J. Org. Chem.*, 2009, **74**, 9222–9224.

424 Z. Li, B. T. Parr and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 10942–10946.

425 V. K. Aggarwal, J. R. Fulton, C. G. Sheldon and J. De Vicente, *J. Am. Chem. Soc.*, 2003, **125**, 6034–6035.

426 T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, **2**, 1011–1014.

427 S. Pilard and M. Vaultier, *Tetrahedron Lett.*, 1984, **25**, 1555–1556.

428 P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 1995, **34**, 2039–2041.

429 S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168–8179.

430 K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem.*, 2011, **76**, 4697–4702.

431 J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 18296–18304.

432 Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem. Int. Ed.*, 2005, **44**, 4212–4215.

433 D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780–784.

434 T. H. Chan, *Acc. Chem. Res.*, 1977, **10**, 442–448.

435 N. A. Petasis and E. I. Bzowej, *J. Am. Chem. Soc.*, 1990, **112**, 6392–6394.

436 L. Shu and Y. Shi, *Tetrahedron*, 2001, **57**, 5213–5218.

437 K. Nagata, Y. Toriizuka and T. Itoh, *Heterocycles*, 2005, **66**, 107–109.

438 S. Liu, J. H. Xie, W. Li, W. L. Kong, L. X. Wang and Q. L. Zhou, *Org. Lett.*, 2009, **11**, 4994–4997.

439 National Research Council (US) Committee on Prudent Practices in the Laboratory, *Prudent Practices in the Laboratory*, National Academies Press, 2011.

440 S. Pramanik and P. Ghorai, *Org. Lett.*, 2014, **16**, 2104–2107.

441 F. Gao, R. Bai, M. Li and Y. Gu, *Green Chem.*, 2021, **23**, 7499–7505.

442 C. Büll, T. Heise, N. van Hilten, J. F. A. Pijnenborg, V. R. L. J. Bloemendal, L. Gerrits, E. D. Kers-Rebel, T. Ritschel, M. H. den Brok, G. J. Adema and T. J. Boltje, *Angew. Chem. Int. Ed.*, 2017, **56**, 3309–3313.

443 J. Waser, B. Gaspar, H. Nambu and E. M. Carreira, *J. Am. Chem. Soc.*, 2006, **128**, 11693–11712.

444 A. Banerjee and H. Yamamoto, *Chem. Sci.*, 2019, **10**, 2124–2129.

445 T. Delcaillau, P. Boehm and B. Morandi, *J. Am. Chem. Soc.*, 2021, **143**, 3723–3728.

446 W. Chen, J. Ren, M. Wang, L. Dang, X. Shen, X. Yang and H. Zhang, *Chem. Commun.*, 2014, **50**, 6259–6262.

447 B. K. Das, N. Shibata and Y. Takeuchi, *J. Chem. Soc. Perkin 1*, 2002, **2**, 197–206.

448 Z. J. Jia, S. Gao and F. H. Arnold, *J. Am. Chem. Soc.*, 2020, **142**, 10279–10283.

449 A. Bellomo, C. Giacomini, B. Brena, G. Seoane and D. Gonzalez, *Synth. Commun.*, 2007, **37**, 3509–3518.

450 P. Reutenauer, M. Kivala, P. D. Jarowski, C. Boudon, J.-P. Gisselbrecht, M. Gross and F. Diederich, *Chem. Commun.*, 2007, 4898–4900.

451 I. Abdelhedi-Miladi, D. Montarnal, M. M. Obadia, H. Ben Romdhane and E. Drockenmuller, *ACS Macro Lett.*, 2014, **3**, 1187–1190.

452 B. M. Casey, C. A. Eakin and R. A. Flowers, *Tetrahedron Lett.*, 2009, **50**, 1264–1266.

453 R. M. H. Rivera, Y. Jang, C. M. Poteat and V. N. G. Lindsay, *Org. Lett.*, 2020, **22**, 6510–6515.

454 K. Ueda, H. Umihara, S. Yokoshima and T. Fukuyama, *Org. Lett.*, 2015, **17**, 3191–3193.

455 D. F. González, J. P. Brand and J. Waser, *Chem. Eur. J.*, 2010, **16**, 9457–9461.

456 M. B. Zhou, R. Pi, M. Hu, Y. Yang, R. J. Song, Y. Xia and J. H. Li, *Angew. Chem. Int. Ed.*, 2014, **53**, 11338–11341.

457 R. A. Bunce and D. A. Irwin, *Synth. Commun.*, 1990, **20**, 2979–2982.

458 A. Liljeblad, H. M. Kavenius, P. Tähtinen and L. T. Kanerva, *Tetrahedron Asymmetry*, 2007, **18**, 181–191.

459 P. Steunenberg, M. Sijm, H. Zuilhof, J. P. M. Sanders, E. L. Scott and M. C. R. Franssen, *J. Org. Chem.*, 2013, **78**, 3802–3813.

460 H. Hebbache, T. Jerphagnon, Z. Hank, C. Bruneau and J. L. Renaud, *J. Organomet. Chem.*, 2010, **695**, 870–874.

461 E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo and C. Palomo, *Chem. Eur. J.*, 2017, **23**, 8185–8195.

462 R. López-González, D. Gnecco, J. R. Juárez, M. L. Orea, V. Gómez-Calvario, S. Bernès, D. M. Aparicio and J. L. Terán, *Tetrahedron Lett.*, 2020, **61**, 151697.

463 B. Majumdar, S. Mandani, T. Bhattacharya, D. Sarma and T. K. Sarma, *J. Org. Chem.*, 2017, **82**, 2097–2106.

464 C. E. Meyet, C. J. Pierce and C. H. Larsen, *Org. Lett.*, 2012, **14**, 964–967.

465 M. Bielawski, M. Zhu and B. Olofsson, *Adv. Synth. Catal.*, 2007, **349**, 2610–2618.

466 J. C. Borghs, Y. Lebedev, M. Rueping and O. El-Sepelgy, *Org. Lett.*, 2019, **21**, 70–74.

467 J. A. Andrews, L. R. E. Pantaine, C. F. Palmer, D. L. Poole and M. C. Willis, *Org. Lett.*, 2021, **23**, 8488–8493.

468 Y. H. Yang and M. Shi, *J. Org. Chem.*, 2005, **70**, 8645–8648.

469 D. J. Hardee, L. Kovalchuke and T. H. Lambert, *J. Am. Chem. Soc.*, 2010, **132**, 5002–5003.

470 J. D. Williams, W. J. Kerr, S. G. Leach and D. M. Lindsay, *Angew. Chem. Int. Ed.*, 2018, **57**, 12126–12130.

471 M. Boyle, K. Livingstone, M. C. Henry, J. M. L. Elwood, J. D. Lopez-Fernandez and C. Jamieson, *Org. Lett.*, 2022, **24**, 334–338.

472 P. V. Ramachandran and H. J. Hamann, *Org. Lett.*, 2021, **23**, 2938–2942.

473 P. Yu, Y. Wang, Z. Zeng and Y. Chen, *J. Org. Chem.*, 2019, **84**, 14883–14891.

474 Q. Zhu and D. G. Nocera, *J. Am. Chem. Soc.*, 2020, **142**, 17913–17918.

475 H. Wang, X. Sun, M. Hu, X. Zhang, L. Xie and S. Gu, *Adv. Synth. Catal.*, 2020, **362**, 3347–3351.

476 P. D. Clayman and T. K. Hyster, *J. Am. Chem. Soc.*, 2020, **142**, 15673–15677.

477 K. P. Shing, Y. Liu, B. Cao, X. Y. Chang, T. You and C. M. Che, *Angew. Chem. Int. Ed.*, 2018, **57**, 11947–11951.

478 H. Yang and R. G. Carter, *Org. Lett.*, 2010, **12**, 3108–3111.

479 V. K. Aggarwal, H. Abdel-Rahman, L. Fan, R. V. H. Jones and M. C. H. Standen, *Chem. Eur. J.*, 1996, **2**, 1024–1030.

480 A. G. Jamieson and A. Sutherland, *Org. Lett.*, 2007, **9**, 1609–1611.

481 Reaxys, https://www.reaxys.com/#/search/advanced, (accessed 10 February 2022).

482 Coconut, https://coconut.naturalproducts.net/, (accessed 20 September 2021).