

Applications of Catalytic C-N Bond Formation From Diazo Compounds



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**Thesis submitted to the University of
Nottingham for the degree of Doctor of
Philosophy**

Declaration of Authorship

I declare that the work embodied in this thesis is the result of my own investigations.

Where the work of other investigators has been used, this is fully acknowledged in
the text.

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Abstract

This thesis describes the development of a new reaction to form indolizines from pyridines, diazo compounds and alkynes, catalysed by commercially available iron catalysts. In addition, new methods for the *in situ* generation of diazo compounds *via* hydrazone oxidation have been developed.

The introduction section introduces indolizidines and indolizines and the synthetic routes towards them, including the reaction of pyridinium ylides with alkenes and alkynes. Subsequently, methods for pyridinium ylide generation and synthesis of diazo compounds are discussed. Methods for the *in situ* generation of diazo compounds are described, specifically hydrazone oxidation. The final section details the use of laccase proteins in conjunction with mediators as oxidation catalysts.

The results and discussions section is divided into three chapters. Chapter one describes the optimisation of catalytic indolizine synthesis, informed by observation of quinolizine and pyrazole by-products. Also discussed is a debromination reaction observed during the substrate scope variation.

Chapter two discusses synthesis of diazo compounds *via* NCS mediated hydrazone oxidation, including the initial optimisation of this process, the synthesis of hydrazone substrates, and the testing of these substrates under the reaction conditions. Finally, the methodology was used to generate diazo compounds *in situ* and react them with anilines *via* NH insertion.

Chapter three describes the biocatalyzed oxidation of hydrazones to diazo compounds and the successful of using this methodology to generate diazo compounds *in situ* and react them *via* NH insertion with aniline. Ultimately, NH insertion products were

obtained without the need for controlled addition of reagents or pre-formation of the diazo compound.

Finally, the experimental chapter describes the procedures by which the compounds in this thesis were synthesised, as well as full spectroscopic data and characterisation.

Acknowledgments

Firstly, I would like to thank my supervisors Dr Anca Pordea and Dr James Dowden for giving me the opportunity to work in their research groups, as well as their input and advice throughout this project.

Secondly, I would like to thank all members of B9, both past and present for making the past three years as enjoyable as they have been, and providing many enjoyable games of Resistance and fruitful discussions about drying agents and aqueous fluorine chemistry. I would also like to thank Holly for her continued and unrelenting support throughout the past three years.

I would like to thank all members of the CDT including Prof. Pete License, Prof. Chris Moody and Peri Williams as well as the EPSRC for providing funding. I would also like to thank my friends and colleagues from the CDT, as well as Simon and Nafeees for providing some of the compounds used during these studies, and Dr Alison Woodward for her assistance with the laccase activity assay.

Finally, I would like to thank all of the technical staff who help keep the department running, including Kev and Shaz for the NMR facilities, as well as Chris, Eric and Jim from stores.

List of Abbreviations

AE	Atom economy
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid)
Ac	Acyl
Ar	Aryl
AZADO	2-Azaadamantane <i>N</i> -Oxyl,
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement by polarization transfer
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAD	Dimethyl acetylenedicarboxylate
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron withdrawing group
h	Hour

HOBt	Hydroxybenzotriazole
ⁱ Pr	Iso-propyl
IR	Infrared
M.p	Melting point
mb	Myoglobin
Me	Methyl
Ms	Mesyl
ⁿ Bu	<i>n</i> -Butyl
NCS	<i>N</i> -Chlorosuccinimide
NMR	Nuclear magnetic resonance
ⁿ Pr	<i>n</i> -Propyl
oct	Octanoate
ox	Oxidised
Ph	Phenyl
r.t.	Room temperature
red	Reduced
RMI	Reaction mass intensity
^t Bu	Tertiary-butyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Triflic
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPP	Tetraphenylporphyrin
Ts	<i>p</i> -Methylbenzyl sulfonyl

TsNIK

Potassium N-iodo p-toluenesulfonamide

UV

UltraViolet

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1. Introduction

1.1. Indolizidines and indolizines

Indolizidines **1** and indolizines **2** are 5,6-bicyclic heterocycles that contain a tertiary nitrogen at the ring junction, and are saturated or unsaturated, respectively (Fig.1). The nomenclature for these heterocycles designates the carbon adjacent to the quaternary carbon at the ring junction as 1, then sequentially numbers carbons in a clockwise manner (as drawn in Figure 1). The quaternary carbon at the ring junction is designated 8a.

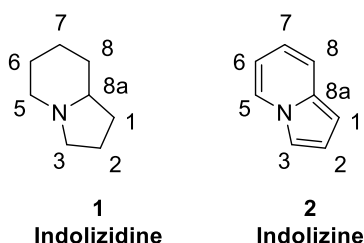


Fig. 1: Numbering pattern for indolizidines **1** and indolizines **2**.

Indolizidines and indolizines are present in a wide range of biologically relevant molecules and natural products (Fig. 2). Securinine **3** is a γ -aminobutyric acid antagonist, has been reported to possess both antibacterial and antimalarial properties.¹ Similarly, the indolizidine alkaloids show activity against an array of biological targets, such as swainsonine **4** which shows promising activity against tumour cell lines *in vitro*.² However, the high monetary cost and synthetic difficulty of accessing large quantities of these molecules has inhibited their development as drug candidates.³

Indolizines have also been reported to have biological activity, and are present in the lamellarin alkaloids **5**, which have potent anticancer activity.⁴ In addition, indolizines

have been reported to have fluorescent properties, making them attractive candidates for incorporation into various materials and chemical probes. Seoul-Fluor **6** in particular has seen considerable literature attention, as its fluorescent properties are highly tuneable by changing the R^1 , R^2 and R^3 substituents.⁵ Indolizines have also been used in medicinal applications such as the bromodomains BAZ2A and BAZ2B probe GSK2801 **7**, which showed high affinity for the domain due to π stacking between the phenyl group of **7** and a tryptophan of the binding pocket.⁶ High expression levels of BAZ2A have been reported in prostate cancer, and BAZ2B in acute lymphoblastic leukemia.⁷

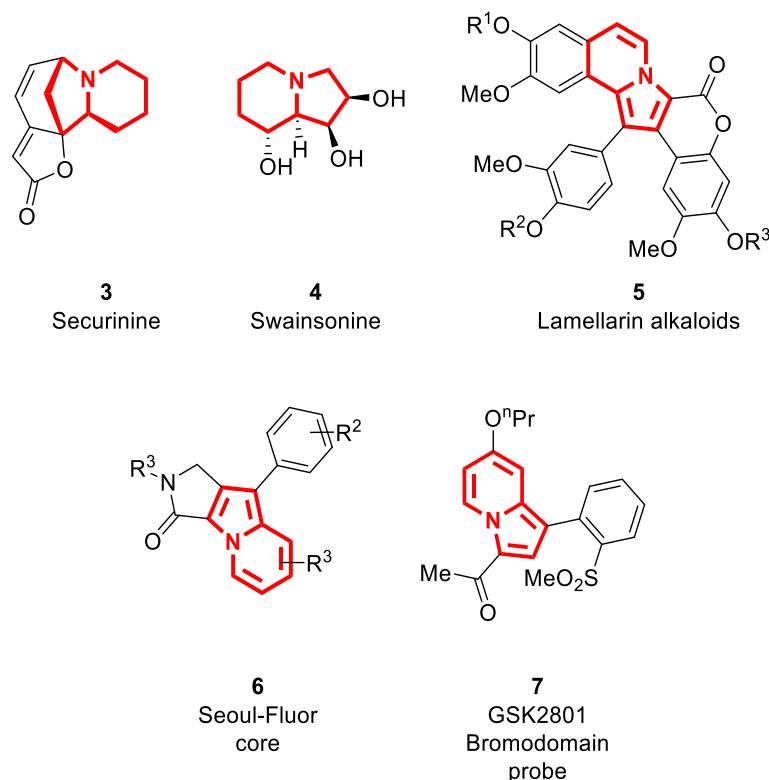
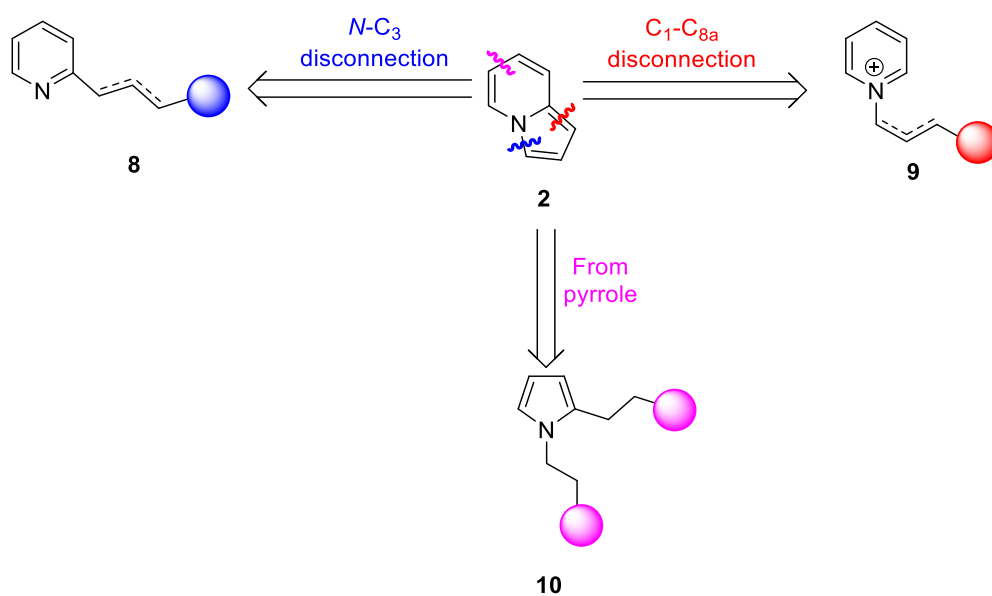


Fig 2: Indolizidine and indolizines of synthetic interest.

There are three main retrosynthetic approaches for the synthesis of indolizines **2** (Scheme 1).⁸ Disconnecting the N -C₃ bond gives a functionalised pyridine **8**, with ring closure occurring *via* nucleophilic attack of the nitrogen lone pair. Typically, a degree

of unsaturation is present on the carbon chain holding the reactive tether, to aid with aromatisation. Alternatively, disconnection at the C₁-C_{8a} bond gives a pyridinium **9**, with ring closure occurring *via* nucleophilic attack into the pyridinium ring. A variety of reagents and approaches are available to prepare the intermediate **9**, which is typically prepared *in situ* owing to its high reactivity. Alternatively, disconnection within the 6 membered ring allows for synthesis from a substituted pyrrole **10**, with ring closure occurring at a greater distance from the indolizine ring juncture. From these approaches, multicomponent methods that do not require pre-functionalisation of starting materials and generate the indolizine **2** from commercially available materials are the most desirable.

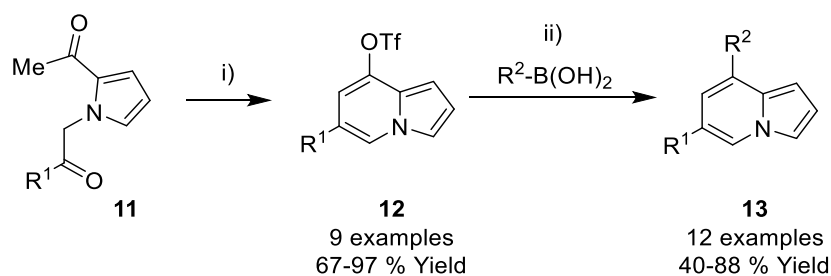


Scheme 1: Retrosynthetic approaches to indolizine **2**.

Kim and co-workers found that cyclisation of the 2-acetyl pyrroles **11** provided access to the 6 and 8 substituted indolizines **12** upon trapping with an external electrophile, such as triflic anhydride (Scheme 2).⁹ The indolizine products **12** were found to react in palladium cross coupling reactions with boronic acids to give the aryl substituted indolizines **13**. The starting material is first prepared *via* alkylation of 2-acetyl pyrrole.

Thus, should additional substitution be required at the C₁, C₂ or C₃ positions of the indolizine ring, synthesis of the starting pyrrole **11** increases in complexity significantly.

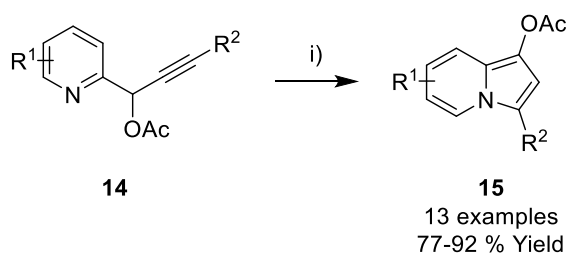
Kim and co-workers (2013)



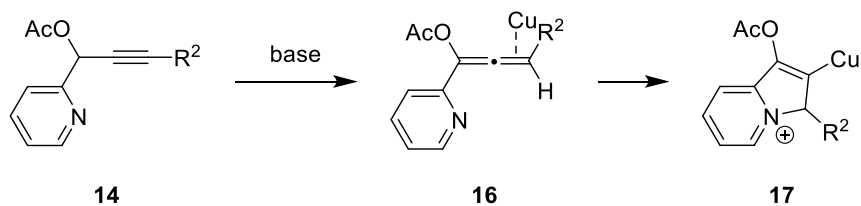
Scheme 2: Intramolecular condensation of pyrroles **11**. Reagents and conditions: i) NaH (2 eq.), THF, triflic anhydride (1.5 eq.), r.t., 1h. ii) $R^2B(OH)_2$ (1.5 eq.), K_3PO_4 (3 eq.), $Pd(PPh_3)_4$ (5 mol %), THF, 90 °C, 2h.

Another stepwise methodology for the synthesis of indolizines was developed by Liu and co-workers (Scheme 3).¹⁰ Under the basic reaction conditions, the propargylic pyridine **14** undergoes tautomerisation to give an allene intermediate **16**. Coordination to the copper catalyst increases the electrophilicity of the allene to allow for C₁-N bond formation and subsequent elimination to give the product **15**. Whilst the authors reported high yields of indolizine products **15**, the propargylic pyridine must first be synthesised, and the indolizine product **15** is prepared with an acetate moiety at the C₃ position, which may not be desired.

Liu and co-workers (2013)



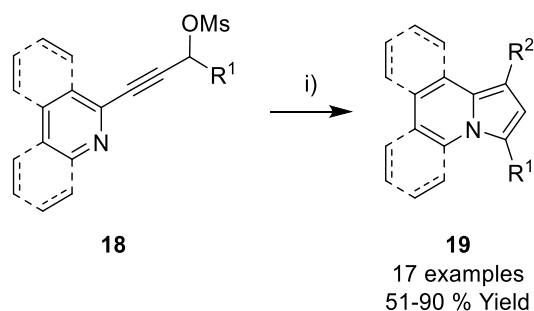
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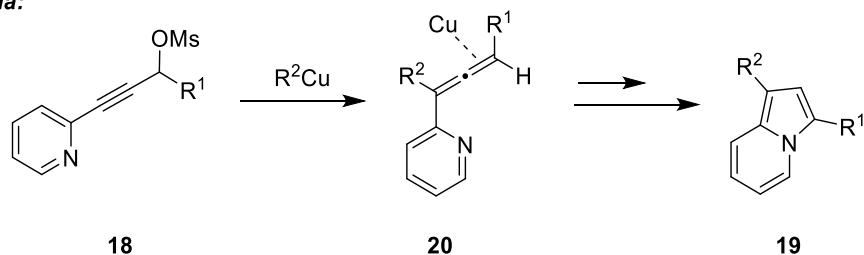
Scheme 3: Synthesis of indolizines **15**. Reagents and conditions: i) CuI (5 mol %), Et₃N (1 eq.), MeCN, reflux, 2 h.

A related method was reported by Gevorgyan and co-workers for the synthesis of the indolizines **19** *via* addition of organocuprate reagents to the propargyl mesylates **18** (Scheme 4).¹¹ Whilst generation of the allene **20** in this manner allows the synthesis of indolizine products **19** that do not possess the acetate group at the 3 position, synthesis of the starting materials **18** still remains a multi-step process.

Gevorgyan and co-workers (2008)



Via:

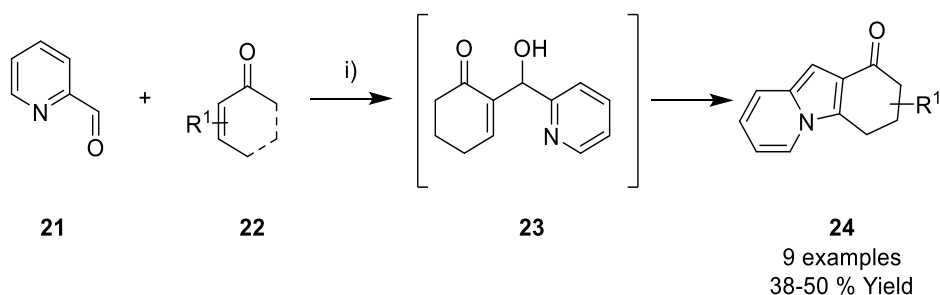


Scheme 4: Two component synthesis of indolizines **19** from propargylic mesylates

18. Reagents and conditions: i) Organocopper reagent (1.2 eq.), THF, -78 °C, 1 h.

Rao and co-workers reported synthesis of the indolizines **24** from the cyclic enones **22** and picolinaldehyde **21** (Scheme 5).¹² Stoichiometric TMSOTf was required to activate the enone **22**, and to accelerate the reaction. The alcohol intermediate **23** was detected by ¹H NMR analysis, but underwent cyclisation to the aromatic indolizine product **24** upon chromatography.

Rao and co-workers (2003)

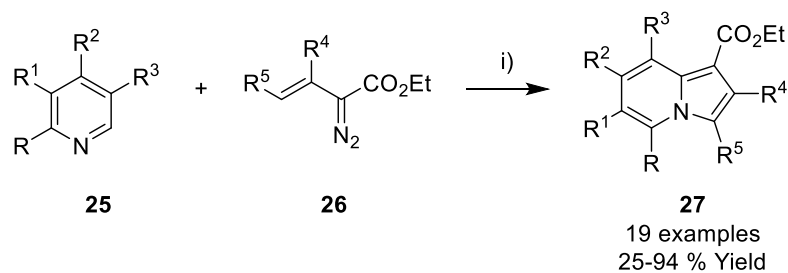


Scheme 5: Indolizine synthesis *via* electrophile induced Baylis-Hillman reaction.

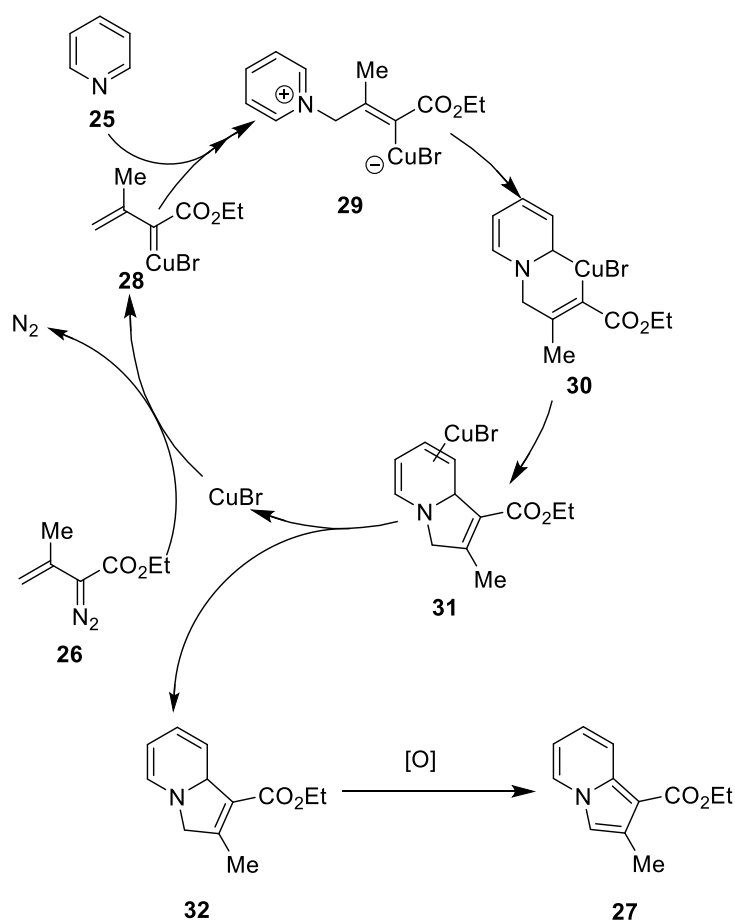
Reagents and conditions: Picolinaldehyde **21** (1 eq.), enone **22** (1 eq.), TMSOTf (1 eq.), MeCN, 0 °C to r.t., 12 h.

Tomás and co-workers reported a catalytic two component synthesis of the indolizines **27** from the pyridines **25** and diazo compounds **26** (Scheme 6).¹³ Catalytic decomposition of the diazo compound **26** gives the copper carbenoid **28**, which was attacked in a 1,4 manner by the pyridine reaction partner to yield the zwitterionic intermediate **29**. Nucleophilic attack at the α position of the pyridinium ion by the cuprate gave the 6,6 bicyclic intermediate **30**, which underwent ring contraction and dissociation of the copper catalyst to give the dihydroindolizine **32**, which then oxidized under air to give the indolizine product **27**.

Tomás and co-workers (2010)



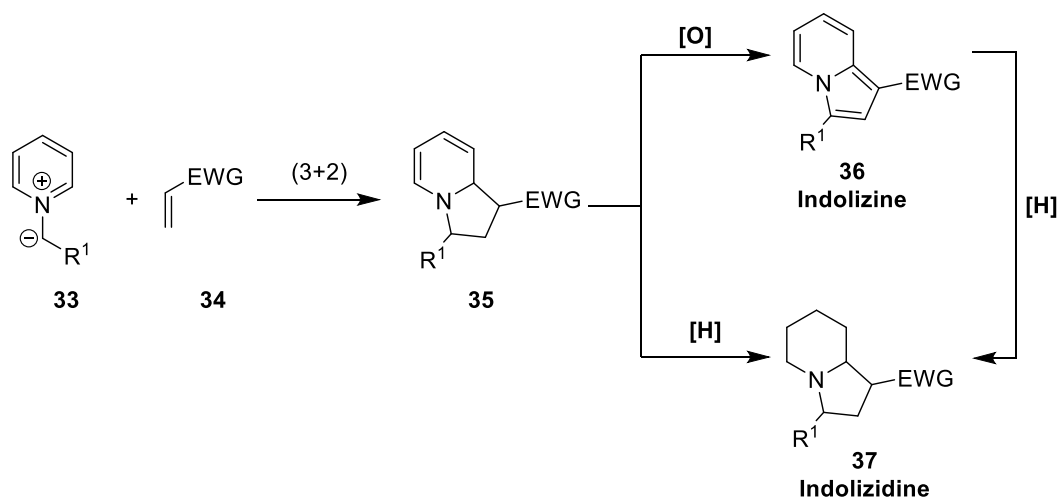
Proposed catalytic cycle



Scheme 6: Catalytic two component synthesis of indolizines **27**. Reagents and conditions: i) Pyridine **25** (1 eq.), diazo compound **28** (1 eq.), CuBr (5 mol %), CH₂Cl₂, r.t., 14 h.

A popular method for indolizine synthesis is the formal [3+2] cycloaddition of a pyridinium ylide **33** with a suitable dipolarophile **34** (Scheme 7). The initial cycloadduct **35** can be further reduced or oxidised to give the desired indolizidine or

indolizine cores **37** and **36** respectively. Alternatively, hydrogenation of the indolizines **36** can be used to access the indolizidines **37**.¹⁴



Scheme 7: Route towards indolizines and indolizidines **36** and **37** via cycloaddition of pyridinium ylide **33** with dipolarophile **34**.

1.2. Synthesis of pyridinium ylides *via* pyridinium salt deprotonation

Pyridinium ylides **33** are aromatic *N*-substituted species that react in a nucleophilic manner at the methine position and absorb strongly in the UV region (Fig. 3).¹⁵ Their high reactivity often precludes isolation, although pyridinium ylides in which the negative charge is highly stabilised or delocalised have been characterised.^{16,17}

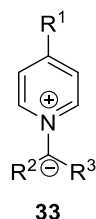
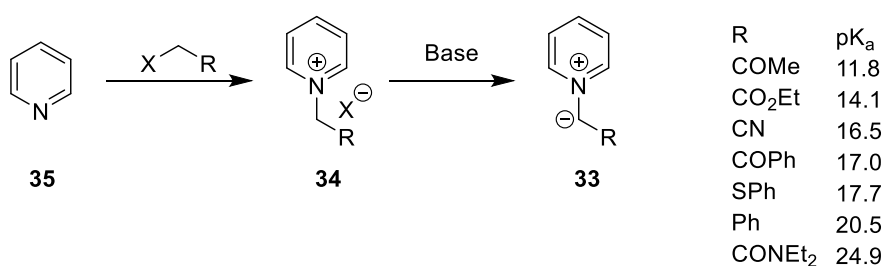


Fig. 3: Generic structure of pyridinium ylides.

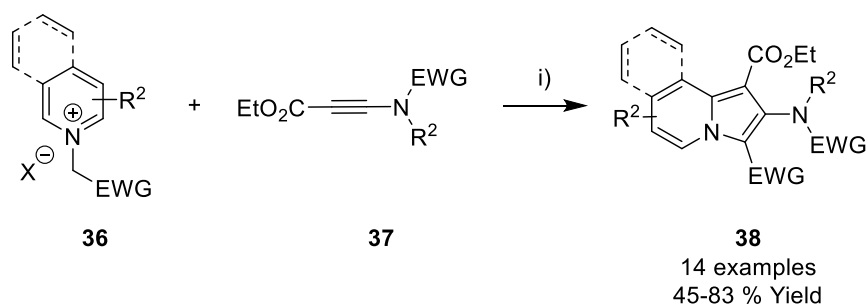
Owing to their high reactivity, pyridinium ylides **33** are typically prepared *in situ* and a common and extensively utilised methodology is the deprotonation of a pyridinium salt **34** (Scheme 8). Alkylation of a suitable pyridine **35** generates a pyridinium salt **34**, which is acidic at the methylene position, allowing for deprotonation with relatively mild bases to generate the pyridinium ylide **33**.¹⁸



Scheme 8: Generation of pyridinium ylide **33** and pK_a values for deprotonation in DMSO.¹⁸

Cossy and co-workers employed deprotonation of the *N*-heterocyclic salts **36** for the synthesis of the 2-aminoindolizines **38**, via formal cycloaddition between the *N*-heterocyclic ylides generated from **36** and electron deficient ynamides **37** (Scheme 9).¹⁹ The cycloaddition was found to proceed at room temperature, with the initial dihydroindolizine undergoing oxidation in air.

Cossy and co-workers (2015)

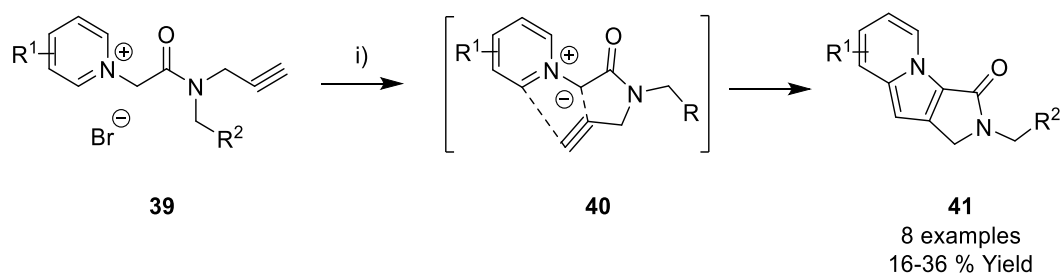


Scheme 9: Employment of ynamides **37** as dipolarophiles. Reagents and conditions:

i) Ynamide **37** (1 eq.), *N*-heterocyclic salt **36** (2.5 eq.), K_2CO_3 (4 eq.), DMF, r.t..

While the presence of an electron withdrawing group on the dipolarophile is typically required for cycloaddition, the release of ring strain in a dipolarophile, such as cyclooctyne,²⁰ or a carbon nanotube wall²¹ can be sufficient to drive reaction. Alternatively, pyridinium ylides can react with dipolarophiles that do not possess an electron withdrawing group if the reaction is intramolecular. Park and co-workers synthesised the Seoul-Fluor derived indolizines **41** via intramolecular reaction of the ylide **40** at elevated temperatures (Scheme 10).²² The addition of either Au^I or Ag^I additives were found to have a positive effect on yield, by raising the electrophilicity of the alkyne. Elevated temperatures have been demonstrated to allow for pyridinium ylide reaction with other electron rich alkynes.²³

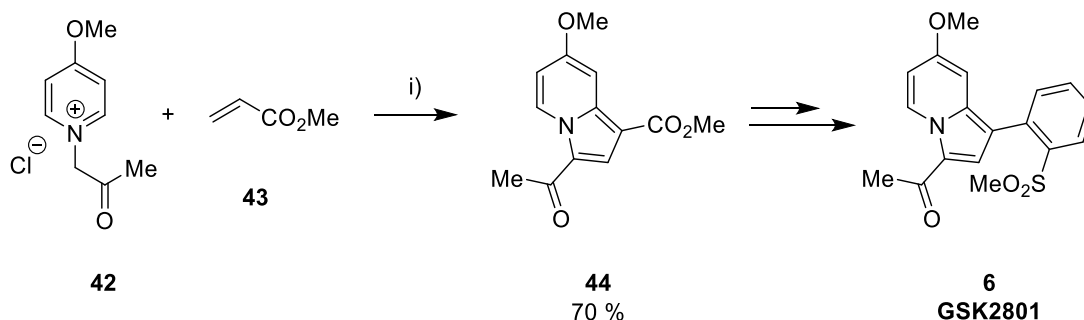
Park and co-workers (2014)



Scheme 10: Intramolecular reaction of **40**. Reagents and conditions: i) Pyridinium salt **39** (1 eq.), DBU (2 eq.), CH_2Cl_2 /toluene (1:1), 80 °C, 16 h.

The reaction of a pyridinium ylide with an electron deficient alkene can also be used to furnish an indolizine product. Drewry and co-workers used the reaction between the ylide generated from deprotonation of the pyridinium salt **42** with methyl acrylate **43** to give the indolizine **44** (Scheme 11). The presence of an additional oxidant, MnO_2 , was required to drive the formation of **44**. Reaction of the ylide with methyl propiolate was also found to give access to the intermediate **44** with the oxidation occurring under air. Further functionalisation *via* decarboxylation of **44** and subsequent cross coupling then gave the desired indolizine GSK2801 **6**.

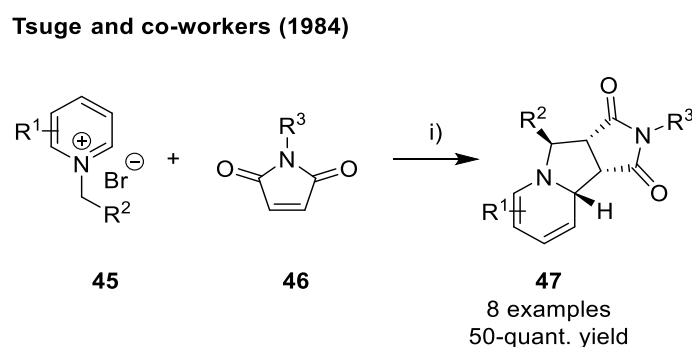
Drewry and co-workers (2015)



Scheme 11: Synthesis of bromodomain probe GSK2801 **6**. Reagents and conditions:

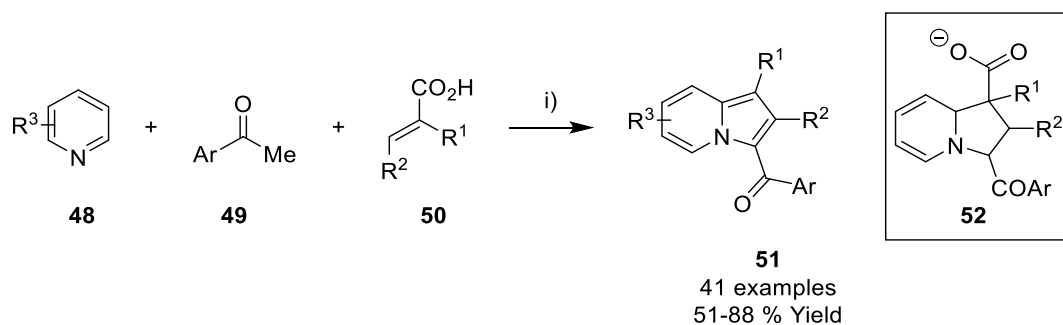
i) Pyridinium salt **42** (1 eq.), methyl acrylate **43** (10 eq.), Et_3N (1.5 eq.), MnO_2 (8 eq.), 90 °C, 1 h.

Tsuge and co-workers reported the cycloaddition of pyridinium ylides generated from deprotonation of **45** with the *N*-substituted maleimide derivatives **46** to give the dihydropyridine cycloadducts **47** (Scheme 12).²⁴ In the absence of a suitable oxidant, the products **47** did not oxidize further to the corresponding indolizine. The cycloadducts themselves were noted to be rather unstable, decomposing upon chromatography, or upon storage beyond 24 hours.



Scheme 12: Tsuge and co-workers synthesis of indolizidine cores **47**. Reagents and conditions: i) Et_3N , CH_2Cl_2 , r.t..

More recently, Liu and co-workers reported a catalytic *in situ* Ortleva-King method to synthesise the indolizines **51** from pyridines **48**, methyl ketones **49** and alkenoic acids **50** (Scheme 13).²⁵ Formation of the indolizine **51** is driven by oxidative decarboxylation of the initial cycloadduct **52**.



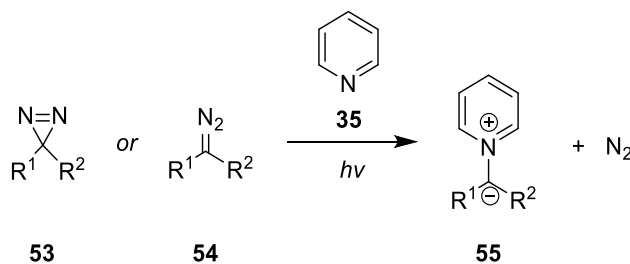
Scheme 13: Three component indolizine synthesis *via* pyridinium ylide intermediate.

Reagents and conditions: i) Pyridine **48** (4 eq.), ketone **49** (2 eq.), alkenoic acid **50** (1 eq.), CuBr (20 mol %), O₂ (1 atm), 80 °C, 12 h.

To conclude, the reaction of a pyridinium ylide with an alkene or alkyne dipolarophile offers an efficient route to indolizines and indolizidines and the deprotonation of a pyridinium salt is a well-developed methodology for *in situ* ylide generation. However, this method for ylide generation generates stoichiometric conjugate acid waste, detracting from the atom economy of an otherwise very efficient route for *N*-heterocycle synthesis.

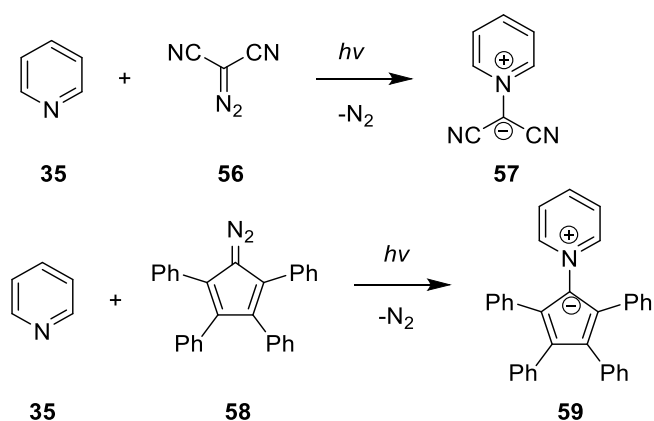
1.3. Synthesis of pyridinium ylides *via* diazo or diazirine decomposition

Whilst the generation of pyridinium ylides from pyridinium salts has received considerable literature attention, a much less explored methodology for ylide generation is the decomposition of a diazirine **53** or diazo **54** compound in the presence of a suitable pyridine.²⁶ Such a method for ylide generation is attractive as it allows for direct ylide formation from pyridine and produces nitrogen as the only by-product. The simplest methodology for accomplishing this is flash photolysis (Scheme 14). Indeed, the formation of UV active pyridinium ylides has been used as a method of detecting carbenes generated by photolysis.²⁷



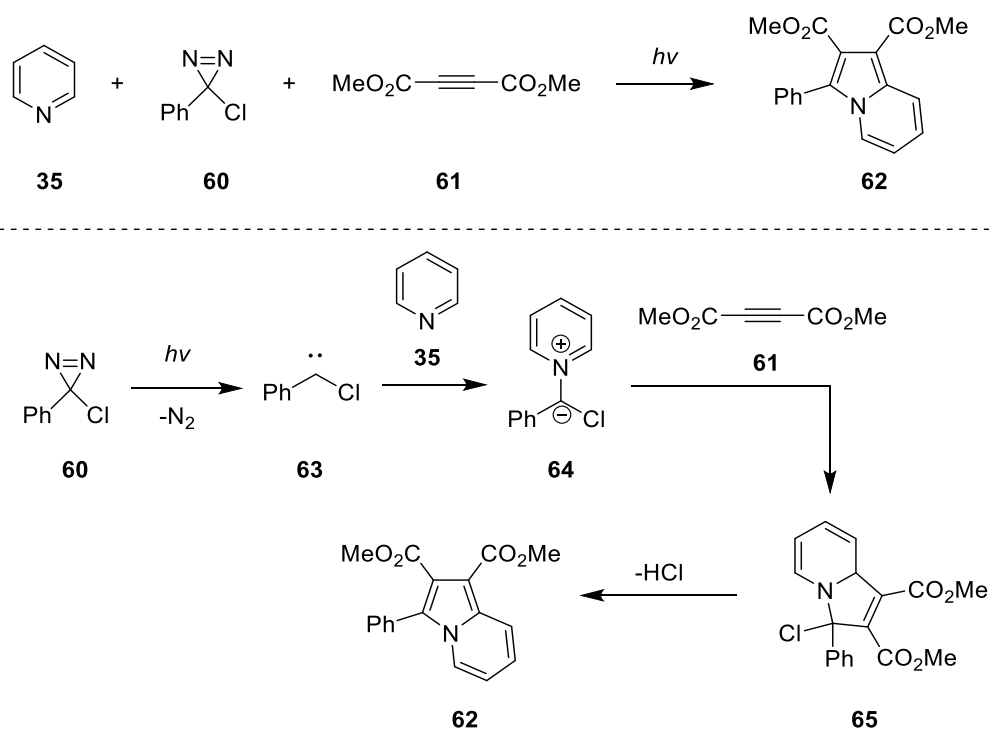
Scheme 14: Pyridinium ylide generation *via* flash photolysis.

Ylides generated *via* photolysis can be isolated, if the negative charge of the ylide is highly stabilised. For example, the highly stabilised ylides **57** and **59** were isolated from photolysis of diazo compounds **56** and **58** respectively in the presence of pyridine **35** (Scheme 15).^{16 17}



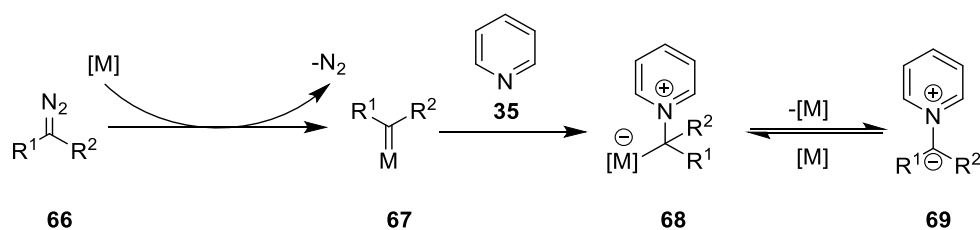
Scheme 15: Synthesis of ylides **57** and **59** *via* diazo photolysis.

Pyridinium ylides generated *via* the photolysis of diazo compounds can also undergo reaction with a suitable dipolarophile to generate indolizines. Liu and co-workers studied the formation of the chlorocarbene **63** from photolysis of the diazirine **60** (Scheme 16).²⁷ Whilst the free chlorocarbene **63** does not possess a chromophore, the pyridinium ylide **64** absorbs strongly in the UV region (λ_{max} 480 nm), allowing for monitoring of its formation. Photolysis of the diazirine **60** generates the free carbene species **63**, which is quenched by pyridine **35** to give the ylide **64**. Cycloaddition with the highly activated dipolarophile DMAD **61** gives the initial cycloadduct **65**. Aromatisation is then driven by the loss of HCl to give the indolizine **62**.



Scheme 16: Synthesis of 2-phenyl indolizine **62** reported by Liu and co-workers.

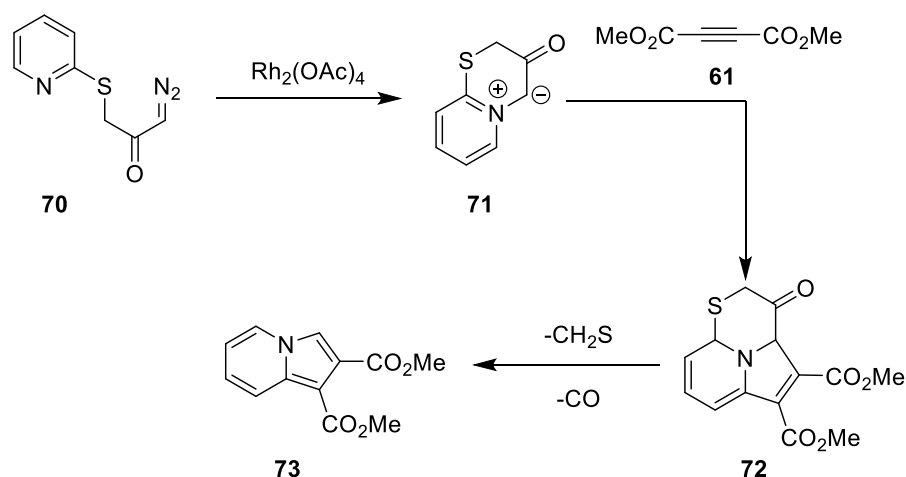
Alternatively, a pyridinium ylide can be generated *via* metal-catalysed decomposition of a diazo compound in the presence of suitable pyridine (Scheme 17). Elimination of nitrogen from the diazo compound **66** yields the carbenoid intermediate **67**, which is attacked by the nucleophilic pyridine **35**. The resulting intermediate **68** may then dissociate to the free ylide **69** or remain as the metal bound complex **68**.



Scheme 17: Catalytic pyridinium ylide generation *via* carbenoid intermediate **67**.

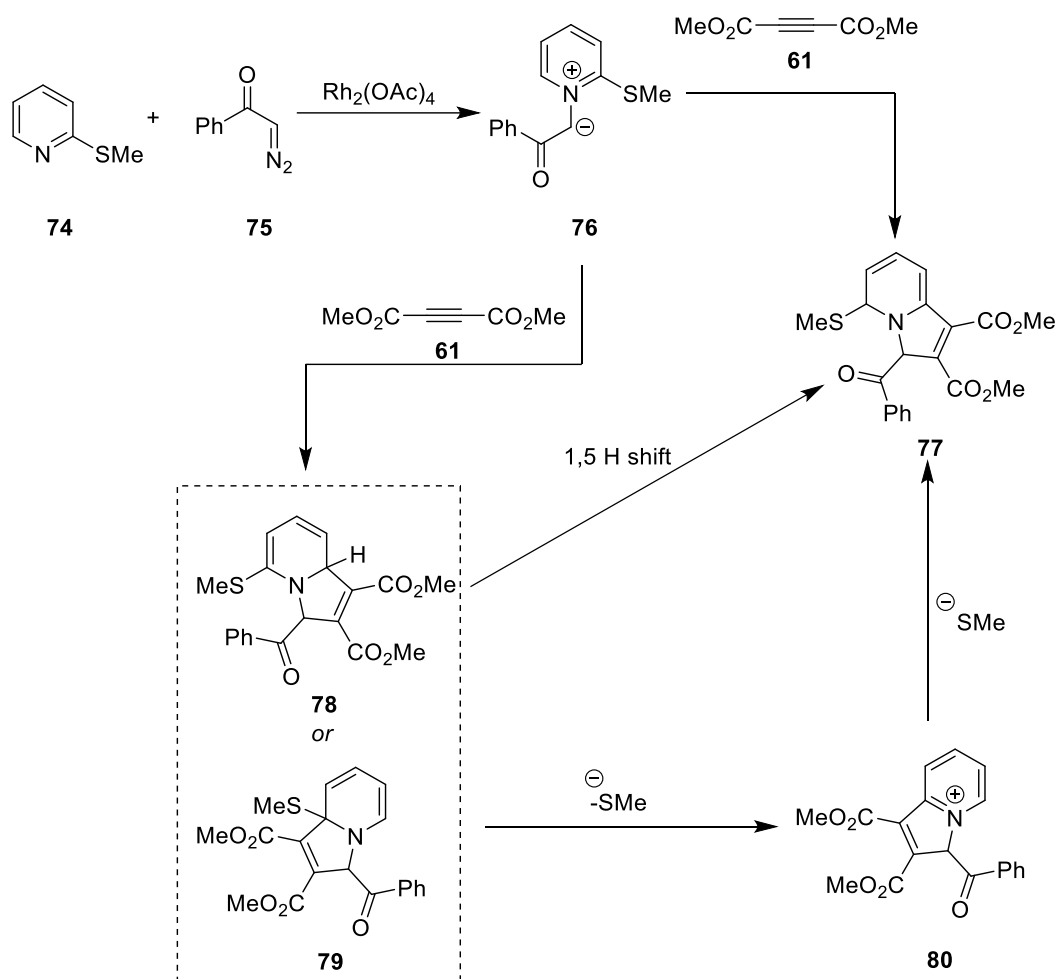
Limited examples of indolizine synthesis involving a carbenoid intermediate generated from a diazo moiety tethered to the pyridine have been reported (Scheme

18).²⁸ Rhodium catalysed decomposition of the diazo moiety of **70** followed by intramolecular ylide formation generates the active ylide species **71**, which undergoes cycloaddition with the dipolarophile DMAD **61** to give the tricyclic cycloadduct **72**. Aromatisation occurs via the loss of carbon monoxide and CH₂S to give the indolizine core **73**.



Scheme 18: Synthesis of indolizine **73** via intramolecular ylide generation.

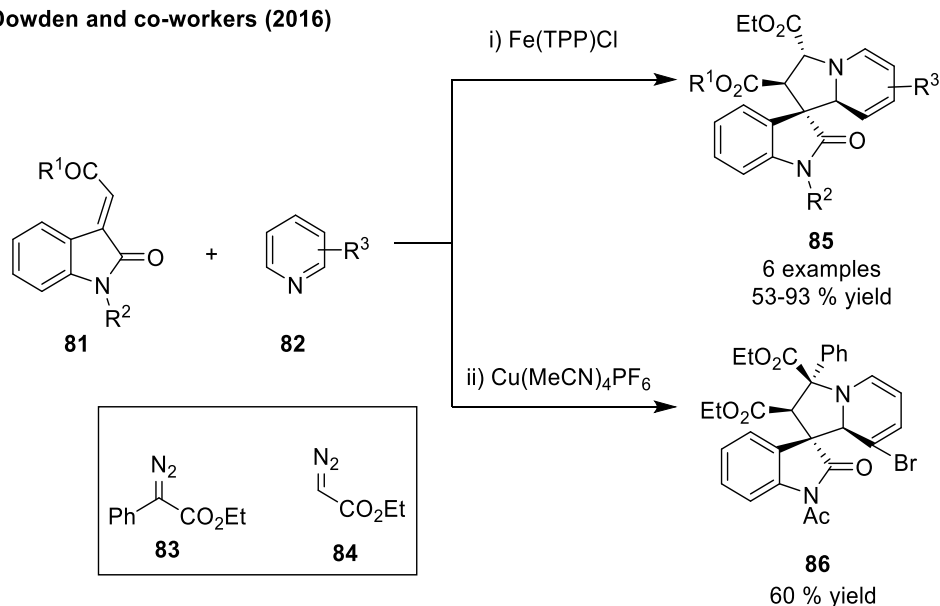
The first example of three component, intermolecular ylide generation and cycloaddition were reported in the same publication, from 2-thiomethyl pyridine **74** and the diazo compound **75** (Scheme 19).²⁸ Reaction of the ylide **76** with DMAD **61** gives observed **77**, or the initial cycloadducts **78** or **79**. A 1,5 hydride shift of **78** will give the observed product **77** and, a thiomethyl shift of **79** will also lead to formation of **77**. The methodology was not general, and substrate variation was not tolerated. Specifically, other pyridines were not compatible with the reaction conditions, leading to ‘a complex mixture of products which was extremely difficult to purify’.



Scheme 19: Intermolecular cycloaddition of pyridinium ylide **76** with DMAD **61**.

More recently, general examples of three component reactions have been reported, in which both ylide generation and cycloaddition were intermolecular. Building upon their previous work,²⁹ Dowden and co-workers reported the three component, catalytic synthesis of the spirooxindoles **85** and **86** (Scheme 20).³⁰ The commercially available iron porphyrin catalyst $\text{Fe}(\text{TPP})\text{Cl}$ was found to display excellent activity with respect to catalysing *in situ* generation of ylides from ethyl diazoacetate **84** and the pyridines **82**. Whilst $\text{Fe}(\text{TPP})\text{Cl}$ was found to be catalytically inactive with respect to ylide formation from the α -substituted diazo compound **83**, employment of tetrakis(acetonitrile)copper(I) hexafluorophosphate gave the corresponding cycloadduct **86** in good yield.

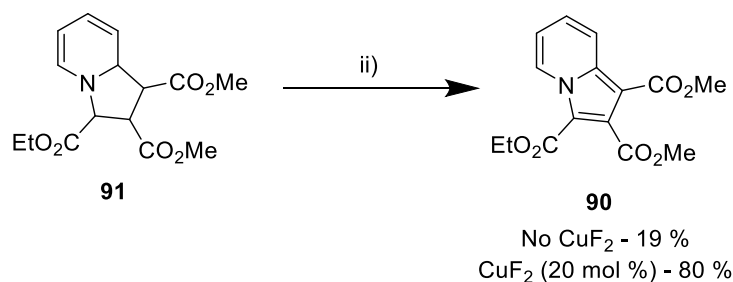
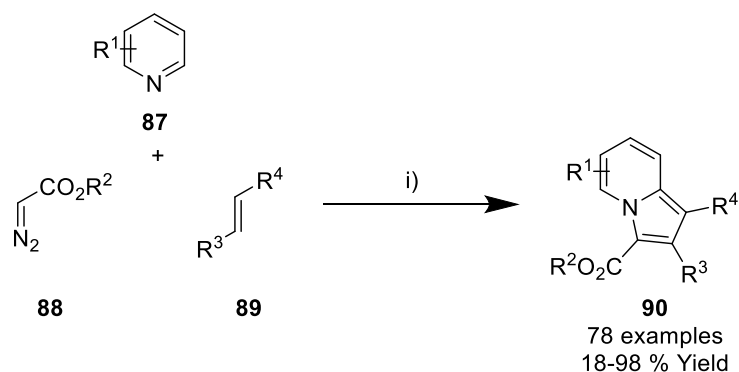
Dowden and co-workers (2016)



Scheme 20: Reagents and conditions i) oxindole **81** (1 eq.), pyridine **82** (3 eq.), ethyl diazoacetate **84** (1.5 eq.), catalyst (1 mol %), CH_2Cl_2 , r.t.; ii) oxindole **81** (1 eq.), pyridine **82** (3 eq.), phenyl ethyl diazoacetate **83** (1.5 eq.), $\text{Cu(MeCN)}_4\text{PF}_6$ (1 mol %), CH_2Cl_2 , r.t.

During the preparation of this thesis, Wan and co-workers reported the copper (II)-catalysed generation of pyridinium ylides from the pyridines **87** and diazo compounds **88** (Scheme 21).³¹ An excess of pyridine **87** was used, with the diazo compound **88** as the limiting reagent, presumably to suppress fumarate or malonate formation, which could potentially compete with the olefin **89** for reaction with the ylide. The copper catalyst was reported to be bifunctional, and was necessary to drive formation of the indolizine products **90** from the initial cycloadduct **91**.

Wan and co-workers (2017)



Scheme 21: CuF_2 catalysed synthesis of indolizines **90**. Reagents and conditions: i) Pyridine **87** (2 eq.), diazo **88** (2 eq.), alkene **89** (1 eq.), CuF_2 (20 mol %), PPh_3 (30 mol %), DCE/ 1,1,2-trichloroethane, 80 °C, 24 h; ii) DCE/ 1,1,2-trichloroethane, 80 °C, 24 h

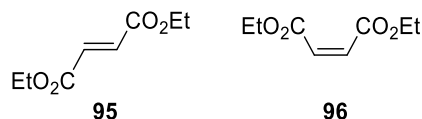
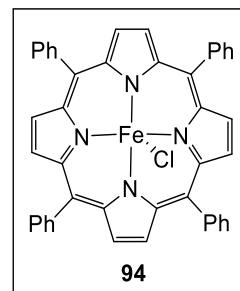
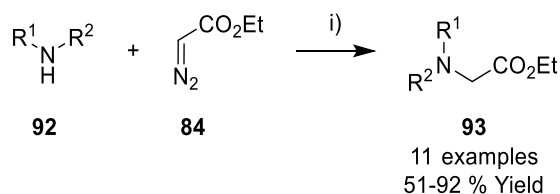
To summarise, the catalytic decomposition of a diazo compound in the presence of pyridine offers an efficient route to pyridinium ylides as the only by-product of the process is nitrogen, and the ylide is generated in one step for commercially available materials. Hitherto, this methodology has received little literature attention compared to reactions involving the preparation of pyridinium ylides from pyridinium salts. Whilst very recent publications indicate that general catalytic routes to pyridinium ylides from diazo compounds and pyridines are possible, to date these remain underexplored.

1.4. Iron and copper catalysed nitrogen ylide formation

Whilst examples of the catalytic generation of pyridinium ylides are limited, the generation of ammonium and iminium ylides *via* diazo decomposition has received considerable literature attention.³² In particular, rhodium has been shown to be highly competent at catalysing ylide formation, although its poor sustainability profile and high monetary cost has led to the investigation of other metals for catalytic activity.³³ Iron and copper catalytic systems have been demonstrated to show promising activity for ylide formation, in addition to having more amenable sustainability profiles.³⁴

Woo and co-workers reported that Fe(TPP)Cl **94** was highly competent with respect to catalysing the NH insertion of ethyl diazoacetate **84** into the amines **92**. (Scheme 22).³⁵ Other catalysts including ruthenium (II) and osmium (II) porphyrins also catalysed the reaction, although the authors concluded that Fe(TPP)Cl **94** was superior given its commercial availability and low monetary cost. In the presence of excess ethyl diazoacetate, formation of malonate **96** and fumarate **95** were observed, although the formation of these side products could be prevented by using only one equivalent of ethyl diazoacetate **84** with respect to the amine **92**, indicating that the amine will outcompete other species for reaction with the carbenoid.

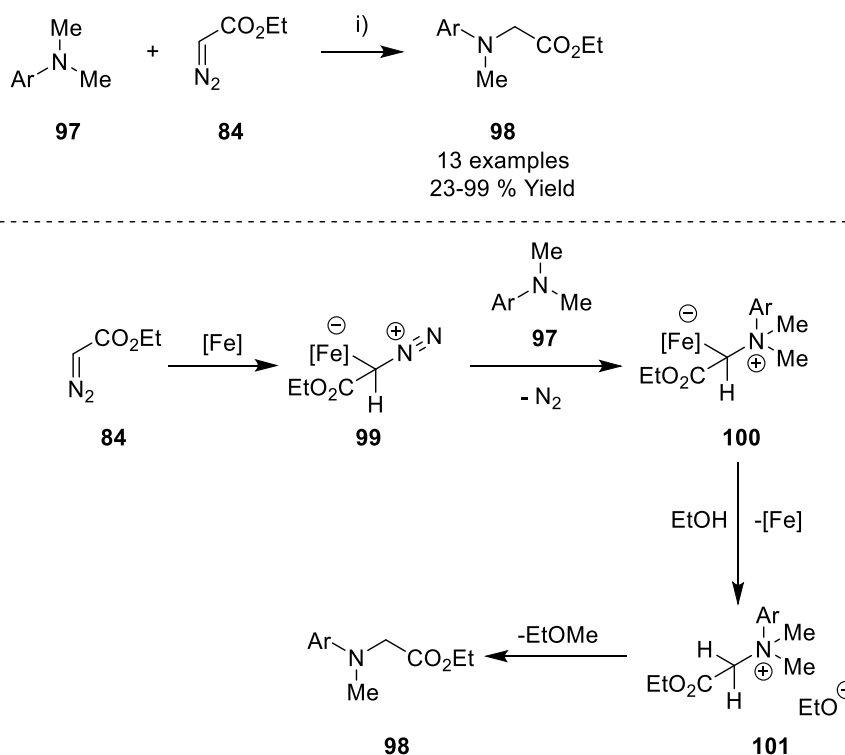
Woo and co-workers (2007)



Scheme 22: Fe(TPP)Cl catalysed NH insertion. Reagents and conditions: i) Amine **92** (1 eq.), ethyl diazoacetate **84** (1 eq.) Fe(TPP)Cl **94** (1 mol %), CH_2Cl_2 , r.t., 16 h.

Takai and co-workers reported synthesis of the glycine derivatives **98** via $FeCl_3$ catalysed reaction of the amines **97** with ethyl diazoacetate **84** (Scheme 23).³⁶ Nucleophilic attack of the tertiary amine **92** into the iron-bound diazonium **99** yields the ylide **100** which contains no appropriate N-H bond to undergo a 1,2 proton shift. Instead, protonation of the ylide **100** by ethanol generates the ethoxide **101**. The ethoxide counterion is then sufficiently nucleophilic to demethylate **101**, leading to the functionalised glycine **98**.

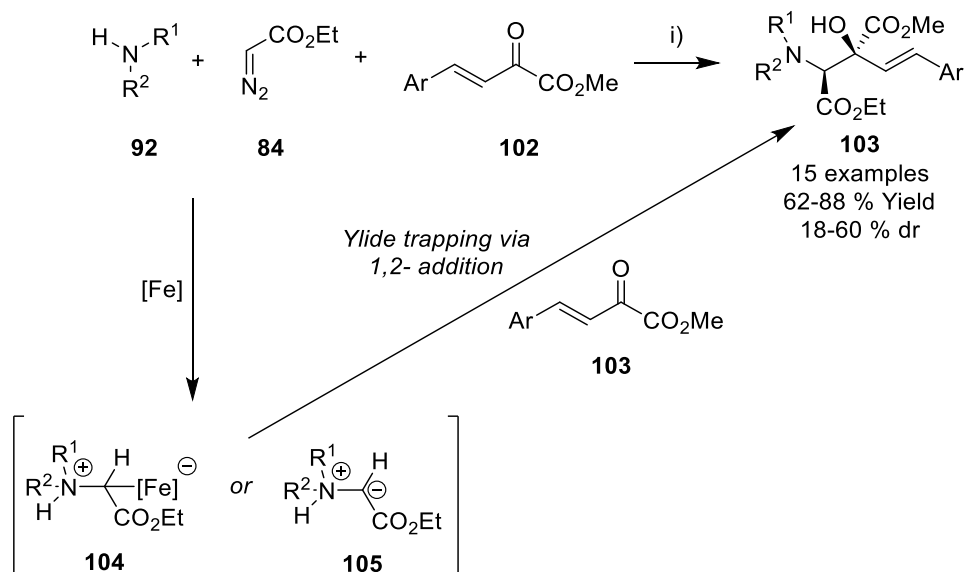
Takai and co-workers (2010)



Scheme 23: Functionalisation of amines *via* demethylation and proposed catalytic cycle. Reagents and conditions: i) Amine **97** (1 eq.), ethyl diazoacetate **84** (2 eq.), FeCl₃ (20 mol %), EtOH, 115 °C.

Ammonium ylides may react with an external electrophile, instead of undergoing a 1,2-hydride shift to give NH insertion products, as reported by Hu and co-workers (Scheme 24).³⁷ Fe(TPP)Cl decomposition of ethyl diazoacetate **84** in the presence of the secondary amine **92** generates either the metal bound or free ylides **104** or **105** respectively, which are trapped *via* 1,2-addition into the keto ester **102** before a 1,2 proton shift can occur. In line with other methodologies,³⁸ the use of DMAP as an additive was found to be essential for successful reaction, due to its binding properties to metalloporphyrins.³⁹

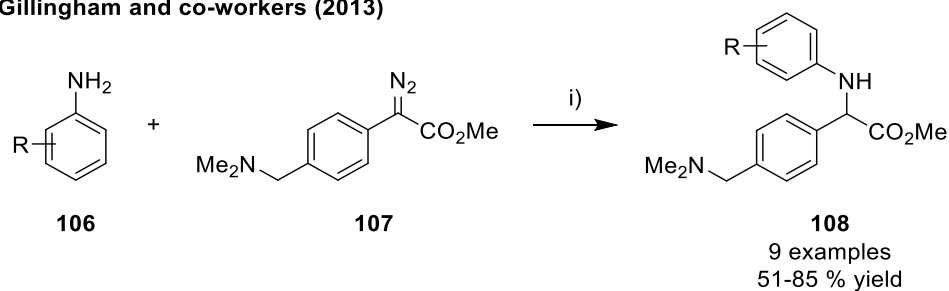
Hu and co-workers (2013)



Scheme 24: Intermolecular ylide trapping *via* 1,2 addition. Reagents and conditions: Keto ester **102** (1 eq.), amine **92** (1.5 eq.), ethyl diazoacetate **84** (1.5 eq.), DMAP (10 mol %), Fe(TPP)Cl (1 mol %), $CHCl_3$, r.t.

Copper is another earth-abundant catalyst that has been demonstrated to be highly competent at catalysing nitrogen ylide formation from diazo compounds.⁴⁰ Gillingham and co-workers found that $CuSO_4$ was effective at catalysing the NH insertion of the anilines **106** with the diazo compounds **107** under aqueous conditions (Scheme 25).⁴¹ While good yields were obtained when anilines **106** were used as reaction partners, aliphatic amines did not react under the reaction conditions.

Gillingham and co-workers (2013)

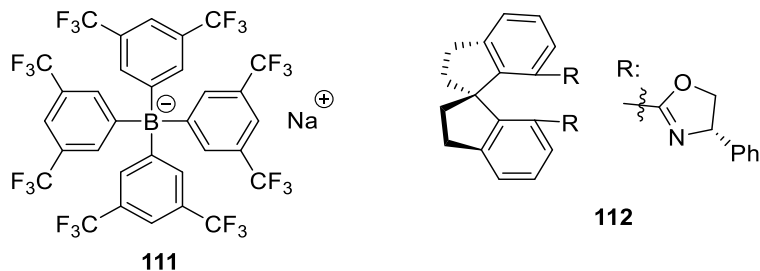
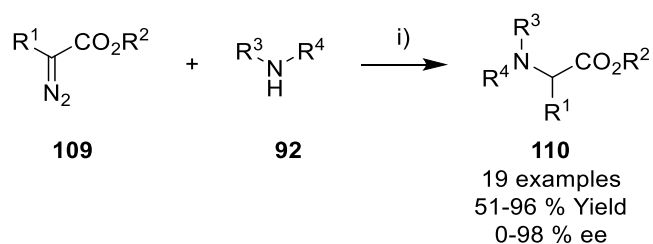


Scheme 25: CuSO₄ catalysed NH insertion of amines **107**. Reagents and conditions:

- i) Diazo compound **107** (1 eq.), aniline **106** (1.1 eq.), CuSO₄ (1 mol %), pH 6
ascorbate MES buffer/ ^tBuOH (8:2), 20 h, r.t..

Zhou and co-workers reported the enantioselective Cu(I)-catalysed NH insertion of the diazo compounds **109** into the amines **92** to yield the amino acids **110** (Scheme 26).⁴² The active copper catalyst was generated *in situ*, with NaBARF **111** as an additive to increase its solubility. The reported enantiomeric excesses suggest that the ammonium ylide remains closely associated with the metal centre during the subsequent proton transfer step. Increasing the steric bulk of the R¹ substituent of the diazo compound was found to have a detrimental effect of the enantiomeric excess observed in the amino acids **110**, with a phenyl substituent at the R¹ position yielding a racemic product.

Zhou and co-workers (2007)

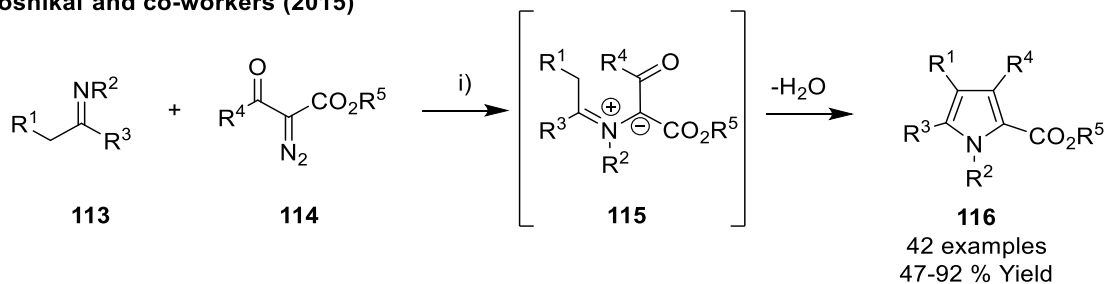


Scheme 26: Enantioselective copper catalysed NH insertion into amines **92**.

Reagents and conditions: i) Amine **92** (1 eq.), diazo compound **109** (1 eq.), CuCl (5 mol %), **112** (6 mol %), NaBARF **111** (6 mol %), CH₂Cl₂, r.t., 16 h.

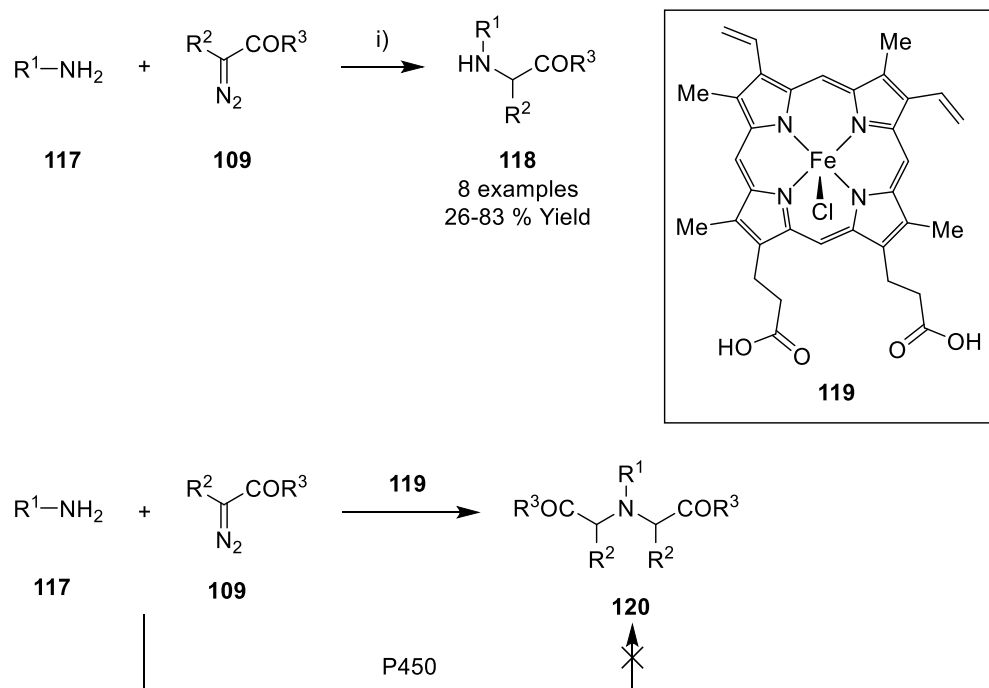
Copper has also been shown to catalyse iminium ylide formation, as reported by Yoshikai and co-workers (Scheme 27).⁴³ The multi-substituted pyrroles **116** were constructed from the imines **113** and diazo compounds **114**, via isomerisation of the iminium ylide **115** followed by intramolecular condensation. Whilst Cu(II) catalysts were found to exhibit excellent catalytic activity with respect to formation of the ylide **115**, Rh₂(OAc)₄ gave ‘an intractable mixture of products, in which the desired product was not detected’.

Yoshikai and co-workers (2015)



Scheme 27: Multi-substituent pyrrole synthesis reported by Yoshikai and co-workers. Reagents and conditions: i) Diazo **114** (1 eq.), imine **113** (1.5 eq.), $\text{Cu}(\text{tfacac})_2$ (10 mol %), 4 Å molecular sieves, toluene, 110 °C, 12 h.

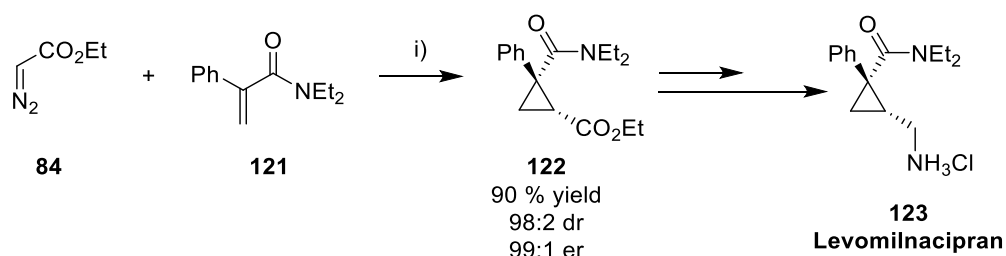
A recent area of development is the biocatalytic reactions of diazo compounds, catalysed by the iron cofactor of either a myoglobin or P450 protein.⁴⁴ Whilst the activity of the wild-type protein to this reaction is typically very low, this can be improved drastically *via* alteration of active site residues.⁴⁵ Arnold and co-workers found that the heme centre of a mutant P450 was effective at catalysing the NH insertion of the anilines **117** with the diazo compounds **109** (Scheme 28).⁴⁶ The reaction was found to be sensitive to additional substitution of the diazo compound, with the lowest yield being obtained when substitution was present at the α -position of the diazo compound **109** ($\text{R}^2 \neq \text{H}$). The reaction was also found to be sensitive to substitution at the R^1 position, with sterically demanding substrates giving poorer yields. Slow addition of the diazo compound was not found to have an effect on yield, and the double NH insertion product **120** was not observed. When free hemin was used as a catalyst, the double NH insertion product **120** was obtained with the desired single NH insertion product **117** in a 1:3 ratio, indicating the protein gives additional selectivity.



Scheme 28: NH insertion of amines **117** into diazo compounds **109** catalysed by P450. Reagents and conditions: i) Aniline **117** (2.4 eq.), diazo compound **109** (1 eq.), $\text{Na}_2\text{S}_2\text{O}_4$ (1.2 eq.), P450 (0.1 mol %), r.t., 12 h.

The iron heme centre of a mutant P450 protein can also catalyse the reaction of a diazo compound with other substrates. One reaction that has received significant literature attention is cyclopropanation.⁴⁷ Arnold and co-workers reported cyclopropanation of the alkene **121** with ethyl diazoacetate **84** to synthesise the cyclopropane **122**, a precursor to the antidepressant Levomilnacipran **123** (Scheme 29).⁴⁸ The authors obtained the cyclopropane **122** in excellent yield and reported enantiomeric and diastereomeric excesses induced by the chirality of the protein active site.

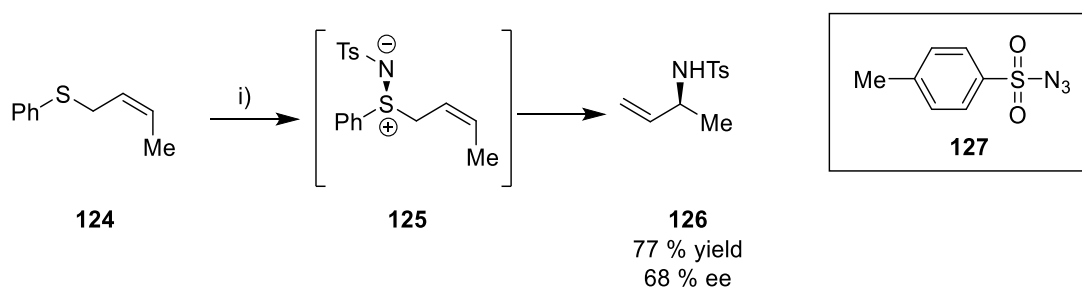
Arnold and co-workers (2014)



Scheme 29: Mutant p450 catalysed cyclopropanation of **121**. Reagents and conditions: i) Olefin **121** (1.1 eq.), ethyl diazoacetate **84** (1 eq.), Na₂S₂O₄ (1 eq.), P450 (1 mol %), pH 8.0 phosphate buffer, r.t., 12 h.

Mutant proteins have also been used to catalyse reactions that conventional metal-ligand complexes perform poorly.⁴⁹ Arnold and co-workers reported the synthesis of the chiral amine **126** via [2,3] rearrangement of the sulfimide **125**, which is formed by biocatalyzed reaction of tosyl azide **127** with the thio ether **124** (Scheme 130). Obtaining the amine **126** in enantioexcess is challenging, as the catalyst must distinguish between the two lone pairs of **124** upon formation of **125**. In addition, should the sulfimide **125** not remain closely associated with the chiral environment of the metal centre, racemization is possible. However, by generating **125** biocatalytically, the secondary co-ordination sphere of the protein active site provides additional enantiocontrol, and a chiral environment should **125** not be closely associated with the metal centre during the reaction.

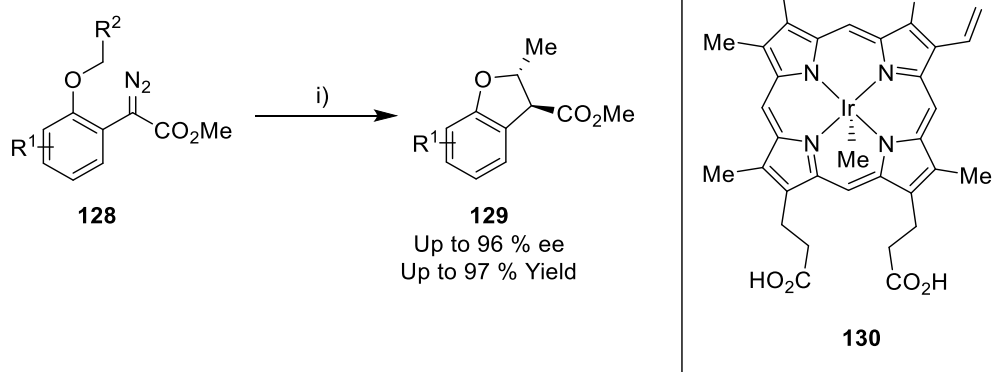
Arnold and co-workers (2016)



Scheme 30: Enantioselective synthesis of allylic amines **126**. Reagents and conditions: i) Allyl sulfide **124** (1 eq.), tosyl azide **127** (1 eq.), NADPH (2 eq.), P450 (2 mol %), pH 8.0 phosphate buffer, r.t., 20 h.

Whilst mutant iron heme proteins have been shown to be effective at catalysing reactions of diazo compounds, similar to free iron heme catalysts, these catalysts have not been reported to show catalytic activity with respect to CH insertion of diazo compounds. Conversely, ruthenium, iridium, and rhodium porphyrin complexes have been shown to possess good catalytic activity for this reaction.⁵⁰ Hartwig and co-workers overcame this substrate scope limitation by incorporating the artificial iridium co-factor **130** into an apo myoglobin (Scheme 31).⁵¹ The artificial metalloprotein was found to show excellent activity with respect to catalysing the intramolecular CH insertion of the diazo compounds **128**. Iron heme proteins have not been reported to show activity for catalysing this reaction.

Hartwig and co-workers (2016)



Scheme 31: Artificial metalloprotein catalysed intramolecular CH insertion.

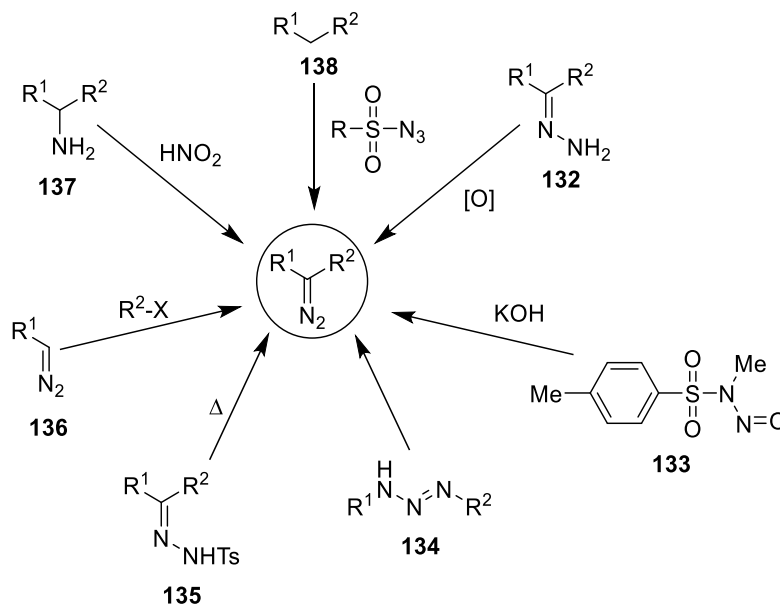
Reagents and conditions: i) Ir(Me)-Myo (0.5 mol %), pH 8.0 Tris buffer/ MeCN
(92:8), 20 °C, 16 h.

To summarise, iron and copper have been demonstrated to be effective at catalysing nitrogen ylide formation from diazo compounds. In some instances, these catalysts outperform conventional rhodium paddlewheel complexes. The advent of mutant heme proteins provides new biocatalysts for the formation of C-N bonds, often with additional selectivity advantages over conventional catalysts. These mutant heme proteins are particularly attractive as catalysts as they operate under mild conditions and their reactivity can be altered drastically by a small number of single residue mutations. The incorporation of achiral metal co-factors into an apo protein is a significant development, as this allows for furnishing of products in high enantiomeric excess due to the secondary co-ordination sphere of the active site.

1.5 Synthesis of diazo compounds

Whilst catalytic diazo decomposition offers a highly efficient method for pyridinium ylide formation, it is important to consider how the diazo moiety is installed, as the lack of commercially available diazo compounds often requires in-house synthesis of the diazo compound. This lack of commercial availability is most likely due to the toxic and potentially explosive nature of molecules containing the diazo moiety.⁵²

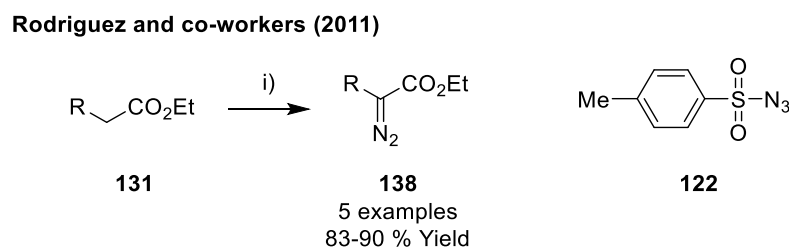
An array of synthetic methodologies are available for the installation of the diazo moiety (Scheme 32).⁵³ These methods include diazo transfer onto an active methylene compound **131**,⁵⁴ oxidation of hydrazones **132**,⁵⁵ decomposition of *N*-alkyl-*N*-nitroso sulfonamides **133**,⁵⁶ triazene **134** fragmentation,⁵⁷ thermolysis of a tosyl hydrazone salts **135**,⁵⁸ synthetic manipulation of an existing diazo compound **136**,⁵⁹ or diazotisation of an electron deficient amine **137**.^{38c, 60}



Scheme 32: Synthetic strategies for installation of the diazo moiety

The method selected for diazo synthesis depends on the electronics of the desired diazo product, and the efficiency of each process differs significantly. Diazo transfer is a

well-developed methodology for the synthesis of diazo compounds bearing one or more electron withdrawing groups. Typical conditions for the transformation are a sulfonyl azide as a source of N_2^+ , as well as a mild stoichiometric base, such as triethylamine or potassium carbonate (Scheme 33).^{54b} The atom economy of this process is poor however, as the by-products of the reaction are stoichiometric sulfonamide and the conjugate acid of the base. Whilst the atom economy of the process can be improved by using lower molecular weight sulfonyl azide, this can present issues given the often unpredictable explosive nature of low molecular weight azides.⁶¹

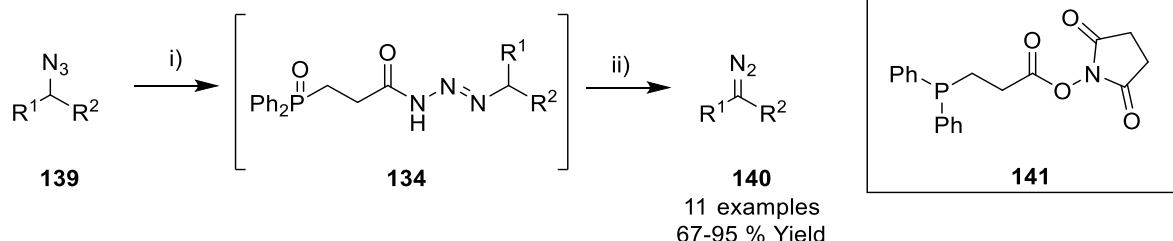


Scheme 33: Diazo synthesis via diazo transfer. Reagents and conditions: i) Active methylene compound **131** (1 eq.), tosyl azide **138** (1 eq.), K_2CO_3 (1.1 eq.), MeCN, r.t., 16 h

Triazene fragmentation has been demonstrated to be effective at generating diazo compounds of varying sterics and electronics, although has not received substantial literature attention.⁵³ Raines and co-workers synthesised the diazo compounds **140** from the azides **139** via the *in situ* generated triazene intermediate **134** (Scheme 34).⁶² Whilst the authors reported high yields of diazo compounds that included synthetically challenging α -diazoacetamides, the reaction suffers from poor atom economy, given the low molecular weight of the diazo compounds **140** relative to the phosphine

reagent **134**. In addition, the commercial availability of azides is limited, thus requiring in-house synthesis of **139**.

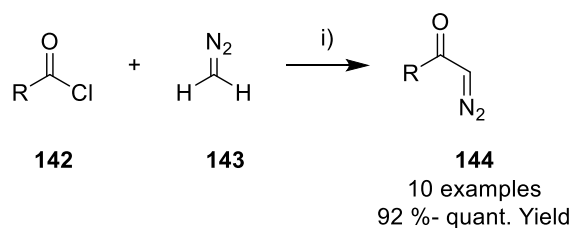
Raines and co-workers (2008)



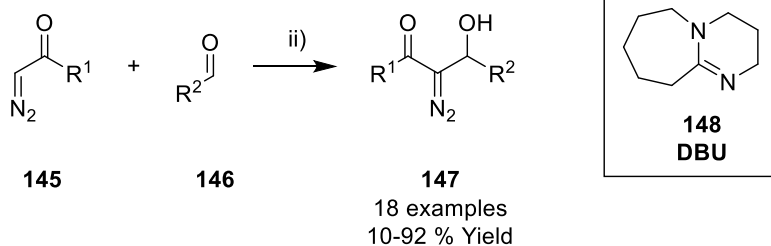
Scheme 34: Synthesis of diazo compounds **140** *via* triazine fragmentation. Reagents and conditions: i) Azide **139** (1 eq.), phosphine **141** (1.05 eq.), THF/H₂O (20:3), 3-12 h. ii) NaHCO₃ (saturated, aq.), 15 min- 12 h.

Modification of an existing diazo compound encompasses a wide range of methods, and typically utilises the inherent nucleophilicity of the diazonium ylide. Kimpe and co-workers synthesised the monosubstituted diazo compounds **143** from nucleophilic attack of diazomethane **143** into the acyl chlorides **142** (Scheme 35, i)).⁶³ Similarly, Wang and co-workers synthesised the diazo compounds **147** from base catalysed addition of the diazo compounds **145** to the aldehydes **146** (scheme 35, ii)).⁶⁴ The reaction of diazo compounds with other electrophiles such as halo alkanes and imines have also been reported.⁵⁹ While the scope of this process is vast, the efficiency of this process is low, as the diazo moiety must still be installed *via* another method.

i) Kimpe and co-workers (2010)



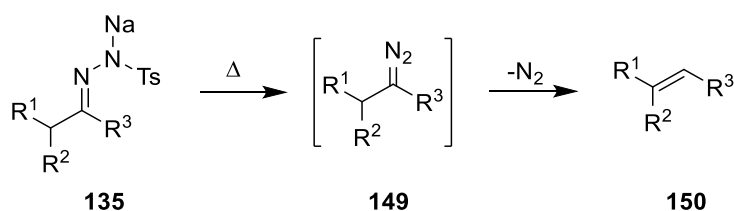
ii) Wang and co-workers (2002)



Scheme 35: Synthesis of diazo compounds *via* modification of an existing diazo compound. Reagents and conditions: i) Acyl chloride **142** (1 eq.), CH_2N_2 **143** (1 eq.), CaO (1.1 eq.), Et_2O , 0 °C, 3 h. ii) Aldehyde **146** (1 eq.), diazo compound **145** (1.2 eq.), DBU **148** (10 mol %), MeCN, 8-24 h.

The decomposition of tosyl hydrazone salts has been developed extensively as a method for *in situ* diazo generation by Aggarwal and co-workers.⁵⁸ In a typical procedure, the tosyl hydrazone salt **135** is added slowly to a heated solution of other reagents, eliminating a sodium sulfinate salt to give the diazo compound **149**. In the Bamford-Stevens reaction, continued heating leads to loss of nitrogen followed by 1,2 H shift to give the alkene **150** (Scheme 36).⁶⁵

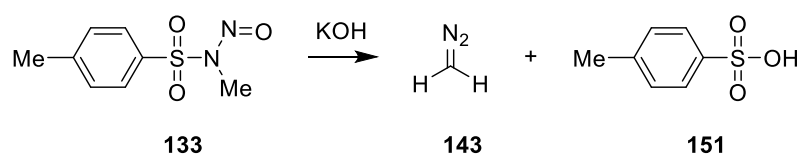
Bamford-Stevens Reaction



Scheme 36: The Bamford-Stevens reaction.

The scope of *N*-alkyl-*N*-nitroso sulfonamide decomposition is exceptionally limited, although it is commonly used to prepare diazomethane **143** from the commercially available Diazald® **133**. A typical procedure would involve heating Diazald® **133** in a mixture of 50 % KOH_(aq) and ether, generating tosic acid **151** and water as by-products (Scheme 37). The reaction mixture would then be distilled to afford an ethereal solution of diazomethane, as the pure diazo compound **143** is exceptionally unstable. The distillation process represents a significant safety risk, and requires the use of specialist glassware and laboratory equipment. The efficiency for this process is low, given the high molecular weight of tosic acid **151** relative to the desired product **143**.

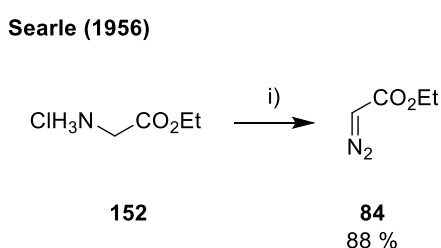
Preparation of diazomethane



Scheme 37: Preparation of diazomethane from Diazald® **133**. Typical reagents and conditions: KOH, H₂O, Et₂O.

The diazotisation of electron deficient amines is a well-established route to diazo compounds, with typical conditions involving a strong mineral acid and either a nitrite salt or alkyl nitrite.⁶⁶ An early example of this was reported by Searle in the synthesis

of ethyl diazoacetate **84** from glycine hydrochloride **152** (Scheme 38).⁶⁷ A biphasic system was used, as the solubility of the nitrous acid generated in organic and chlorinated solvents is low, and the stability of ethyl diazoacetate **84** to the strong acid is also low. Controlling the temperature of the reaction was found to be crucial, with decomposition of ethyl diazoacetate **84** occurring above 1 °C, and formation of solid methylene chloride dihydrate was observed at lower temperatures, which interfered with the reaction.

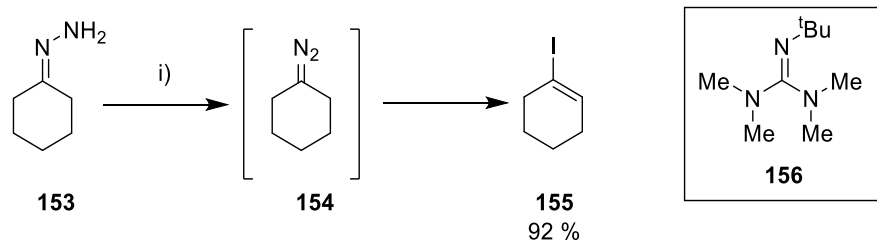


Scheme 38: Preparation of ethyl diazoacetate **84** *via* diazotisation of glycine hydrochloride **152**. Reagents and conditions: i) Glycine hydrochloride **152** (1 eq.), NaNO₂ (1 eq.), H₂SO₄, H₂O, CH₂Cl₂, -9 °C, 10 min.

Hydrazone oxidation is used for the synthesis of diazo compounds of varying electronics and sterics. Typically metal based oxidants are used, although metal free oxidants have also been shown to be effective at facilitating the reaction. Describing the efficiency of the process is difficult, given the diversity of oxidants that have been used to affect this transformation. Whilst catalytic methods have been reported, general methods for catalytic hydrazone oxidation remain rare compared with catalytic methods for alcohol oxidation. An early example of hydrazone oxidation was reported by Barton and co-workers, who described iodine mediated oxidation of the hydrazone **153** to give the diazo compound **154** (Scheme 39).⁶⁸ Under the reaction conditions, nucleophilic attack of the diazo compound **154** into iodine at elevated temperature and

subsequent elimination of nitrogen from the resulting diazonium under the basic reaction conditions gave the observed vinyl iodide product **155**.

Barton Reaction

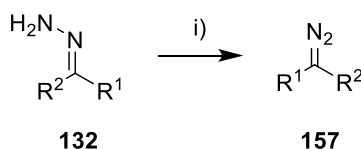


Scheme 39: Iodine mediated oxidation of hydrazone **153**: Reagents and conditions: i) I₂, **156**, Et₂O, r.t.to 90°C.

In conclusion, many methodologies for the synthesis of diazo compounds have significant issues from a sustainability perspective, in particular efficiency and function group tolerance. Hydrazone oxidation offers an attractive method for the synthesis of diazo compounds, as the reaction can take place under neutral pH and at room temperature. The abundance of, and preference for, stoichiometric metal based oxidants for this reaction is undesirable, although methodologies that use more benign oxidants have been reported.

1.6 Hydrazone oxidation

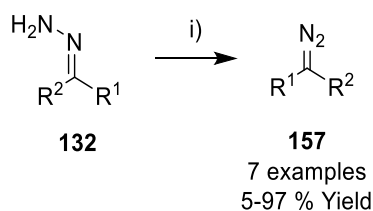
Early methodologies for hydrazone oxidation required the use of stoichiometric heavy metal based oxidants, such as mercury⁶⁹ or lead,^{55b} although super stoichiometric MnO_2 ⁷⁰ has also been shown to be effective at facilitating this oxidation (Scheme 40).



Scheme 40: Hydrazone oxidations. Reagents and conditions: i) MnO_2 or $\text{Pb}(\text{OAc})_4$ or HgO

More recently, methodologies for hydrazone oxidation have moved towards metal free conditions, and use of less toxic reagents. Brewer and co-workers reported the successful oxidation of the hydrazones **132** under Swern conditions utilising DMSO as an oxidant, with the resulting diazo compounds **157** being obtained in >95 % purity after filtration under argon at cryogenic temperatures (Scheme 41).⁷¹

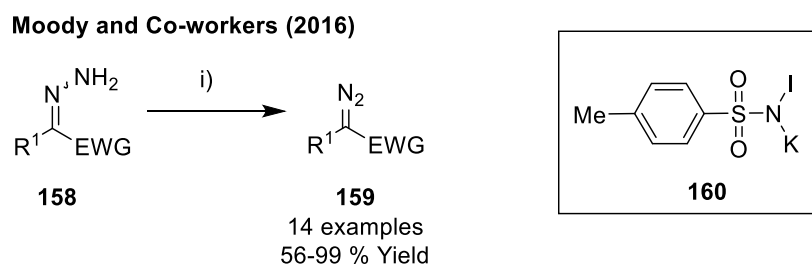
Brewer and co-workers (2007)



Scheme 41: Oxidation of hydrazones under Swern conditions. Reagents and conditions: i) Hydrazone **132** (1 eq.), oxalyl chloride (1.05 eq.), DMSO (1.1 eq.), Et_3N (2.1 eq.), CH_2Cl_2 , -78°C .

Similarly, Moody and co-workers reported potassium *N*-iodo *p*-toluenesulfonamide (Ts-NIK) **160** to be an effective reagent for the oxidation of the hydrazones **158**

(Scheme 42).^{55a} The bench stable oxidant **160** could be prepared from the corresponding sulfonamide, iodine and potassium iodide under basic conditions.

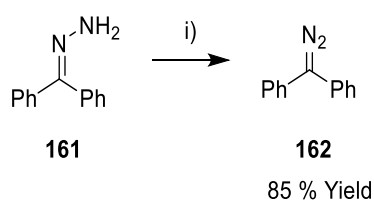


Scheme 42: TsNIK **160** oxidation of hydrazones **158**. Reagents and conditions: i)

Hydrazone **158** (1 eq.), TsNIK **160** (2 eq.), THF, r.t..

Whilst catalytic methodologies for alcohol oxidation have been developed extensively,⁷² catalytic methodologies for hydrazone oxidation are poorly described in the literature. A Glaxo Laboratories Ltd. patent describes biphasic iodine catalysed, peracetic acid oxidation of benzophenone hydrazone **161** using trioctylpropylammonium chloride as a phase transfer catalyst (Scheme 43). An excess of aqueous base is used to neutralise the acetic acid produced, as well as to suppress any side reactions of the unstable diazo compound **162**. The patent also describes catalytic oxidation of hydrazones with peracids, halogens, hypochlorite, catalysed by iodide, transition metals, or quinone in the presence of a phase transfer catalyst.

Glaxo Laboratories Ltd. (1976)

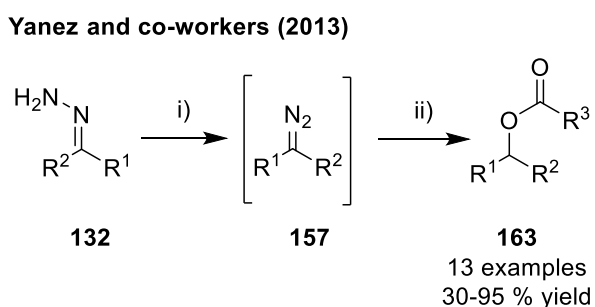


Scheme 43: Catalytic oxidation of benzophenone hydrazone. Reagents and conditions: i) Benzophenone hydrazone **161** (1 eq.), trioctylpropylammonium chloride (3 mol %), iodine (1 mol %), peracetic acid (1 eq.), NaOH, CH₂Cl₂/ H₂O (2:1), 40 minutes, 0 °C.

To conclude, whilst hydrazone oxidation offers a mild and effective route to diazo compounds, typical conditions employ stoichiometric high molecular weight reagents, and catalytic methods are rare. Given the intrinsically hazardous nature of the diazo compound, it would be advantageous to generate and react the diazo compound *in situ*, to minimize user exposure and improve the safety profile of the reaction.

1.7 *In situ* synthesis of diazo compounds via hydrazone oxidation

Some methods have been developed for *in situ* diazo generation via hydrazone oxidation. Given that hydrazones are highly nucleophilic and can compete for reaction with a carbene, ⁷³ typical *in situ* methods require complete conversion of the hydrazone to the diazo compound before the addition of other reagents. Yanez and co-workers reported a TEMPO/ NaOCl catalytic system for the oxidation of the hydrazones **132** to the diazo compounds **157** (Scheme 44).⁷⁴ After complete conversion hydrazone **132** to the diazo compound **157**, addition of a carboxylic acid to the reaction mixture reacted gave the esters **163**.



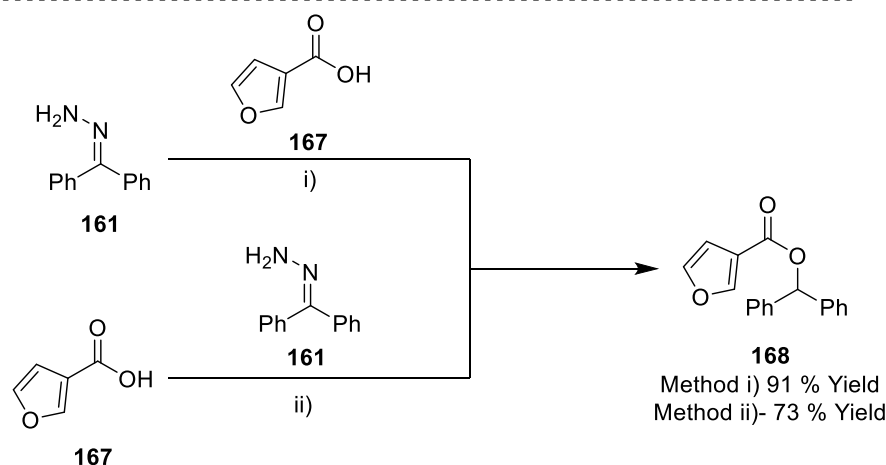
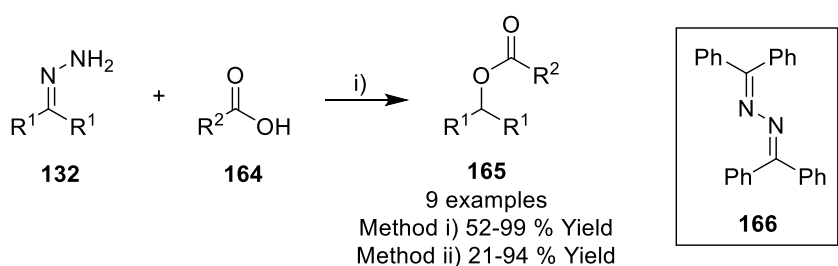
Scheme 44: TEMPO/NaOCl oxidation of hydrazones **132**. Reagents and conditions:

- i) Hydrazone **132** (1 eq.), NaHCO₃ (0.6 eq.), KBr (0.2 eq.), TEMPO (2 mol %), NaOCl (3.5 eq.), CH₂Cl₂, -5 °C. ii) Acid (1 eq.), -5 °C to r.t.

Shaw and co-workers developed hydrazone oxidation conditions for the continuous *in situ* generation and reaction of diazo compounds by OH insertion *via* hydrazone oxidation (Scheme 45).⁷⁵ The authors reported two sets of conditions. In the first set of conditions (i), the hydrazone **161** was stirred with MnO₂, with the acid **164** being added after complete consumption of the hydrazone **161**. In the second set of conditions (ii), all the reagents were added at the start of the reaction, without pre-formation of the diazo compound. By monitoring the reaction by ReactIR, the authors

determined that the concentration of diazo was lower using conditions ii), although the concentration of each reagent during the reaction was not quantified. Unfortunately, the authors did not indicate if the expected side product azine **166**, produced from NH insertion of the hydrazone **161** with the resulting diazo compound, was observed. The azine is a side product produced during the preparation of some of hydrazones **132**, which were not purified before use.

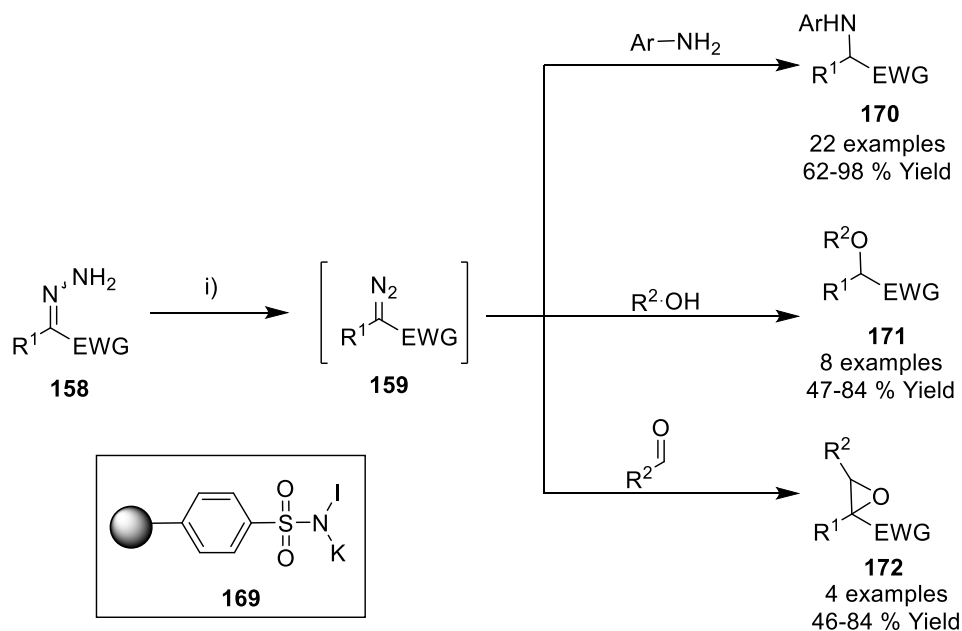
Shaw and co-workers (2016)



Scheme 45: *In situ* and trapping of diazo compounds reported by Shaw and co-workers. Reagents and conditions: i) Hydrazone **161** (1.2 eq.) MnO_2 (8 eq.), KH_2PO_4 (8 eq.), CH_2Cl_2 , r.t., 10 min., *then* acid **167** (1 eq.), r.t., 18 h; ii) Acid **167** (1 eq.), MnO_2 (8 eq.), KH_2PO_4 (8 eq.), CH_2Cl_2 , r.t., 10 min., *then* hydrazone **161** (1.2 eq.), r.t., 18 h.

A common method for mitigating the hazards associated with use of highly toxic or potentially dangerous reactants is to generate them in continuous flow.⁷⁶ This approach has been used extensively to mitigate the hazards associated with diazo compounds. As the diazo compound is continuously consumed and generated, user exposure and the quantity of reagent present at one time is greatly minimized.⁷⁷ A popular methodology for generating diazo compounds in continuous flow is hydrazone oxidation.

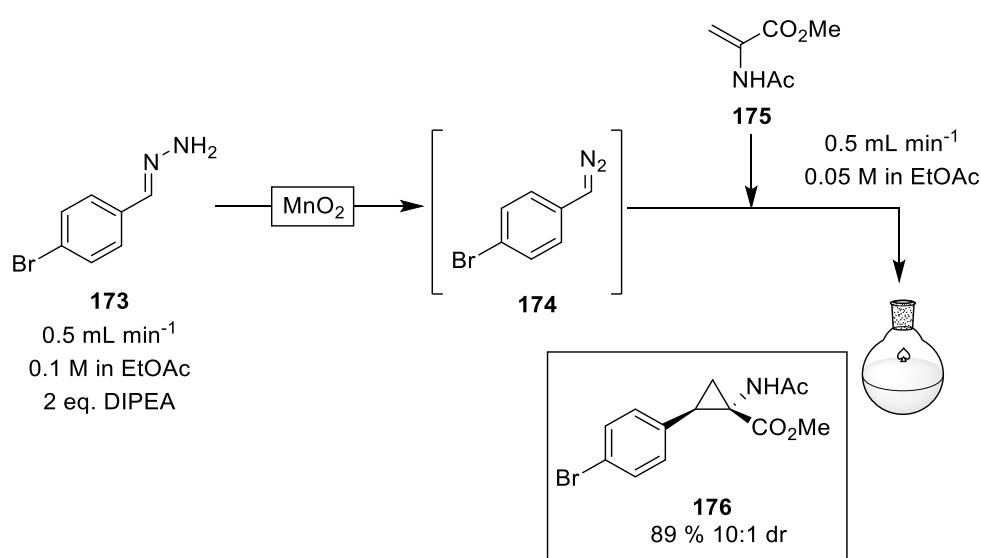
Moody and co-workers found that the immobilised TsNIK resin **169** was effective at facilitating the oxidation of the hydrazone **158** to the diazo compounds **159** in flow (Scheme 46).⁷⁸ The diazo compounds **159** could either be isolated, or added to a solution containing catalyst and an additional reagent to give the amines **170**, alcohols **171** or epoxides **172**.



Scheme 46: In flow oxidation of hydrazones **158**. Reagents and conditions: i)

Hydrazone **158** (1 eq.), **169** (2 eq.), substrate (1.2 eq.), Rh₂(OAc)₄, CH₂Cl₂.

Another example of diazo synthesis in continuous flow was reported by Ley and co-workers using MnO_2 (Scheme 47).⁷⁰ Once generated, the diazo **174** was mixed with a stream of the olefin **175** and fed into a stirred round bottom flask to generate the cyclopropane **176**. An excess of DIPEA was used to suppress protonation of the basic diazo compound **174**, which would lead to decomposition. Stirring the reagents at room temperature for 24 h afforded the cyclopropane **176** in excellent yield (89 %) on a 1.14 gram scale.

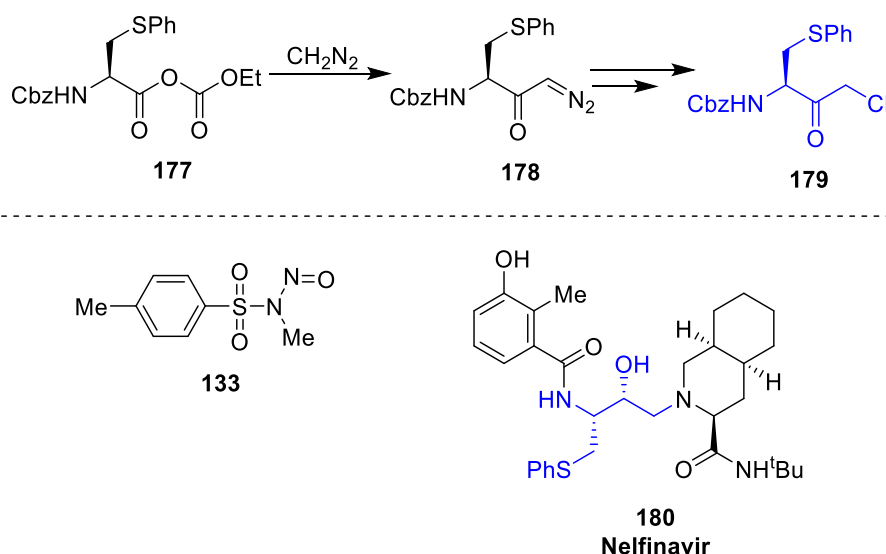


Scheme 47: MnO_2 oxidation of hydrazone **173** in flow reported by Ley and co-workers.

In summary, whilst hydrazone oxidation in flow has been to be useful in mitigating the use of hazardous compounds, it often requires cost-prohibitive equipment. Whilst *in situ* methods for diazo generation *via* hydrazone oxidation in batch have been reported, these typically require complete consumption of the hydrazone before addition of other reagents, meaning a large amount of diazo is present in the reaction at one time.

1.8 Other methods for the *in situ* generation of diazo compounds

Other methods have been reported to be effective at generating diazo compounds *in situ*. Ethyl diazoacetate generated *via* glycine diazotisation has been used in the synthesis of fine chemicals⁷⁹ and Phoenix chemicals utilise diazomethane in the multi-tonne synthesis of **178** (Scheme 48).⁸⁰ A typical procedure for the use of diazomethane involves hydroxide mediated decomposition of Diazald® **133** and distillation of the resulting diazomethane. Even on small scale this presents a significant safety risk which would be unfeasible on large scale. Phoenix chemicals developed a methodology for generation of diazomethane from Diazald® **133** for the synthesis of the HIV protease inhibitor Nelfinavir **180**. Despite the process generating 50-60 tonnes of **178** annually, the total amount of diazomethane present at any one time is 80 g.

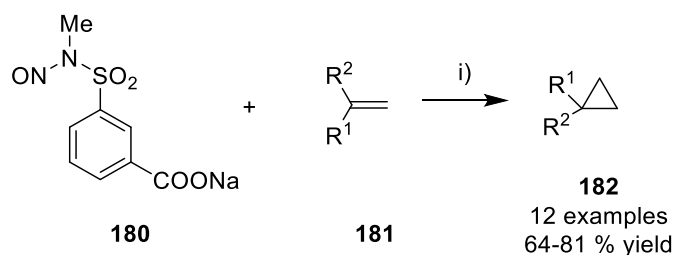


Scheme 48: Synthesis of intermediate **112** reported by Phoenix chemicals.

Carreira and co-workers reported that the water soluble nitrosamide derived **114** was an exceptionally efficient precursor for *in situ* diazomethane generation (Scheme 49).⁸¹ Under the biphasic reaction conditions, decomposition of the water soluble **180** in the highly basic aqueous phase yields diazomethane, which is rapidly extracted into

the organic reaction phase. The diazomethane is then quickly consumed *via* Fe(TPP)Cl catalysed cyclopropanation with the styrene derivatives **181**. Slow addition of **180** to the biphasic reaction conditions also aided in preventing accumulation of the potentially explosive diazomethane.

Carreira and co-workers (2012)

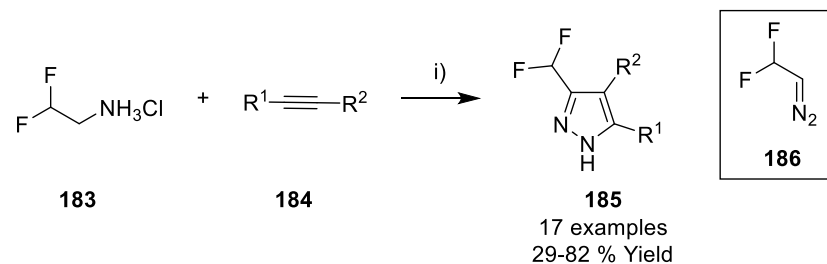


Scheme 49: *In situ* generation of diazomethane reported by Carreira and co-workers.

Reagents and conditions: i) **180** (3 eq. added over 4 h), styrene **181** (1 eq.), KOH (6M), Fe(TPP)Cl (2 mol %), r.t.

The diazotisation of electron deficient amines has also been used for *in situ* generation of diazo compounds.^{38c} Mykhailiuk reported that diazotisation of difluoroethylamine hydrochloride **183** with ^tBuONO and acetic acid was effective for generating difluoromethyl diazomethane **186** *in situ* (Scheme 50).⁶⁰ Heating at 40 °C for 10 minutes was sufficient to generate **186**, which was consumed upon addition of the alkyne **184** to provide access to the fluorinated pyrazoles **185**.

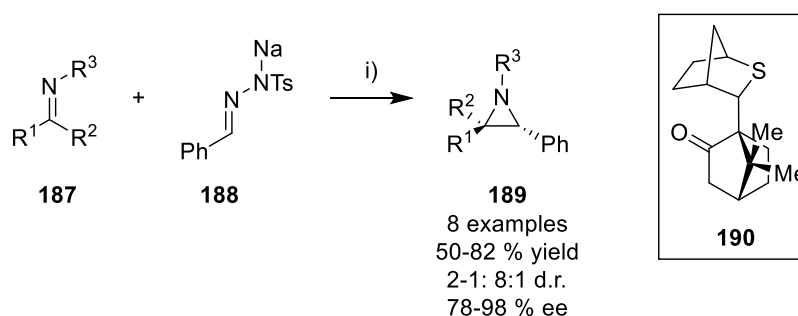
Mykhailiuk (2017)



Scheme 50: *In situ* generation of difluoromethyl diazomethane **186**. Reagents and conditions: i) Difluoroethylamine hydrochloride **183** (2 eq.), $^t\text{BuONO}$ (2.4 eq.), acetic acid (0.4 eq.), CHCl_3 , 40 °C, 10 min; alkyne **184** (1 eq.), r.t., 24 h.

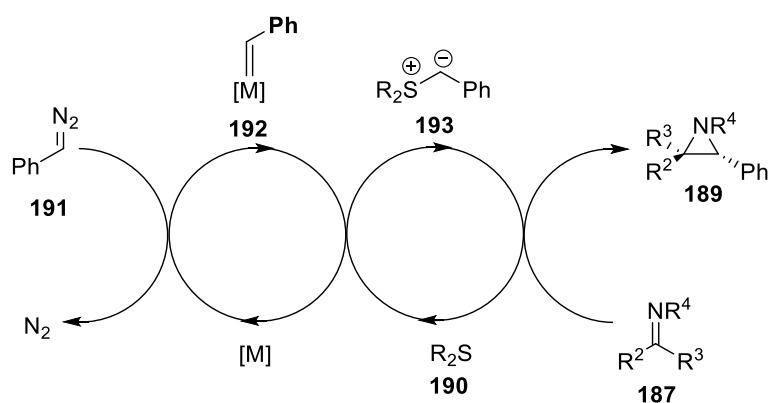
A well-developed methodology for *in situ* diazo generation is the decomposition of tosylhydrazone salts.⁵⁸ A typical experimental procedure consists of adding a solution of the tosylhydrazone salt slowly to a heated solution of other reagents. In one example, Aggarwal and co-workers reported the enantioselective synthesis of the aziridines **189** from the imines **187** and diazo compounds generated from the decomposition of the tosylhydrazone salts **188** in the presence of the sulfide catalyst **190** (Scheme 51).⁸² Similar methodologies have also been used in the synthesis of cyclopropanes,⁸³ epoxides,⁸⁴ and olefins.⁸⁵

Aggarwal and co-workers (2001)



Scheme 51: In situ generation of diazo compounds *via* decomposition of tosylhydrazone salts **188**. Reagents and conditions: i) Tosylhydrazone salt **188** (1.5 eq.), imine **187** (1 eq.), BnNEt₃Cl, **190** (10 mol %), Rh₂(OAc)₄ (1 mol %), 1-4 dioxane, 40 °C.

A tandem catalytic cycle was proposed (Scheme 52). Thermolysis of the tosylhydrazone **188** gives the diazo compound **191**, which undergoes rhodium catalysed decomposition to give the electrophilic carbenoid **192**. Nucleophilic attack of the sulfide **190**, followed by dissociation yields the chiral free ylide **193** which reacts with the imine **187** to aziridine product **189** and regenerate the sulfide **190**.

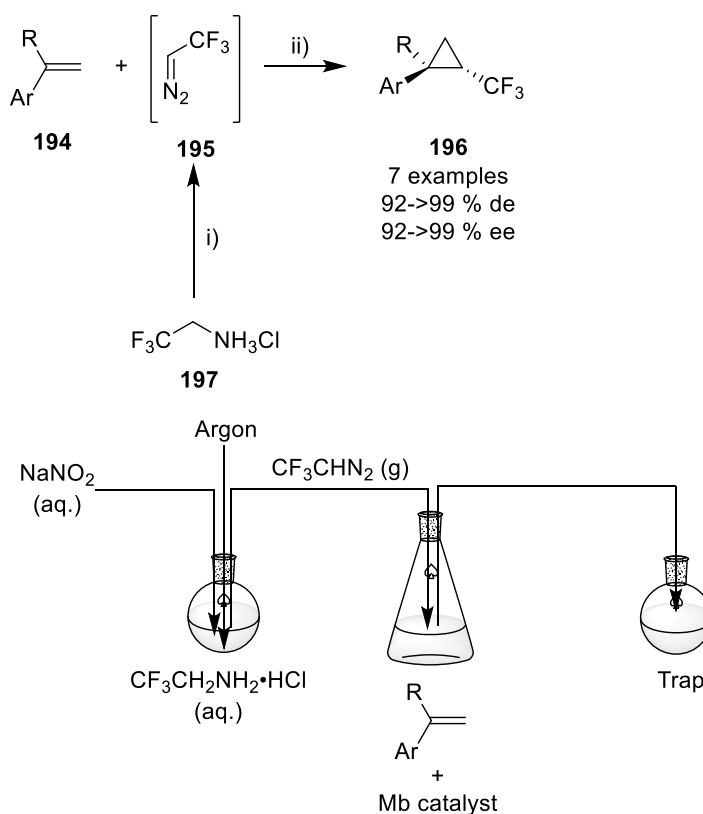


Scheme 52: Proposed tandem catalytic cycle.

Whilst the *in situ* generation of diazo compounds has received considerable literature attention, a method that would allow for *in situ* diazo generation in a reaction involving

a metalloprotein has not been developed. Possessing such a method would allow for upscaling of a powerful synthetic transformation, and also operate under exceptionally mild conditions. In particular, whilst *in situ* diazo generation *via* diazotisation and tosylhydrazone salt decomposition have received considerable literature attention, these methods are highly unlikely to be biocompatible given the need for heating or highly acidic conditions. However, the diazotisation of amines was used by Fasan and co-workers to generate trifluoromethyl diazomethane **195** *ex situ* in the biocatalytic synthesis of the cyclopropanes **196** (Scheme 53).⁸⁶ Given the instability of the myoglobin (Mb) to the highly acidic reaction conditions, the diazo compound **195** was generated *ex situ* in a separate reaction vessel and allowed to evaporate into the reaction vessel containing the styrene derivative **194** and the mutant myoglobin protein.

Fasan and co-workers (2017)



Scheme 53: Myoglobin catalysed synthesis of fluorinated cyclopropanes **131**.

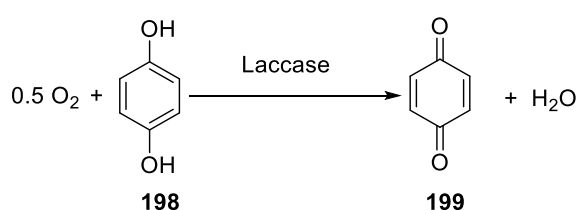
Reagents and conditions: i) Amine **197** (1 eq.), NaOAc (0.1 eq.), DMAP (0.06 eq.), H_2SO_4 (0.06 eq.), NaNO_2 (1.2 eq.), H_2O . ii) Styrene **194** (3 eq.), myoglobin (1 mol %), pH 7.0 phosphate buffer, r.t., 12 h.

To summarise, whilst an array of *in situ* methods are available to limit user exposure to diazo compounds, these typically require either full consumption of the precursor before addition of other reagents, or adding the precursor slowly to the reaction mixture to prevent unwanted side reactions. To date, a biocompatible method for *in situ* continuous generation and consumption of diazo compounds has not been reported. Generating such a method would have several difficulties, including biocompatibility of reagents and reaction conditions. One possible approach to achieve this would be to use a protein as a mild oxidation catalyst to generate the diazo

compound. The protein would be able to function in the aqueous conditions required and would be less likely to have an adverse interaction with the metalloprotein than current *in situ* methods.

1.9 Laccases as Oxidation Catalysts

Laccases are part of a family of multicopper oxidases (MCOs) that are effective at catalysing the oxidation of substrates such as catechols, (poly)phenols and aromatic amines using oxygen from air as a terminal oxidant (Scheme 54).⁸⁷ The most studied is the laccase from the wood rot fungi *Trametes Versicolor*, where the protein catalyses the oxidative depolymerisation of lignin, although laccase proteins are also found in bacteria and plants.⁸⁸



Scheme 54: Oxidation of catechol **198** by laccase.

The laccase active site consists of four copper atoms (Fig.3). A trigonal type 1 (T₁) copper is ligated by two histidine and one cysteine residues and axially ligated with either methionine, leucine or phenylalanine.⁸⁹ The remaining three copper atoms, one type 2 (T₂) and two type 3 (T₃), exist in a cluster co-ordinated by two and three histidine residues, respectively. Substrate oxidation occurs at the type 1 copper centre, due to its accessibility and high redox potential of *ca.* 790 mV.⁸⁹

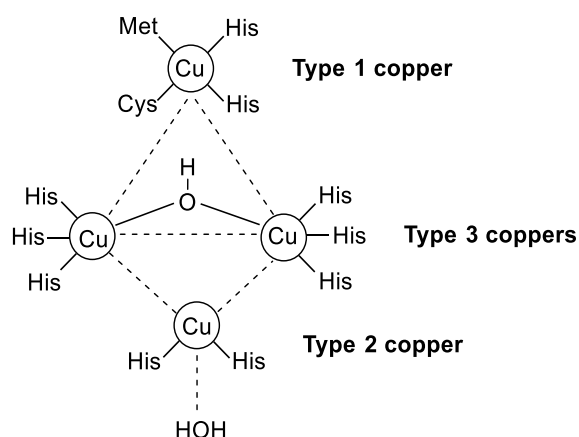
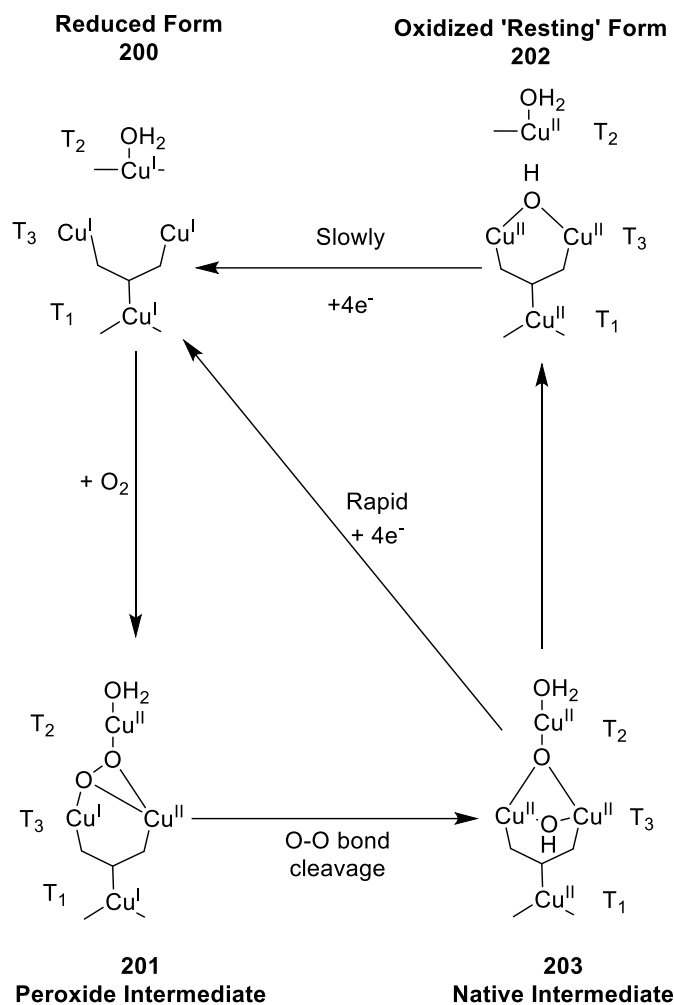


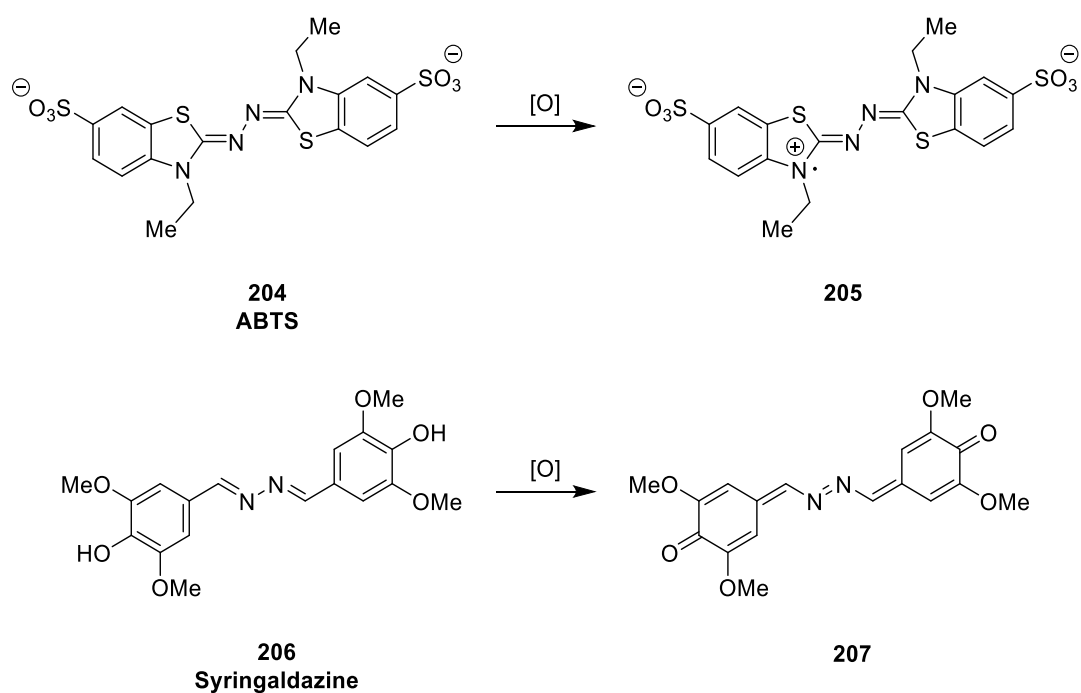
Fig 3: Laccase active site

The mechanism for the catalytic activity shown by laccase has been shown to consist of four intermediates (Scheme 55). From the reduced form **200**, oxygen reacts with the type 2 and type 3 copper atoms *via* a 2 electron transfer to give the peroxide intermediate **201**.⁹⁰ The peroxide intermediate **201** then undergoes a further two electron transfer in which the O-O bond breaks to give the fully oxidized native intermediate **203**. Four electron oxidation of the substrate(s) then regenerates the reduced form **200**. In the absence of a suitable substrate, the native intermediate **203** can slowly convert to the oxidized 'resting' state **202**.⁹¹ The typical pH range that laccases operate in is between 3.5 and 5.0, due to the inhibition of the T₁ copper active site by hydroxide binding at high pH.⁹²



Scheme 55: Laccase catalytic cycle

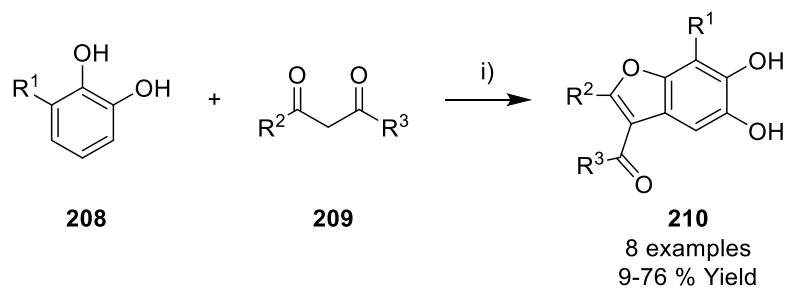
The catalytic activity of laccase proteins is expressed as units (U), which is defined as the quantity of laccase required to oxidize 1 μmol of substrate per minute. The substrates used for this assay are either 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) **204** or syringaldazine **206**. The rate at which the substrates **204** and **206** are oxidized are determined by measuring the absorbance of **205** and **207** at 405 nm or 530 nm respectively (Scheme 56).⁹³



Scheme 56: Substrates used to quantify activity of laccase during assay

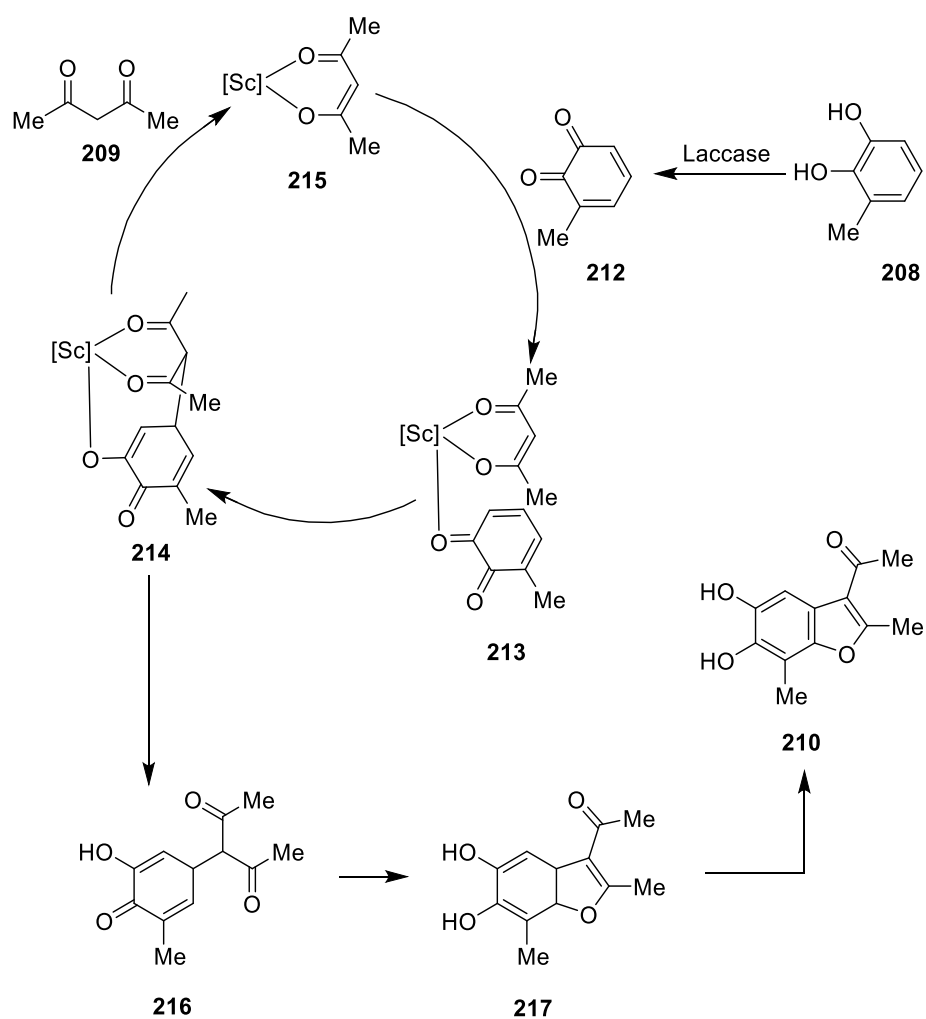
Laccase systems have been shown to tolerate the presence of additional reagents and catalyst, allowing for oxidised substrates to undergo further reactions *in situ*. Ragauskas and co-workers reported the synthesis of benzofuran derivatives **210** from the catechols **208** and the 1,3-diketones **209** (Scheme 57).⁹⁴ The authors reported that whilst high pH was required to drive the deprotonation of **209**, laccase activity dropped drastically at pH 9 and above. The addition of bases were found not to increase reaction efficiency, however satisfactory yields were obtained in pH 7.0 phosphate buffer.

Ragauskas and co-workers (2007)



Scheme 57: Use of laccase with an additional lewis acid catalyst. Reagents and conditions: i) **208** (1 eq.), **209** (2 eq.), SDS (0.2 eq.), Sc(OTf)₃ (20 mol %), laccase (100 U mmol⁻¹), 0.1 M pH 7.0 phosphate buffer, r.t., 4 h.

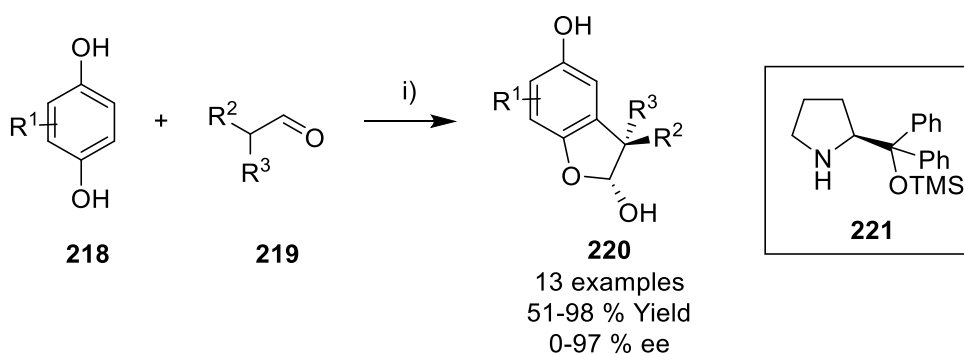
A catalytic cycle was proposed in which laccase catalysed oxidation of catechol **143** yields the highly electrophilic benzoquinone **212** (Scheme 58). Binding of **212** to the enolate complex **215** enhances the electrophilicity of **213**, which then undergoes Michael addition to give **214**. Dissociation from the metal centre gives the ketone **216**, which undergoes intramolecular Michael addition and aromatization to yield the benzofuran **210**.



Scheme 58: Postulated mechanism for formation of **210**.

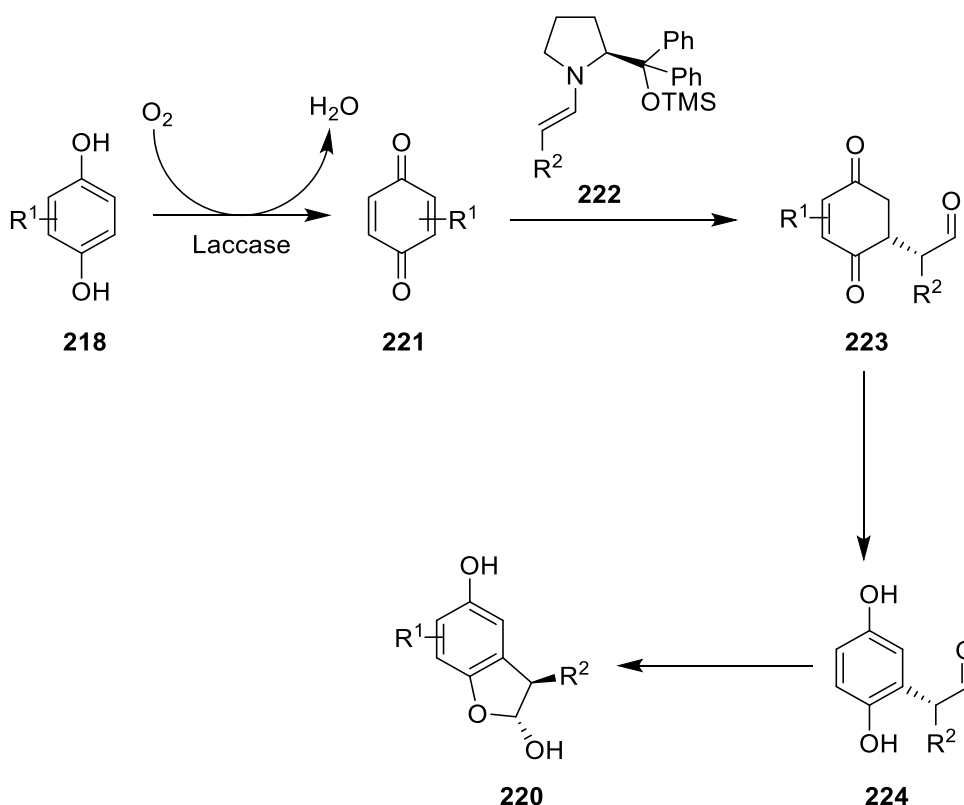
Worgull and co-workers reported a dual catalytic reaction, catalysed by laccase from *Agaricus bisporus* and the proline derived organocatalyst **221** (Scheme 59).⁹⁵ The yields obtained proved to be sensitive to solvent choice, and decreased significantly when ethanol was used as a co-solvent, or when water was used instead of buffer. The authors attributed this drop in yield to the lower stability of laccase in these solvent systems.

Worgull and co-workers (2015)



Scheme 59: Laccase catalysed cascade reaction. Reagents and conditions: i) **152** (1 eq.), **153** (5 eq.) **155** (10 mol %), laccase (60 U mmol⁻¹), 0.2 M pH 6.0 phosphate buffer, 22 °C, 72 h.

The reaction pathway was reported to proceed *via* oxidation of the diphenol **218** to the quinone **221** which is electrophilic enough to undergo Michael addition with the enamine **222**, generated from condensation of the aldehyde **219** with the catalyst **221** (Scheme 60). After aromatisation of the resulting intermediate **223** to give the diphenol **224**, cyclisation yielded the observed **220**.



Scheme 60: Proposed mechanism for formation of **220**.

Synthetically, the substrates that laccases can oxidize have typically been limited to aromatic amines, catechols and (poly)phenols.⁹⁶ The substrate scope of oxidation with laccases can be increased greatly, however, *via* the addition of a mediator (Fig.4). In the presence of a suitable mediator, the laccase will fulfil a different role, driving the oxidation of the mediator instead of the substrate.⁹⁷ In turn, the mediator will perform substrate oxidation outside the active site.

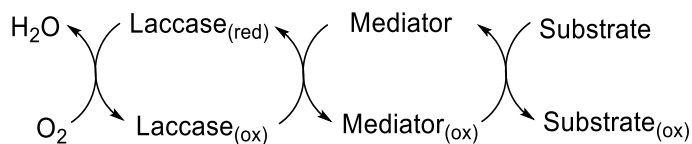


Fig. 4: Catalytic cycle for laccase/mediator substrate oxidation

Various mediators that have been reported to be compatible with laccase, including HOBt **225**, ABTS **204** and TEMPO **226** (Fig. 5).⁹⁸ In particular, a catalytic system containing a laccase and a nitroxyl radical mediator, such as TEMPO **226**, has been shown to offer a mild, efficient methodology to selectively furnish aldehydes from the corresponding alcohols.⁹⁹ In such a laccase / mediator catalytic system the laccase does not interact with the substrate, and functions only to promote the mediator, either *via* hydrogen abstraction, or by one or two electron oxidation.

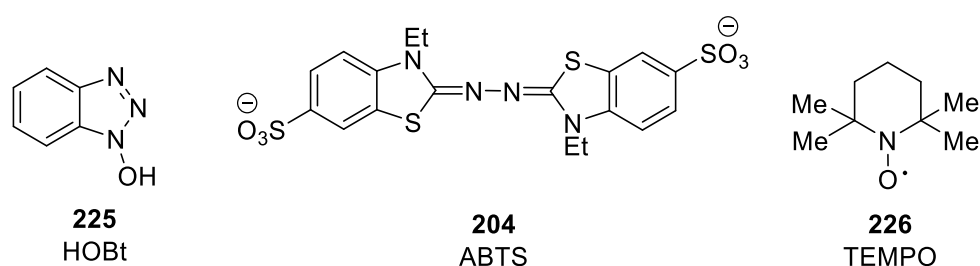
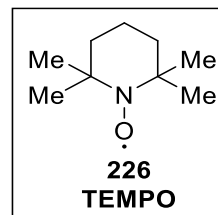
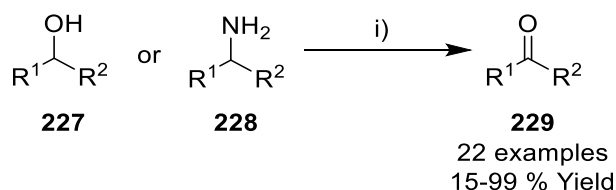


Fig.5: Mediators reported to be compatible with laccase

Macchitella and co-workers reported that laccase from *Trametes villosa* and TEMPO **226** were effective at catalysing the oxidation of the alcohols **227** to the carbonyls **229** (Scheme 61).¹⁰⁰ Whilst benzylic alcohols were tolerated well under the reaction conditions, aliphatic alcohols gave the corresponding aldehydes in poorer yields. The utilisation of amines **228** as substrates led to isolation the ketones **229** *via* hydrolysis of the resulting unstable iminium intermediate.

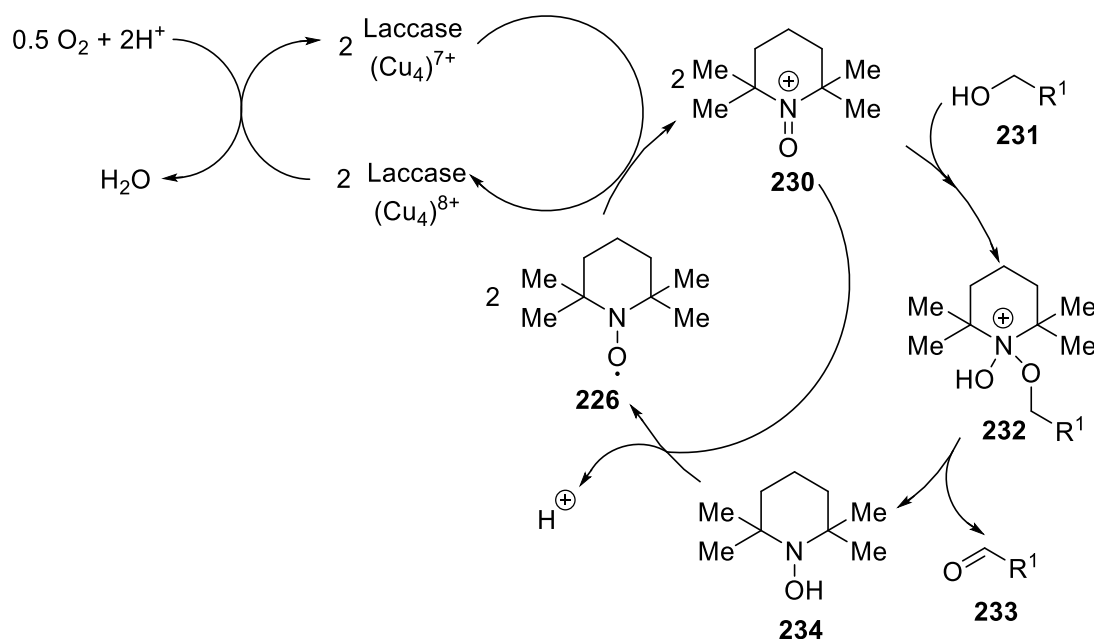
Macchitella and co-workers (2001)



Scheme 61: Oxidation of alcohols and amines catalysed by laccase/ TEMPO system.

Reagents and conditions: i) Alcohol **227** or amine **228** (1 eq.), TEMPO (30 mol %),
laccase (0.5 U mmol⁻¹), pH 4.5 0.1 M citrate buffer, r.t., 24 h.

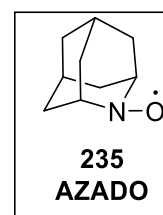
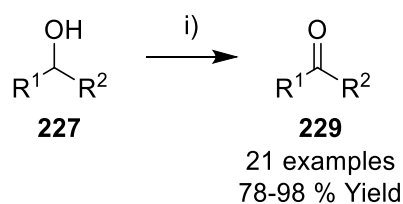
The mechanism of the laccase/ TEMPO oxidation of benzyl alcohol was studied by de Vries and co-workers (Scheme 62).¹⁰¹ The authors proposed that the active oxyl ammonium intermediate **230** was generated by single electron oxidation of two equivalents of TEMPO **226** by laccase. One equivalent of **230** would then react with the alcohol substrate to give **232**, which would eliminate the aldehyde product **233** and produce the hydroxylamine product **234**. Comproportionation of **234** with an equivalent of the oxyl ammonium **230** then regenerates TEMPO **226** upon elimination of a proton.



Scheme 62: Proposed catalytic cycle of laccase/ TEMPO catalysed oxidation of benzyl alcohol

Whilst TEMPO **226** has been demonstrated to effectively oxidize activated alcohols, the steric hindrance of the two geminal dimethyl groups limits substrate scope, resulting in poor activity with respect to the oxidation of more sterically encumbered substrates. Ying and co-workers reported an improved catalytic system for oxidation of the alcohols **227** with laccase from *Trametes versicolor* (Scheme 63).¹⁰² Whilst TEMPO **226** was found to give the corresponding carbonyls **229** in poor (< 10 %) yield, the use of AZADO **235** as a mediator was highly efficient at catalysing the oxidations of **227**. Both primary and secondary benzylic and aliphatic alcohols were tolerated under the reaction conditions. The use of a fluorinated co-solvent was required to increase the solubility of **227**.

Ying and co-workers (2014)

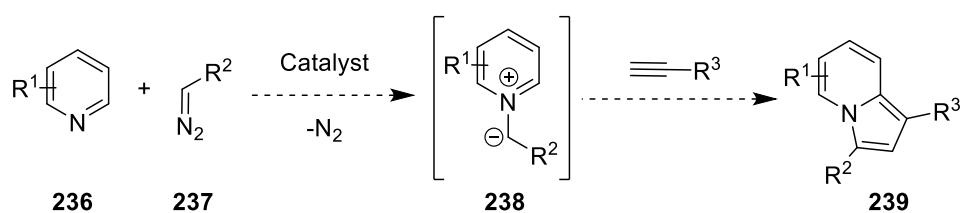


Scheme 63: AZADO **235** mediated oxidation of alcohols **227**. Reagents and conditions: i) Alcohol **227** (1 eq.), laccase (40 U mmol⁻¹), AZADO **235** (10 mol %), 0.2 M pH 4.5 citrate buffer, PhCF₃ (10 %), r.t., 24 h.

To summarise, a laccase protein in conjunction with an *N*-oxyl mediator has been shown to be an effective catalytic system for furnishing ketones and aldehydes from the corresponding amine or aldehydes under mild, biocompatible conditions. The substrate scope of this transformation, however, has not been expanded to include other heteroatom containing products. In addition, a laccase/ mediator catalytic system has not been used to generate an intermediate *in situ* for use in a subsequent reaction with an additional catalyst and reagent.

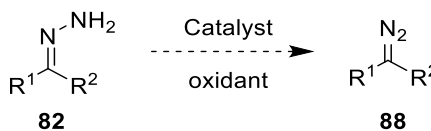
2. Aims and Objectives

1) Develop a new methodology for indolizine synthesis. The metal catalysed decomposition of diazo compounds offers a faster and more atom economical method for *in situ* pyridinium ylide generation than conventional pyridinium salt methods. The reduced step count and efficiency of this process has not been fully exploited, as the scope of dipolarophiles that are compatible with the catalytic reaction conditions have not been explored to a large degree. The feasibility of reacting a pyridinium ylide **238**, generated *via* diazo decomposition, with an alkyne to give an indolizine **239** was planned (Scheme 64). A range of catalysts and solvents were evaluated to determine optimised conditions, followed by variation of substituents on the pyridine, diazo compound and alkyne to ascertain the generality of the optimised conditions.



Scheme 64: Proposed indolizine synthesis

2) Develop a new methodology for the synthesis of diazo compounds. Although hydrazone oxidation offers an attractive method for the synthesis of diazo compounds, most methods involve the use of stoichiometric oxidants, despite the advantages that catalytic methods would offer. Thus, the second aim of this project will be to develop a new, catalytic method for diazo synthesis *via* oxidation of a hydrazone **88** (Scheme 65). Various catalysts and oxidants will be screened for activity, and the stability of the resulting diazo compound to the reaction conditions will be studied. Particular attention will be paid to the atom economy of the process, and ideally the reaction conditions will be biocompatible.

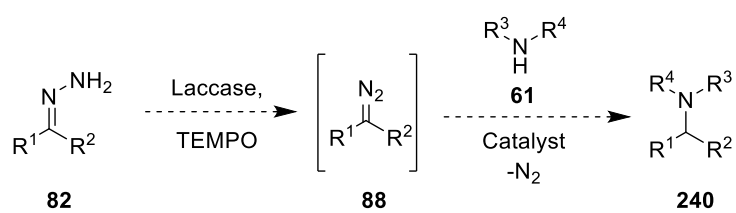


Scheme 65: Catalytic hydrazone oxidation

3) Develop a biocompatible methodology for *in situ* diazo generation.

Metalloproteins have been shown to be effective at catalysing the reactions of diazo compounds, however an obstacle to their widespread use is the intrinsic hazards of the diazo compound. Typical methods for *in situ* generation of diazo compounds would mitigate these hazards, but current methods use either extremely acidic or basic conditions that are not compatible with a protein. The final aim of this project was therefore to generate a mild and general method for the *in situ* generation of diazo compounds that is biocompatible with enzymes and does not require pre-formation of the diazo compound or controlled addition of reagents. Specifically, it is envisaged that a catalytic system involving the copper centre of a laccase with TEMPO as a mediator would catalyse the oxidation of a hydrazone to a diazo compound, which could then undergo a subsequent reaction (Scheme 66).

Evaluation of this reaction required a second reaction to consume the diazo compound, ideally under catalytic conditions. Initially NH insertion was explored as a subsequent reaction, as this reaction has been reported to proceed under aqueous conditions, although ideally other reactions such as OH insertion and cyclopropanation were to be investigated.

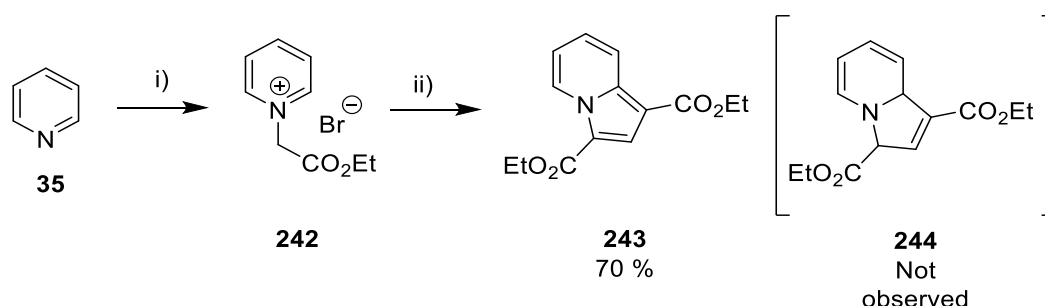


Scheme 66: Proposed *in situ* generation of diazo compounds and subsequent reaction.

3. Results and discussion

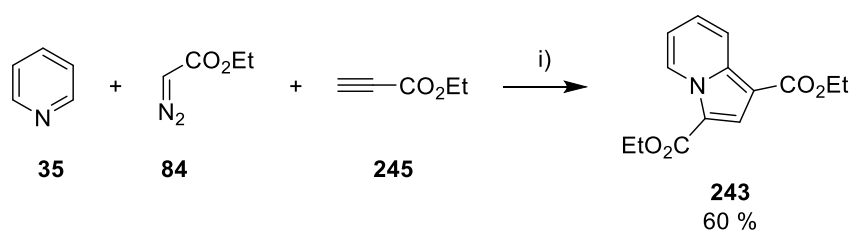
3.1. Indolizine synthesis

Initially, the indolizine **243** was synthesised in the absence of a catalyst, because an understanding of the reaction was highly desirable (Scheme 67). The presence of a metal catalyst could complicate analysis of the crude reaction mixture by ^1H NMR spectroscopy and performing the reaction in the absence of a metal catalyst would clarify if the initial cycloadduct **244** could oxidize to the desired indolizine **243** in air. Thus, indolizine **243** was synthesised by combination of the pyridinium salt **242** with ethyl propiolate (Scheme 67). Addition of excess potassium carbonate (3 eq.) to a colourless suspension of **242** in CH_2Cl_2 afforded a bright yellow solution, suggesting pyridinium ylide formation, which rapidly faded after addition of the alkyne reaction partner. After stirring the reaction mixture under air at room temperature for 16 h according to literature precedent,¹⁹ the desired indolizine **243** was obtained in good yield (70 %). The initial cycloadduct **244** was not observed, indicating that oxidation of **244** to **243** would occur under air without the need for an additional reagent or catalyst, as reported previously.¹⁹



Scheme 67: Reagents and conditions i): Ethyl bromoacetate (1 eq.), ethyl acetate, r.t., 16 h. ii) K_2CO_3 (3 eq.), CH_2Cl_2 , ethyl propiolate (1 eq.), r.t., 16 h.

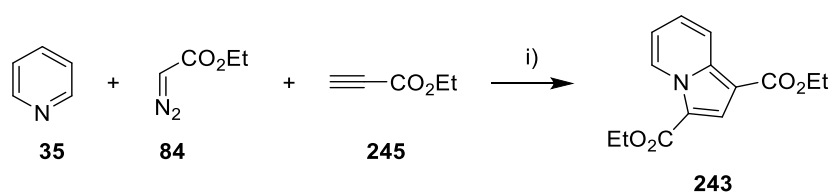
Confident that oxidation would occur under open-flask conditions, the feasibility of carrying out indolizine synthesis *via* catalytic pyridinium ylide generation was investigated. Initially, Fe(TPP)Cl was used as catalyst, as this complex had been reported to show excellent activity for pyridinium ylide formation previously,³⁰ and ethyl diazoacetate **84** was added to a solution of other reagents in CH₂Cl₂ *via* syringe pump over 2 h, to minimize side-product formation.¹⁰³ Under these conditions, the desired indolizine product **243** was obtained in good yield (60 %) (Scheme 68).



Scheme 68. Reagents and conditions: Pyridine **35** (3 eq.), ethyl diazoacetate **84** (1.5 eq., added over 2 h *via* syringe pump), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

Encouraged by this initial result, various potential catalysts were evaluated, but none gave yields superior to Fe(TPP)Cl (Scheme 69, Table 1). Rh₂(OAc)₄ performed poorly in this reaction, with indolizine **243** being obtained in only 11 % yield (entry 1). Similarly, Padwa and co-workers also observed poor catalytic activity of Rh₂(OAc)₄ with respect to intermolecular pyridinium ylide generation from pyridines and diazo compounds.²⁸ Copper salts also gave the indolizine **243** in poor yield (entries 3-5). Formation of **243** was not observed whatsoever when Cu(MeCN)₄PF₆ (entry 5) was used as a catalyst in this reaction, despite its reported activity for pyridinium ylide generation in the group.³⁰ Formation of the indolizine product **243** was not observed when simple iron and cobalt salts were used (entries 6-9). In later examples (entries 6 and 7), the use of ethanol and acetonitrile as solvents was required due to the poor

solubility of the cobalt catalysts in dichloromethane. Direct addition of ethyl diazoacetate in one portion, rather than slow addition *via* syringe pump, to the reaction mixture containing Fe(TPP)Cl, ethyl propiolate **245** and pyridine **35**, gave superior yields (92 %, entry 10). The high yield of indolizine **243** obtained under these conditions (entry 10) indicates that pyridine is sufficiently reactive to allow for ylide formation over other undesired reactions, such as carbene dimerization.¹⁰³

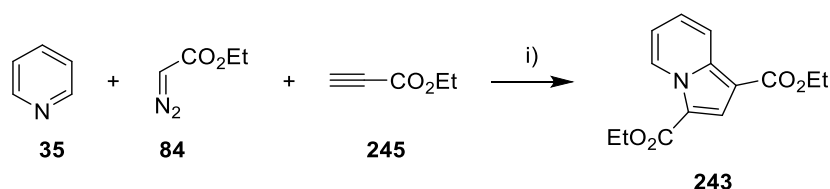


Scheme 69: Reagents and conditions: Pyridine **35** (3 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), catalyst (1 mol %), solvent, r.t., 16 h.

Entry	Catalyst	Solvent	Yield of 165 (%)
1	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	11
2	RuCl ₃	CH ₂ Cl ₂	26
3	CuCl	CH ₂ Cl ₂	10
4	CuCl ₂	CH ₂ Cl ₂	7
5	CuPF ₆ (MeCN) ₄	CH ₂ Cl ₂	0
6	CoCl ₂ •6H ₂ O	EtOH	0
7	CoCl ₃ • 6H ₂ O	MeCN	0
8	FeNO ₃ •9H ₂ O	CH ₂ Cl ₂	0
9	Fe(OAc) ₂	CH ₂ Cl ₂	0
10	Fe(TPP)Cl	CH ₂ Cl ₂	92

Table 1: Catalyst screen for reaction detailed in Scheme 69

Additional catalysts were examined next, in particular porphyrin and phthalocyanine complexes due to their reported activity for diazo decomposition (Scheme 70, Table 2).¹⁰⁴ Whilst indolizine formation was not observed when copper and cobalt (II) phthalocyanines were employed as catalysts (entries 1-3), both iron (II) and iron (III) phthalocyanine gave the indolizine **243** in excellent yield (entries 4 and 5). Ru(TPP)CO also gave the desired product **243** in good yield (71 %, entry 4), although the use of Fe(TPP)Cl with one equivalent of pyridine **35** afforded better results for the formation of **243** (87 %, entry 7). The effect of the catalyst loading was also examined. Whilst a decrease in the amount of Fe(TPP)Cl from 1 mol % to 0.25 mol % led to a minor reduction in yield (82 %, entry 8), decreasing the amount further to 0.1 mol % led to a significant drop in product yield (27 %, entry 9). Given the excellent yield (87 %, entry 7) of indolizine **243** obtained with 1 equivalent of pyridine **35** and 1 mol % of Fe(TPP)Cl, this stoichiometry was used for future studies.

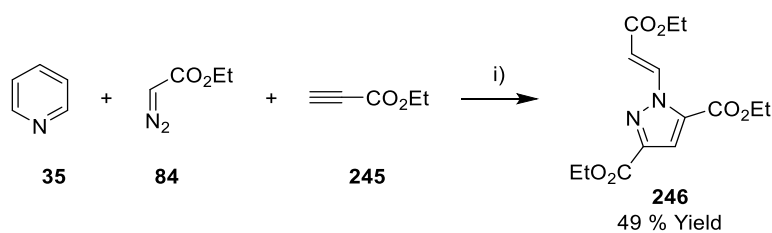


Scheme 70: Additional catalyst screening. Reagents and conditions: i) Pyridine **35** (3 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), catalyst (1 mol %), CH_2Cl_2 , r.t., 16 h.

Entry	Catalyst loading (mol %)	Catalyst	Yield (%)
1	1	CuPc	-
2	1	F ₁₆ CuPc	-
3	1	CoPc	-
4	1	Ru(TPP)CO	71
5	1	FePc	80
6	1	FePcCl	86
7	1	Fe(TPP)Cl	87 ^a
8	0.25	Fe(TPP)Cl	82
9	0.1	Fe(TPP)Cl	27

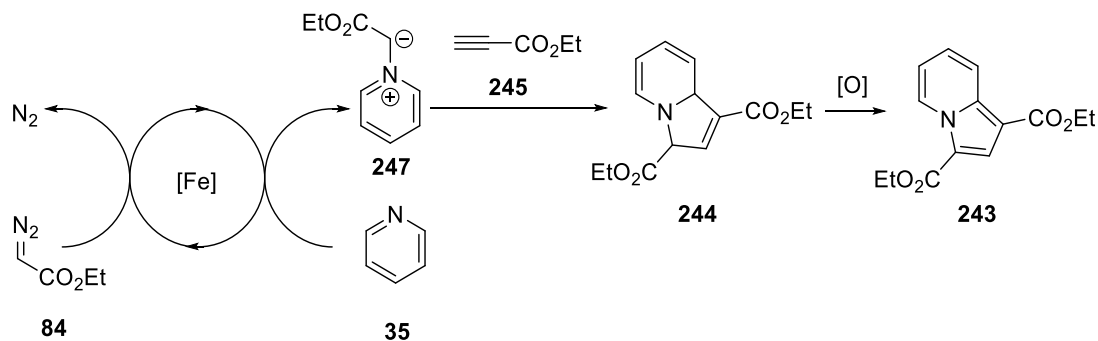
Table 2: Catalyst screen for reaction detailed in Scheme 70. ^a One equivalent of pyridine was used.

Next, the reaction was examined in the absence of a catalyst, to determine whether indolizine formation was possible *via* a pathway that did not involve metal catalysed decomposition of ethyl diazoacetate **84** (Scheme 71). The indolizine product **243** was not observed, and instead this control reaction gave a complex mixture of products that included the pyrazole **246**, which was obtained in 49 % yield. Presumably, cycloaddition between ethyl diazoacetate **84** and ethyl propiolate **245** gives an initial cycloadduct, which then undergoes conjugate addition with an additional equivalent of ethyl propiolate **245** to give the observed pyrazole **246**.¹⁰⁵



Scheme 71: Pyrrole **246** formation in the absence of Fe(TPP)Cl. Reagents and conditions: i) Pyridine **14** (1 eq.), ethyl propiolate **178** (1 eq.), ethyl diazoacetate **61** (1.5 eq.), CH₂Cl₂, r.t., 16 h.

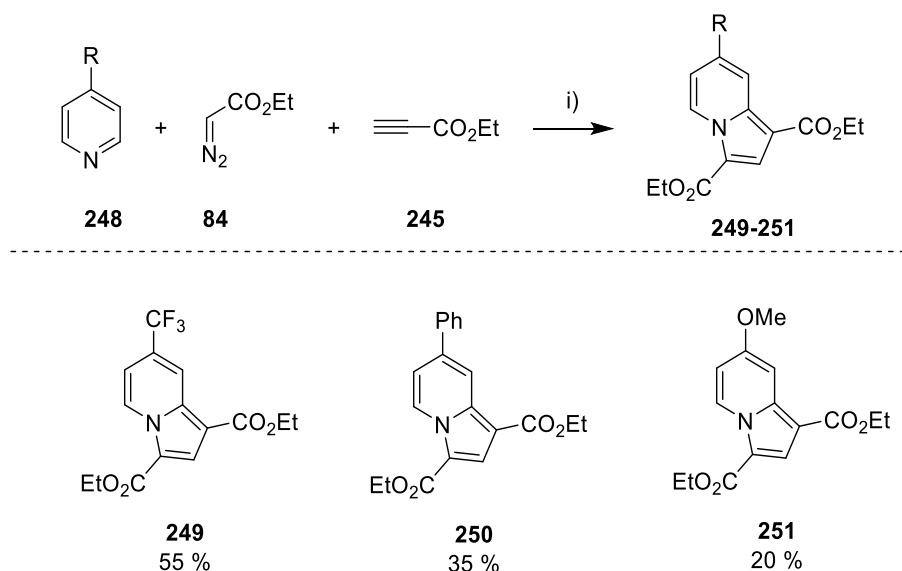
Based upon the lack of indolizine formation in the absence of Fe(TPP)Cl, we propose the ylide **247** is formed catalytically from iron catalysed decomposition of ethyl diazoacetate **84** in the presence of pyridine **35**, generating nitrogen as a by-product (Scheme 72). Reaction of **247** with the alkyne **245** then gives an initial cycloadduct **244**, which aromatises readily under air to give the observed indolizine product **243**.



Scheme 72: Proposed mechanism for indolizine formation

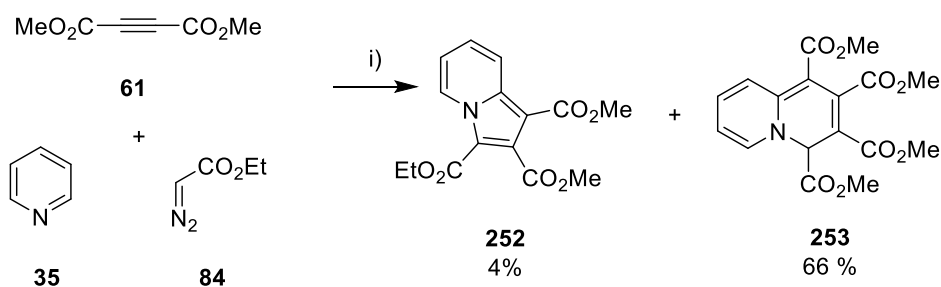
With optimised conditions for the formation of **243** in hand, the substrate scope of catalytic indolizine synthesis was next explored. The effect of electron donating and electron withdrawing substituents at the 4 position of the pyridine were first examined (Scheme 73). Whilst the electron deficient 4-trifluoromethyl pyridine gave the corresponding indolizine **249** in satisfactory yield (55 %), yields of other indolizines were more modest, with the electron rich 4-methoxy and 4-phenyl pyridine giving the

corresponding indolizines **251** and **250** in relatively poor yield (20 % and 35 %, respectively). From this decrease in observed yield of indolizine, it was concluded that the reaction is sensitive to electronic changes in the pyridine and further optimisation was required in order to obtain a general methodology.



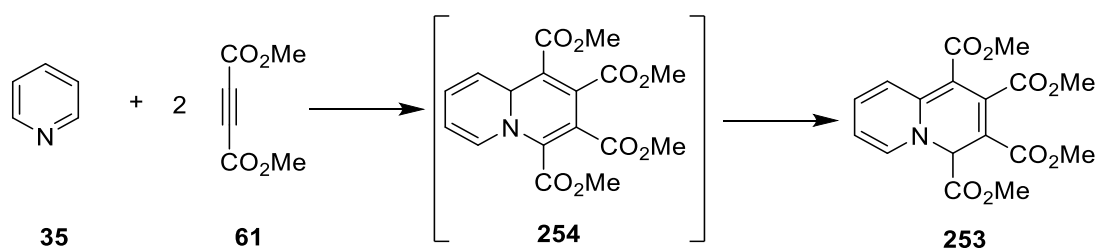
Scheme 73: Variation of pyridine reaction partner. Reagents and conditions: i) Pyridine **248** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

In addition, utilisation of DMAD **61** as a dipolarophile gave the desired indolizine **252** in exceptionally poor yield (4 %) (Scheme 74). The major product isolated from the reaction mixture was the quinolizine **253** (66 % yield), which was formed from reaction of pyridine **35** reacting with two equivalents of DMAD **61**.¹⁰⁶



Scheme 74: Formation of quinolizine **253**. Reagents and conditions: Pyridine **35** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), DMAD **61** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

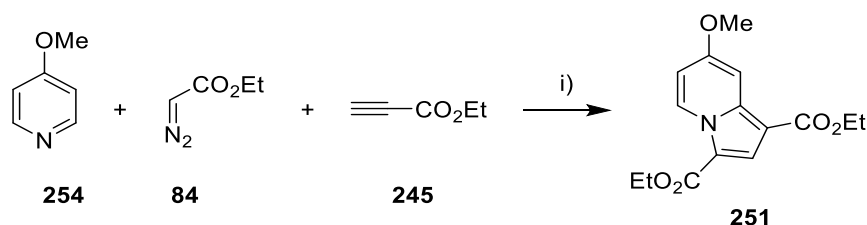
Formation of quinolizine **253** occurs *via* initial reaction of pyridine **35** with 2 equivalents of DMAD **61** to give the initial quinolizine **254**, which tautomerizes to give the more conjugated observed quinolizine **253** (Scheme 75). As the reaction is reported to be favoured for highly electrophilic alkynes, reaction most likely involves the first step of this reaction conjugate addition of pyridine **35** with DMAD **61**.¹⁰⁷



Scheme 75: Formation of quinolizine **253**.

The low to moderate yields of indolizines **249-251** indicated that further optimisation was required. The indolizine **251** was selected for optimisation (Scheme 76, Table 3), as this was obtained in the lowest yield. It was found that by lowering the temperature to -20 °C and adding a combined solution of diazo **84** and pyridine **254** to a solution containing ethyl propiolate **245** and Fe(TPP)Cl led to a significant increase in chemical yield (77 %, entry 2). This compares to a yield of 20 % when ethyl diazoacetate **84** was added to a solution of alkyne **245**, pyridine **245** and Fe(TPP)Cl at room

temperature (entry 1). Adding a solution of diazo **84** and pyridine **254** to a solution containing ethyl propiolate **245** and Fe(TPP)Cl at lower temperature of -63 °C was not beneficial, and afforded **251** in a lower yield (38 %, entry 3).

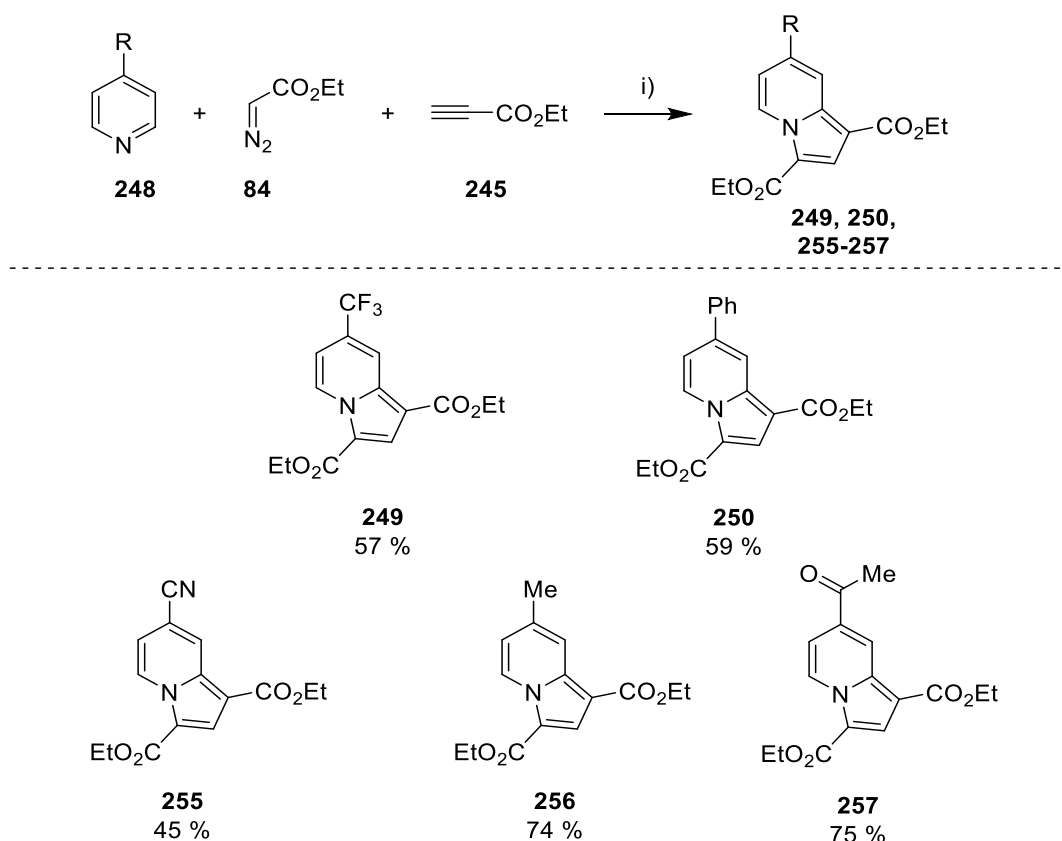


Scheme 76: Optimisation of cycloaddition to give indolizine **251**. Reagents and conditions: i) 4-methoxypyridine **254** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, temperature, 16 h.

Entry	Temperature	Yield of 251 (%)
1	r.t.	20
2	-20 °C	77
3	-63 °C	38

Table 3: Temperature screening for reaction detailed in Scheme 46.

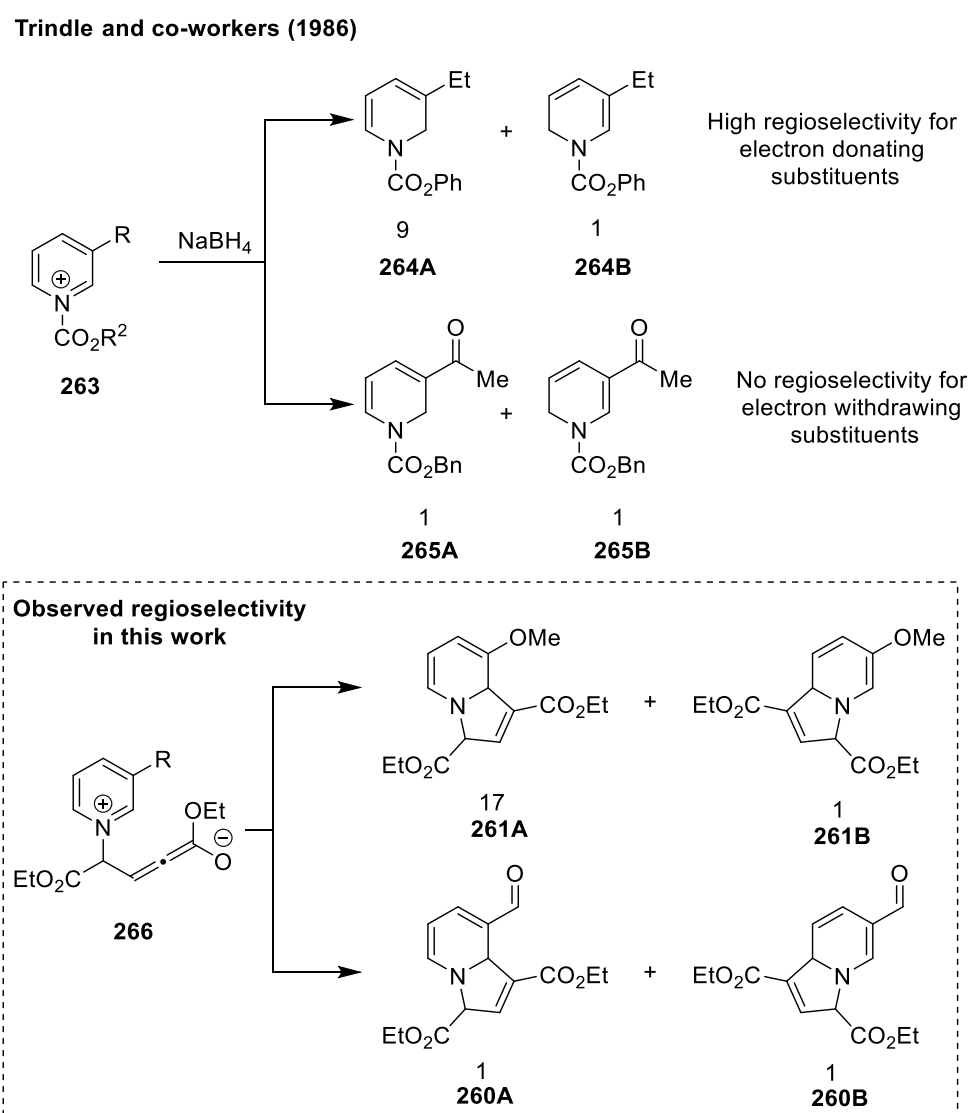
Having optimised the reaction conditions with the most reactive pyridine, substrate scope investigation was resumed, by further variation of the 4-substituent of the pyridine reaction partner (Scheme 77). A range of electron rich and poor pyridines were used, to give the corresponding 7-substituted indolizines in moderate to good yield. The indolizine **257** was isolated in 74 % yield on a 1.1 mmol scale.



Scheme 77: Utilisation of 4-substituted pyridines. Reagents and conditions: i) para-substituted pyridine **248** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), $\text{Fe}(\text{TPP})\text{Cl}$ (1 mol %), CH_2Cl_2 , -20°C , 16 h.

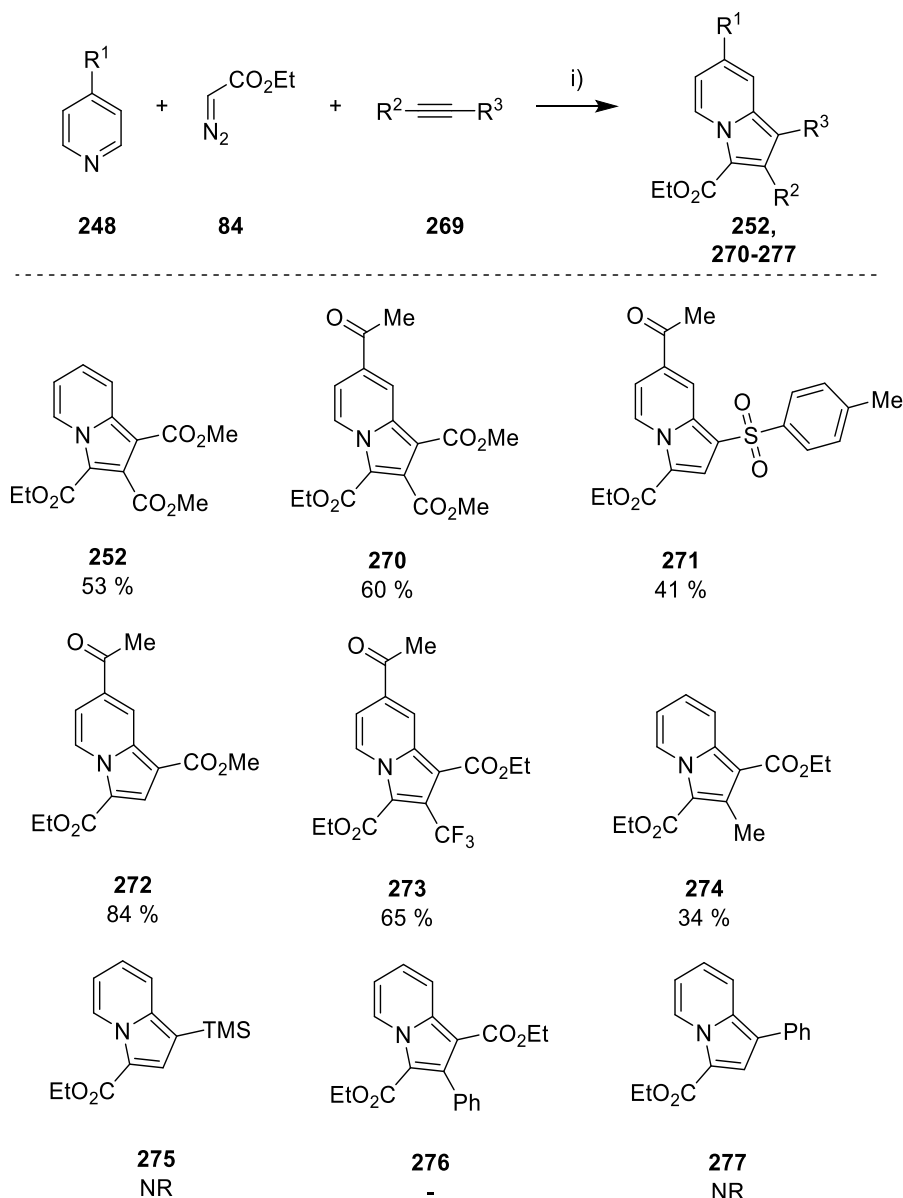
Next, 3-substituted pyridines were used as reaction partners (Scheme 78). Whilst 3-methoxypyridine displayed good selectivity for the 8-substituted indolizine **261A**, with the 6-substituted indolizine **261B** being obtained as a minor product other pyridines of both electron rich and electron poor character gave much lower regioselectivity. Both 3-fluoropyridine and 3-picoline showed moderate regioselectivity for the 8-substituted indolizines **262A** and **259A**, however 3-acetylpyridine showed no regioselectivity, with the indolizines **260A** and **260B** being isolated as a 1:1 mixture.

indicates that the directing effect was electronic, and not steric, in nature. The authors postulated that the additional resonance stabilisation of **264A** accounted for the exceptional regioselectivities of strongly electron donating substrates. Electron withdrawing substituents provided only a weak regiodirecting effect, and no regioselectivity was observed, such as the 3-acetyl substituted **265A** and **265B**. This is consistent with the result obtained when nicotinaldehyde was used as a substrate (Scheme 78).



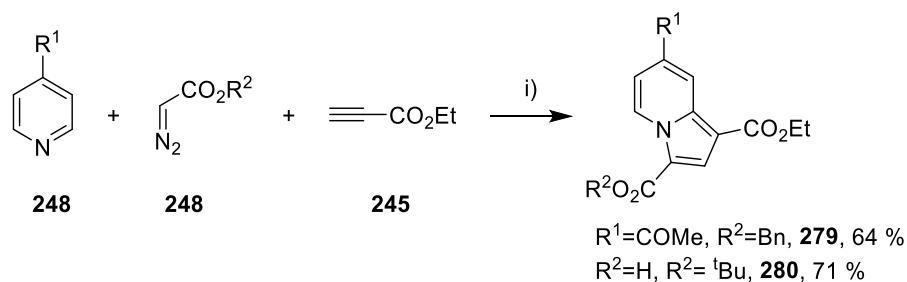
Scheme 79: Comparison of observed regioselectivity and Trindle and co-workers

conversion or yield of **274**. Increasing the steric bulk further to a phenyl group led to partial conversion of alkyne to a complex mixture of products that were inseparable by chromatography, as previously reported.¹⁰⁹ Disappointingly, electron rich alkynes such as trimethylsilylacetylene and phenylacetylene did not react under the reaction conditions employed and the desired indolizines **274** and **277** were not observed.



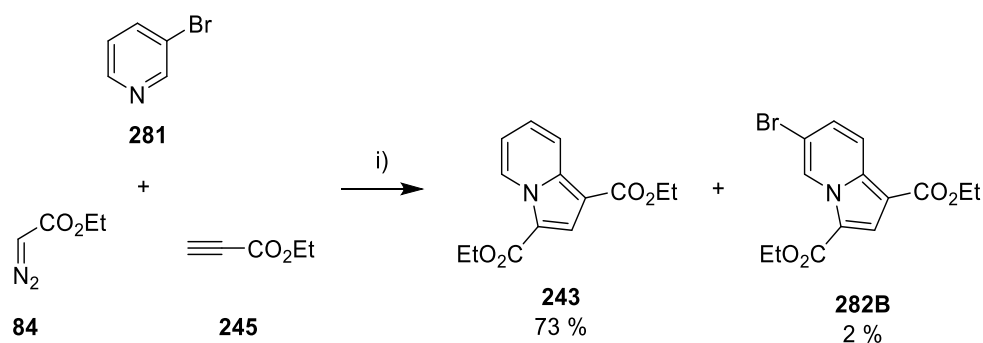
Scheme 81: Variation of alkyne reaction partner. Reagents and conditions: i) Pyridine **248** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), alkyne **269** (1 eq.), Fe(THP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

The diazo reaction partner was next varied. The commercially available benzyl and *tert*-butyl diazoacetate **248** were employed, as these esters could be selectively deprotected and functionalised, allowing for further library generation. Both the benzyl and *tert*-butyl protected indolizine cores **279** and **280** were obtained in good yield under the reaction conditions (Scheme 82).



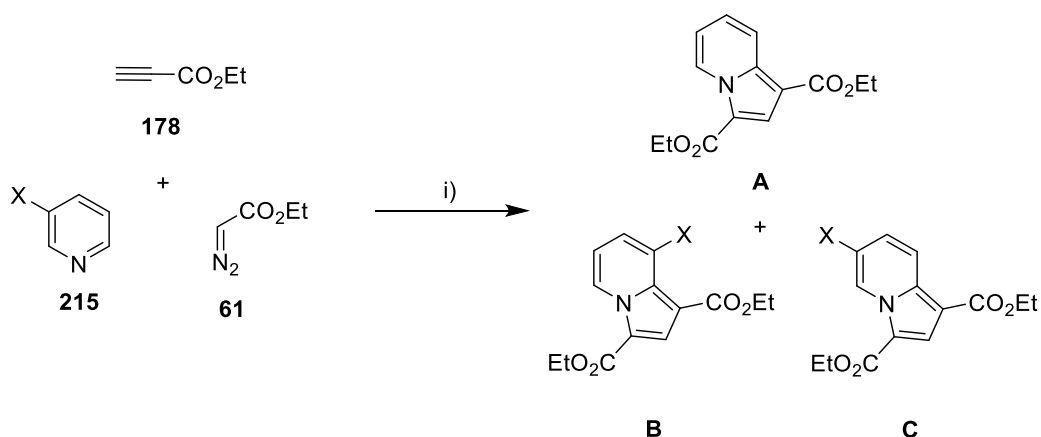
Scheme 82: Variation of diazo reaction partner. Reagents and conditions i) Pyridine **248** (1 eq.), ethyl propiolate **245** (1 eq.), diazo compound **248** (1.5 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, - 20 °C, 16 h.

During the variation of the pyridine reaction partner, an unexpected side reaction was observed. It was envisaged that the incorporation of a halogen amenable to subsequent cross couplings would allow for rapid generation of indolizine libraries. However, when 3-bromo-pyridine **281** was used as a reaction partner, the expected brominated indolizine **282B** was isolated in very low yield and the major product isolated from the reaction mixture was the debrominated indolizine **243** (Scheme 83).



Scheme 83: Dehalogenation reaction. Reagents and conditions: 3-Bromo pyridine **281** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), CH_2Cl_2 , - 20 °C, 16 h.

The unusual nature of this dehalogenation was further investigated. Initial experiments sought to establish if this dehalogenation was unique for bromide, or if the dehalogenation would occur for other halogens (Scheme 84, Table 4). The reaction with 3-fluoropyridine gave a mixture of the fluorinated indolizine products **262A** and **262B** in moderate yield (entry 1). When 3-iodopyridine (entry 3) was used as a reaction partner, the dehalogenated indolizine **243** was isolated, albeit in poor yield (20 %). These results indicated that although the process was not unique for bromine, dehalogenation was dependent upon the nature of halogen at the 3-position. It is likely the isolation of the fluorinated indolizines **262A** and **262B** are due to the strength of the carbon-fluorine bond, and the poor performance of fluorine as a leaving group.¹¹⁰

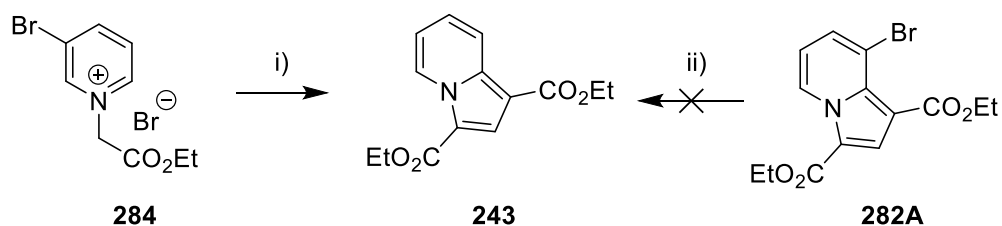


Scheme 84: Further dehalogenation experiments. Reagents and conditions: i) Pyridine **283** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

Entry	X	Yield of A	Yield of B	Yield of C
1	F	0	33	19
2	Br	73	0	2
3	I	20	0	0

Table 4: Further dehalogenation experiments

Further experiments sought to establish whether Fe(TPP)Cl was involved in the dehalogenation. Generation of the ylide *via* deprotonation of the pyridinium salt **284**, and subsequent reaction with ethyl propiolate **245** led to the selective formation of the debrominated indolizine **243** in 40 % yield (Scheme 85). In addition, the brominated indolizine **282A** did not undergo dehalogenation when subjected to the reaction conditions, indicating that the debromination occurs prior to aromatisation, and in the absence of the iron catalyst.

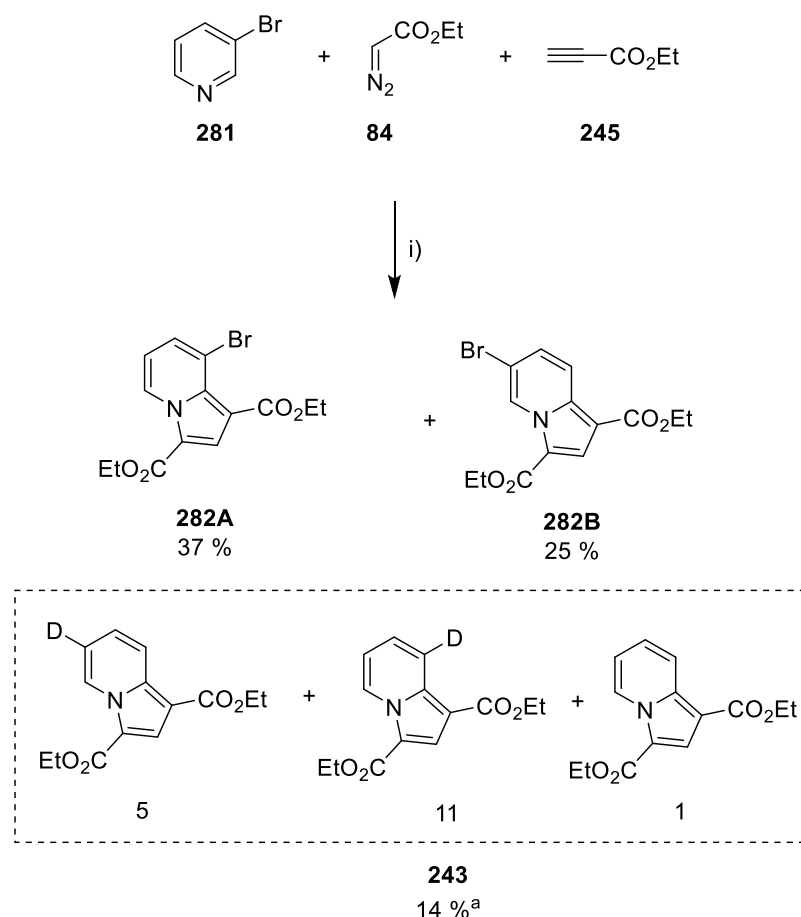


Scheme 85: Dehalogenation in the absence of Fe(TPP)Cl. Reagents and conditions i)

284 (1 eq.), ethyl propiolate **245** (1 eq.), K₂CO₃ (1 eq.), CH₂Cl₂, r.t., 16 h; ii)

Fe(TPP)Cl (1 mol %), CH₂Cl₂, r.t., 16 h.

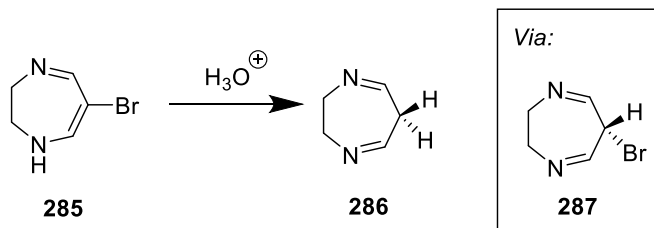
From these results it was concluded that the dehalogenation occurred before aromatisation of any intermediates, and in the absence of Fe(TPP)Cl. To investigate the dehalogenation further, the reaction was performed in a 1:1 mixture of deuterium oxide and dichloromethane (Scheme 86), to ascertain if deuterium incorporation would be observed. The presence of dichloromethane was used to ensure adequate dissolution of the reagents, given the low aqueous solubility of reagents and catalyst. Saturating the reaction solvent in deuterium, by performing the reaction in a 3:1 mixture of dichloromethane and deuterium oxide led to the isolation of the debrominated indolizines **243** in a combined yield of 12 %, with deuterium incorporation at either the 6 or 8 position (Scheme 86). Notably, the regioisomeric brominated indolizines **282A** and **282B** were isolated in significantly higher quantities (combined yield 55 %) under the biphasic conditions. The ratio of these brominated isomers and the ratio of deuterium incorporation in **243** is analogous to ratios when other 3 substituted pyridines were used in earlier studies (Scheme 78).



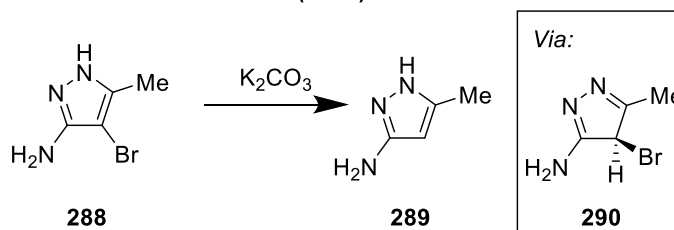
Scheme 86: Regioselective deuterium incorporation. ^a The product ratio was estimated by relative integration of protons at the indolizine 5-, 6-, and 8-positions by ¹H NMR spectroscopy. Reagents and conditions: i) 3-Bromo pyridine **281** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂/ D₂O (1:1), r.t., 16 h.

Similar debrominations have been described previously (Scheme 87). Duffield and co-workers reported the acid mediated dehalogenation of the 6-halogeno-2,3-dihydro-1*H*-1,4-diazepine **285**, with debromination occurring *via* loss of bromonium from the intermediate **287** to give **286**.¹¹¹ More recently, Cankar and co-workers reported base mediated dehalogenation of the pyrazole **288**, with the suggested mechanism proceeding in an analogous manner, *via* loss of bromonium from **290**, followed by *N*-protonation of the resulting pyrazole.¹¹²

Duffield and co-workers (1969)

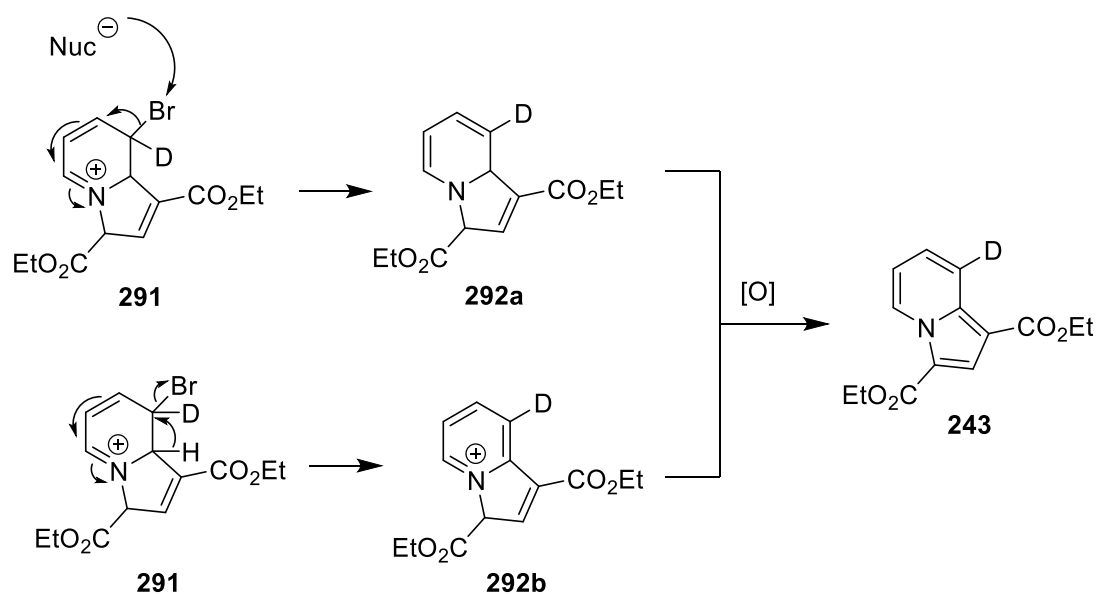


Cankar and co-workers (2017)



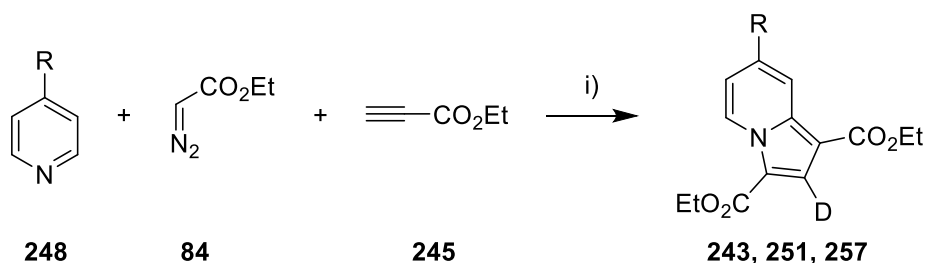
Scheme 87: Dehalogenation of 1,3 brominated enamines reported to proceed *via* a bromonium mechanism

Based upon the deuterium incorporation pattern observed, as well as the aforementioned dehalogenation examples, it was postulated that the protonated cycloadduct **291** undergoes loss of bromonium to an external nucleophile, perhaps the pyridinium ylide, to give the deuterated cycloadduct **292A** (Scheme 88). Aromatisation of **292A** then gives the deuterated indolizine product **243**. Alternatively, elimination of HBr from **291** gives the pyridinium intermediate **292B**, which also give the observed deuterated product **243** upon aromatisation.



Scheme 88: Postulated mechanism for deuterium incorporation

When other pyridines **248** were subjected to the biphasic reaction conditions, deuteration was not observed at the 6 or 8 position, but at the 2 position instead (Scheme 89, Table 5).



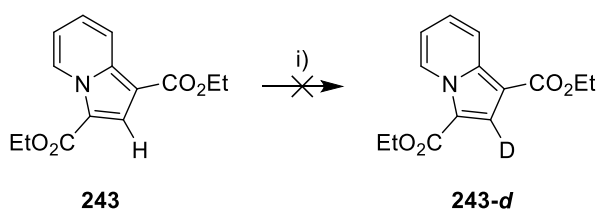
Scheme 89: Observed deuterium incorporation of indolizines. Reagents and conditions: i) Pyridine **248** (1 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂/D₂O (1:1), r.t., 16 h.

Entry	Indolizine	R	Yield	D/H ratio
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1	243	H	79	4:6
2	257	COMe	59	6:4
3	251	OMe	50	9:1

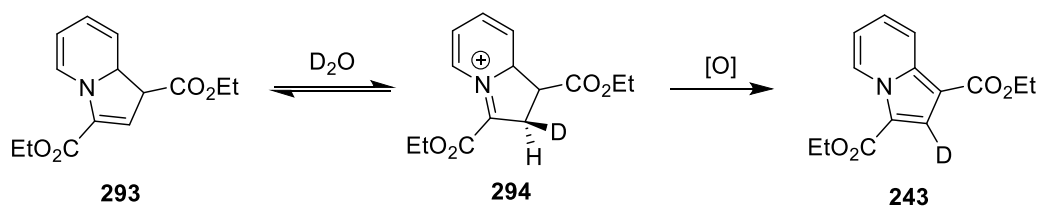
Table 5: Deuterium incorporation of indolizines

It was found that deuterium incorporation at the 2 position did not occur upon subjecting the indolizine **243** to the deuterating reaction conditions (Scheme 90), indicating that deuterium incorporation occurs prior to formation of the indolizine core.



Scheme 90: Lack of deuterium incorporation. Reagents and conditions: i) Indolizine **243** (1 eq.), Fe(TPP)Cl (1 mol %), CH₂Cl₂/D₂O, r.t., 16 h.

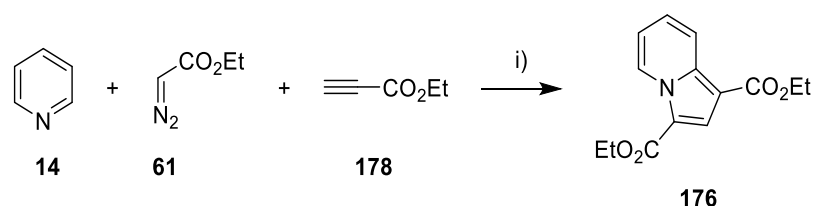
It was postulated that deuterium incorporation occurred prior to aromatisation, perhaps *via* the intermediate **294** (Scheme 91).



Scheme 91: Postulated mechanism for deuterium incorporation

Finally, although the use of Fe(TPP)Cl in dichloromethane as a solvent yielded the indolizine product **243** in excellent yield, the poor sustainability profile of this solvent merited the investigation of alternative solvents (Scheme 92, Table 6).¹¹³ Generally,

yields of **243** in more environmentally benign solvents were respectable, although the yield of **243** in water was poor (13 %). This drop in chemical yield can be attributed to the poor aqueous solubility of the reagents and catalyst, as yields of **243** in an 8:2 water/ethanol mixture were much higher (82 %, entry 6). Whilst the use of dichloromethane ultimately gave superior yields (92 % entry 7), the reaction still proceeds smoothly in other solvents, giving **243** in good yields.



Scheme 92: Solvent screening of for formation of **243**. Reagents and conditions:

Pyridine **34** (3 eq.), ethyl diazoacetate **84** (1.5 eq.), ethyl propiolate **245** (1 eq.),

Fe(TPP)Cl , solvent, r.t., 16 h.

Entry	Solvent	Yield (%)
1	MeCN	80
2	Acetone	82
3	Toluene	79
4	EtOAc	70
5	H ₂ O	13
6	H ₂ O/ EtOH (8:2)	82
7	CH ₂ Cl ₂	92

Table 6: Solvent screen for reaction detailed in Scheme 92

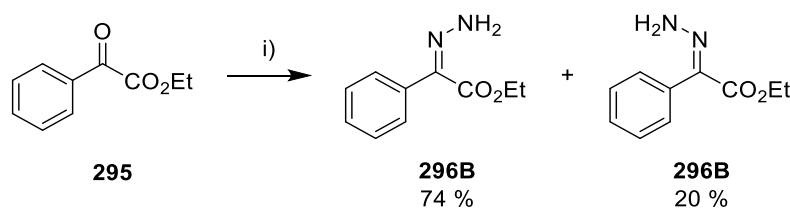
In summary, a catalytic methodology for the synthesis of indolizines from pyridines, diazo compounds and alkynes has been developed. The catalytic system uses an earth

abundant catalyst and shows good tolerance to solvents. The dehalogenation of dihydroindolizine intermediates has been observed, and after mechanistic investigation has been postulated to occur *via* loss of bromonium from a protonated dihydroindolizine.

3.2 N-Chlorosuccinimide Mediated Oxidation of Hydrazones

With a new methodology for the catalytic indolizine synthesis from pyridines, diazo compounds and alkynes developed, attention was next focused upon *in situ* generation of the diazo compound. The greatest drawback to this catalytic method was the use of the diazo compound, due to its toxicity and high reactivity and mitigating these hazards would be highly desirable. A methodology was sought that would allow for *in situ* continuous diazo consumption and generation. To optimise the atom economy of reagents, a catalytic methodology was desirable. Therefore, from the methods discussed in section 1.5, hydrazone oxidation was selected as this method had been demonstrated to function catalytically, and typical conditions are mild, involving neutral pH and room temperature.

The hydrazone **296** was selected as a model substrate due to its ease of preparation from the commercially available keto ester **295** and relevance to other research undertaken in the group (Scheme 93).³⁰ Benzoic acid mediated condensation with hydrazine hydrate afforded the hydrazone **296** as two isomers, with preference shown for the *Z* isomer **296A** as previously reported.^{55a}

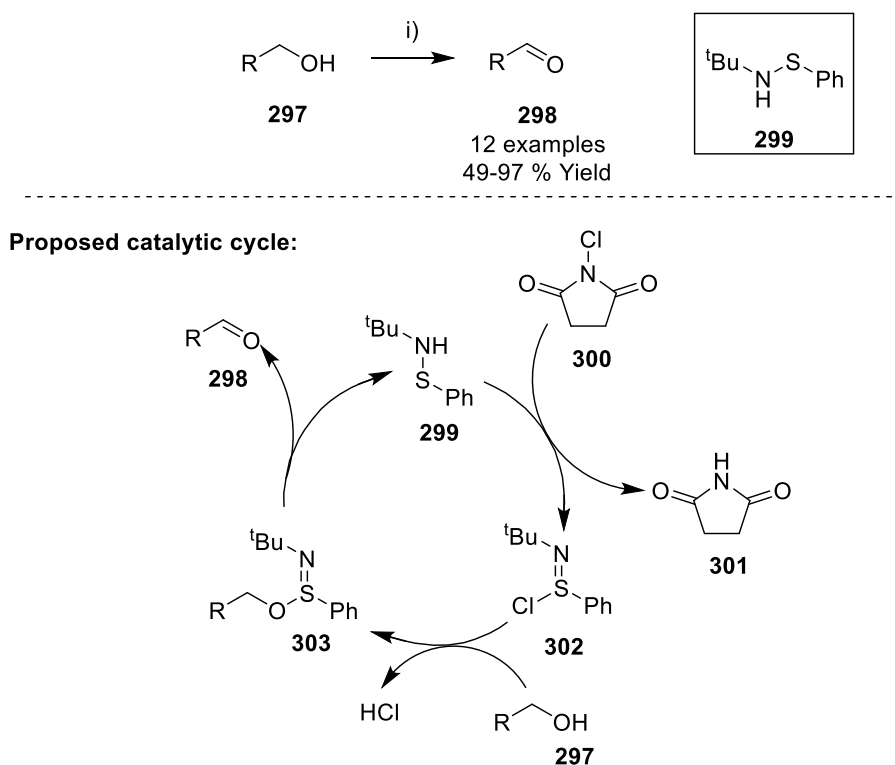


Scheme 93: Synthesis of model substrate **296**. Reagents and conditions: i) Keto ester **295** (1 eq.), N₂H₄·X H₂O (1 eq.), benzoic acid (1 eq.), THF, r.t., 14 h.

Initially, a single hydrazone isomer of **296** was used, to simplify reaction monitoring. The (*E*) hydrazone **296B** was selected as a substrate, as its conversion to the

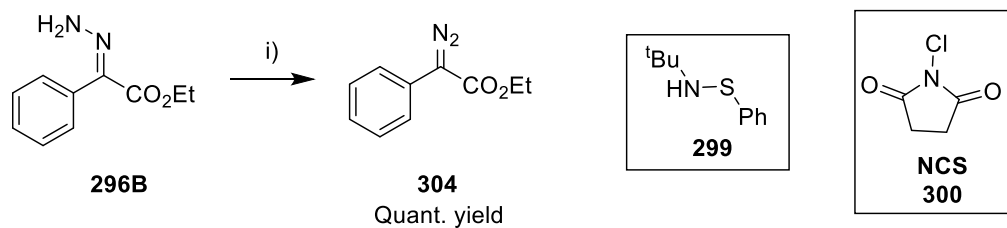
corresponding diazo compound could be monitored quantitatively by observing the loss of the NH₂ signal at 6.23 ppm in the ¹H NMR spectrum. In addition, the (*E*) isomer **296B** was obtained as a solid, making manipulation and handling easier than the corresponding (*Z*) isomer **296A**, which was collected a thick oil.

Initially, the sulfenamide catalyst **299** and *N*-chlorosuccinimide (NCS) **300** were chosen as the oxidative system, as this catalytic system had been reported to be effective at alcohol oxidation by Kitagawa and co-workers (Scheme 94).¹¹⁴ The authors suggested that the catalytic cycle proceeded *via* initial nucleophilic attack of the sulfenamide catalyst **299** into the electrophilic chlorine substituent of NCS **300**, giving the active intermediate **302**. Nucleophilic attack of the alcohol substrate, followed by elimination of HCl gives **303**, which is regenerated to the sulfenamide catalyst **299** upon elimination of the desired aldehyde product **298**.



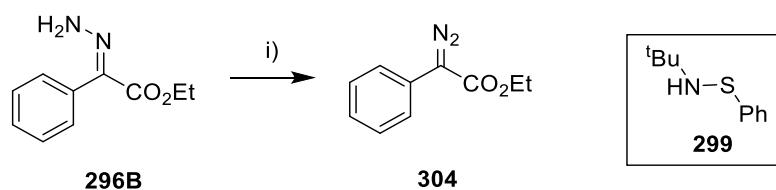
Scheme 94: Sulfenamide catalysed oxidation of alcohols **297**. Reagents and conditions: i) NCS **300** (1 eq.), **299** (10 mol %), K₂CO₃ (10 eq.), MgSO₄ (10 eq.), CH₂Cl₂, 0 °C, 3.5 h.

The method was adapted for use in this work, and hydrazone **296B** was used as a substrate (Scheme 95). A large excess of base was used to ensure the HCl generated was neutralised, as decomposition of the diazo product **304** could potentially occur at low pH. Additionally, MgSO₄ was used as a drying agent to prevent water from potentially interfering in the catalytic cycle. Pleasingly, under these conditions the diazo compound **304** was obtained in quantitative yield.



Scheme 95: Catalytic hydrazone oxidation. Reagents and conditions: i) Hydrazone **296B** (1 eq.), NCS (1.1 eq.), **299** (10 mol %), K_2CO_3 (10 eq.), $MgSO_4$ (10 eq.), CH_2Cl_2 , 0 °C, argon atmosphere 3.5 h

Encouraged by the quantitative yield of **304**, the reaction was developed further. Different solvents were evaluated, to ascertain if more environmentally benign solvents would be compatible with the reaction (Scheme 96, Table 7). Of the solvents screened, only acetonitrile and *tert*-butanol produced satisfactory conversion of **296B** to **304** (82 % and quant., entries 2 and 5). This is most likely due to the poor solubility of *N*-chlorosuccinimide (NCS) in the other solvents. The conversion of **296B** in acetonitrile could be increased from 82 % (entry 3) to 97 % (entry 9) by increasing the reaction time to 24 h, but superior yields were obtained from performing the reaction in *tert*-butanol. Satisfied by the low toxicity, environmental impact and monetary cost of this solvent, *tert*-butanol was used for further reactions.¹¹⁵

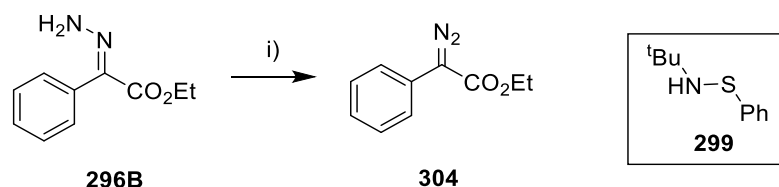


Scheme 96: Solvent optimisation for organocatalytic hydrazone oxidation. Reagents and conditions: i) Hydrazone **296B** (1 eq.), NCS **300** (1.1 eq.), **299** (10 mol %), K_2CO_3 (10 eq.), $MgSO_4$ (10 eq.), solvent, temperature, time.

Entry	Solvent	Temperature (°C)	Time (h)	Conversion (%)
1	CH ₂ Cl ₂	0	3	Quant.
2	Ethyl acetate	0	3	50
3	MeCN	0	3	82
4	Toluene	0	3	19
5	^tBuOH	r.t.	3	Quant.
6	THF	0	3	59
7	2-Me-THF	0	3	36
8	DMSO	r.t.	24	NR
9	MeCN	r.t.	24	97
10	Acetone	r.t.	24	83

Table 7: Solvent optimisation for organocatalytic hydrazone oxidation

Next, the stoichiometry of the reagents was varied, to ascertain whether the atom economy of the process could be improved (Scheme 97, Table 8). Whilst a decrease in conversion was observed in the absence of MgSO₄ and an argon atmosphere (entries 3 and 5), a 92 % conversion was observed in the absence of the catalyst **299** (entry 4). This very high conversion in the absence of a catalyst indicates that a reaction pathway for oxidation exists that does not require the catalyst **299**.

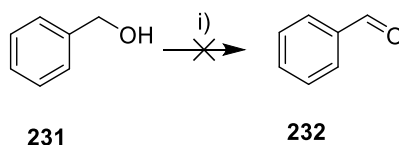


Scheme 97: Control experiments for organocatalytic hydrazone oxidation. Reagents and conditions: i) Hydrazone **296B** (1 eq.), **299** (10 mol %) NCS (1.1 eq.), K₂CO₃ (10 eq.), MgSO₄ (10 eq.), ^tBuOH, r.t., 3.5 h.

Entry	Base eq.	MgSO ₄	Atmosphere	Cat loading (mol %)	Conversion (%)
1	10	Yes	Argon	10	Quant.
2	5	Yes	Argon	10	80
3	10	No	Argon	10	65
4	10	Yes	Argon	0	92

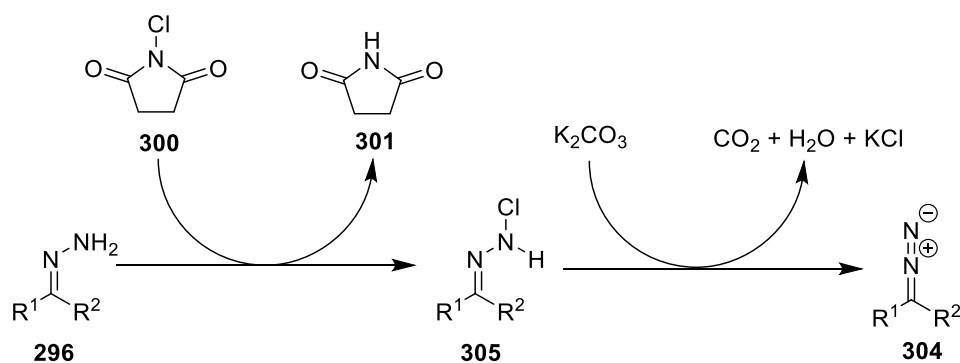
Table 8: Control experiments for organocatalytic hydrazone oxidation

The methodology reported by Kitagawa and co-workers was re-examined, to ensure that the sulfenamide catalyst **299** was required for alcohol oxidation.⁷⁷ Subjecting benzyl alcohol **231** to reported conditions in the absence of **299** did not lead to formation of benzaldehyde **232**, even upon heating the reaction mixture at 50 °C for 4 h (Scheme 98).



Scheme 98: Unsuccessful oxidation of benzyl alcohol **231**. Reagents and conditions: Benzyl alcohol **231** (1 eq.), NCS (1.1 eq.), K₂CO₃ (10 eq.), MgSO₄ (10 eq.), CH₂Cl₂, r.t., 3.5 h.

Oxidation of the hydrazone could occur *via* a pathway that does not involve the sulfenamide catalyst **299** (Scheme 99). Should the substrate be nucleophilic enough, direct attack of the substrate to electrophilic chlorine would yield the *N*-chlorinated intermediate **302** and succinimide **301**. Elimination of HCl from **305** would then yield the diazo compound **304**. It could be postulated that this pathway is only accessible to highly nucleophilic substrates, and thus an alcohol, lacking sufficient nucleophilicity to react directly with NCS, requires the catalyst **299** to undergo oxidation. Given that hydrazones are significantly more nucleophilic than alcohols, the hydrazone **296** does not require the sulfenamide **299**, and can react directly with NCS **300**.

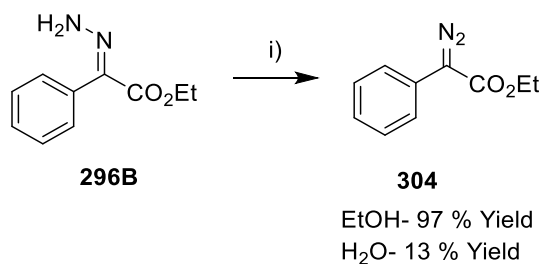


Scheme 99: Postulated mechanism for NCS mediated hydrazone oxidation

The catalyst-free oxidation of hydrazones to diazo compounds with NCS has not been reported previously, so this methodology was further explored. The optimisation of this reaction continued, with a particular emphasis placed upon atom economy of the process. In addition, tolerance to water and air would be highly desirable.

Given that NCS would not oxidize alcohols in the absence of a catalyst, the use of ethanol as a solvent was investigated, as the sustainability profile of this solvent is excellent, and is obtained from renewable sources.¹¹⁵ Heating the hydrazone **296B** with two equivalents of NCS and super stoichiometric potassium carbonate in ethanol

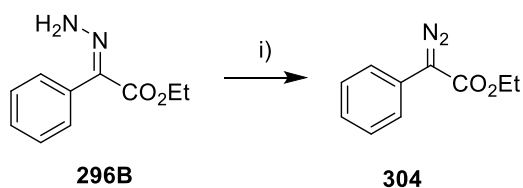
for 16 h gave the diazo compound in 97 % yield without the need for MgSO_4 as a drying agent or an argon atmosphere (Scheme 100). The use of water as a reaction medium led to poor conversion, even after 16 h. This poor conversion is attributed to the poor aqueous solubility of the hydrazone **296B**.



Scheme 100: Catalyst free oxidation of hydrazone **296B**. Reagents and conditions: i)

Hydrazone **296B** (1 eq.), NCS (2 eq.), K_2CO_3 (10 eq.), solvent, 50 °C, 16 h.

With the yield of **304** at a satisfactory level, further optimisation was undertaken (Scheme 101, Table 9). It was found that the amount of NCS used could be lowered from 2 to 1.3 equivalents without any loss in conversion (entry 2), although a slight drop in yield of **304** was observed when the excess was decreased to 1.2 (entry 3). Similarly, the amount of K_2CO_3 used could be decreased from 10 to 1 equivalents without any depreciation in yield (entry 7).



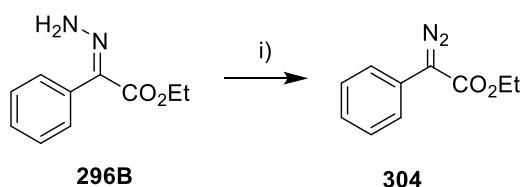
Scheme 101: Catalyst free oxidation of hydrazone **296B**. Reagents and conditions: i)

Hydrazone **296B** (1 eq.), NCS (eq.), K_2CO_3 (eq.), EtOH, 50 °C, 16 h.

Entry	NCS (eq.)	K ₂ CO ₃ (eq.)	Conversion (%)	Yield (%)
1	2	10	Quant.	97
2	1.3	10	Quant.	Quant.
3	1.2	10	90	NR
4	1.2	2	85	NR
5	1.5	5	Quant.	Quant.
6	1.3	2.5	Quant.	Quant.
7	1.3	1	Quant.	Quant.

Table 9: Optimisation of NCS mediated hydrazone oxidation

With the stoichiometry of the process now optimised, the effects of varying temperature and time were investigated (Scheme 102, Table 10). Decreasing the reaction temperature from 50 °C to room temperature did not lead to drop in conversion (entry 2), and the diazo compound **304** was furnished in quantitative yield after 4 h at room temperature (entry 3).



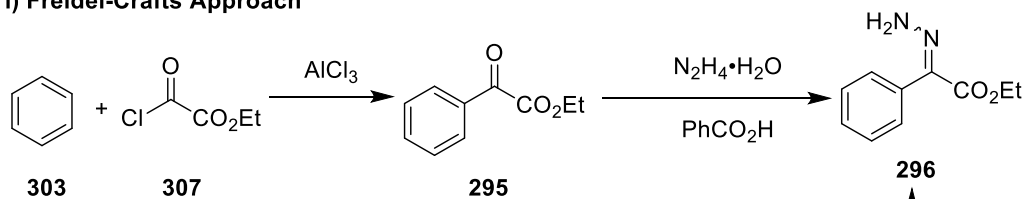
Scheme 102: Further optimisation of NCS mediated hydrazone oxidation. Reagents and conditions: i) Hydrazone **296B** (1 eq.), NCS (1.3 eq.), K₂CO₃ (eq.), EtOH, temperature, time.

Entry	K ₂ CO ₃	Temperature	Time	Conversion	Yield
1	2.5	40	16	Quant.	-
2	1	r.t.	16	Quant.	Quant.
3	1	r.t.	4	Quant.	Quant.

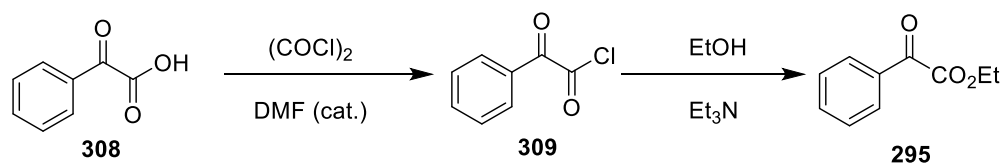
Table 10: Further optimisation of NCS mediated hydrazone oxidation

With optimised conditions for hydrazone oxidation in hand, the substrate scope of the methodology was next investigated. It was decided that the most efficient methodology for synthesis of the required hydrazone substrates would be condensation of hydrazine hydrate with the required keto compound (Scheme 103).^{55a} Whilst the commercial availability of keto compounds is modest, their synthesis could also be accomplished *via* Friedel-Crafts acylation of an arene **303** with ethyl chlorooxoacetate **307**, or condensation of the desired alcohol with commercially available benzoylformic acid **308**.¹¹⁶

i) Freidel-Crafts Approach

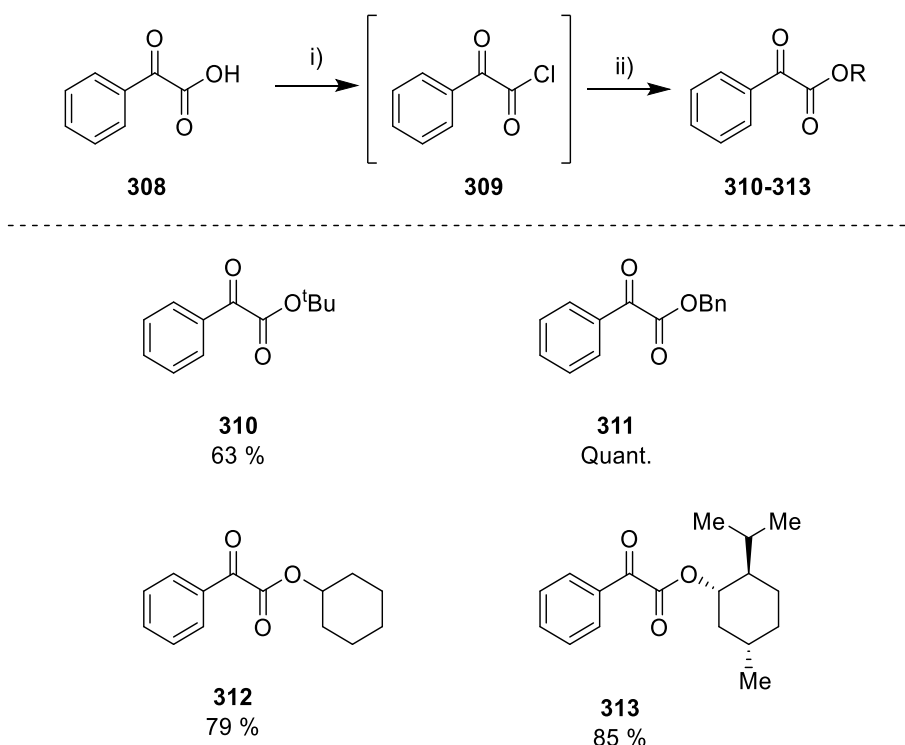


ii) Condensation Approach



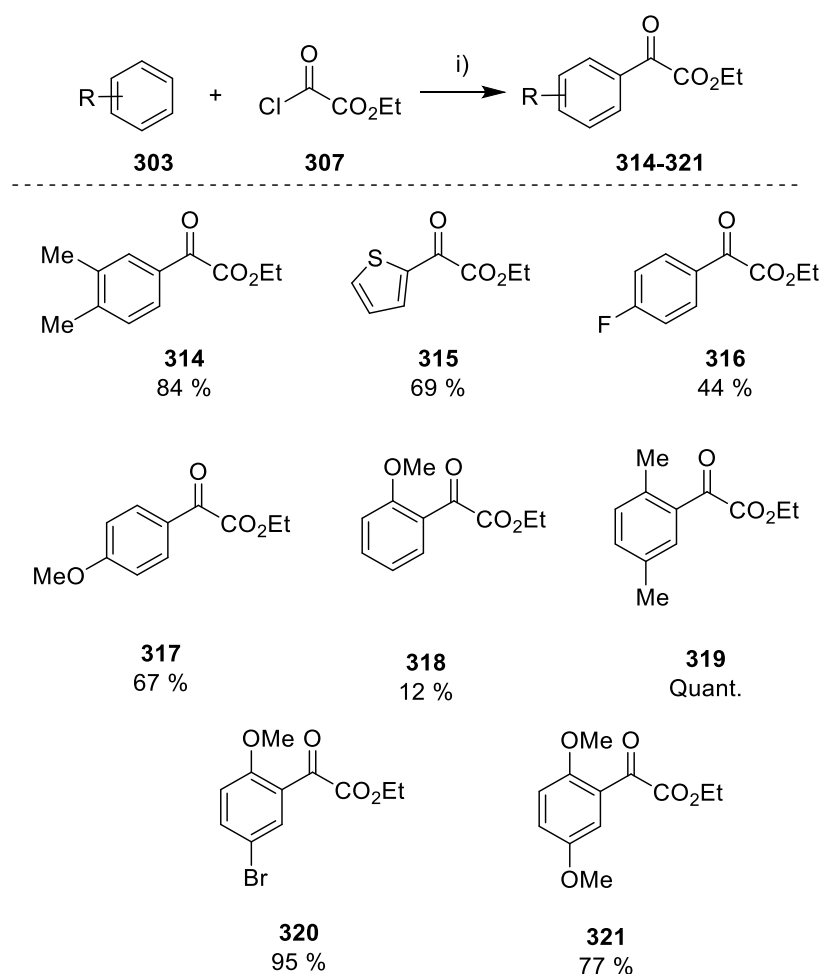
Scheme 103: Proposed synthetic route to keto compounds and corresponding hydrazones.

A variety of keto esters were thus prepared according to literature methods (Scheme 104).^{55a} Stirring a solution of benzoylformic acid **308** with oxalyl chloride in CH_2Cl_2 with catalytic DMF for 4 h afforded a stock solution of the acyl chloride **309** that could be stored at 0 °C until required. An aliquot of this was then added dropwise to a solution of the required alcohol and triethylamine under argon at 0 °C to afford the desired keto esters **310-313**.



Scheme 104: Keto ester synthesis. Reagents and conditions: i) **308** (1 eq.), oxalyl chloride (1 eq.), DMF (cat.), CH₂Cl₂, 0 °C-r.t., 4 h; ii) Alcohol (1 eq.), Et₃N (2 eq.), CH₂Cl₂, 0 °C-r.t., 16 h.

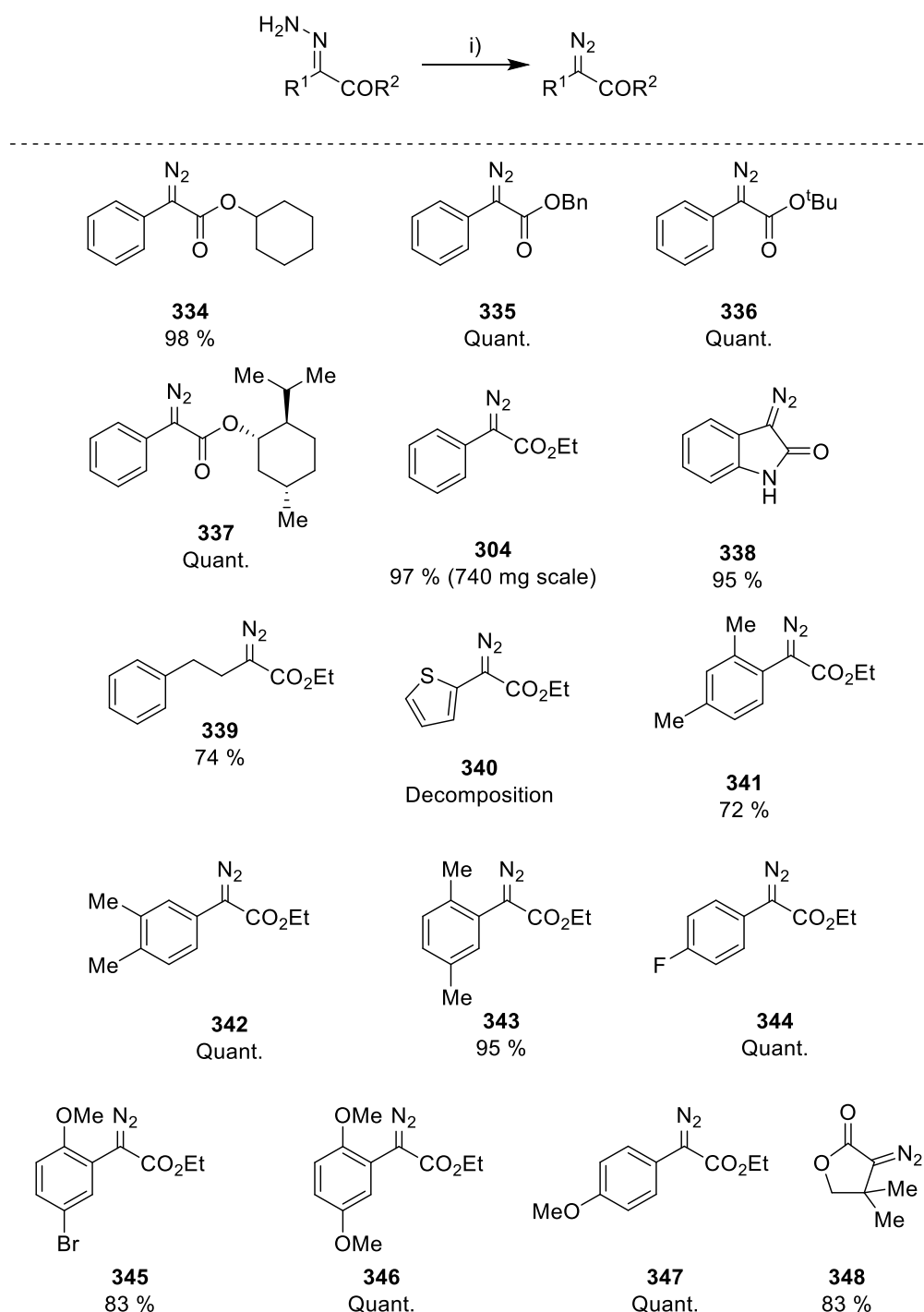
Similarly, keto esters with varied substitution patterns on the arene substituent were prepared *via* Friedel-Crafts acylation of commercially available ethyl oxalyl chloride **307** with the desired arene **303** (Scheme 105).¹¹⁶ Reaction of *o*-xylene gave the corresponding 4-substituted keto ester **314** in excellent yield (84 %). Thiophene reacted exclusively at the 2-position, giving the keto ester **315** in moderate yield (69 %). When anisole was employed, the 4-substituted keto ester **317** was isolated as the major product (67 %), along with the 2-substituted **318** in lower yield (12 %). 1,4-substituted arenes also reacted smoothly, providing access to 2-substituted keto esters **319**, **320** and **321** in excellent yields.



Scheme 105: Preparation of keto esters **314-321**. Reagents and conditions: Arene **303** (1 eq.), ethyl oxalyl chloride **307** (1.9 eq.), AlCl_3 (1.9 eq.), CH_2Cl_2 , 0 °C- r.t., 4 h.

The resulting keto esters were then reacted with hydrazine hydrate in the presence of benzoic acid to give the desired hydrazones (Scheme 106). Hydrazones of varying ester substituents bearing α -aromatic substituents gave the corresponding hydrazones in good yields, with preference typically shown for the (*Z*) isomer. The geometry of the C=N bond was assigned by comparison of data to literature reports and the chemical shift of the NH_2 peak in the ^1H spectrum.^{55a} Substituents at the two position of the phenyl ring led to a switch in selectivity and the (*E*) hydrazone was isolated as the major product (**330** and **332**), which is consistent with literature reports.^{55a}

the arene ring, the diazo compound was still furnished in excellent yield. Sterically hindered esters, such as *t*-butyl, and menthol were tolerated well, furnishing the corresponding diazo compounds **335**, **336** and **337** in quantitative yield. The reaction conditions gave the diazo compound **304** in 97 % yield on a 740 mg scale. The methodology also provided access to cyclic diazo compounds, including the isatin derived **338**, from oxidation of the *Z* hydrazone corresponding (95 %), and the germinal dimethyl cyclic diazo **358** (83 %). Disappointingly, the thiophene derived diazo compound **340** decomposed under the reaction conditions. The xylene derived diazo compounds **341-343** were also obtained in good yield, as was the electron poor fluorinated diazo compound **344** (Quant.). In instances where substituents could undergo further reactions *via* CH insertion, diazo compounds **355** and **356** were isolated in excellent yields. Oxidation of the hydrazone **333B** also proceeded smoothly, with the diazo compound **339** being obtained in good yield (74 %).



Scheme 107: NCS mediated hydrazone oxidation substrate scope. Reagents and conditions: i) Hydrazone **322B-333B** (1 eq.), NCS (1.3 eq.), K₂CO₃ (1 eq.), EtOH, r.t., 16 h

With the substrate scope of the methodology adequately demonstrated, a more in depth analysis of the efficiency of the process was undertaken. After consideration, it was

decided that the metrics that should be used to compare this work with literature methods for hydrazone oxidation would be atom economy (AE) and reaction mass intensity (RMI) (Equation 1). The selection of metrics that do not involve reaction solvent or purification is deliberate, as these processes are not optimised in other methodologies, meaning comparison would give misleading results. In addition, the volume of silica, chromatography eluent or drying agent is seldom reported in literature experimental procedures.

$$(1) \text{ Reaction mass intensity (RMI)} = \frac{\text{Mass of product}}{\text{Mass of all reagents}} \times 100 \%$$

$$(2) \text{ Atom economy (AE)} = \frac{\text{Molecular weight of product}}{\text{Molecular weight of all reagents}} \times 100 \%$$

Equation 1: Metrics selected for comparison

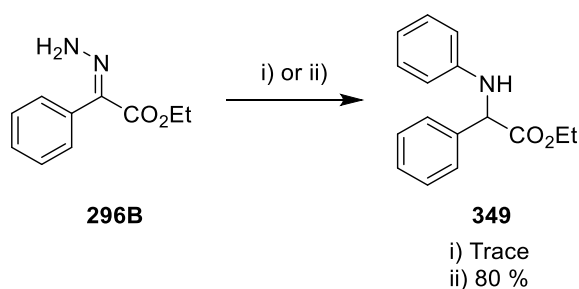
The methodology for hydrazone oxidation generated during this work compares favourably to literature methods for diazo synthesis commonly used (Table 11). The atom economy and RMI of the developed methodology were similar (entry 1, 41 % and 37 %), indicating a close to optimal reaction stoichiometry. With respect to RMI, this work performed better than existing conditions for hydrazone oxidation including TsNIK^{55a} and Swern conditions⁷¹ (entries 2 and 3). Whilst oxidation with MnO₂ had a significantly higher atom economy (69 %, entry 4) than this work (41 %, entry 1), the excess (5 eq.) of this oxidant typically used in hydrazone oxidation reactions led to a lowered RMI (30 %). A common methodology for the preparation of donor-acceptor diazo compounds is diazo transfer, and thus the metrics of diazo transfer for this reaction were also compared. Diazo transfer using both mesyl and tosyl azide gave the same RMI (35 %, entry 5), as a larger excess of base is used with the lower molecular weight mesyl azide. Whilst diazotransfer with mesyl azide gave an improved atom

economy (49 %), the explosive nature of low molecular weight azides makes use of this reagent undesirable.¹¹⁷

Entry	Methodology	Atom economy (%)	Reaction mass intensity (%)
1	NCS/K ₂ CO ₃	41	37
2	TsNIK ^{55a}	36	26
3	DMSO (COCl) ₂ ⁷¹	38	31
4	MnO ₂ ⁷⁰	69	30
5	Diazo transfer ^{61,}	38 ^a /49 ^b	35 ^a /35 ^b

Table 11: Comparison of this work to other methods for preparation of diazo compound **304**. ^a with mesyl azide ^b with tosyl azide

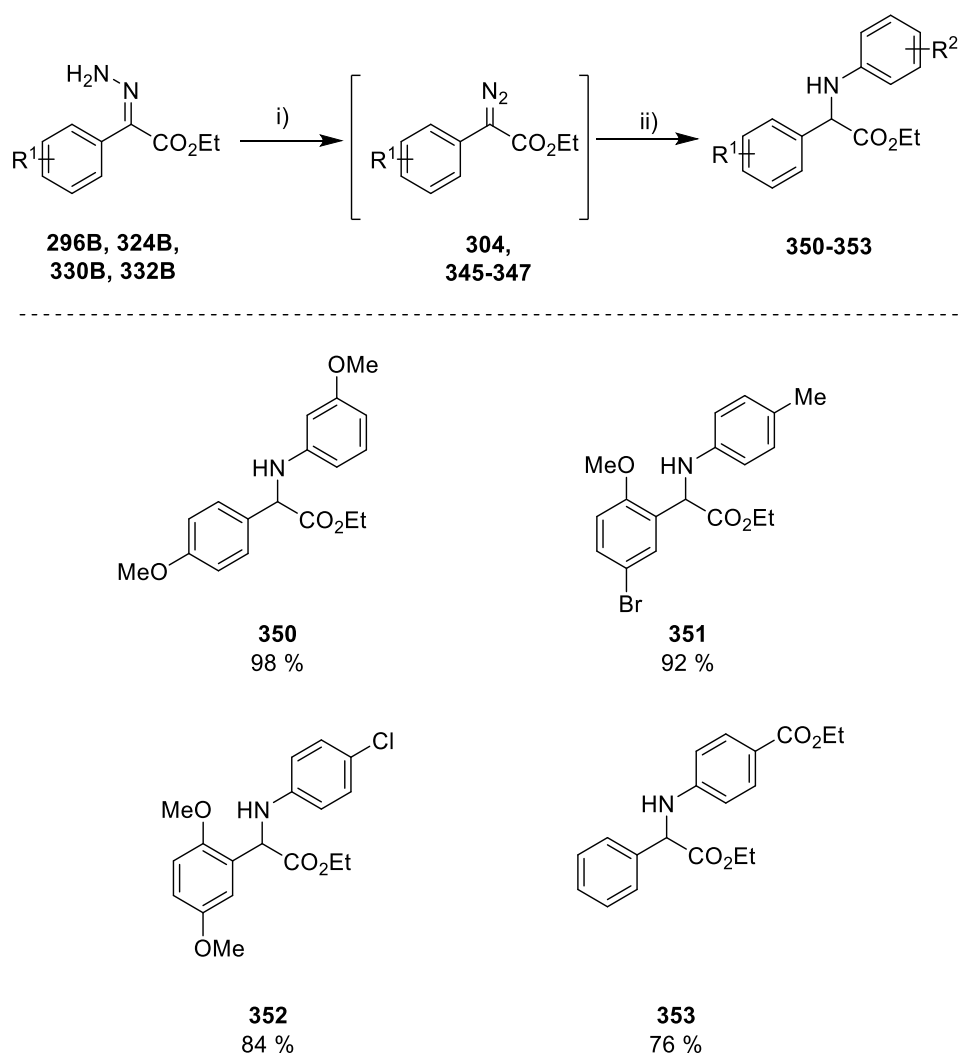
Finally, *in situ* reaction of the diazo compound **304** was investigated. Ideally, generation and consumption of the diazo compound would occur contemporaneously, avoiding its accumulation and build up. This would be highly desirable, as diazo compounds are potentially toxic and explosive and minimizing the quantity present during the reaction would greatly improve the safety profile of the process. Reaction with aniline was selected, as this NH insertion reaction is a robust and well established reaction. Adding rhodium acetate and aniline at the start of the reaction (Scheme 106, conditions i)), led to a black precipitate forming rapidly, and only traces of the desired amine **359**. Most likely, the rhodium catalyst was unstable to the reaction conditions. However, the NH insertion product **359** was obtained in excellent yield (80 %) if the hydrazone **296B** was stirred for 4 h in a suspension of NCS and K₂CO₃ in ethanol, and a solution of rhodium acetate and aniline in ethanol was added after complete consumption of **296B** as judged by TLC (Scheme 108, conditions ii)).



Scheme 108: One pot NH insertion from hydrazone **296B**: Reagents and conditions:

- i) Hydrazone **296B** (1 eq.), NCS (1.3 eq.), K_2CO_3 (1 eq.), $\text{Rh}_2(\text{OAc})_4$ (20 mol %), aniline (3 eq.), EtOH, r.t., 16 h. ii) Hydrazone **296B** (1 eq.), NCS (1.3 eq.), K_2CO_3 (1 eq.), EtOH, r.t., 4 h, *then* $\text{Rh}_2(\text{OAc})_4$ (10 mol %), aniline (3 eq.), r.t., 16 h.

This one pot NH insertion methodology was explored further, to ascertain if other hydrazones and anilines would be tolerated under the reaction conditions (Scheme 109). The electron rich **324B** reacted with *m*-methoxyaniline to give the corresponding amine **350** in near quantitative yield, and the electron rich, sterically encumbered **332B** reacted with *p*-toluidine to give **351** in excellent yield. The reaction also proceeded smoothly with electron deficient anilines, such as *p*-chloroaniline, which reacted smoothly with the electron rich hydrazone **330B** to give the desired secondary amine **3652** in excellent yield (84 %). Similarly, combination of **296B** with benzocaine furnished the amine **353** in good yield (76 %).



Scheme 109: One pot synthesis of amines **350-353**. Reagents and conditions: i) Hydrazone (1 eq.), NCS (1.3 eq.), K₂CO₃ (1 eq.), EtOH, r.t., 4 h; ii) Rh₂(OAc)₄ (10 mol %), aniline (3 eq.), r.t., 16 h.

In summary, an efficient and user-friendly route for the dehydrogenation of hydrazones has been developed. The diazo compounds were obtained in high yields, producing succinimide, potassium chloride and carbon dioxide as the only by-products. Whilst contemporaneous generation and consumption of the diazo compound was not successful under the conditions employed, addition of anilines and rhodium acetate to the crude reaction mixture afforded the corresponding NH insertion products in excellent yields.

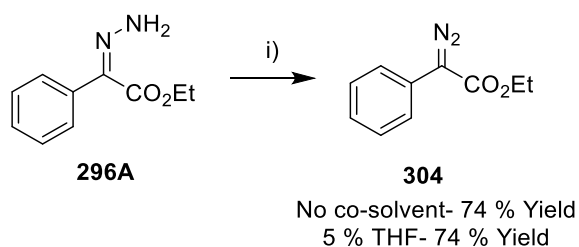
3.3 Biocatalytic Oxidation of Hydrazones

Whilst a new method for hydrazone oxidation had been developed in the preceding chapter, initial results indicated that successful *in situ* reactions relied upon prior formation of the diazo compound, as attempts to continuously generate and consume the diazo compound had been unsuccessful. In addition, the NCS mediated oxidation of hydrazones was an unsuitable method for biocompatible *in situ* diazo generation as the reaction performed poorly in water.

Thus, the focus was shifted towards a new catalytic system. Recent advances in the area of biocatalysed reactions involving diazo compounds suggest that possessing a catalytic system that could generate the diazo compound under biocompatible conditions would be highly desirable. To date, a method for generating diazo compounds *in situ* that is likely biocompatible has not been developed, thus hindering the employment of these biocatalysed reactions on scale due to the hazards associated with the large scale use of diazo compounds. In order for an *in situ* method to be viable, the reaction would have to proceed at ambient conditions (or with mild heating), and the reagents used to effect diazo formation would have to be compatible with all of the reagents, especially the protein used to transform the diazo compound.

A copper/TEMPO catalytic system is a popular and mild catalytic system for alcohol oxidation. Given the mild conditions that these systems can operate under, it was envisaged that such a catalytic system could be applied for hydrazone oxidation. However, it is possible that copper would react with the diazo compound generated, as copper has been demonstrated to show activity for diazo decomposition.

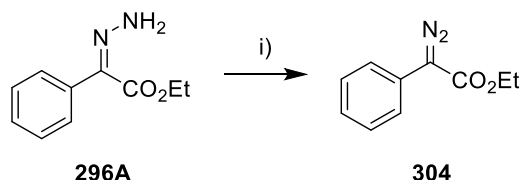
Laccase/TEMPO systems have also been reported to oxidize alcohols under very mild conditions, which are biocompatible. Although the presence of copper in the laccase active site could potentially catalyse unwanted side reactions, it was envisaged that the catalytic activity of these copper centres with respect to diazo decomposition would be low or nil due to encapsulation within the laccase active site. Thus, commercially available laccase from *Trametes versicolor* in conjunction with TEMPO as a mediator was selected as the catalytic system for initial screening for hydrazone oxidation. For ease of reaction monitoring by TLC and NMR, the (Z) isomer **296A** was used exclusively as a substrate as a large amount of this hydrazone was available from earlier studies (section 3.2). Pleasingly, stirring a solution of laccase from *Trametes versicolor* and TEMPO in water gave the diazo compound **304** in 74 % yield and conversion from the (Z) hydrazone **296A** after 4 h (Scheme 110). The presence of a co-solvent (THF) was not found to increase conversion or yield.



Scheme 110: Laccase/TEMPO catalysed hydrazone oxidation. Reagents and conditions: i) Hydrazone **296A** (1 eq.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), water/co-solvent (95:5), r.t., 3 h.

Encouraged by this preliminary result, the biocatalytic oxidation of **296A** was examined further (Scheme 111, Table 12). While performing the reaction over a longer time frame did not lead to quantitative conversion to **304** (entry 1), increasing the temperature to 30 °C gave the desired diazo compound **304** in quantitative yield after 4 h (entry 2). Performing the reaction under an atmosphere of oxygen led to a

discernible increase in conversion (84 %) compared to stirring under air (74 %, entry 3), but the hazards of using oxygen gas did not justify the modest increase in conversion. Further reactions were heated at 30 °C to obtain satisfactory conversion of the hydrazone **296A**.



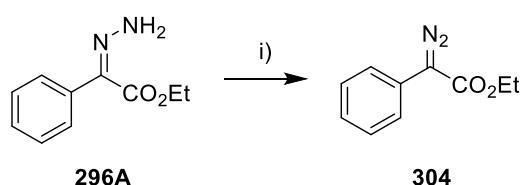
Scheme 111: Optimisation of laccase/TEMPO hydrazone oxidation. Reagents and conditions: i) Hydrazone **296A** (1 eq.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), water/ THF (95:5), r.t, 3.5 h.

Entry	Deviation from standard conditions ^a	Conversion (%)
1	16 h	80
2	O ₂ atmosphere	84
3	30 °C	Quant.

Table 12: Optimisation of laccase/TEMPO hydrazone oxidation.^a Standard conditions: Hydrazone **296A** (1 eq.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), water/ THF (95:5), r.t, 3.5 h.

With conversion of **296A** to **304** at a satisfactory level, the reaction solvent was next examined. If the catalytic system was to be used with an additional protein catalyst, it is likely that the optimal reaction medium for the subsequent reaction would be aqueous buffer, and not pH 7 deionised water. To investigate the pH range of the laccase/ TEMPO system, the reaction was performed in a variety of buffers (Scheme 112, Table 13). The reaction proceeded very slowly in pH 4 citrate and acetate buffer (entries 1 and 2), although performing the reaction in pH 5 acetate buffer gave

quantitative conversion to the desired diazo compound **304** after 6 h (entry 3). Pleasingly, in pH 8 phosphate buffer, the reaction proceeded to 93 % conversion after 2 h and quantitative yield after 4 h (entries 4 and 5). Whilst the drop in activity observed at pH levels lower than 5 was undesirable, the excellent performance of the reaction at higher pH was encouraging, as many biocatalysed reactions of diazo compounds are performed in basic buffer. Ultimately, phosphate buffer was selected for further studies due to the high conversion of **296A** and the stability and activity of p450 proteins in this solvent.^{44b}



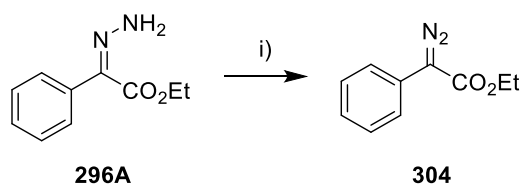
Scheme 112: Solvent optimisation of laccase/ TEMPO catalysed hydrazone oxidation. Reagents and conditions: i) Hydrazone (1 eq.), Laccase (700 U mmol⁻¹), TEMPO (20 mol %), solvent/THF (95:5), 30 °C, 3.5 h.

Entry	Buffer	pH	Time (h)	Conversion (%)
1	Citrate	4.0	7	50
2	Acetate	4.0	6	53
3	Acetate	5.0	6	100
4	Phosphate	8.0	1	78
5	Phosphate	8.0	2	93
6	Phosphate	8.0	4	100

Table 13: Solvent screens for laccase/ TEMPO oxidation of hydrazones

Further optimisation was undertaken to investigate the use of co-solvents (Scheme 113, Table 14). Whilst THF had been used so far, ideally the methodology would allow

for the use of co-solvents that had greater biocompatibility. It was found that the reaction conditions tolerated a range of co-solvents (entries 1-3), in particular *n*-butanol, which was selected for further use due to its good sustainability profile and biocompatibility. The catalytic loading of TEMPO could be lowered to 10 mol % without a loss of conversion (entry 4), although a drop from quantitative to 69 % conversion was observed at 5 mol % loading of TEMPO (entry 5). A concurrent drop in laccase loading to 105 U mmol⁻¹ also furnished the diazo compound **304** in quantitative yield (entry 6). Thus, a laccase loading of 350 U mmol⁻¹ and a TEMPO loading of 10 mol % was used in future reactions.

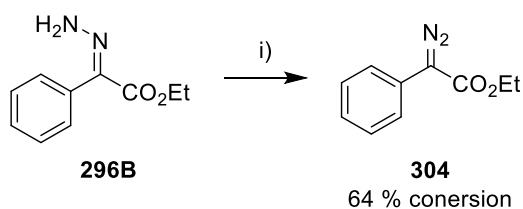


Scheme 113: Further optimisation of laccase/TEMPO catalysed hydrazone oxidation. Reagents and conditions: i) Hydrazone **296A** (1 equiv.), TEMPO, laccase, phosphate buffer/co-solvent (95:5), 30 °C, r.t.

Entry	Co-solvent	TEMPO (mol %)	Laccase (U mmol ⁻¹)	Conversion
1	THF	20	700	Quant.
2	Propanol	20	700	Quant.
3	ⁿ BuOH	20	700	Quant.
4	ⁿ BuOH	10	700	Quant.
5	ⁿ BuOH	5	700	69
6	ⁿ BuOH	20	350	Quant.
7	ⁿ BuOH	20	175	67

Table 14: Optimisation of laccase/ TEMPO hydrazone oxidation

With optimised conditions for hydrazone oxidation in hand, the substrate scope of this transformation was explored. The oxidation of the (*E*) isomer of the model substrate was first examined (Scheme 114). Interestingly, under the reaction conditions, **296B** reacted slowly, giving a 64 % conversion to **304** after 4 h, compared to quantitative conversion when the (*Z*) isomer **296A** was used. This slower reaction can be attributed to the very poor solubility of **296B** in the aqueous reaction medium. During the course of the reaction, **296B** remained as a precipitate on the surface of the solvent.

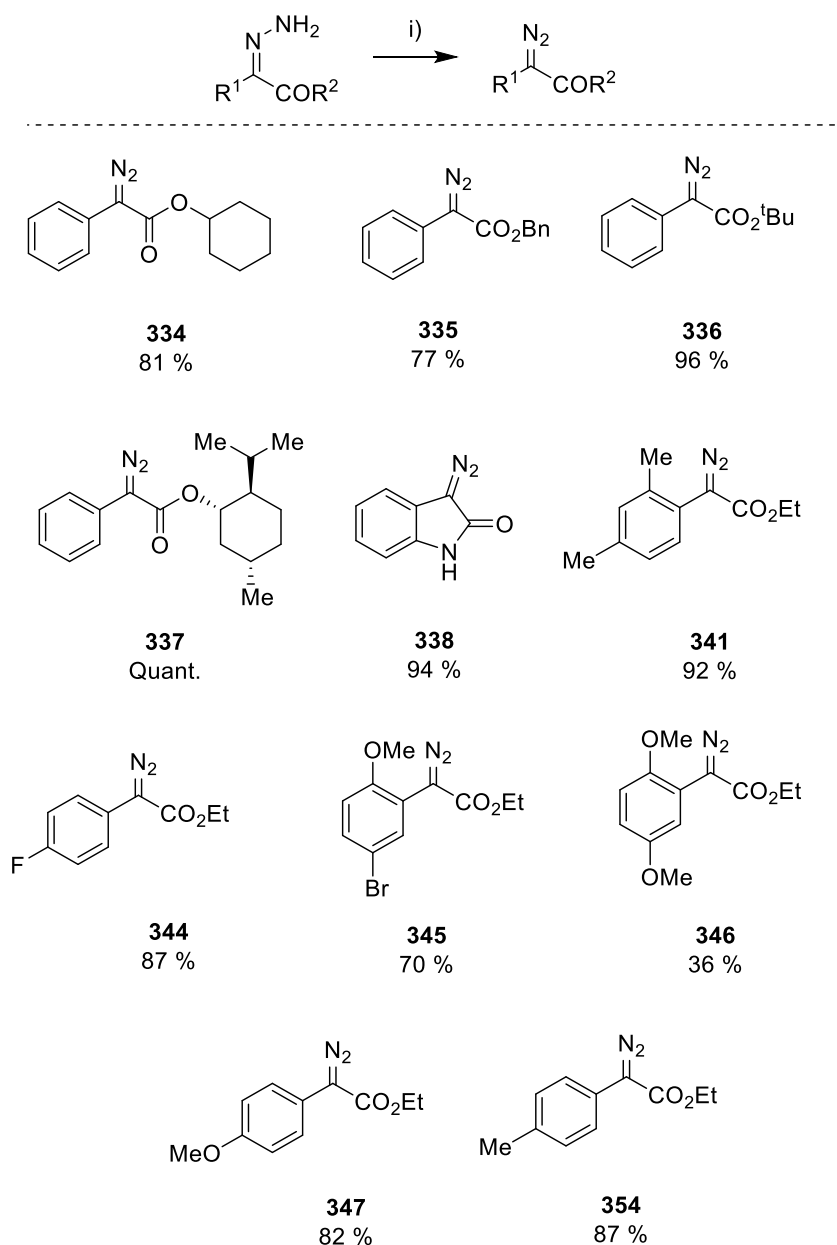


Scheme 114: Oxidation of (*E*) hydrazone **296B**. Reagents and conditions: i)

Hydrazone **296B** (1 eq.), laccase (350 U mmol⁻¹), TEMPO (10 mol %), pH 8.0

phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4h.

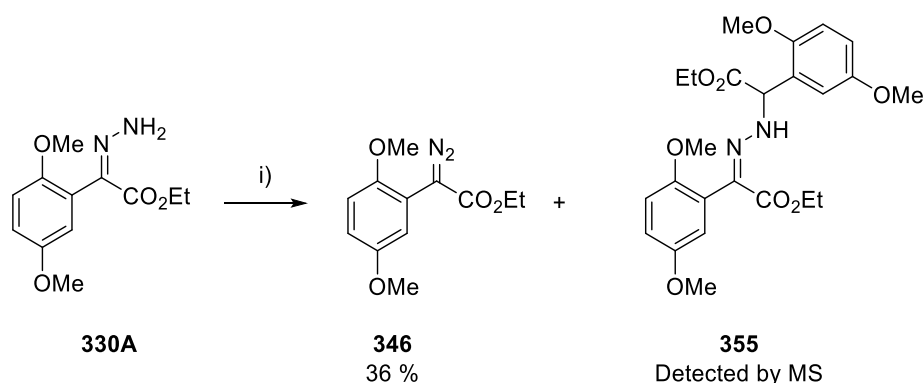
Next, a range of (*Z*)-hydrazones derived from the keto esters prepared in section 3.2 were tested for diazo formation in the laccase/ TEMPO system. (Scheme 115). Electron donating and electron withdrawing aryl substituents were generally tolerated well, and gave the corresponding diazo compounds **344**, **345** and **347** in good yields (87 %, 70 % and 82 % respectively). Esters of differing substitutions were also tolerated under the reactions conditions and gave the corresponding diazo compound in good to excellent yields.



Scheme 115: Substrate scope for hydrazone oxidations. Reagents and conditions: i) Hydrazone (1 eq.), laccase (350 U mmol⁻¹), TEMPO (10 mol %), pH 8.0 phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4h.

When the hydrazone **330A** was used as a substrate, the highly electron rich **346** was obtained in a much lower yield of 36 % from a complex mixture of products (Scheme 116). The azine product **355** was detected by mass spectrometry, although we were unable to isolate this product. An explanation for this lower yield could be the very

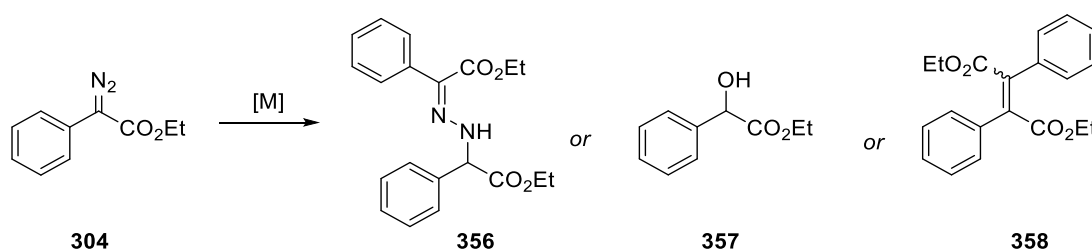
electron rich aryl substituent of **330B** increasing the nucleophilicity of the diazo α -carbon, making it more susceptible to decomposition *via* a diazonium intermediate.



Scheme 116: Use of hydrazone **330A** as a substrate. Reagents and conditions: i) Hydrazone (1 eq.), laccase (350 U mmol⁻¹), TEMPO (10 mol %), pH 8.0 phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4h.

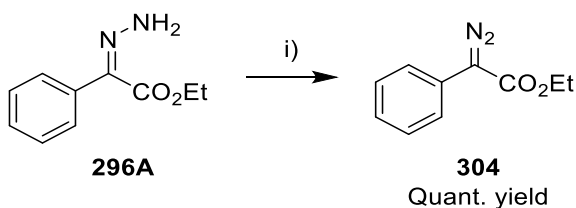
Given the mostly high yields of diazo compounds obtained thus far, and their stability to the reaction conditions, we set out to evaluate whether encapsulation within the laccase active site was preventing the copper centres of the laccase from reacting with the diazo compounds.

Should encapsulation within the laccase active site be preventing reaction of copper with the diazo compound, it would be expected that using a copper salt/ TEMPO system for hydrazone oxidation would give either an OH or NH insertion product **356** or **357**, or carbene dimer **358** as the copper salt would decompose the diazo product **304** (Scheme 117).



Scheme 117: Potential reaction products upon decomposition of **304** under the reaction conditions

To test this, a copper salt that had been reported to show catalytic activity for diazo decomposition was used as the copper source, instead of laccase. Copper sulfate was selected as the copper source, as it was been reported by Gillingham and co-workers to show good activity for catalysing reactions of similar diazo compounds in buffer.⁴¹ When CuSO₄ was used the diazo compound **304** was obtained in quantitative yield. Products associated with side reactions such as carbenoid dimers **358**, azines **356** or OH insertion products **357** were not observed, even at high catalytic copper loadings (Scheme 118). This indicated that the origin of the stability of the diazo compound to the laccase/TEMPO catalytic system was not due to a shielding of the copper centre by the active site of the enzyme.



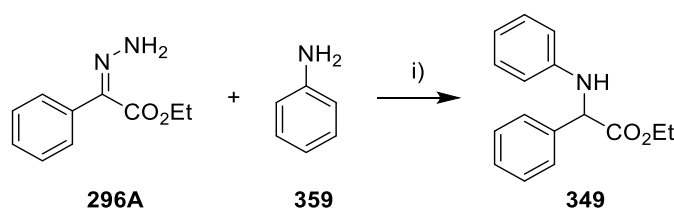
Scheme 118: CuSO₄/ TEMPO catalysed hydrazone oxidation. Reagents and conditions: i) Hydrazone **296A** (1 eq.), CuSO₄ (20 mol %), TEMPO (20 mol %), phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4 h.

It has been reported that diazo compounds can be highly stable in the presence of copper in the absence of a reaction partner, and will not react.³⁴ To test if this was the origin of the stability observed, the reaction was performed in the presence of suitable reaction partner, aniline (Scheme 119).¹¹⁸ The amount of both TEMPO and laccase were increased to allow for easier observation of any reaction with aniline, and also to ensure that hydrazone oxidation would be rapid, to prevent undesired azine formation. After stirring the reactants for 16 h, the corresponding the NH insertion product **349** was obtained in 23 % yield. Whilst this yield is low, it is worth noting that the copper loading during the reaction, when accounting for the four copper centres within the active sites, is 2 mol % which is significantly lower than optimal copper loadings reported for NH insertion.^{40d} This indicates that whilst the catalytic system gives poor yields of **349** at the amounts used during the reaction, the laccase is capable of catalysing undesired reactivity with the diazo compound in the presence of an amine reaction partner.

Scheme 119: One pot hydrazone oxidation / NH insertion. Reagents and conditions:

Next, performing the reaction in the presence of aniline **359** and an additional catalyst was explored, to ascertain if an increased yield of amine would be obtained under these conditions, and whether the reaction would tolerate an additional catalyst (Scheme

120, Table 15). When Fe(TPP)Cl was used as a catalyst, the desired NH insertion product **349** was isolated in very poor yield (10 %, entry 1), even with a large amount of catalyst (20 mol %). This corresponds with lack of literature uses of Fe(TPP)Cl with respect to reaction of aniline **359** with **304**. On the other hand, Rh₂(OAc)₄ and CuSO₄ gave the desired NH insertion product in excellent yields (86 % and 84 % respectively).



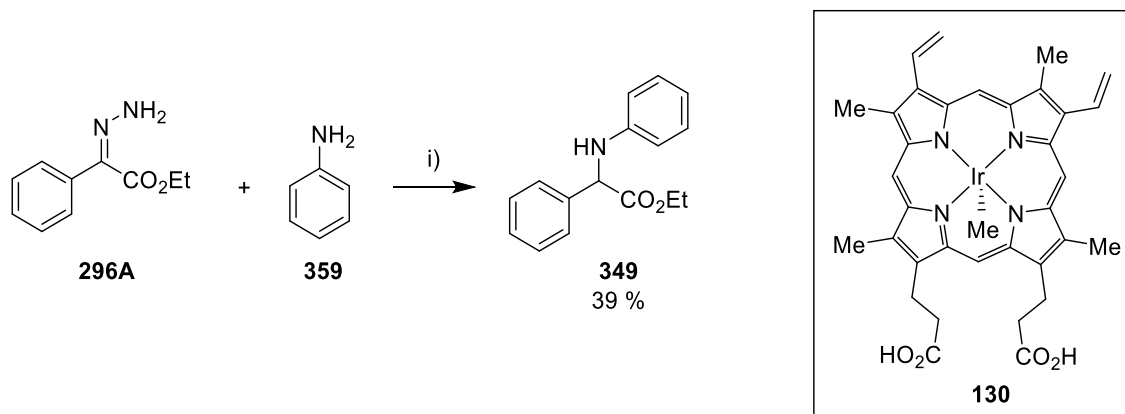
Scheme 120: Optimisation of one pot hydrazone oxidation/ NH insertion. Reagents and conditions: i) Hydrazone **296A** (1 equiv.), aniline **359** (3 equiv.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), catalyst (20 mol %), phosphate buffer/ⁿBuOH (95:5), 30 °C, 16 h.

Entry	Catalyst	Yield (%)
1	Fe(TPP)Cl	10
2	Rh ₂ (OAc) ₄	86
3	CuSO ₄	84

Table 15: Optimisation of one pot hydrazone oxidation/ NH insertion.

The iridium methyl protoporphyrin **130** was also investigated for catalytic activity, as it possible to incorporate this catalyst in the active site of an apoprotein (Scheme 121).⁵¹ Apoproteins containing this catalyst have been reported by Hartwig and co-workers to show good activity for catalysing enantioselective reactions of diazo compounds, and a quantity of this catalyst was on hand from concurrent work being

performed within the group. Under the reaction conditions, the iridium catalyst **130** showed moderate catalytic activity at 1 mol %, giving the amine product in 39 % yield. This lower yield compared to CuSO₄ and Rh₂(OAc)₄ is attributable to the poorer aqueous solubility of the catalyst **130**.



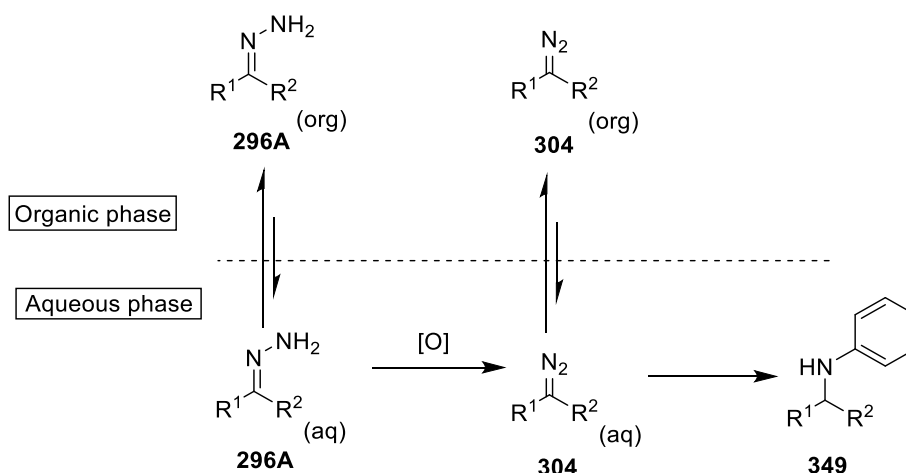
Scheme 121: Iridium catalysed NH insertion. Reagents and conditions: i) Hydrazone **296A** (1 eq.), aniline **359** (3 eq.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), **130** (1 mol %), pH 8.0 phosphate buffer/ ⁿBuOH (95:5), 30 °C, 16 h.

The high yield of the NH insertion product **349** that could be obtained under the reaction conditions was surprising, as it would be expected the hydrazone **296A** could compete significantly with the aniline during any step involving nucleophilic attack, given its high nucleophilicity due to the alpha effect.⁷³

Shaw and co-workers reported high yields of OH insertion products under conditions in which diazo compounds were continuously generated because the starting hydrazone was partially protonated, preventing reaction with the diazo compound.⁷⁵ However, given the basic conditions of the reaction mixture, this rationale is unlikely to explain the high yields obtained and absence of azine product. However, given the exceptionally poor solubility of the hydrazone **296A** under the reaction conditions, the reaction forms a biphasic mixture, with the hydrazone **296A** existing as an oil on top

of the aqueous reaction mixture. One possibility is that hydrazone **296A** is released slowly into the reaction mixture where it undergoes rapid dehydrogenation to the diazo compound **304** (Scheme 122). Thus, the concentration of hydrazone **296A** in the reaction mixture relative to the aniline **358** is very low, and the aniline will outcompete the hydrazone **296A** for NH insertion. The aqueous solubility of **296A** at 30 °C was measured by ^1H NMR. After stirring **296A** at 30 °C in D_2O the dissolution of **296A** in D_2O was measured to be 4 mg mL^{-1} . As the reaction conditions are 42 mg of **296A** in 3.5 mL of buffer and 200 μL of n-butanol, the aqueous concentration of **296A** is very low.

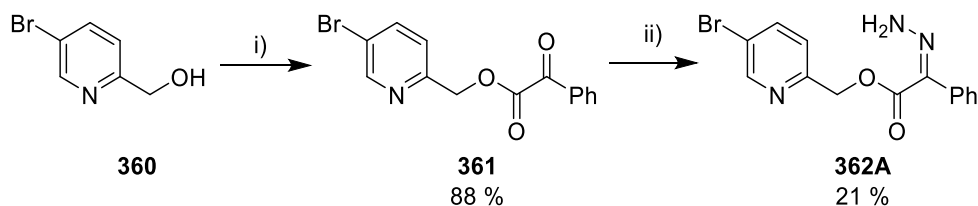
Postulated biphasic model:



Scheme 122: Postulated biphasic model

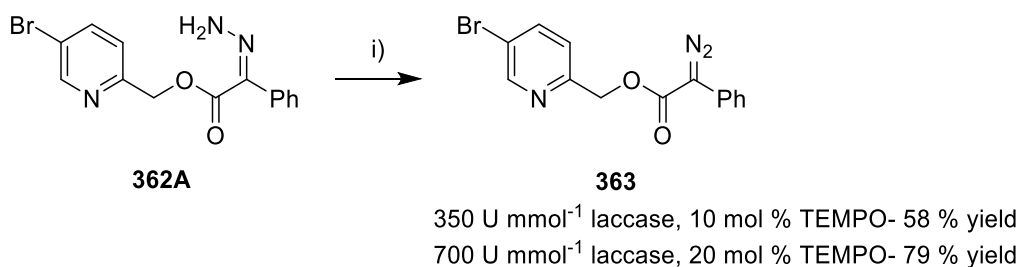
Finally, the possibility of using the laccase/ TEMPO system to generate diazo compounds for use in other reactions was investigated. Given the work already undertaken in Section 3.1 on the generation of pyridinium ylides from diazo compounds, the generation of pyridinium ylides was investigated next. The hydrazone **362A** selected as a substrate, as the corresponding diazo compound could react intramolecularly, increasing the probability of successful ylide generation. Maleimide

was selected as the dipolarophile, as reaction of the ylide with maleimide has been successful previously within the group.³⁰ Reaction of the alcohol **360** with phenylglyoxylic acid under the standard reaction conditions used in Section 3.2 gave the keto ester **361** in good yield, which in turn furnished the hydrazone **362A** as a single isomer in moderate yield (Scheme 123).



Scheme 123: Synthesis of hydrazone **362A**. Reagents and conditions: i) Alcohol **360** (1 eq.), oxalyl chloride (1 eq.), phenylglyoxylic acid (1 eq.), DMF (cat.), CH₂Cl₂, 0 °C to r.t., 16 h. ii) Keto-ester **361** (1 eq.), benzoic acid (1 eq.), N₂H₄·H₂O (1 eq.), THF, r.t., 24 h.

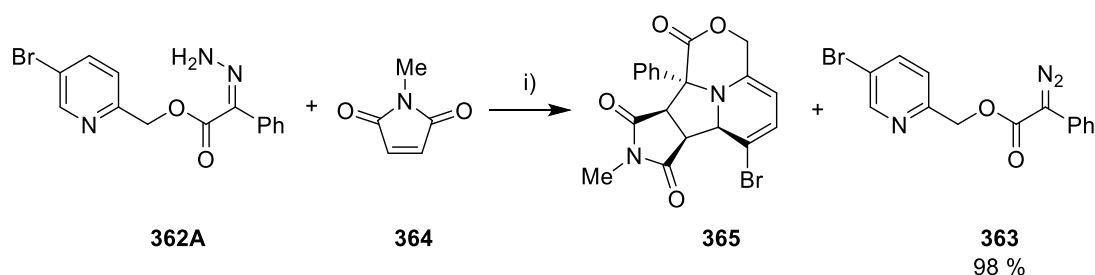
With the required starting material in hand, the hydrazone **362A** was subjected to the laccase/TEMPO reaction conditions. The initial isolated yield of **363** was modest (58 %) although this could be improved to 79 % if the amount of laccase and TEMPO being used were increased (Scheme 124). This reduced conversion of **363** compared to other substrates could be due to the pyridine binding to the copper within the laccase active site, hindering the reaction.



Scheme 124: Oxidation of hydrazone **362A**. Reagents and conditions: i) Hydrazone

362A (1 eq.), laccase, TEMPO, phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4 h.

With the knowledge that the oxidation of **362A** to **363** would proceed under the reaction conditions, subsequent ylide generation from the diazo compound was investigated. Reaction with *N*-methyl maleimide was attempted, as reaction with this dipolarophile had been reported to be high yielding by Dowden and co-workers.³⁰ Using Cu(MeCN)₄PF₆ as a catalyst, with the same reaction stoichiometry as reported by Dowden co-workers, formation of the desired cycloadduct **365** was not observed and the diazo compound **363** was isolated from the reaction mixture in near quantitative yield (Scheme 125). The increased conversion of **362A** under the reaction conditions is most likely due to the increased amount of copper present during the reaction being able to compensate for the pyridine binding.



Scheme 125: Attempted *in situ* generation of pyridinium ylide. Reagents and conditions: i) *N*-Methylmaleimide **364** (1 eq.), hydrazone **363A** (1 eq.), laccase (700 U mmol⁻¹), TEMPO (20 mol %), Cu(MeCN)₄PF₆ (10 mol %), phosphate buffer/ ⁿBuOH (95:5) 30 °C, 8 h.

The isolation of the diazo compound **363** was surprising, as $\text{Cu}(\text{MeCN})_4\text{PF}_6$ was reported to show good catalytic activity with respect to decomposition of the diazo compound **363**, albeit it in toluene or dichloromethane.³⁰ In the future, the feasibility of performing this reaction under the aqueous reaction conditions will require further investigation, as the catalytic activity of copper can be hindered under lewis basic conditions.³⁴

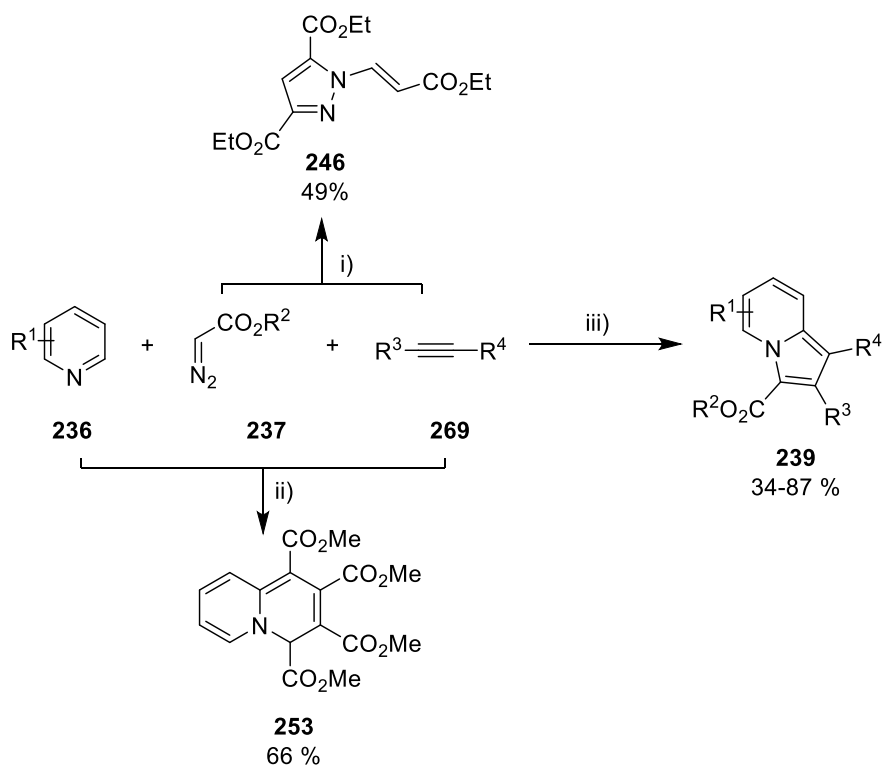
To summarise, a new, biocatalytic methodology for hydrazone oxidation has been developed that uses atmospheric oxygen as the terminal oxidant. The resulting diazo compounds are stable to the reaction conditions in the absence of an amine reaction partner. Whilst catalytic activity of the laccase drops significantly at pH 4, the reaction proceeds smoothly at pH 5 to 8, with optimal results being obtained in pH 8 phosphate buffer. The substrate scope of this reaction has been investigated, and whilst highly electron rich substrates were tolerated poorly, a range of diazo compounds were obtained in good yield.

The presence of an additional catalyst, such as rhodium acetate or copper sulfate, and aniline allows for *in situ* reaction of the diazo compound *via* NH insertion under aqueous conditions. To our knowledge, this represents the first catalytic example of *in situ* diazo generation and reaction that does not require controlled addition of reagents, or prior formation of the diazo compound.

Moreover, the catalytic activity of $\text{Ir}(\text{PIX})\text{Me}$ **130** under the reaction conditions bodes well for the prospect of reacting the diazo compounds generated *in situ* with a metalloprotein. Whilst the yield of amine obtained with this catalyst was modest (39 %), the poor aqueous solubility, we believe that incorporating the catalyst into an apoprotein will increase this, as the aqueous solubility of the catalyst is very low.

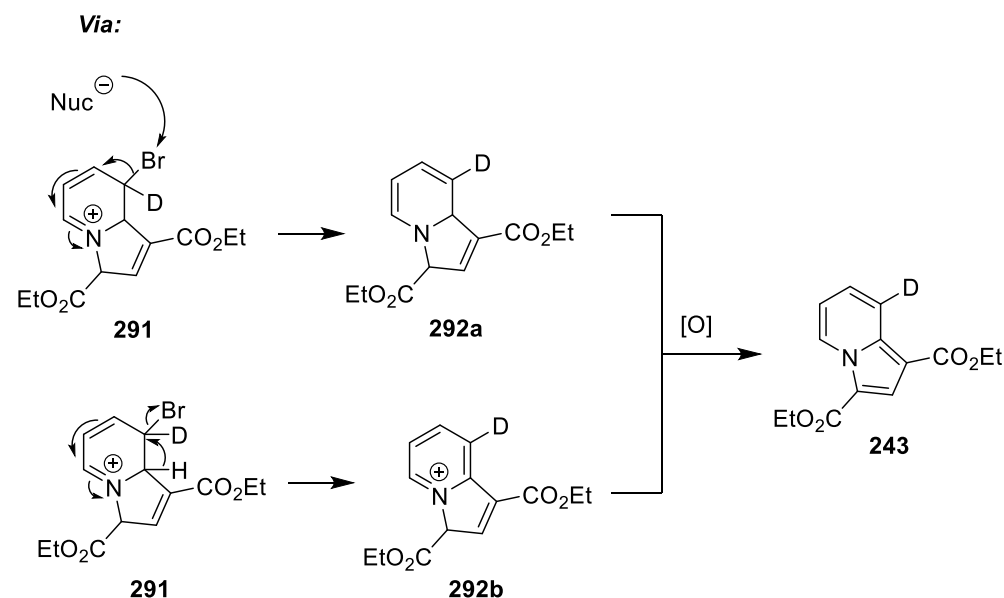
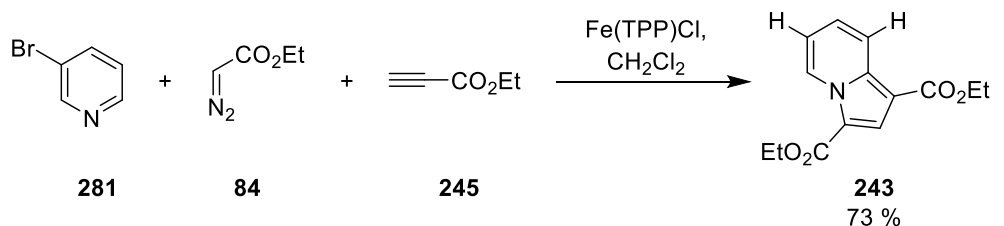
3.4 Summary

A novel, iron catalysed, three component route to indolizines has been developed in this project. The key pyridinium ylide intermediate is generated catalytically from a pyridine **236** and diazo compound **237**, and then reacts with an electron deficient alkyne **269** to give an indolizine **239** product after oxidation (Scheme 124). Marshalling the high reactivity of the alkyne was key for successful reaction, as the electrophilic character of **269** allowed for other, undesired reactions to occur, namely pyrazole **246** and quinolizine **253** formation. These products have been isolated and characterised, and their formation minimized *via* optimisation of the reaction conditions (Scheme 126). Unfortunately, electron rich alkynes were found to be poor dipolarophiles, and did not react under the conditions developed.



Scheme 126: Different reaction pathways of the electrophilic alkyne. Reagents and conditions: i) CH_2Cl_2 , r.t., 16 h; ii) $Fe(TPP)Cl$, CH_2Cl_2 , r.t., 16 h; iii) $Fe(TPP)Cl$, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$, 16 h.

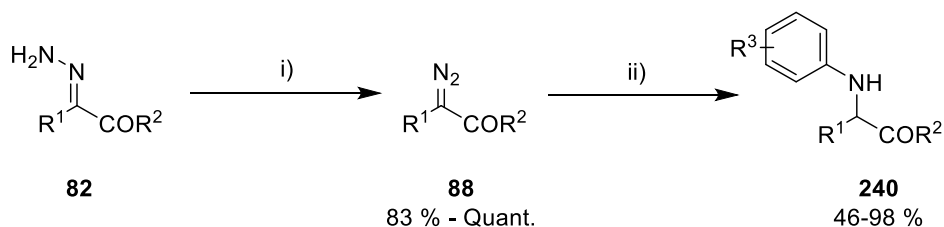
During the course of substrate scope investigation, an unexpected side reaction was observed. The major product isolated when 3-bromopyridine **281** was used as a reaction partner was the dehalogenated indolizine **243** (Scheme 127). From the results of deuterium labelling experiments, it is postulated that debromination occurs *via* elimination of HBr or bromonium from the initial protonated cycloadduct **291**.



Scheme 127: Observed debromination of cycloadducts.

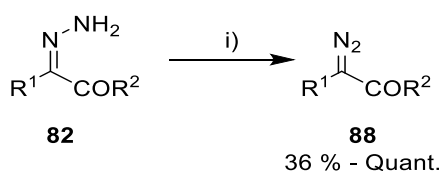
Subsequently, new methods for the synthesis and *in situ* generation of diazo compounds *via* hydrazone oxidation were investigated. Initially, *N*-chlorosuccinimide and a sulfimide catalyst were found to effectively oxidize hydrazones **82**, however control experiments demonstrated that oxidation would occur in the absence of a catalyst (Scheme 128). A range of diazo compounds **88** were synthesised from the corresponding hydrazones **82** using this method. Addition of an aniline and rhodium

catalyst after complete oxidation of the hydrazone **82** was found to give access to NH insertion products **240** in excellent yields. Unfortunately, pre-formation of the diazo compound **88** was required for successful reaction and adding the aniline and catalyst at the beginning of the reaction did not give the desired amine **240**.



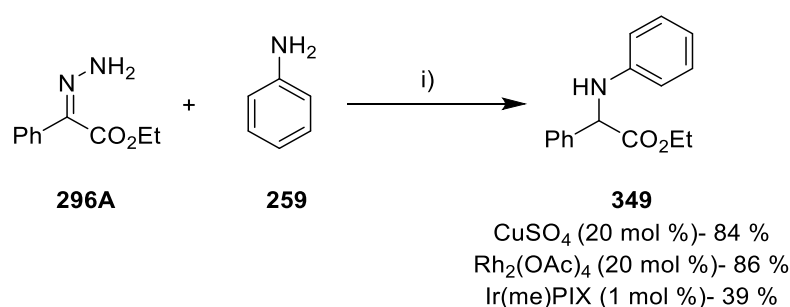
Scheme 128: NCS mediated oxidation of hydrazones **82**. Reagents and conditions: i) Hydrazone **82** (1 eq.), NCS (1.3 eq.), K₂CO₃ (1 eq.), EtOH, 4 h; ii) Aniline (3 eq.), Rh₂(OAc)₄ (10 mol %), 16 h.

In addition, a biocatalytic system for hydrazone oxidation has been developed. The use of a laccase protein with TEMPO as a mediator and air as the terminal oxidant was found to give diazo compounds **88** in high yield from the corresponding hydrazones **82** (Scheme 129). The catalytic system operates under conditions that are likely to be biocompatible, under aqueous conditions at 30 °C. The reaction operated optimally in pH 8 phosphate buffer, although the reaction could proceed at lower pH over longer timeframes. In addition, the use of organic co-solvents was found to have a negligible effect on yield, and were tolerated well by the catalytic system.



Scheme 129: Biocatalysed oxidation of hydrazones **82**. Reagents and conditions: i) Laccase/ TEMPO, pH 8.0 phosphate buffer/ ⁿBuOH (95:5), 30 °C, 4 h.

Finally, subsequent reaction *via* NH insertion of the diazo compound under the laccase/ TEMPO system was achieved (Scheme 130). It was found that addition of either a copper or rhodium catalyst and aniline at the start of the reaction gave the NH insertion product **349** in excellent yield. In addition, Ir(PIX)Me was found to show catalytic activity for the NH insertion reaction, raising the prospect of using the methodology in conjunction with an artificial metalloprotein.

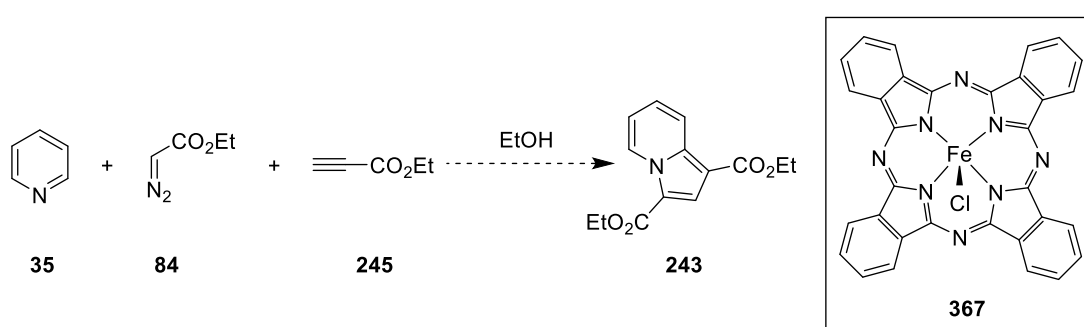


Scheme 130: Use of laccase/ TEMPO catalytic system as an *in situ* methodology.

Reagents and conditions: i) Hydrazone **296A**, aniline **259** (3 eq.), Laccase/ TEMPO, pH 8.0 phosphate buffer/ $n\text{BuOH}$ (95:5), 30 °C, 16 h.

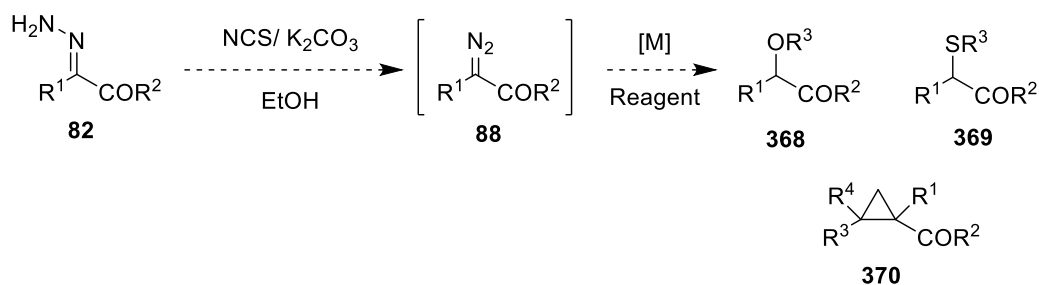
3.5 Future Work

Increasing the sustainability profile of our method for indolizine synthesis is highly desirable, and the use of more environmentally benign solvents should be investigated (Scheme 131). The performance of the reaction in ethanol and water (8:2) indicates that solvents with better sustainability profiles could be tolerated. In addition, the excellent catalytic activity of iron phthalocyanine **367** merits further investigation of this catalyst, given its low monetary cost.



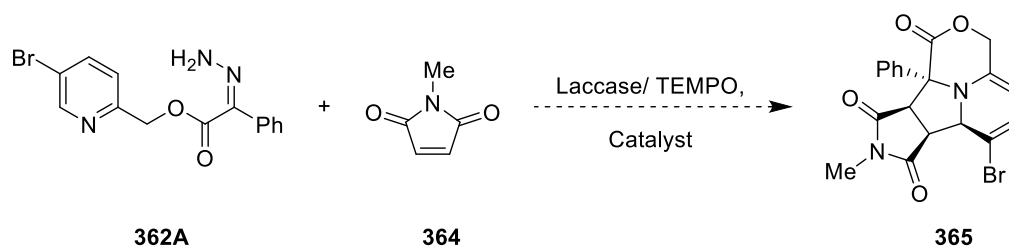
Scheme 131: Proposed FePcCl catalysed synthesis of **243** in EtOH

Expanding the scope of subsequent transformations that are tolerated with the *in situ* diazo methods would greatly increase the versatility of the reaction, and therefore merits further study (Scheme 132). Whilst reaction of the *in situ* generated diazo compound with anilines has been shown to proceed smoothly, reaction with alcohols thiols and alkenes has not been investigated. This would allow a large range of synthetically desirable products to be accessed without user handling of the diazo compound.



Scheme 132: Expansion of substrate scope for *in situ* diazo generation.

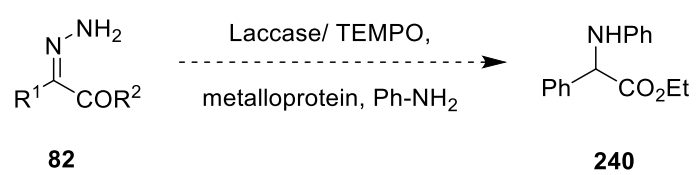
The generation of pyridinium ylides from the diazo compounds generated from laccase/TEMPO catalysed hydrazone oxidation should be investigated further. (Scheme 133). When $\text{Cu}(\text{MeCN})_4\text{PF}_6$ was used as a catalyst for the ylide formation, ylide formation was not observed, thus investigation of other catalysts may be necessary.



Scheme 133: Generation of pyridinium ylide from laccase/TEMPO catalysed oxidation of **362A**.

One of the long term aims to of this project is to possess a biocompatible method for the *in situ* generation of a diazo compound. The catalytic activity of $\text{Ir}(\text{Me})\text{PIX}$ with respect to NH insertion the laccase/TEMPO reaction conditions bodes well for the prospect of using this as an *in situ* method for diazo generation in conjunction with an artificial metalloprotein. Thus, the next stage of this project would be to attempt this reaction using a metalloprotein with an iridium co-factor, given the activity that the free heme showed for NH insertion (Scheme 134).

Future work:



Scheme 134: Biocatalyzed oxidation of hydrazones as an *in situ* method for diazo generation.

4 Experimental

4.1 General Experimental

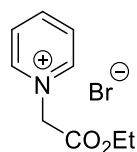
All reagents and solvents were from commercial suppliers and used as supplied. Reactions were performed in open round bottomed flasks. Room temperature reflects ambient laboratory conditions ranging from 18-22 °C. Analytical thin layer chromatography was carried out on aluminium backed plates coated with Merck Kieselgel 60 GF254 and visualized under UV light at 254 and/or 360 nm. Flash chromatography was carried out using Davisil silica 60Å at medium pressure, with the eluent specified. Melting points were measured on a RiechertKofler and are uncorrected. Infrared spectra were recorded using Nicolet Avatar 320 FTR-IR spectrometer equipped with an OMNI-Sampler™ smart accessory for HATR (Germanium crystal, DTGS detector) over the range 4000-600 cm⁻¹. NMR spectra were recorded at 298 K using a Bruker AV(III)400, AV400, DPX400 (400 MHz ¹H frequency, 100 MHz ¹³C frequency) or DPX300 instrument (300 MHz ¹H frequency, 75 MHz ¹³C frequency). Chemical shifts are quoted in parts per million (ppm), referenced to residual chloroform (7.26 ppm for ¹H NMR, 77.16 ppm for ¹³C NMR), dimethylsulfoxide (2.50 ppm for ¹H NMR, 39.51 ppm for ¹³C NMR), as internal standards and coupling constants, *J*, are quoted in Hz. Multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; app, apparent; br, broad or combinations thereof. In the ¹³C NMR spectra, signals corresponding to C, CH, CH₂ and CH₃ were assigned from DEPT experiments. High resolution mass spectrometry experiments were recorded on a Bruker MicroTOF (ESI) mass spectrometer. The diazo compounds **338**, **341** and **343** were synthesised from hydrazones provided by Dr Simon Niccole.^{55a} Ir(Me)PIX **130** was synthesised by Mujtaba ‘Nafees’ Mohammed according to literature procedures.⁵¹

4.2 Determination of Laccase Activity

Laccase activity was determined to be 2.34 U mg^{-1} by oxidation of 2,2'-azinobis-(3-ethyl benzthiazoline-6-sulphonate) (ABTS), according to the method of Wolfenden and Wilson.¹¹⁹ The reaction mixture consisting of 0.5 mM ABTS, 0.2 M sodium acetate buffer and a suitable amount of enzyme were mixed at 30 °C and pH 4.0. Oxidation of ABTS was accompanied by an increase in absorbance at 420 nm, and the rate thus determined using an extinction co-efficient of $36000 \text{ M}^{-1} \text{ cm}^{-1}$. One unit of enzyme activity was defined as the amount of enzyme which catalysed the oxidation of 1 μmol of ABTS per min at 37°C.

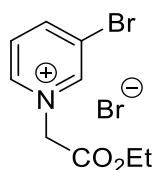
4.2 Compound Characterisation

1-(2-Ethoxy-2-oxoethyl)pyridin-1-ium bromide 242



To a solution of pyridine (2 mL, 25 mmol) in ethyl acetate (10 mL) was added bromo ethyl acetate (2.75 mL, 25 mmol) at room temperature under argon. The resulting solution was stirred at room temperature for 16 h. The reaction mixture was filtered, and the precipitate was washed with ether (2×15 mL) to give *the title compound 19* as a white solid (4.1 g, 67 %): Found $M\text{-Br}^+$ 166.0873. $\text{C}_9\text{H}_{12}\text{NO}_2^+$ requires 166.0863; ^1H (400 MHz, DMSO-d_6): 9.31-9.20 (2H, m, *ArH*), 8.77 (1H, tt, J 7.8, 1.4, *ArH*), 8.35-8.17 (2H, m, *ArH*), 5.91 (2H, s, CH_2), 4.20 (2H, q, J 7.1, OCH_2), 1.21 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, DMSO-d_6) δ 166.8 (COO), 147.3 (CH) 146.7 (CH), 128.3 (CH), 62.8 (CH_2), 60.7 (CH_2), 14.5 (CH_3). The data were in agreement with literature values.²⁹

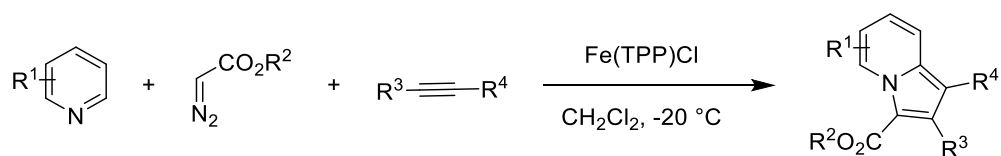
1-(2-Ethoxy-2-oxoethyl)pyridin-1-ium bromide 284



A solution of 3-bromo pyridine (0.78 mL, 8.1 mmol) and ethyl bromoacetate (2 mL, 8.1 mmol) in ethyl acetate (10 mL) was stirred under argon for 16 h. The reaction mixture was filtered, and the precipitate washed with ether (2×20 mL) to give the title compound **188** as a white solid (1.3 g, 31 %): Found: $M\text{-Br}^+$, 243.9975. $\text{C}_9\text{H}_{11}\text{NO}_2^+$ requires 243.9968; IR_{solid} ($\nu_{\text{max}}/\text{cm}^{-1}$): 3080, 1565, 1452, 1179, 1030; ^1H (400 MHz, DMSO-d_6): δ 9.61 (1H, s, *ArH*), 9.20 (1H, d, J 6.1, *ArH*), 9.03 (1H, ddd,

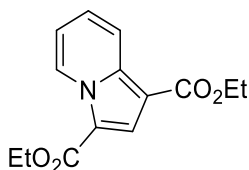
J 8.5, 2.0, 1.1 Ar*H*), 8.26 (1*H*, dd, *J* 8.4, 6.1, Ar*H*), 5.75 (2*H*, s, CH₂), 4.24 (2*H*, q, *J* 7.1, CH₂), 1.26 (3*H*, t, *J* 7.1, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 166.5 (C), 149.7 (CH), 147.8 (CH), 145.9 (CH), 129.1 (CH), 122.0 (C), 62.9 (CH₂), 60.7 (CH₂), 14.4 (CH₃). The data were in agreement with literature values.²⁹

4.3 General Procedure For Preparation of Indolizines



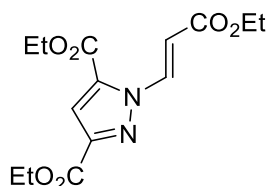
A solution of the appropriate pyridine (0.58 mmol, 1 equiv.) and ethyl diazoacetate (1.5 equiv.) in dichloromethane was added in one portion to a stirring solution of Fe(TPP)Cl (1 mol %) and alkyne (1 equiv.) in dichloromethane (4 mL) at -20 °C and the reaction was stirred for 16 h whilst gradually warming to room temperature. Silica gel (0.5 g) was added to the reaction, the mixture evaporated to dryness and then loaded onto a silica gel column with subsequent elution using the specified solvents affording the desired indolizine.

Diethyl indolizine-1,3-dicarboxylate 243



A solution of ethyl diazoacetate (180 μ L, 1.68 mmol), in dichloromethane was added in one portion to a stirring solution of pyridine (90 μ L, 1.12 mmol), Fe(TPP)Cl (8 mg, 1 mol %) and ethyl propiolate (120 μ L, 1.12 mmol) in CH₂Cl₂ (8 mL) and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then concentrated onto silica (0.5 g) and evaporated to dryness prior to loading onto a silica gel column and eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). Off-white solid (261 mg, 89 %). m.p.109-110°C (lit. 128-130°C), (Found: MNa⁺, 284.0892. C₁₅H₁₅NaNO₄ requires 284.0899); IR (ν_{max} /cm⁻¹): 2977, 1673, 1528, 1435, 1374, 1194, 1022; ¹H (400 MHz; CDCl₃): δ 9.49 (1H, dt, *J* 7.0, 1.2, Ar*H*), 8.31 (1H, dt, *J* 9.0, 1.2, Ar*H*), 7.96 (1H, s, Ar*H*), 7.26 (1H, ddd, *J* 9.0, 7.0, 1.2, Ar*H*), 6.95 (1H, app.td, *J* 7.0, 1.2, Ar*H*), 4.37 (4H, app. q, *J* 7.1, CH₂), 1.41 (3H, *J* 7.1, CH₃), 1.40 (3H, *J* 7.1, CH₃); ¹³C (100 MHz, CDCl₃): δ 164.2 (C), 161.1 (C), 139.0 (C), 127.8 (CH), 125.4 (CH), 124.1 (CH), 119.5 (CH), 114.6 (C), 114.3 (CH), 105.1 (C), 60.2 (CH₂), 59.9 (CH₂), 14.5 (CH₃), 14.4 (CH₃). The data were in agreement with the literature.¹²⁰

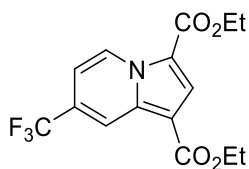
Diethyl (E)-1-(3-ethoxy-3-oxoprop-1-en-1-yl)-1H-pyrazole-3,5-dicarboxylate 246



A solution of ethyl diazoacetate (91 μ L, 0.84 mmol), pyridine (60 μ L, 0.77 mmol) and ethyl propiolate (60 μ L, 0.58 mmol) in CH₂Cl₂ (4 mL) was stirred at room temperature

for 16 h. Silica gel was added to the reaction, and the mixture evaporated to dryness. The reaction mixture was then concentrated onto silica (0.5 g) and evaporated to dryness prior to loading onto a silica gel column and eluting with ethyl acetate and petroleum ether (2:8). The title compound **246** was collected as a pale-yellow oil (44 mg, 49 %): (Found MH^+ 311.1233. $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_6$ requires 311.1238); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2983, 1721, 1650, 1539, 1445, 1385, 1289, 1160; ^1H (400 MHz, CDCl_3): δ 8.94 (1H, d, J 13.9, CH), 7.43 (1H, s, CH), 6.83 (1H, d, J 13.9, CH), 4.43 (2H, q, J 7.1, CH_2), 4.41 (2H, q, J 7.1, CH_2), 4.25 (2H, q, J 7.1, CH_2), 1.41 (3H, t, J 7.1, CH_3), 1.40 (3H, t, J 7.1, CH_3), 1.32 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 165.8 (C), 160.9 (C), 158.4 (C), 145.2 (C), 137.4 (CH), 134.7 (C), 115.7 (CH), 112.2 (CH), 62.2 (CH_2), 61.8 (CH_2), 60.8 (CH_2), 14.2 (2 x CH_3), 14.1 (CH_3).

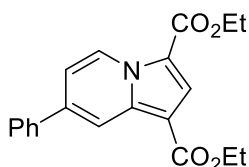
Diethyl 7-(trifluoromethyl)indolizine-1,3-dicarboxylate 249



Following general procedure for preparation of indolizines, using 4-trifluoromethylpyridine (1.12 mmol) and ethyl propiolate (1.12 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:99 to 5:95 gradient). Buff solid (210 mg, 57 %): m.p. 86-89 °C; (Found: MH^+ , 330.0992, $\text{C}_{15}\text{H}_{15}\text{F}_3\text{NO}_4^+$ requires 330.0953); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3148, 2983, 1684, 1531, 1473, 1351, 1205, 1068, 1037; ^1H (400 MHz, CDCl_3): δ 9.61 (1H, d, J 7.4, ArH) 8.63 (1H, dt, J 1.9, 1.0, ArH), 8.02 (1H, s, ArH), 7.04 (1H, dd, J 7.4, 2.0, ArH), 4.40 (2H, J 7.1, CH_2), 4.40 (2H, J 7.1, CH_2), 1.43 (3H, J 7.1, CH_3), 1.42 (3H, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 163.7 (C), 161.0 (C), 136.8 (C) 128.5 (CH), 126.9 (q, J C-F 34, CCF_3) 124.7 (CH), 123.3 (q, J^{CF}

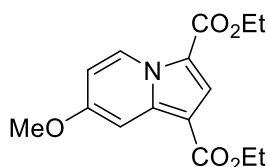
270, CF₃), 117.4 (q, J^{CF} 5.0, CCF₃), 109.9 (C), 110.0 (q, J^{CF} 3.0, CCF₃), 108.0 (C), 60.8 (CH₂), 60.4 (CH₂), 14.44 (CH₂), 14.39 (CH₃).

Diethyl 7-phenylindolizine-1,3-dicarboxylate 250



Following general procedure for preparation of indolizines, with 4-phenylpyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). Pale yellow solid (116 mg, 59 %): m.p. 115-118 °C; (Found: MH⁺, 338.1393. C₂₀H₂₀NO₄⁺ requires 338.1387); IR (ν_{max} /cm⁻¹): 2982, 1672, 1527, 1462, 1350, 1262, 1157, 1059; ¹H (300 MHz; CDCl₃): δ 9.51 (1H, dd, J 7.4, 1.0, ArH), 8.57 (1H, dd, J 2.1, 1.0, ArH), 7.99 (1H, s, ArH), 7.77-7.68 (2H, m, ArH), 7.54-7.38 (3H, m, ArH), 7.26 (1H, dd, J 7.4, 2.1, ArH), 4.40 (2H, q, J 7.1, CH₂), 4.39 (2H, q, J 7.1, CH₂), 1.43 (3H, t, J 7.1, CH₃), 1.42 (3H, t, J 7.1, CH₃); ¹³C (75 MHz, CDCl₃) δ 164.3 (C), 161.2 (C), 139.5 (C), 138.3 (C), 138.2 (C), 129.2 (CH), 128.7 (CH), 128.0 (CH), 127.0 (CH), 124.7 (CH), 116.4 (CH), 114.6 (C), 113.8 (CH), 105.6 (C), 60.4 (CH₂), 60.0 (CH₂), 14.7 (CH₃), 14.6 (CH₃).

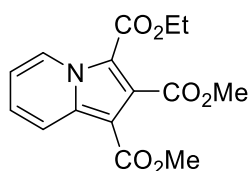
Diethyl 7-methoxyindolizine-1,3-dicarboxylate 251



Following general procedure for preparation of indolizines, with 4-methoxypyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and

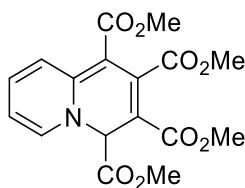
petroleum ether (40-60 °C) (1:9). Yellow solid (130 mg, 77 %): m.p. 87-90 °C; (Found: MNa^+ 314.1012. $\text{C}_{15}\text{H}_{17}\text{NNaO}_5$ requires 314.1004); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3140, 2974, 1670, 1641, 1460, 1343, 1239, 1103; ^1H (400 MHz; CDCl_3): δ 9.32 (1H, dd, J 7.7, 0.7, ArH), 7.86 (1H, s, ArH), 7.64 (1H, dd, J 2.8, 0.7 ArH), 6.63 (1H, dd, J 7.7, 2.8, ArH), 4.49 (2H, q, J 7.2, CH_2), 4.40 (2H, q, J 7.2, CH_2), 3.91 (3H, s, OCH_3), 1.44 (3H, t, J 7.2, CH_3), 1.43 (3H, t, J 7.2, CH_3); ^{13}C (100 MHz; CDCl_3): δ 164.6 (C), 161.2 (C), 158.4 (C), 141.6 (C), 129.1 (CH), 124.4 (CH), 113.7 (C), 108.6 (CH), 103.2 (C), 97.3 (CH), 60.2 (CH_2), 59.7 (CH_2), 55.6 (CH_3), 14.7 (CH_3), 14.6 (CH_3).

3-Ethyl 1,2-dimethyl indolizine-1,2,3-tricarboxylate 252



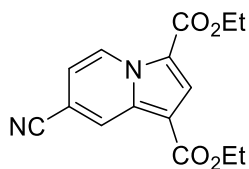
Following general procedure for preparation of indolizines, using pyridine (0.58 mmol) and dimethyl acetylenedicarboxylate (0.58 mmol), eluting with ethyl acetate: petroleum ether (40-60 °C) (2:8). Recrystallisation from hexane: ethyl acetate (9:1) gave a colourless solid (90 mg, 53 %): m.p. 105-106 °C (lit. 112-114 °C); (Found MH^+ 306.0977 $\text{C}_{15}\text{H}_{16}\text{NO}_6$ requires 306.0972); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2994, 2942, 1738, 1689, 1535, 1454, 1421, 1380, 1271, 1250, 1084; ^1H (300 MHz, CDCl_3): δ 9.55 (1H, dt, J 7.1, 1.1, ArH), 8.35 (1H, dt, J 9.0, 1.3, ArH), 7.39 (1H, ddd, J 9.0, 6.8, 1.1, ArH), 7.06 (1H, td, J 7.1, 1.3, ArH), 4.38 (2H, q, J 7.1, CH_2), 4.01 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 1.39 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 166.3 (C), 163.4 (C), 160.1 (C), 137.8 (C), 130.5 (C), 128.0 (CH), 126.7 (CH), 119.9 (CH), 115.4 (CH), 112.0 (C), 103.0 (C), 60.9 (CH_2), 52.8 (OCH_3), 51.7 (OCH_3), 14.1 (CH_3). The data were in agreement with the literature.³¹

Tetramethyl 4*H*-quinolizine-1,2,3,4-tetracarboxylate 253



Ethyl diazoacetate (129 μL (1.22 mmol)) was added to a solution of DMAD (100 μL , 0.81 mmol), Fe(TPP)Cl (5 mg, 7.45 μmol) and pyridine (200 μL , 2.5 mmol) in CH_2Cl_2 (4 mL) then stirred at room temperature for 16 h. The reaction mixture was dry loaded onto silica and purified by column chromatography, eluting with ethyl acetate and light petroleum (3:7). The title compound **253** was collected as a red oil (99 mg, 66 %): (Found MH^+ 364.1032. $\text{C}_{17}\text{H}_{18}\text{NO}_8$ requires 364.1027) IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2954, 1738, 1672, 1571, 1482, 1392, 1290, 1062; ^1H (400 MHz, CDCl_3): δ 8.65 (1H, dd, J 7.4, 1.4, CH), 7.62-7.47 (2H, m, 2 $\times$ CH), 6.85 (1H, td, J 6.8, 1.4, CH), 6.05 (1H, s, CH), 3.93 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.72 (3H, s, OCH_3); ^{13}C (100 MHz, CDCl_3): δ 169.3 (C), 168.8 (C), 165.4 (C), 164.0 (C), 149.5 (C), 143.3 (C), 138.2 (CH), 136.8 (CH), 124.0 (CH), 115.7 (CH), 95.5 (C), 92.8 (C), 64.0 (CH), 53.6 (OCH_3), 52.6 (OCH_3), 52.3 (OCH_3), 51.3 (OCH_3). The data were in agreement with the literature.¹²¹

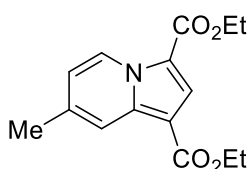
Diethyl 7-cyanoindolizine-1,3-dicarboxylate 255



Following general procedure for preparation of indolizines, with 4-cyanopyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 $^{\circ}\text{C}$) (5:95- 1:9 gradient). Off white solid (75 mg, 45 %): m.p.

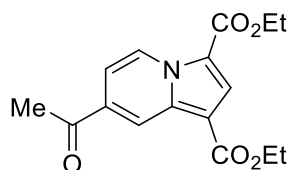
112-116 °C; (Found: MH^+ , 287.1038, $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_4^+$ requires 287.1032); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3130, 2981, 2894, 2227, 1689, 1529, 1349, 1234, 1142, 1102, 1054, 1036; ^1H (400 MHz; CDCl_3): δ 9.53 (1H, dd, J 7.3, 1.0, ArH), 8.70 (1H, dd, J 1.9, 1.0, ArH), 8.02 (1H, s, ArH), 7.05 (1H, dd, J 7.3, 1.9, ArH), 4.40 (4H, app. q, J 7.1, CH_2), 1.42 (3H, t, J 7.1 CH_3), 1.41 (3H, t, J 7.1 CH_3); ^{13}C (100 MHz, CDCl_3) δ 163.2 (C), 160.7 (C), 136.1 (C), 128.2 (CH), 125.8 (CH), 124.9 (CH), 117.5 (C), 117.2 (C), 114.0 (CH), 108.9 (C), 107.9 (C), 61.1 (CH_2), 60.7 (CH_2), 14.6 (CH_3), 14.5 (CH_3).

Diethyl 7-methylindolizine-1,3-dicarboxylate 256



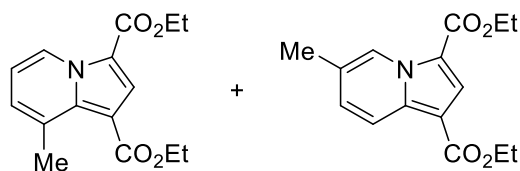
Following general procedure for preparation of indolizines, with 4-methylpyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). Off white solid (118 mg, 74 %). m.p. 83-85 °C; (Found: MNa^+ , 298.1040, $\text{C}_{15}\text{H}_{17}\text{NNaO}_4^+$ requires 298.1055); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3103, 1678, 1237, 1168, 1032; ^1H (300 MHz; CDCl_3): δ 9.37 (1H, dd, J 7.2, 0.9, ArH), 8.13-8.09 (1H, m, ArH), 7.91 (1H, s, ArH), 6.78 (1H, dd, J 7.2, 1.9, ArH), 4.36 (2H, q, J 7.1 CH_2), 4.35 (2H, q, J 7.1 CH_2), 2.44 (3H, s, CH_3), 1.40 (3H, t, J 7.1, CH_3), 1.39 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 164.5 (C), 161.4 (C), 139.7 (C), 137.1 (C), 127.4 (CH), 124.5 (CH), 118.4 (CH), 117.0 (CH), 114.3 (C), 104.0 (C), 60.3 (CH_2), 59.9 (CH_2), 21.6 (CH_3), 14.7 (CH_3), 14.6 (CH_3).

Diethyl 7-acetylindolizine-1,3-dicarboxylate 257



Following general procedure for preparation of indolizines, with 4-acetylpyridine (120 μ L, 1.12 mmol) and ethyl propiolate (120 μ L, 1.12 mmol) eluting with ethyl acetate and petroleum ether (40-60 $^{\circ}$ C) (EtOAc 2:8 petroleum ether to EtOAc 3:7 petroleum ether). Pale yellow solid (263 mg, 75 %): m.p.: 117- 119 $^{\circ}$ C; IR (ν_{max} /cm $^{-1}$): 2982, 1680, 1516, 1431, 1374, 1253, 1138, 1070, 1034; (Found: MH $^{+}$ 304.1187. C $_{16}$ H $_{18}$ NO $_5^{+}$ requires 304.1185); ^1H (300 MHz, CDCl $_3$): δ 9.34 (1H, dd, J 7.4, 1.0, ArH), 8.73 (1H, dd J 2.0, 1.0, ArH), 7.85 (1H, s, ArH), 7.39 (1H, dd, J 7.4, 2.0, ArH), 4.39 (4H, app. q, J 7.1, 2 x CH $_2$), 2.66 (3H, s, CH $_3$), 1.43 (3H, t, J 7.1, CH $_3$), 1.41 (3H, t, J 7.1, CH $_3$); ^{13}C (75 MHz, CDCl $_3$): δ 195.9 (COCH $_3$), 163.8 (C), 160.8 (C), 137.3 (C), 132.6 (C), 127.4 (CH), 124.5 (CH), 121.3 (CH), 116.6 (C), 111.6 (CH), 108.8 (C), 60.8 (CH $_2$), 60.4 (CH $_2$), 26.1 (CH $_3$), 14.5 (OCH $_3$), 14.4 (OCH $_3$).

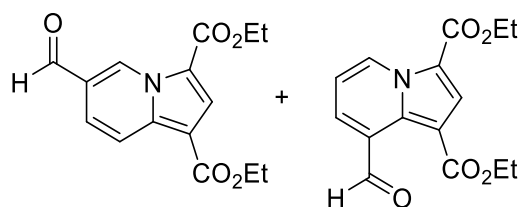
Diethyl 8-methylindolizine-1,3-dicarboxylate 259A and diethyl 6-methylindolizine-1,3-dicarboxylate 259B



Following general procedure for preparation of indolizines, with 3-methylpyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), gradient elution with ethyl acetate and petroleum ether (40-60 $^{\circ}$ C) (from 5-95 to 1:9 gradient). Yellow solid (110 mg, 69 %, 5:3 ratio of regioisomers 14a to 14b): 4 (Found: MNa $^{+}$, 298.1062. C $_{15}$ H $_{17}$ NNaO $_4^{+}$

requires 298.1055); IR ($\nu_{\max}/\text{cm}^{-1}$): 2985, 1681, 1525, 1476, 1218, 1188, 1044; ^1H (300 MHz, CDCl_3): 9.46 (1H, d, J 7.0, ArH), 9.34 (1H, app. q, J 1.2, ArH*), 8.20 (1H, d, J 9.0, ArH*), 7.98 (1H, s, ArH), 7.91 (1H, s, ArH*), 7.14 (1H, dd, J 9.0, 1.6, ArH*), 7.02 (1H, dt, J 7.0, 1.1 ArH), 6.85 (1H, t, J 7.0, ArH), 4.43-4.30 (8H, m, $4 \times \text{CH}_2$ and CH_2^*), 2.78 (3H, s, CH_3^*), 2.38 (3H, s, CH_3), 1.402 (3H, t, J 7.1, CH_3), 1.397 (3H, t, J 7.1, CH_3) (12H, m, $4 \times \text{CH}_3$ and CH_3^*); ^{13}C NMR (75 MHz, CDCl_3): δ 164.4 (C), 164.2 (C), 161.4 (C), 161.2 (C), 138.2 (C), 137.9 (C), 130.1 (C), 128.7 (CH), 126.8 (CH), 126.1 (CH), 126.0 (CH), 125.8 (CH), 124.3 (C), 124.0 (CH), 118.9 (CH), 114.2 (C), 114.1 (CH), 114.0 (C), 107.2 (C), 105.0 (C), 60.31 (CH_2), 60.28 (CH_2), 59.97 (CH_2), 59.93 (CH_2), 22.1 (CH_3), 18.6 (CH_3), 14.73 (CH_3), 14.68 (CH_3), 14.6 (CH_3).

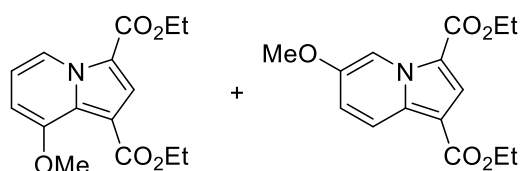
Diethyl 8-formylindolizine-1,3-dicarboxylate 260A and diethyl 6-formylindolizine-1,3-dicarboxylate 260B



Following general procedure for preparation of indolizines, with 3-formylpyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). Pale yellow solid (83 mg, 51 %, 1:1 mixture of regioisomers): (Found: MNa^+ , 312.0853. $\text{C}_{15}\text{H}_{15}\text{NO}_5\text{Na}^+$ requires 312.0848); IR ($\nu_{\max}/\text{cm}^{-1}$): 2934, 1682, 1632, 1528, 1350, 1167, 1136, 1036; ^1H (300 MHz, CDCl_3): δ 10.89 (1H, s, $\text{CH}=\text{O}$), 9.98 (1H, m, ArH), 9.95 (1H, s, $\text{CH}=\text{O}$), 9.74 (1H, dd, J 7.1, 1.2, ArH), 8.33 (1H, dd, J 9.4, 0.9, ArH), 8.05 (1H, s, ArH), 8.02 (1H, s, ArH), 7.86 (1H, dd, J 7.1, 1.2, ArH), 7.69 (1H, dd, J 9.4, 1.5, ArH), 7.07 (1H, app. t, J 7.1, ArH), 4.47- 4.33 (8H, m, $4 \times \text{CH}_2$) 1.49 - 1.36 (12H, m, $6 \times \text{CH}_3$); ^{13}C (75 MHz, CDCl_3): δ

190.9 (CH=O), 188.8 (CH=O), 164.2 (C), 163.6 (C), 161.0 (C), 160.9 (C), 139.6 (C), 136.1 (CH), 135.9 (C), 131.8 (CH), 128.6 (C), 127.6 (CH), 126.2 (CH), 125.9 (CH), 125.4 (C), 121.4 (CH), 120.1 (CH), 116.4 (C), 115.6 (C), 113.8 (CH), 107.4 (C), 106.6 (C), 70.0 (CH₂), 60.81 (CH₂), 60.77 (CH₂), 60.5 (CH₂), 14.6 (CH₃), 14.51 (CH₃), 14.48 (2 x CH₃).

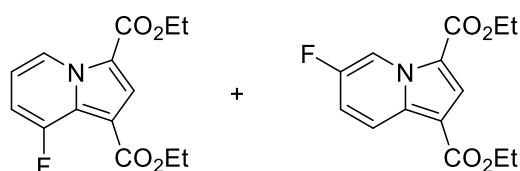
Diethyl 8-methoxyindolizine-1,3-dicarboxylate 261A and diethyl 6-methoxyindolizine-1,3-dicarboxylate 261B



Following general procedure for preparation of indolizines, with 3-methoxypyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (10:90 to 25:75 gradient). **Diethyl 8-methoxyindolizine-1,3-dicarboxylate 261A** as a yellow oil (115 mg, 68 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2940, 1722, 1524, 1467, 1315, 1222, 1177, 1037; (Found MH^+ 292.1190, $\text{C}_{15}\text{H}_{18}\text{NO}_5^+$ requires 292.1185); ^1H (300 MHz, CDCl_3): 9.15 (1H, dd, J 7.0, 1.0, ArH), 7.87 (1H, s, ArH), 6.80 (1H, app. dd, J 7.8, 7.0, ArH), 6.53 (1H, d, J 7.8, 1.0, ArH), 4.33 (2H, q, J 7.1, CH₂), 4.32 (2H, q, J 7.1, CH₂), 3.97 (1H, s, OCH₃), 1.36 (6H, app. t, J 7.1, 2 x CH₃); ^{13}C (75 MHz, CDCl_3) δ 163.8 (C), 161.1 (C), 151.8 (C), 130.8 (C), 124.9 (CH), 120.8 (CH), 114.9 (C), 114.0 (CH), 107.4 (C), 102.8 (CH), 60.31 (CH₂), 60.28 (CH₂), 55.9 (OCH₃), 14.51 (CH₃), 14.49 (CH₃). Further elution gave **Diethyl 6-methoxyindolizine-1,3-dicarboxylate 261B** as a yellow oil (6 mg, 4 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2940, 1693, 1548, 1466, 1372, 1316, 1238, 1130, 1083; (Found MH^+ 292.1189, $\text{C}_{15}\text{H}_{18}\text{NO}_5^+$ requires 292.1185); ^1H (300 MHz, CDCl_3): δ 9.19 (1H, dd, J 2.3, 0.8,

ArH), 8.21 (1H, dd, *J* 9.7, 0.8, ArH), 7.90 (1H, s, ArH), 7.12 (1H, dd, *J* 9.7, 2.3, ArH), 4.38 (2H, q, *J* 7.1, CH₂), 4.37 (4H, q, *J* 7.1, CH₂), 3.88 (3H, s, OCH₃), 1.410 (3H, t, *J* 7.1, CH₃), 1.408 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃): δ 164.5 (C), 161.4 (C), 139.7 (C), 137.1 (C), 127.4 (CH), 124.5 (CH), 118.4 (CH), 117.0 (CH), 114.3 (C), 104.0 (C), 60.3 (CH₂), 59.9 (CH₂), 21.6 (OCH₃), 14.7 (CH₃), 14.6 (CH₃).

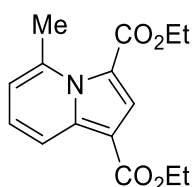
Diethyl 8-fluoroindolizine-1,3-dicarboxylate 262A and diethyl 6-fluoroindolizine-1,3-dicarboxylate 262B



Following general procedure for preparation of indolizines, with 3-fluoropyridine (0.58 mmol) and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). **Diethyl 8- fluoroindolizine-1,3-dicarboxylate 262A** as a yellow solid (54 mg, 33 %): m.p: 44 °C; IR (ν_{max}/cm⁻¹): 2966, 1726, 1692, 1526, 1484, 1417, 1358, 1225, 1133, 1066; (Found MH⁺ 280.0991. C₁₄H₁₅FNO₄⁺ requires 280.0985); ¹H (300 MHz, CDCl₃): 9.40 (1H, dd, *J* 6.9, 1.0, ArH), 7.99 (1H, s, ArH), 7.10-6.84 (2H, m, ArH), 4.41 (2H, q, *J* 7.1 Hz, CH₂), 4.37 (2H, q, *J* 7.1, CH₂), 1.41 (3H, t, *J* 7.1, CH₃), 1.39 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃): ¹³C (75 MHz, CDCl₃) δ 162.9 (C), 160.9 (C), 153.9 (d, *J*^{CF} 254, CF), 129.2 (d, *J*^{CF} 33.8, C), 125.34 (CH), 124.2 (d, *J*^{CF} 5.3, CH), 116.0 (C), 113.4 (d, *J*^{CF} 7.5, CH), 109.2 (d, *J*^{CF} 20.3, CH) 106.5 (d, *J*^{CF} 6.0, C), 60.6 (CH₂), 60.4 (CH₂), 14.40 (CH₃), 14.37 (CH₃). Further elution gave **diethyl 6-fluoroindolizine-1,3-dicarboxylate 262B** as a yellow solid (30 mg, 19 %): M.p: 96-98 °C; IR (ν_{max}/cm⁻¹): 3095, 2930, 1638, 1527, 1428, 1324, 1129, 1116, 1036; (Found MH⁺ 280.0986. C₁₄H₁₅NO₄F⁺ requires 280.0985); ¹H (300 MHz,

CDCl₃): 9.50 (1H, ddd, *J* 5.5, 2.3, 0.8, Ar*H*), 8.31 (1H, ddd, *J* 9.8, 5.8, 0.8, Ar*H*), 7.97 (1H, s, Ar*H*), 7.21 (1H, ddd, *J* 9.8, 7.5, 2.3, Ar*H*), 4.39 (2H, q, *J* 7.1, CH₂), 4.37 (2H, q, *J* 7.1, CH₂), 1.411 (3H, t, *J* 7.1, CH₃), 1.408 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃) δ 164.0 (C), 161.2 (C), 154.5 (d, *J*^{CF} 238, CF) 136.4 (C), 124.3 (d, *J*^{CF} 3.0, CH), 124.0 (C), 120.2 (d, *J*^{CF} 8.3, CH), 117.3 (d, *J*^{CF} 24.4, CH), 115.2 (d, *J*^{CF} 42.7, CH), 106.2 (C), 60.6 (CH₂), 60.2 (CH₂), 14.7 (CH₃), 14.6 (CH₃).

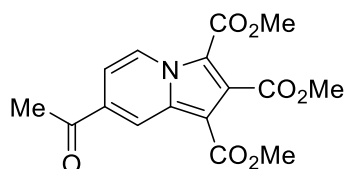
Diethyl 5-methylindolizine-1,3-dicarboxylate 268



A solution of 2-picoline (280 μL, 2.80 mmol, 5 equiv.) and ethyl diazoacetate (91 μL, 0.84 mmol, 1.5 equiv.) in dichloromethane was added in one portion to a stirring solution of Fe(TPP)Cl (1 mol %) and ethyl propiolate (60 μL, 0.56 mmol) in dichloromethane at -20 °C and the reaction was stirred for 16 h whilst gradually warming to room temperature. Silica gel was added to the reaction, the mixture evaporated to dryness and then loaded onto a silica gel column and eluted using eluting with ethyl acetate and petroleum ether (40-60°C) (5:95) afforded diethyl 5-methylindolizine-1,3-dicarboxylate 12 as a red oil (93 mg, 58 %): (Found: MH⁺, 276.1233. C₁₅H₁₈NO₄⁺ requires 276.1236); IR (ν_{max}/cm⁻¹): 2979, 1692, 1635, 1524, 1401, 1366, 1297, 1189; ¹H (400 MHz, CDCl₃): δ 8.28 (1H, ddd, *J* 8.9, Ar*H*), 7.96 (1H, s, Ar*H*), 7.25 (1H, dd, *J* 8.9, 6.9, Ar*H*), 6.76 (1H, d, *J* 6.9, Ar*H*), 4.37 (2H, q, *J* 7.1, CH₂), 4.34 (2H, q, *J* 7.1, CH₂), 2.69 (3H, s, CH₃), 1.40 (6H, app. t, *J* 7.1, 2 × CH₃); ¹³C (100 MHz, CDCl₃) δ 164.2 (C), 160.8 (C), 141.3 (C), 138.9 (C), 129.9 (C), 126.8

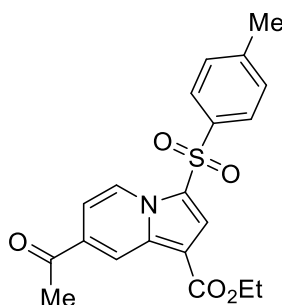
(CH), 126.1 (CH), 117.3 (CH), 116.3 (CH), 104.9 (C), 60.9 (CH₂), 60.0 (CH₂), 22.7 (CH₃), 14.6 (CH₃), 14.5 (CH₃).

3-Ethyl 1,2-dimethyl 7-acetylindolizine-1,2,3-tricarboxylate 270



Following general procedure for preparation of indolizines, with 4-acetylpyridine (0.58 mmol) and dimethyl acetylenedicarboxylate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (10-25 % gradient). Yellow solid (120 mg, 60 %): (Found MNa⁺ 370.0902. C₁₇H₁₇NNaO₇⁺ requires 370.0903); IR (ν_{max}/cm⁻¹): 3134, 2945, 1699, 1440, 1373, 1254, 1140, 1052, 1032; ¹H (300 MHz, CDCl₃): δ 9.52 (1H, dd, *J* 7.4, 1.0, ArH), 8.89 (1H, dd, *J* 2.0, 1.0, ArH), 7.56 (1H, dd, *J* 7.4, 2.0, ArH), 4.39 (2H, q, *J* 7.1, CH₂), 3.99 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 2.70 (3H, s, COCH₃), 1.39 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃): δ 195.8 (COCH₃), 165.8 (C), 163.1 (C), 159.9 (C), 136.4 (C), 133.8 (C), 131.0 (C), 127.8 (CH), 121.6 (CH), 113.9 (C), 112.9 (CH), 106.4 (C), 61.5 (CH₂), 53.0 (CH₃), 52.1 (CH₃), 26.3 (CH₃), 14.2 (CH₃).

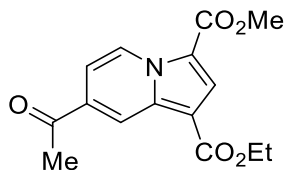
Ethyl 7-acetyl-1-tosylindolizine-3-carboxylate 271



Following general procedure for preparation of indolizines, with 4-acetylpyridine (0.58 mmol) and phenylsulfonyl acetylene (0.58 mmol), elution with ethyl acetate and

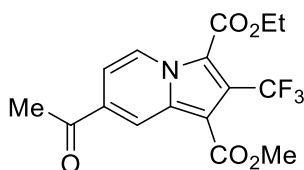
petroleum ether (40-60 °C) (gradient elution from 2:8 to 3:7 gradient). Light yellow solid (91 mg, 41 %): m.p: 121-124 °C; (Found MH^+ 386.1050. $\text{C}_{20}\text{H}_{20}\text{NO}_5\text{S}^+$ requires 386.1057); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3127, 2983, 1703, 1689, 1516, 1503, 1347, 1298, 1144; ^1H (300 MHz, CDCl_3): δ 9.48 (1H, dd, J 7.4, 1.0, ArH), 8.73 (1H, dd, J 1.9, 1.0, ArH), 7.88 (2H, d, J 8.3, ArH), 7.52 (1H, dd, J 7.4, 1.9, ArH), 7.29 (2H, dt, J 8.3, ArH), 4.39 (2H, q, J 7.1, CH_2), 2.70 (3H, s, OCH_3), 2.38 (3H, s, CH_3), 1.41 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3): δ 195.6 (CO), 160.5 (C), 144.2 (C), 140.2 (C), 134.7 (C), 133.2 (C), 130.1 (CH), 127.9 (CH), 126.8 (CH), 123.7 (CH), 119.5 (CH), 117.6 (C), 117.2 (C), 112.4 (CH), 61.2 (CH_2), 26.4 (CH_3), 21.7 (CH_3), 14.5 (CH_3).

3-Ethyl 1-methyl 7-acetylindolizine-1,3-dicarboxylate 272



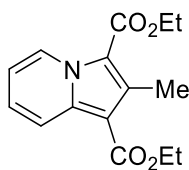
Following general procedure for preparation of indolizines, with 4-acetylpyridine (0.58 mmol) and methyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9 to 15:85 gradient). Yellow solid (142 mg, 85 %): (Found MH^+ 290.1026. $\text{C}_{15}\text{H}_{16}\text{NO}_5^+$ requires 290.1023.); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3133, 2944, 1680, 1678, 1439, 1372, 1278, 1195, 1071, 954. ^1H (300 MHz, CDCl_3): δ 9.34 (1H, dd, J 7.4, 1.0, ArH), 8.73 (1H, dd, J 2.0, 1.0, ArH), 7.85 (1H, s, ArH), 7.39 (1H, dd, J 7.4, 2.0, ArH), 4.35 (1H, q, J 7.1, CH_2), 3.89 (3H, s, OCH_3), 2.63 (3H, s, CH_3), 1.38 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3): δ 195.8 (C), 164.1 (C), 160.7 (C), 137.2 (C), 132.6 (C), 127.4 (CH), 124.5 (CH), 121.1 (CH), 116.6 (C), 111.6 (CH), 108.4 (C), 60.8 (CH_2), 51.5 (CH_3), 26.1 (CH_3), 14.4 (CH_3).

Diethyl 7-acetyl-2-(trifluoromethyl)indolizine-1,3-dicarboxylate 273



Following general procedure for preparation of indolizines, with 4-acetylpyridine (0.58 mmol) and ethyl 3- trifluoromethylpropiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (10-20 % gradient). Red oil (140 mg, 65 %): (Found MNa^+ 394.0872. $C_{17}H_{16}F_3NNaO_5^+$ requires 394.0878); IR (ν_{max}/cm^{-1}): 2986, 1723, 1687, 1495, 1381, 1306, 1135, 1073, 1058, 1023; ^1H (300 MHz, $CDCl_3$): δ 9.07 (1H, dd, J 7.5, 1.0, ArH), 8.74 (1H, dd, J 2.0, 1.0, ArH), 7.51 (1H, dd, J 7.5, 2.0, ArH), 4.58-4.35 (4H, m, $2 \times CH_2$), 2.68 (3H, s, $COCH_3$), 1.47-1.40 (6H, m, $2 \times CH_3$); ^{13}C (100 MHz, $CDCl_3$): δ 195.5 ($COCH_3$), 163.0 (C), 160.4 (C), 135.1 (C), 132.8 (C), 126.6 (CH), 122.7 (q, J^{CF} 38, C), 121.8 (q, J^{CF} 270, CF_3), 121.82 (CH), 116.9 (q, J^{CF} 3.0, C) 112.7 (CH), 109.1 (C), 62.4 (CH_2), 61.6 (CH_2), 26.1 (CH_3), 14.1 (CH_3), 13.9 (CH_3).

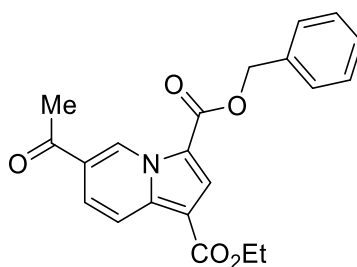
Diethyl 2-methylindolizine-1,3-dicarboxylate 274



Following general procedure for preparation of indolizines, with pyridine (0.58 mmol) and methyl 2-butynoate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9). Off white solid (58 mg, 34 %): m.p. 90-91 °C; (Found: MH^+ 276.1234. $C_{15}H_{18}NO_4$ requires 276.1230); IR (ν_{max}/cm^{-1}): 2974, 1666, 1517, 1466, 1413, 1253, 1112; ^1H (300 MHz, $CDCl_3$): δ 9.58 (1H, d, J 7.0, ArH), 8.29 (1H, d, J

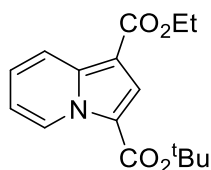
9.0, ArH), 7.24 (1H, ddd, *J* 9.0, 7.0, 1.1 ArH), 6.90 (1H, app. td, *J* 7.0, 1.4, ArH), 4.41 (2H, q, *J* 7.1, CH₂), 4.39 (2H, q, *J* 7.1, CH₂), 2.84 (1H, s, CH₃), 1.43 (6H, app. t, *J* 7.1, 2 × CH₃); ¹³C (75 MHz, CDCl₃) δ 165.3 (C), 162.5 (C), 139.2 (C), 138.4 (C), 128.1 (CH), 125.7 (CH), 119.4 (CH), 114.0 (C), 113.8 (CH), 104.9 (C), 60.3 (CH₂), 59.8 (CH₂), 14.7 (CH₃), 14.6 (CH₃), 13.5 (CH₃).

3-Benzyl 1-ethyl 6-acetylidolizine-1,3-dicarboxylate 279



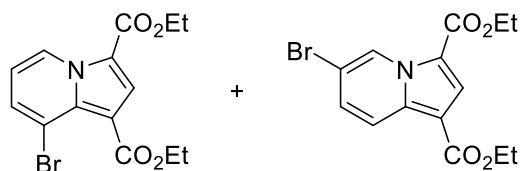
Following general procedure for preparation of indolizines, with 4-acetylpyridine (0.58 mmol), benzyl diazoacetate (0.87 mmol) (in place of ethyl diazoacetate), and ethyl propiolate (0.58 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (1:9 to 2:8 gradient). Yellow solid (136 mg, 64 %): M.p: 109-111 °C; IR (ν_{max} /cm⁻¹): 2933, 1688, 1677, 1515, 1428, 1348, 1275, 1188, 1066, 1022; (Found: MH⁺ 366.1349. C₂₁H₂₀NO₅⁺ requires 366.1341); ¹H (300 MHz, CDCl₃): δ 9.47 (1H, dd, *J* 7.4, 1.0, ArH), 8.88 (1H, dd, *J* 2.0, 1.0, ArH), 8.01 (1H, s, ArH), 7.56-7.31 (6H, m, ArH), 5.38 (2H, s, CH₂), 4.40 (2H, q, *J* 7.1, CH₂), 2.67 (3H, s, COCH₃), 1.43 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃): δ 195.9 (COMe), 163.7 (C), 160.5 (C), 137.5 (C), 135.8 (C), 132.8 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 124.8 (CH), 121.3 (CH), 116.3 (C), 111.7 (CH), 109.0 (C), 66.4 (CH₂), 60.4 (CH₂), 26.0 (CH₃), 14.5 (CH₃).

3-(tert-butyl) 1-Ethyl indolizine-1,3-dicarboxylate 280



Following general procedure for preparation of indolizines, with pyridine (0.58 mmol), ethyl propiolate (0.58 mmol), and tert-butyl diazo acetate (0.87 mmol), eluting with ethyl acetate and petroleum ether (40-60 °C) (5:95). Pale yellow oil (118 mg, 71 %): Found MH^+ 290.1394. $C_{16}H_{20}NO_4$ requires 190.1396; IR (ν_{max}/cm^{-1}): 3982, 1680, 1516, 1431, 1252, 1190, 1070, 1034; ^1H (300 MHz, $CDCl_3$): δ 8.87 (1H dt, J 7.1, 1.1, ArH), 7.67 (1H, dt, J 9.0, 1.1, ArH), 7.26 (1H, s, ArH), 6.63 (1H, ddd, J 9.0, 7.1, 1.1, ArH), 6.29 (1H, td, J 7.1, 1.4, ArH), 3.75 (2H, q, J 7.1, CH_2), 0.98 (9H, s, CH_3), 0.78 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 164.5 (C), 160.9 (C), 128.0 (CH), 125.4 (CH), 124.2 (CH), 119.6 (CH), 116.1 (C), 114.2 (CH), 104.9 (C), 81.3 (CH_2), 60.0 (C), 28.6 (CH_3), 14.7 (CH_3).

Diethyl 6-bromoindolizine-1,3-dicarboxylate 282A, diethyl 8-bromoindolizine-1,3-dicarboxylate 282B and (mixed fraction containing diethyl indolizine-1,3-dicarboxylate 243, diethyl indolizine-1,3-dicarboxylate-6-d, Diethyl indolizine-1,3-dicarboxylate-8-d)

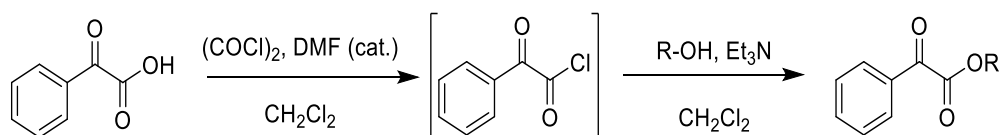


To a solution of 3-bromopyridine (168 μL , 1.74 mmol), ethyl propiolate (170 μL , 1.70 mmol) and Fe(TPP)Cl (12 mg, 0.017 mmol) in dichloromethane (10 mL) and D_2O (3 mL) was added ethyl diazoacetate (270 μL , 2.59 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was dry loaded onto silica and purified using column chromatography, eluting with ethyl acetate and petroleum ether (40-60 $^{\circ}\text{C}$) (1:9). **Diethyl 6-bromoindolizine-1,3-dicarboxylate 282B** was collected as an off-white solid (144 mg, 25 %): (Found MH^+ 340.0176. $\text{C}_{14}\text{H}_{15}\text{BrNO}_4^+$ requires 340.0179.); ^1H (300 MHz, CDCl_3): δ 9.66 (1H, dd J 1.8, 0.9, ArH), 8.18 (1H, dd, J 9.5, 0.9, ArH), 7.90 (1H, s, ArH), 7.37 (1H, dd, J 9.5, 1.8, ArH), 4.38 (2H, q, J 7.1, CH_2), 4.36 (2H, q, J 7.1, CH_2), 1.40 (6H, app t, J 7.1, $2 \times \text{CH}_3$); ^{13}C (75 MHz, CDCl_3): δ 163.9 (C), 161.0 (C), 137.0 (C), 128.7 (CH), 127.9 (CH), 124.0 (CH), 120.1 (CH), 115.0 (C), 109.6 (C), 106.1 (C), 60.6 (CH_2), 60.2 (CH_2), 14.5 (CH_3), 14.4 (CH_3). Further elution gave a mixture of **Diethyl indolizine-1,3-dicarboxylate 243, diethyl indolizine-1,3-dicarboxylate-6-d, diethyl indolizine-1,3-dicarboxylate-8-d** (62 mg, 14 % 5:3 ratio of 6-d to 8-d) - this ratio components was estimated by relative integration of the protons at 6- or 8- indolizine position by ^1H NMR spectroscopy) Further elution gave **Diethyl 8-bromoindolizine-1,3-dicarboxylate 282A** as a colourless oil (212 mg, 37 %): (Found MH^+ 340.0175. $\text{C}_{14}\text{H}_{15}\text{BrNO}_4^+$ requires

340.0179); IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2978, 1737, 1687, 1520, 1476, 1415, 1300, 1225, 1193, 1078, 1014; ^1H (300 MHz CDCl_3): δ 9.55 (1H, dd, J 7.2, 1.0, ArH), 7.89 (1H, s, ArH), 7.46 (1H, dd, J 7.2, 1.0, ArH), 6.75 (1H, t, J 7.2, ArH), 4.36 (2H, q, J 7.1, CH_2), 4.36 (2H, q, J 7.1, CH_2), 1.39 (3H, t, J 7.1, CH_3), 1.38 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 163.9 (C), 160.8 (C), 134.5 (C), 129.8 (CH), 126.8 (CH), 125.4 (CH), 114.7 (C), 113.8 (C), 112.2 (C), 109.0 (C), 60.9 (CH_2), 60.6 (CH_2), 14.43 (CH_3), 14.38 (CH_3).

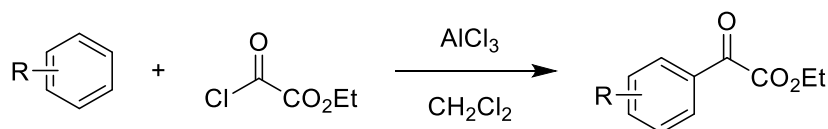
4.4 General Method for Preparation of Keto-esters

4.5 General Method 1 For Keto-Ester Preparation



To a solution of phenylglyoxylic acid (5.26 g, 35.0 mmol) and DMF (*ca.* 200 μL) in dry dichloromethane (35 mL) was added oxalyl chloride (3.0 mL, 35 mmol) dropwise at 0 °C under argon. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, until gas evolution ceased. The solution was stored at 0 °C under argon until required: IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3067, 1773, 1687, 1580, 1451, 1256, 1177, 1094, 1000. A solution of 2-oxo-2-phenylacetyl chloride in dry dichloromethane (1M, 1 eq.) was added dropwise to a solution of alcohol (1 eq.), and trimethylamine (2 eq.) in dichloromethane (1 mL per mmol of alcohol) dropwise at 0 °C under argon. The reaction mixture was allowed to warm to room temperature, and stirred for 16 h. The reaction mixture was added to water (30 mL) and extracted with dichloromethane (3 $\times$ 50 mL). The chlorinated extracts were combined, and washed with HCl (1M, 50 mL), K_2CO_3 (aq., saturated, 50 mL), brine (50 mL), dried over MgSO_4 and filtered. The solvent was removed *in vacuo*, and the resulting residue purified by column chromatography to give the desired keto ester.

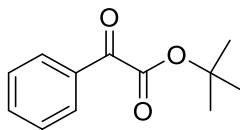
4.6 General Procedure 2 For Keto-Ester Preparation



To a suspension of AlCl_3 (3.7 g, 28 mmol) in anhydrous CH_2Cl_2 (35 mL) was added ethyl oxalyl chloride (3.1 mL, 28 mmol) dropwise at 0 °C under argon. The reaction

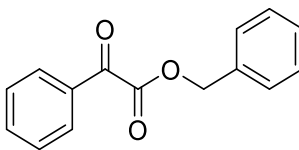
mixture was stirred for 15 min, then the arene (15 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C 1 h, then 3 h at room temperature. The reaction mixture was added to crushed ice (300 g) and concentrated HCl (100 mL), and the resulting mixture was extracted with CH₂Cl₂ (3 ×50 mL). The chlorinated extracts were combined, washed with aqueous saturated potassium carbonate (50 mL) and brine (50 mL), dried over MgSO₄ and filtered. The solvent was removed *in vacuo* and the resulting residue purified by column chromatography to give the desired keto ester.

tert-Butyl 2-oxo-2-phenylacetate 310



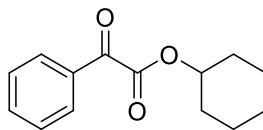
Following general procedure 2 for keto-ester preparation, with *t*-butanol (960 μ L, 10 mmol), eluting with ethyl acetate and light petroleum (1:9). Yellow oil (1.3 g, 63 %): Found MNa^+ 229.0836. $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}$ requires 229.0841 ; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2982, 1726, 1684, 1579, 1501, 1450, 1394, 1277, 1025; ^1H (400 MHz, CDCl_3): δ 7.90-7.80 (2H, m, ArH), 7.54-7.45 (1H, m, ArH), 7.37 (2H, dd, J 8.4, 7.2, ArH), 1.51 (9H, s, CH_3); ^{13}C (100 MHz, CDCl_3) δ 186.6 (C), 163.6 (C), 134.5 (CH), 132.2 (C), 129.5 (CH), 128.7 (CH), 84.4 (C), 27.7 (CH_3). The data were in agreement with the literature.¹²²

Benzyl 2-oxo-2-phenylacetate 311



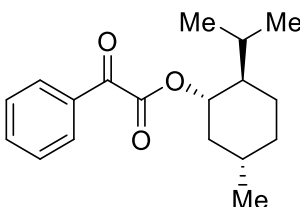
Following general procedure 2 for keto-ester preparation, with benzyl alcohol (570 μ L, 5.5 mmol), eluting with ethyl acetate and light petroleum (1:9). Pale yellow oil (1.2 g, quant.): Found MNa^+ 263.0679 $\text{C}_{15}\text{H}_{13}\text{O}_3\text{Na}$ requires 263.0684; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3066, 1733, 1686, 1580, 1451, 1321, 1192, 1028, 989; ^1H (300 MHz, CDCl_3): δ 8.01-7.96 (2H, m, ArH), 7.64-7.51 (1H, m, ArH), 7.48-7.30 (7H, m, ArH), 5.41 (2H, s, CH_2); ^{13}C (75 MHz, CDCl_3): δ 185.9 (C), 163.5 (C), 134.7 (CH), 134.4 (C), 132.1 (C), 129.7 (CH), 128.7 (CH), 128.52 (CH), 128.47 (CH), 128.3 (CH), 67.4 (CH_2). The data were in agreement with the literature.¹²³

Cyclohexyl 2-oxo-2-phenylacetate 312



Following general procedure 2 for keto-ester preparation, with cyclohexanol (570 μ L, 5.0 mmol). Yellow oil (990 mg, 85 %): Found MNa^+ 255.0984. $C_{14}H_{16}O_3Na$ requires 255.0997; IR (ν_{max}/cm^{-1}): 2935, 1726, 1687, 1596, 1450, 1321, 1295, 1199, 1121, 1072, 1001; ^1H (300 MHz, $CDCl_3$): 7.92-7.82 (2H, m, *ArH*), 7.61-7.46 (1H, m, *ArH*), 7.43-7.33 (2H, m, *ArH*), 4.98 (1H, tt, *J* 9.1, 3.9, *CH*), 1.97-1.05 (8H, m, *CH*₂); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.6 (C), 163.5 (C), 134.6 (CH), 132.3 (C), 129.6 (CH), 128.7 (CH), 75.1 (CH), 31.1 (CH₂), 24.9 (CH₂), 23.3 (CH₂). The data were in agreement with the literature.^{55a}

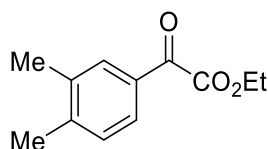
(1S*,2R*,5S*)-2-Isopropyl-5-methylcyclohexyl 2-oxo-2-phenylacetate 313



Following general procedure 2 for keto-ester preparation, with $\pm$ menthol (1.6 g, 10 mmol), eluting with ethyl acetate and light petroleum (9:1). Pale yellow oil (2.3 g, 79 %): Found MNa^+ 311.1615. $C_{18}H_{24}NaO_3$ requires 311.1623; IR (ν_{max}/cm^{-1}): 2595, 1726, 1689, 1595, 1451, 1319, 1294, 1201, 1175, 1097, 1002; ^1H (400 MHz, $CDCl_3$) δ 7.94 – 7.80 (2H, m, *ArH*), 7.54 – 7.46 (1H, m, *ArH*), 7.42 – 7.33 (2H, m, *ArH*), 4.91 (1H, td, *J* 10.9, 4.4, *CH*), 2.12 – 2.00 (2H, m, *CH*₂), 1.92 – 1.79 (1H, m, *CH*), 1.66 – 1.51 (2H, m, *CH*₂), 1.48 – 1.31 (2H, m, 2 $\times$ *CH*), 1.13 – 0.91 (2H, m, *CH*₂), 0.87 – 0.67 (9H, m, 3 $\times$ *CH*₃); ^{13}C (100 MHz, $CDCl_3$) δ 186.4 (C), 163.6 (C), 134.6 (CH),

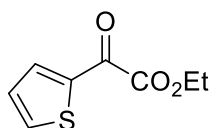
132.3 (C), 129.5 (CH), 128.7 (CH), 76.4 (CH), 46.6 (CH), 40.4 (CH₂), 33.8 (CH₂), 31.2 (CH), 25.9 (CH), 23.1 (CH₂), 21.7 (CH₃), 20.4 (CH₃), 15.9 (CH₃). The data were in agreement with the literature.¹²⁴

Ethyl 2-(3,4-dimethylphenyl)-2-oxoacetate 314



Following general procedure 1 for keto-ester preparation, with *o*-xylene (1.8 mL, 15 mmol), eluting with ethyl acetate and light petroleum (5:95). Pale yellow oil (2.6 g, 84 %): Found MNa⁺ 229.0848 C₁₂H₁₄O₃Na requires 229.0841; IR (ν_{max}/cm⁻¹): 2981, 1733, 1679, 1605, 1571, 1410, 1368, 1281, 1164, 1034; ¹H (400 MHz, CDCl₃): δ 7.71 (1H, app. s, ArH), 7.68 (1H, dd, *J* 7.8, 1.9, ArH), 7.20 (1H, d, *J* 7.8, ArH), 4.40 (2H, q, *J* 7.2, CH₂), 2.28 (3H, s, CH₃), 2.26 (3H, s, CH₃), 1.37 (3H, t, *J* 7.2, CH₃); ¹³C (100 MHz, CDCl₃) δ 186.4 (C), 164.2 (C), 145.0 (C), 137.4 (C), 130.7 (CH), 130.3 (C), 130.1 (CH), 127.8 (CH), 62.1 (CH₂), 20.2 (CH₃), 19.6 (CH₃), 14.1 (CH₃). The data were in agreement with the literature.¹²⁵

Ethyl 2-oxo-2-(thiophen-2-yl)acetate 315

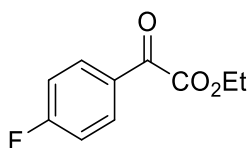


Following general procedure 1 for keto-ester preparation, with thiophene (1.2 mL, 15 mmol), eluting ethyl acetate and light petroleum (5:95). Yellow oil (1.9 g, 69 %): Found MNa⁺ 207.0087 C₈H₈O₃SNa requires 207.0092; IR (ν_{max}/cm⁻¹): 2982, 1730, 1659, 1508, 1467, 1409, 1356, 1229, 1112, 1053; ¹H (400 MHz, CDCl₃) δ 7.84 (1H,

dd, J 3.9, 1.2, ArH), 7.63 (1H, dd, J 5.0, 1.2, ArH), 6.94 (1H, dd, J 5.0, 3.9, ArH), 4.17 (2H, q, J 7.1 Hz, CH₂), 1.15 (3H, t, J 7.1, CH₃); ¹³C (100 MHz, CDCl₃) δ 176.0 (C), 161.1 (C), 138.5 (C), 137.2 (CH), 136.8 (CH), 128.3 (CH), 62.2 (CH₂), 13.4 (CH₃).

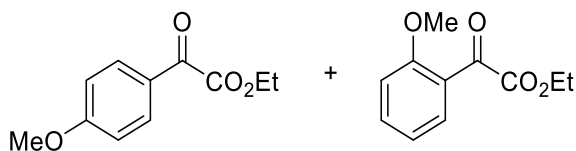
The data were in agreement with the literature.^{55a}

Ethyl 2-(4-fluorophenyl)-2-oxoacetate 316



Following general procedure 1 for keto-ester preparation, with fluorobenzene (1.3 mL). Colourless oil (1.3 g, 44 %): Found MNa⁺ 219.0426. C₁₀H₉O₃FNa requires 219.0433 ; IR (ν_{max} /cm⁻¹): 2985, 1732, 1685, 1597, 1447, 1370, 1299, 1194, 1154, 1100; ¹H (400 MHz, CDCl₃): δ 7.97-7.86 (2H, m, ArH), 7.10-6.97 (2H, m, ArH), 4.30 (2H, q, J 7.1, CH₂), 1.26 (3H, t, J 7.1, CH₃); ¹³C (100 MHz, CDCl₃) δ 184.4 (C), 166.5 (d, J^{CF} 260, C), 163.2 (C), 132.7 (d, J^{CF} 10, CH), 128.8 (C), 116.0 (d, J^{CF} 22, CH) 62.2 (CH₂), 13.7 (CH₃). The data were in agreement with the literature.¹²⁵

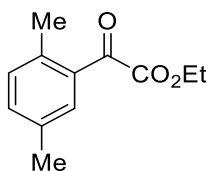
Ethyl 2-(4-methoxyphenyl)-2-oxoacetate 317 and ethyl 2-(2-methoxyphenyl)-2-oxoacetate 318



Following general procedure 1 for keto-ester preparation, with anisole (1.6 mL, 15 mmol), eluting with ethyl acetate and light petroleum (5:95 to 1:9 gradient). **Ethyl 2-(4-methoxyphenyl)-2-oxoacetate 317** was obtained as a colourless oil (2.0 g, 67 %): Found MNa⁺ 231.0627. C₁₁H₁₂O₄Na requires 231.0633 ; IR (ν_{max} /cm⁻¹): 2981, 1731,

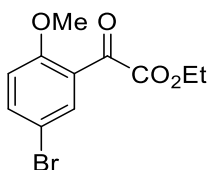
1672, 1596, 1510, 1444, 1369, 1264, 1159; ^1H (400 MHz, CDCl_3): δ 7.86-7.60 (2H, m, ArH), 6.81-6.56 (2H, m, ArH), 4.19 (2H, q, J 7.1, CH_2), 3.60 (3H, s, OCH_3), 1.15 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 184.6 (C), 164.6 (C), 163.9 (C), 131.9 (CH), 124.8 (C), 113.8 (CH), 61.6 (CH_2), 55.0 (OCH_3), 13.5 (CH_3). Further elution gave **ethyl 2-(2-methoxyphenyl)-2-oxoacetate 318** as a colourless oil (360 mg, 12 %): Found MNa^+ 231.0626. $\text{C}_{11}\text{H}_{12}\text{O}_4\text{Na}$ requires 231.0633 ; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2981, 1735, 1597, 1467, 1369, 1243, 1190, 1018; ^1H (400 MHz, CDCl_3): 7.80 (1H, dd, J 7.9, 1.8, ArH), 7.51 (1H, ddd, J 8.4, 7.3, 1.8, ArH), 7.00 (1H, dd, J 7.9, 7.3, ArH), 6.93 (1H, d, J 8.4, ArH), 4.32 (2H, q, J 7.1, CH_2), 3.79 (3H, s, OCH_3), 1.32 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 186.6 (C), 165.3 (C), 160.3 (C), 136.4 (CH), 130.5 (CH), 122.6 (C), 121.2 (CH), 112.1 (CH), 61.7 (CH_2), 55.9 (CH_3), 14.1 (CH_3). The data were in agreement with the literature.¹²⁶

Ethyl 2-(2,5-dimethylphenyl)-2-oxoacetate 319



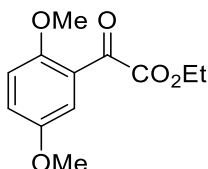
Following general procedure 1 for keto-ester preparation, with *p*-xylene (1.8 mL, 15 mmol), eluting with ethyl acetate and light petroleum (5:95). Pale yellow oil (3.1 g, quant.): Found MNa^+ 229.0837 $\text{C}_{12}\text{H}_{14}\text{O}_3\text{Na}$ requires 229.0841; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2981, 1732, 1679, 1562, 1498, 1368, 1314, 1275, 1208, 1162, 1095; ^1H (400 MHz, CDCl_3): δ 7.48 – 7.43 (1H, m, ArH), 7.27 – 7.22 (1H, m, ArH), 7.14 (1H, d, J 7.8, ArH), 4.40 (2H, q, J 7.1, CH_2), 2.52 (3H, s, CH_3), 2.32 (3H, s, CH_3), 1.38 (3H, t, J 7.2, CH_3); ^{13}C (100 MHz, CDCl_3) δ 188.5 (C), 164.4 (C), 137.5 (C), 135.1 (C), 134.1 (CH), 132.2 (CH), 131.8 (CH), 130.5 (C), 61.6 (CH_2), 20.3 (CH_3), 20.1 (CH_3), 13.5 (CH_3). The data were in agreement with the literature.¹²⁷

Ethyl 2-(5-bromo-2-methoxyphenyl)-2-oxoacetate 320



Following general procedure 1 for keto-ester preparation, with *p*-bromo anisole (1.9 mL, 15 mmol), eluting with ethyl acetate and light petroleum (2:8). Colourless solid (4.1 g, 95 %): M.p. 95-98 °C; Found MNa^+ 308.9733. $\text{C}_{11}\text{H}_{11}\text{O}_4\text{BrNa}$ requires 308.9738; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2983, 1729, 1676, 1591, 1481, 1391, 1313, 1271, 1178, 1014; ^1H (400 MHz, CDCl_3) δ 7.80 (1H, d, J 2.6, ArH), 7.53 (1H, dd, J 9.0, 2.6, ArH), 6.81 (1H, d, J 9.0 Hz, ArH), 4.28 (2H, q, J 7.1, CH_2), 3.75 (3H, s, OCH_3), 1.28 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 185.1 (C), 164.4 (C), 159.0 (C), 138.6 (CH), 132.6 (CH), 124.0 (C), 114.1 (CH), 113.4 (C), 61.8 (CH_2), 56.2 (OCH_3), 13.9 (CH_3).

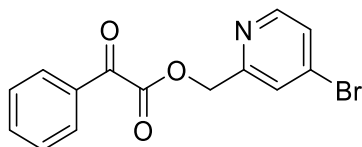
Ethyl 2-(2,5-dimethoxyphenyl)-2-oxoacetate 321



Following general procedure 1 for keto-ester preparation, eluting with ethyl acetate and light petroleum (1:9- 2:8 gradient). Yellow oil (3.0 g, 77 %): Found MNa^+ 261.0734 $\text{C}_{12}\text{H}_{14}\text{O}_5\text{Na}$ requires 261.0739; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3001, 1731, 1662, 1584, 1467, 1388, 1302, 1224, 1176, 1095; ^1H (300 MHz, CDCl_3): δ 7.13 (1H, d, J 3.3, ArH), 6.93 (1H, dd, J 9.0, 3.3, ArH), 6.75 (1H, d, J 9.0, ArH), 4.18 (2H, q, J 7.1, CH_2), 3.60 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 1.17 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 185.9 (C), 165.0 (C), 154.6 (C), 153.6 (C), 123.3 (CH), 122.3 (C), 113.72 (CH),

112.31 (CH), 61.3 (CH₂), 56.2 (OCH₃), 55.2 (OCH₃), 13.6 (CH₃). The data were in agreement with the literature.¹²⁷

(4-bromopyridin-2-yl)methyl 2-oxo-2-phenylacetate 361



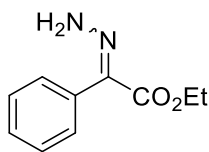
Following general procedure 2 for keto-ester preparation, with (5-bromopyridin-2-yl)methanol (940 mg, 5 mmol). Yellow oil (1.4 g, 88 %): Found MH⁺ 319.9920. C₁₄H₁₁BrNO₃⁺ requires 319.9922; IR (ν_{max}/cm⁻¹): 3063, 1737, 1684, 1595, 1560, 1470, 1299, 1191, 1171, 1091, 1004; ¹H (400 MHz, CDCl₃): δ 8.63 (1H, dd, *J* 2.3, 0.7, ArH), 8.08 – 7.94 (2H, m, ArH), 7.81 (1H, dd, *J* 8.3, 2.3, ArH), 7.68 – 7.58 (1H, m, ArH), 7.47 (2H, t, *J* 7.8, ArH), 7.31 (1H, dd, *J* 8.3, 0.7, ArH), 5.44 (2H, s, CH₂); ¹³C (100 MHz, CDCl₃): δ 185.7 (C), 163.2 (C), 153.0 (C), 150.7 (CH), 139.5 (CH), 135.2 (CH), 132.3 (C), 130.2 (CH), 129.0 (CH), 123.1 (CH), 120.3 (C), 67.1 (CH₂).

4.7 General Procedure For Hydrazone Preparation



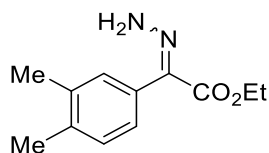
A solution of keto ester (1 eq.), hydrazine hydrate (1 eq.) and benzoic acid (1 eq.) in THF (15 mL) was stirred at room temperature for 24 h. The reaction mixture was added to ethyl acetate (50 mL) and aqueous saturated potassium carbonate (50 mL), and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried over MgSO₄ and filtered. The solvent was removed *in vacuo* and the resulting residue purified by column chromatography, eluting with the eluent specified.

Ethyl 2-hydrazono-2-phenylacetate 296



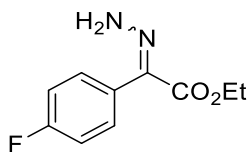
Following general procedure for preparation of hydrazones, with ethyl 2-oxo-2-phenylacetate **295** (2.00 mL, 12.6 mmol), eluting with ethyl acetate and light petroleum (9:1 to 4:6 gradient). **Ethyl (Z)-2-hydrazono-2-phenylacetate 296A** was obtained as a colourless oil (1.74 g, 72 %): Found MNa^+ 215.0789. $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2\text{Na}$ requires 215.0796; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3453, 3281, 2983, 1684, 1562, 1493, 1391, 1335, 1291, 1142, 1019; ^1H (300 MHz, CDCl_3) δ 8.51 (2H, s *br.*, NH_2), 7.68 – 7.54 (2H, m, *ArH*), 7.47 – 7.28 (3H, m, *ArH*), 4.34 (2H, q, J 7.1 CH_2), 1.35 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 162.9 (C), 136.7 (C), 130.7 (C), 128.1 (CH), 127.8 (CH), 127.4 (CH), 60.6 (CH_2), 14.1 (CH_3). Further elution gave **ethyl (E)-2-hydrazono-2-phenylacetate 296B** as a colourless solid (494 mg, 20 %): M.p. 82-85 °C; Found MNa^+ 215.0790. $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2\text{Na}$ requires 215.0796; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3409, 3280, 2984, 1699, 1563, 1492, 1369, 1311, 1229, 1141, 1047; ^1H (300 MHz, CDCl_3) δ 7.61 – 7.34 (3H, m, *ArH*), 7.31-7.26 (2H, m, *ArH*), 6.23 (2H, s *br.*, NH_2), 4.29 (2H, q, J 7.1, CH_2), 1.32 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 164.5 (C), 137.5 (C), 129.7 (C), 129.4 (CH), 129.3 (CH), 128.9 (CH), 61.4 (CH_2), 14.4 (CH_3). The data were in agreement with the literature.^{55a}

Ethyl 2-(3,4-dimethylphenyl)-2-hydrazonoacetate 322



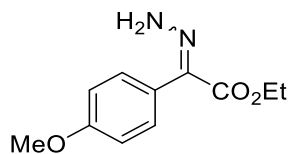
Following general procedure for preparation of hydrazones, with **ethyl 2-(3,4-dimethylphenyl)-2-oxoacetate 314** (2.60 g, 12.6 mmol), eluting with ethyl acetate and light petroleum (1:9 to 3:7 gradient). **Ethyl (Z) 2-(3,4-dimethylphenyl)-2-hydrazonoacetate 322A** as a colourless solid (1.0 g, 36 %): M.p.: 89-91 °C; Found MH^+ 221.1297. $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$ requires 221.1290; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3405, 3266, 2944, 1684, 1533, 1441, 1365, 1269, 1159, 1044; ^1H (400 MHz, CDCl_3): δ 8.27 (2H, s *br.*, NH_2), 7.31 (1H, d, J 2.1, *ArH*), 7.27 – 7.23 (1H, m, *ArH*), 7.12 (1H, d, J 7.6, *ArH*), 4.32 (2H, q, J 7.1, CH_2), 2.28 (3H, s, CH_3), 2.28 (3H, s, CH_3), 1.34 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 163.1 (C), 136.2 (C), 134.3 (C), 131.8 (C), 129.31 (CH), 129.28 (C), 129.25 (CH), 125.7 (CH), 60.7 (CH_2), 19.9 (CH_3), 19.6 (CH_3), 14.3 (CH_3). Further elution gave **ethyl (E) 2-(3,4-dimethylphenyl)-2-hydrazonoacetate as a colourless solid 322B** (400 mg, 14 %): M.p.: 95- 96 °C; Found MH^+ 221.1297. $\text{C}_{12}\text{H}_{17}\text{N}_2\text{O}_2$ requires 221.1290; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3412, 3285, 2981, 1698, 1500, 1452, 1369, 1235, 1143, 1050; ^1H (400 MHz, CDCl_3): δ 7.20 (1H, d, J 7.7, *ArH*), 7.02 (1H, d, J 1.7, *ArH*), 6.99 (1H, dd, J 7.7, 1.7, *ArH*), 6.27 (2H, s *br.*, NH_2), 4.26 (2H, q, J 7.1, CH_2), 2.26 (6H, s, $2 \times \text{CH}_3$), 1.30 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 164.6 (C), 137.9 (C), 137.5 (C), 137.5 (C), 130.3 (CH), 129.7 (CH), 126.9 (C), 126.1 (CH), 61.1 (CH_2), 19.8 (CH_3), 19.7 (CH_3), 14.3 (CH_3).

Ethyl 2-(4-fluorophenyl)-2-hydrazonoacetate 323



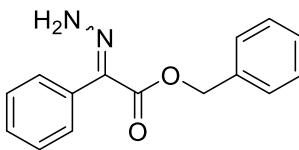
Following general procedure for preparation of hydrazones, with ethyl **2-(4-fluorophenyl)-2-oxoacetate 316** (860 mg, 4.4 mmol), eluting with ethyl acetate and light petroleum (8:2 to 1:1 gradient). **(Z)-Ethyl 2-(4-fluorophenyl)-2-hydrazonoacetate 323A** as a pale yellow oil (530 mg, 62 %): Found MH^+ 211.0890. $C_{10}H_{12}FN_2O_2^+$ requires 211.0883; IR (ν_{max}/cm^{-1}): 3454, 3284, 2981, 1687, 1600, 1508, 1465, 1368, 1306, 1261, 1144, 1020; ^1H (400 MHz, $CDCl_3$): δ 8.54 (2H, s *br.*, NH_2), 7.68-7.37 (2H, m, *ArH*), 7.03 (2H, t, J 8.8, *ArH*), 4.30 (2H, q, J 7.1, CH_2), 1.30 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$): δ 162.7 (C), 162.2 (d, J^{CF} 245, C), 132.9 (d, J^{CF} 3.4, C), 129.9 (d, J^{CF} 8.0, CH), 129.6 (C), 114.6 (d, J^{CF} 22.0, CH), 60.6 (CH_2), 14.0 (CH_3). Further elution gave **(E)-Ethyl 2-(4-fluorophenyl)-2-hydrazonoacetate 323B** as a colourless oil (320 mg, 37 %): Found MH^+ 211.0887. $C_{10}H_{12}FN_2O_2^+$ requires 211.0883; IR (ν_{max}/cm^{-1}): 3418, 3288, 3210, 2939, 1693, 1600, 1544, 1475, 1366, 1296, 1216, 1100, 1014; ^1H (400 MHz, $CDCl_3$): δ 7.29-7.24 (2H, m, *ArH*), 7.18-7.11 (2H, m, *ArH*), 6.31 (2H, s *br.*, NH_2), 4.25 (2H, q, J 7.1, CH_2), 1.29 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$): δ 164.4 (C), 163.0 (d, J^{CF} 163.0, C), 136.2 (C), 131.0 (d, J^{CF} 8.4, CH), 125.4 (d, J^{CF} 4.0, C), 116.4 (d, J^{CF} 22.0, CH), 61.4 (CH_2), 14.3 (CH_3).

Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate 324



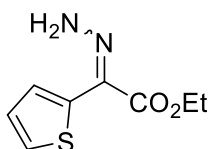
Following general procedure for preparation of hydrazones, with **Ethyl 2-(4-methoxyphenyl)-2-oxoacetate 317** (1.5 g, 7.2 mmol), eluting with ethyl acetate and light petroleum (2:8 to 7:3 gradient): **(Z)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate 324A** as a pale yellow oil (1.1 g, 69 %): Found MNa^+ 245.0887 $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ requires 245.0902; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3418, 3287, 3210, 2940, 1692, 1545, 1478, 1388, 1295, 1138, 1037; ^1H (400 MHz, CDCl_3): δ 8.39 (2H, s *br.*, NH_2), 7.54-7.42 (2H, m, *ArH*), 6.98-6.82 (2H, m, *ArH*), 4.30 (2H, q, J 7.1, CH_2), 3.79 (3H, s, OCH_3), 1.31 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 162.8 (C), 158.9 (C), 130.6 (C), 129.21 (C), 129.19 (CH), 113.1 (CH), 60.4 (CH_2), 55.0 (OCH_3), 14.0 (CH_3). Further elution gave **(E)-Ethyl 2-hydrazono-2-(4-methoxyphenyl)acetate 324B** as a colourless solid (300 mg, 19 %): Found MNa^+ 245.0906. $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3\text{Na}$ requires 245.0902; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3418, 3287, 3210, 2940, 1692, 1545, 1478, 1388, 1295, 1138, 1037; ^1H (400 MHz, CDCl_3): δ 7.25-7.17 (2H, m, *ArH*), 7.01-6.95 (2H, m, *ArH*), 6.23 (2H, s *br.*, NH_2), 4.27 (2H, q, J 7.1, CH_2), 3.81 (3H, s, OCH_3), 1.31 (3H, t, CH_3); ^{13}C (100 MHz, CDCl_3) δ 164.7 (C), 160.2 (C), 137.4 (C), 130.36 (CH), 121.5 (C), 114.6 (CH), 61.3 (CH_2), 55.4 (OCH_3), 14.4 (CH_3). The data were in agreement with the literature.^{55a}

Benzyl-2-hydrazineylidene-2-phenylacetate 325



Following general procedure for preparation of hydrazones, with **benzyl 2-oxo-2-phenylacetate 311** (790 mg, 3.3 mmol), eluting with ethyl acetate and light petroleum (2:8 to 4:6 gradient). **Benzyl (Z)-2-hydrazineylidene-2-phenylacetate 325A** was collected as a pale yellow oil (490 mg, 58 %): Found MH^+ 255.1129. $C_{15}H_{15}N_2O_3$ requires 255.1134; IR (ν_{max}/cm^{-1}): 3408, 3377, 3035, 1678, 1601, 1560, 1496, 1422, 1324, 1265, 1149, 1073; ^1H (300 MHz, $CDCl_3$) δ 8.52 (2H, s br., NH_2), 7.64 – 7.54 (2H, m, ArH), 7.46 – 7.30 (8H, m, ArH), 5.34 (2H, s, CH_2); ^{13}C (75 MHz, $CDCl_3$): δ 162.7 (C), 136.6 (C), 135.5 (C), 130.5 (C), 128.6 (CH), 128.3 (2 $\times$ CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 66.3 (CH_2). Further elution gave **benzyl (E)-2-hydrazineylidene-2-phenylacetate 325B** as a pale yellow oil (120 mg, 14 %): Found MH^+ 277.0947. $C_{15}H_{14}N_2O_3Na$ requires 277.0953; IR (ν_{max}/cm^{-1}): 3397, 3270, 2954, 1698, 1582, 1490, 1441, 1379, 1291, 1179, 1127, 1042; ^1H (300 MHz, $CDCl_3$) δ 7.54 – 7.27 (10H, m, ArH), 6.27 (2H, s br., NH_2), 5.29 (2H, s, CH_2); ^{13}C (75 MHz, $CDCl_3$) δ 164.4 (C), 137.2 (C), 136.1 (C), 129.6 (CH), 129.5 (C), 129.3 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 66.9 (CH_2).

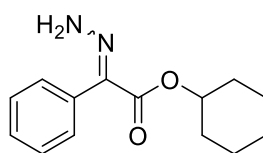
Ethyl 2-hydrazono-2-(thiophen-2-yl)acetate 326



Following general procedure for preparation of hydrazones, with **ethyl 2-oxo-2-(thiophen-2-yl)acetate 315** (1.4 g, 7.6 mmol), eluting with ethyl acetate and light

petroleum (1:9 to 1:1 gradient). **Ethyl (E)-2-hydrazono-2-(thiophen-2-yl)acetate 326A** as a yellow oil (650 mg, 43 %): Found MNa^+ 221.0356 $\text{C}_8\text{H}_{10}\text{N}_2\text{SO}_2\text{Na}$ requires 221.0361; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3403, 3225, 2937, 1684, 1555, 1473, 1366, 1290, 1202, 1115, 1090; ^1H (400 MHz, CDCl_3) δ 8.47 (2H, s *br.*, NH_2), 7.40 (1H, dd, J 3.7, 1.2, *ArH*), 7.17 (1H, dd, J 5.2, 1.2, *ArH*), 6.98 (1H, dd, J 5.2, 3.7, *ArH*), 4.37 (2H, q, J 7.1, CH_2), 1.42 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 162.1 (C), 141.0 (C), 127.3 (CH), 126.2 (C), 125.2 (CH), 124.8 (CH), 61.2 (CH_2), 14.3 (CH_3). Further elution gave **ethyl (Z)-2-hydrazono-2-(thiophen-2-yl)acetate 326B** as a yellow oil (213 mg, 14 %): Found MNa^+ 221.0359 $\text{C}_8\text{H}_{10}\text{N}_2\text{SO}_2\text{Na}$ requires 221.0361; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3402, 3269, 2980, 1700, 1557, 1472, 1399, 1268, 1128, 1111, 1047; ^1H (400 MHz, CDCl_3) δ 7.48 (1H, dd, J 5.1, 1.1, *ArH*), 7.26 (1H, dd, J 3.6, 1.1, *ArH*), 7.11 (1H, dd, J 5.1, 3.6, *ArH*), 6.78 (2H, s *br.*, NH_2), 4.27 (2H, q, J 7.1, CH_2), 1.30 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 164.3 (C), 129.9 (C), 129.0 (CH), 128.6 (C), 128.3 (CH), 126.9 (CH), 61.5 (CH_2), 14.3 (CH_3). The data were in agreement with the literature.^{55a}

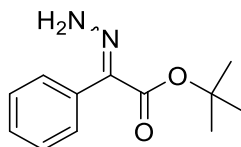
Cyclohexyl 2-hydrazono-2-phenylacetate 327



Following general procedure for preparation of hydrazones, with **cyclohexyl 2-oxo-2-phenylacetate 312** (490 mg, 2.1 mmol), eluting with ethyl acetate and light petroleum (2:8 to 3:7 gradient). **Cyclohexyl (Z) 2-hydrazono-2-phenylacetate 327A** as a colourless oil (320 mg, 62 %): Found MNa^+ 269.1266. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{NaO}_2$ requires 269.1266; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3456, 3280, 2934, 1680, 1563, 1516, 1493, 1372, 1292, 1159, 1119; ^1H (400 MHz, CDCl_3): δ 8.47 (2H, s *br.*, NH_2), 7.64 – 7.55 (2H, m, *ArH*), 7.41 – 7.29 (3H, m, *ArH*), 5.05 (1H, tt, J 8.6, 3.8, CH), 1.98-1.66 (2H, m, CH_2), 1.62

– 1.25 (6H, m, CH₂); ¹³C (100 MHz, CDCl₃): δ 162.3 (C), 136.8 (C), 131.2 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 73.1 (CH), 31.3 (CH₂), 25.2 (CH₂), 23.4 (CH₂). Further elution gave **cyclohexyl (E) 2-hydrazono-2-phenylacetate 327B** as colourless solid (170 mg, 33 %): M.p. 105-108 °C; Found MH⁺ 247.1441. C₁₄H₁₉N₂O₂ requires 247.1447; IR (ν_{max}/cm⁻¹): 3393, 3273, 2922, 2586, 1697, 1493, 1378, 1334, 1281, 1137, 1075, 1017; ¹H (400 MHz, CDCl₃): δ 7.51 – 7.43 (2H, m, ArH), 7.43 – 7.37 (1H, m, ArH), 7.31 – 7.26 (2H, m, ArH), 6.22 (2H, s br., NH₂), 4.90 (1H, tt, J 9.5, 4.0 Hz, CH), 1.99 – 1.59 (4H, m, CH₂), 1.58 – 1.11 (6H, m, CH₂); ¹³C (100 MHz, CDCl₃): δ 163.9 (C), 138.1 (C), 130.0 (C), 129.3 (CH), 129.2 (CH), 128.9 (CH), 73.8 (CH), 31.7 (CH₂), 25.4 (CH₂), 24.0 (CH₂). The data were in agreement with the literature.^{55a}

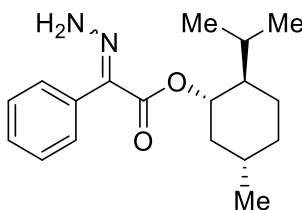
tert-Butyl-2-hydrazono-2-phenylacetate 328



Following general procedure for preparation of hydrazones, with **tert-butyl 2-oxo-2-phenylacetate 310** (880 mg, 4.60 mmol), eluting with ethyl acetate and light petroleum (1:9 to 1:0 gradient). **Tert-butyl (Z)-2-hydrazono-2-phenylacetate 328A** was obtained as a pale yellow oil (550 mg, 54 %): Found MH⁺ 221.1285. C₁₂H₁₇N₂O₂ requires 221.1290; IR (ν_{max}/cm⁻¹): 3459, 3372, 3005, 1682, 1553, 1493, 1391, 1320, 1250, 1073; ¹H (400 MHz, CDCl₃): δ 8.32 (2H, s, NH₂), 7.62-7.56 (2H, m, ArH), 7.43-7.28 (3H, m, ArH), 1.59 (9H, s, CH₃); ¹³C (100 MHz, CDCl₃) δ 162.4 (C), 137.0 (C), 132.5 (C), 128.0 (CH), 127.6 (CH), 127.2 (CH), 82.3 (C), 28.1 (CH₃). Further elution gave **tert-Butyl (E)-2-hydrazono-2-phenylacetate 328B** as a colourless solid (230 mg, 23 %): M.p. 85-87 °C; Found MNa⁺ 243.1108. C₁₂H₁₆N₂NaO₂ requires 243.1109;

IR ($\nu_{\max}/\text{cm}^{-1}$): 3394, 3265, 3001, 1703, 1576, 1489, 1365, 1274, 1165, 1015; ^1H (400 MHz, CDCl_3): 7.51-7.42 (2H, m, ArH), 7.41-7.36 (2H, m, ArH), 7.30-7.23 (2H, m, ArH), 6.09 (2H, s br., NH_2), 1.50 (9H, s, CH_3); ^{13}C (100 MHz, CDCl_3) δ 163.7 (C), 138.8 (C), 130.1 (CH), 129.11 (CH), 129.05 (CH), 128.9 (C), 81.5 (C), 28.2 (CH_3).

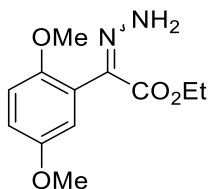
(1S*,2R*,5S*)-2-isopropyl-5-methylcyclohexyl 2-hydrazono-2-phenylacetate 329



Following general procedure for preparation of hydrazones, with **(1S*,2R*,5S*)-2-isopropyl-5-methylcyclohexyl 2-oxo-2-phenylacetate 313** (1.3 g, 4.3 mmol), eluting with ethyl acetate and light petroleum **(1S*,2R*,5S*)-2-isopropyl-5-methylcyclohexyl (Z)-2-hydrazono-2-phenylacetate 329A** was collected as a pale yellow oil (930 mg, 72 %): (Found MNa^+ 325.1885. $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ requires 325.1892; IR ($\nu_{\max}/\text{cm}^{-1}$): 3457, 3394, 2955, 1702, 1556, 1490, 1388, 1329, 1260, 1142, 1076, 1010; ^1H (400 MHz, CDCl_3): δ 8.38 (2H, s br., NH_2), 7.67 – 7.46 (2H, m, ArH), 7.39 – 7.22 (3H, m, ArH), 4.94 (1H td, J 10.9, 4.4, CH), 2.33 – 1.98 (m, 1H), 1.92-1.81 (1H, m, CH), 1.76 – 1.65 (m, 2H), 1.55 (1H, ttd, J = 11.9, 6.6, 6.0, 3.2, CH), 1.49 – 1.36 (1H, m, CH), 1.20 – 1.03 (2H, m, CH_2), 0.99 – 0.76 (10H, m); ^{13}C (100 MHz, CDCl_3) δ 162.8 (C), 136.8 (C), 132.1 (C), 128.21 (CH), 127.9 (CH), 127.6 (CH), 75.2 (CH), 46.9 (CH), 40.9 (CH_2), 34.2 (CH_2), 31.6 (CH), 26.3 (CH), 23.4 (CH_2), 22.1 (CH_3), 20.9 (CH_3), 16.2 (CH_3). Further elution gave **(1S*,2R*,5S*)-2-isopropyl-5-methylcyclohexyl (E)-2-hydrazono-2-phenylacetate 329B** as a colourless oil (300 mg, 23 %) Found MNa^+ 325.1893. $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ requires 325.1892; ($\nu_{\max}/\text{cm}^{-1}$): 3399, 3279, 2956, 1864, 1706, 1575, 1454, 1333, 1273, 1178, 1096; ^1H (400 MHz, CDCl_3): δ 7.47 (2H, tt, J 6.8, 1.2, ArH), 7.44 – 7.36 (1H, m, ArH), 7.34 – 7.22 (2H,

m, ArH), 5.93 (2H, s *br.*, NH₂) 4.85 (1H, td, *J* 10.9, 4.3, CH), 2.10-2.02 (1H, m, CH), 1.88 (1H, m, CH), 1.66 (2H, m, CH₂), 1.47 (2H, m, CH₂), 1.15 – 0.97 (2H, m, CH₂), 0.95 – 0.80 (7H, m, 2 × CH₃, CH), 0.78-0.73 (3H, m, CH₃); ¹³C (100 MHz, CDCl₃) δ 164.1 (C), 138.1 (C), 130.0 (C), 129.3 (CH), 129.2 (CH), 128.9 (CH), 75.2 (CH), 46.9 (CH), 40.9 (CH₂), 34.3 (CH₂), 31.6 (CH), 26.3 (CH), 23.5 (CH₂), 22.2 (CH₃), 20.8 (CH₃), 16.4 (CH₃).

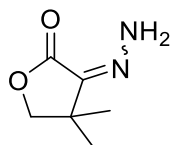
Ethyl 2-(2,5-dimethoxyphenyl)-2-hydrazonoacetate 330



Following general procedure for preparation of hydrazones, with **ethyl 2-(2,5-dimethoxyphenyl)-2-oxoacetate 321** (1.0 g, 4.2 mmol), eluting with ethyl acetate and light petroleum (2:8 to 1:1 gradient). **(Z) Ethyl 2-(2,5-dimethoxyphenyl)-2-hydrazonoacetate 330A** as a yellow oil (405 mg, 37 %): Found MH⁺ 253.1181. C₁₂H₁₇N₂O₄ requires 253.1188; IR (ν_{max}/cm⁻¹): 3448, 3291, 2834, 1692, 1582, 1492, 1421, 1261, 1173, 1044; ¹H (300 MHz, CDCl₃): 8.16 (2H, s *br.*, NH₂), 7.26 (1H, s, ArH), 6.87-6.75 (2H, m, ArH), 4.21 (2H, q, *J* 7.1, CH₂), 3.76 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 1.21 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃) δ 162.8 (C), 153.5 (C), 151.8 (C), 130.4 (C), 127.2 (C), 115.3 (CH), 114.5 (CH), 111.7 (CH), 60.2 (CH₂), 55.9 (OCH₃), 55.6 (OCH₃), 14.1 (CH₃). Further elution gave **(E) Ethyl 2-(2,5-dimethoxyphenyl)-2-hydrazonoacetate 330B** as colourless oil (480 mg, 44 %): Found MH⁺ 253.1184. C₁₂H₁₇N₂O₄ requires 253.1188; IR (ν_{max}/cm⁻¹): 3411, 3296, 3214, 1699, 1614, 1563, 1494, 1369, 1268, 1178, 1112, 1036; ¹H (300 MHz, CDCl₃): δ 6.90 (2H, app. d, *J* 7.1, ArH), 6.69 (1H, t, *J* 1.7, ArH), 6.18 (2H, s *br.*, NH₂), 4.25

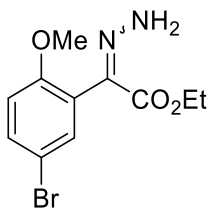
(2H, q, J 7.1, CH_2), 3.73 (3H, s, OCH_3), 3.71, s, OCH_3), 1.28 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3): δ 164.5 (C), 153.9 (C), 151.1 (C), 135.3 (C), 119.3 (C), 116.1 (CH), 115.3 (CH), 113.0 (CH), 61.1 (CH_2), 56.4 (OCH_3), 55.8 (OCH_3), 14.4 (CH_3).

3-Hydrazono-4,4-dimethyldihydrofuran-2(3H)-one 331



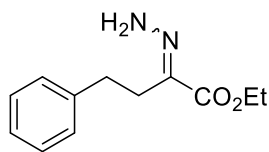
Following general procedure for preparation of hydrazones, with 4,4-dimethyldihydrofuran-2,3-dione (1.0 g, 7.8 mmol), eluting with ethyl acetate and light petroleum (1:1 to 1:0 gradient). **(Z)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3H)-one 331A** as a colourless oil (220 mg, 20 %): Found MH^+ 143.0822. $\text{C}_6\text{H}_{11}\text{N}_2\text{O}_2$ requires 143.0821; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3445, 3287, 2966, 1726, 1582, 1462, 1370, 1282, 1180, 1064, 1004; ^1H (300 MHz, $\text{DMSO}-d_6$): 8.96 (2H, s br., NH_2), 4.13 (2H, s, CH_2), 1.16 (6H, s, CH_3); ^{13}C (75 MHz, $\text{DMSO}-d_6$) δ 164.4 (C), 131.4 (C), 78.3 (CH_2), 37.3 (C), 26.0 (CH_3); Further elution gave **(E)-3-Hydrazono-4,4-dimethyldihydrofuran-2(3H)-one 331B** as a colourless solid (150 mg, 14 %): M.p. 160-165 °C; Found MH^+ 143.0824. $\text{C}_6\text{H}_{11}\text{N}_2\text{O}_2$ requires 143.0821; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3410, 3295, 3232, 1726, 1574, 1476, 1376, 1315, 1263, 1193, 1057; ^1H (300 MHz, $\text{DMSO}-d_6$): 7.96 (2H, s br., NH_2), 3.95 (2H, s, CH_2), 1.32 (6H, s, CH_3); ^{13}C (75 MHz, $\text{DMSO}-d_6$) δ 167.5 (C), 132.9 (C), 77.3 (CH_2), 36.4 (C), 21.3 (CH_3). The data were in agreement with the literature.^{55a}

Ethyl 2-(5-bromo-2-methoxyphenyl)-2-hydrazonoacetate 332



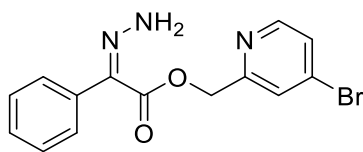
Following general procedure for preparation of hydrazones, with ethyl **2-(5-bromo-2-methoxyphenyl)-2-oxoacetate 320** (3.60 g, 12.6 mmol), eluting with ethyl acetate and light petroleum (2:8 to 1:1 gradient). **Ethyl (Z)-2-(5-bromo-2-methoxyphenyl)-2-hydrazonoacetate 332A** as a pale yellow solid (1.07 g, 28 %): M.p. 95-98 °C; Found MH⁺ 301.0188. C₁₁H₁₄O₃BrN₂ requires 301.0188; IR (ν_{max}/cm⁻¹): 3598, 3265, 2883, 1687, 1562, 1482, 1438, 1365, 1259, 1169, 1136, 1026; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (2H, s *br.*, NH₂), 7.44–7.37 (2H, m, ArH), 6.74 (1H, d, *J* 8.6, ArH), 4.21 (2H, q, *J* 7.1, CH₂), 3.76 (3H, s, OCH₃), 1.22 (3H, t, *J* 7.1, CH₃); ¹³C (100 MHz, CDCl₃) δ 162.7 (C), 156.9 (C), 132.9 (CH), 132.0 (CH), 128.9 (C), 128.6 (C), 112.9 (C), 112.3 (CH), 60.5 (CH₂), 55.7 (OCH₃), 14.3 (CH₃). Further elution gave **Ethyl (E)-2-(5-bromo-2-methoxyphenyl)-2-hydrazonoacetate 332B** as a pale pink solid (2.0 g, 52 %): M.p. 105-107 °C; Found MH⁺ 301.0187. C₁₁H₁₄O₃BrN₂ requires 301.0188; IR (ν_{max}/cm⁻¹): 3384, 3272, 2978, 701, 1571, 1484, 1324, 1267, 1220, 1153, 1040; ¹H (400 MHz, CDCl₃) δ 7.43 (1H, dd, *J* 8.8, 2.5, ArH), 7.22 (1H, d, *J* 2.5, ArH), 6.83 (1H, d, *J* 8.8, ArH), 6.26 (2H, s *br.*, NH₂), 4.21 (2H, q, *J* 7.1, CH₂), 3.72 (3H, s, OCH₃), 1.25 (3H, t, *J* 7.1, CH₃); ¹³C (100 MHz, CDCl₃) δ 164.1 (C), 156.1 (C), 133.6 (CH), 133.3 (C), 132.7 (CH), 120.6 (C), 113.3 (CH), 113.0 (C), 61.1 (CH₂), 55.9 (OCH₃), 14.3 (CH₃).

Ethyl 2-hydrazineylidene-4-phenylbutanoate 333



Following general procedure for preparation of hydrazones, with ethyl 2-oxo-4-phenylbutanoate (1.0 mL, 5.3 mmol), eluting with ethyl acetate and light petroleum (2:8 to 1:1 gradient). **Ethyl (Z)-2-hydrazineylidene-4-phenylbutanoate 333A** was obtained as a colourless oil (82 mg, 7 %): Found MH^+ 221.1291. $C_{12}H_{17}N_2O_2$ requires 221.1290; IR (ν_{max}/cm^{-1}): 3459, 3294, 2981, 1690, 1570, 1496, 1390, 1298, 1243, 1172, 1071; ^1H (400 MHz, $CDCl_3$): δ 8.09 (2H, s *br.*, NH_2), 7.32 – 7.26 (2H, m, *ArH*), 7.23 – 7.16 (3H, m, *ArH*), 4.22 (2H, q, J 7.1, CH_2), 2.87 – 2.80 (2H, m, CH_2), 2.73 – 2.66 (2H, m, CH_2), 1.33 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 163.0 (C), 142.1 (C), 130.8 (C), 128.6 (CH), 128.5 (CH), 126.0 (CH), 60.4 (CH_2), 35.3 (CH_2), 34.4 (CH_2), 14.3 (CH_3). Further elution gave **ethyl (E)-2-hydrazineylidene-4-phenylbutanoate 333B** as a colourless oil (220 mg, 19 %): Found MH^+ 221.1293. $C_{12}H_{17}N_2O_2$ requires 221.1290; IR (ν_{max}/cm^{-1}): 3409, 3309, 3228, 2980, 1694, 1578, 1496, 1395, 1328, 1256, 1168, 1096; ^1H (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (2H, m, *ArH*), 7.23 – 7.18 (3H, m, *ArH*), 5.78 (2H, s *br.*, NH_2), 4.27 (2H, q, J 7.1, CH_2), 2.84 – 2.78 (2H, m, CH_2), 2.77 – 2.71 (2H, m, CH_2), 1.33 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 164.9 (C), 141.0 (C), 139.8 (C), 128.8 (CH), 128.4 (CH), 126.6 (CH), 61.3 (CH_2), 31.4 (CH_2), 26.4 (CH_2), 14.4 (CH_3). The data were in agreement with the literature.^{55a}

(4-bromopyridin-2-yl)methyl (Z)-2-hydrazineylidene-2-phenylacetate 362A



Following general procedure for hydrazones, with **pyridin-2-ylmethyl 2-oxo-2-phenylacetate 361** (1.0 g, 3.0 mmol), eluting with ethyl acetate and light petroleum (2:8 to 1:1 gradient). Pale yellow oil (210 mg, 21 %): M.p. 95-96 °C; Found MH^+ 334.0192. $C_{14}H_{13}BrN_3O_2^+$ requires 334.0192; IR (ν_{max}/cm^{-1}): 3421, 3241, 3058, 1689, 1516, 1472, 1363, 1319, 1296, 1244, 1149, 1089, 1007; ^1H (400 MHz, $CDCl_3$): δ 8.64 (1H, dd, J 2.4, 0.7, ArH), 8.54 (2H, s *br.*, NH_2), 7.79 (1H, dd, J 8.3, 2.3, ArH), 7.64 – 7.49 (2H, m, ArH), 7.41 – 7.28 (3H, m, ArH), 7.16 (1H, dd, J 8.3, 0.7, ArH), 5.34 (2H, s, CH_2); ^{13}C (100 MHz, $CDCl_3$): δ 162.3 (C), 154.1 (C), 150.6 (CH), 139.5 (CH), 136.5 (C), 130.1 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 122.8 (CH), 112.0 (C), 66.1 (CH₂).

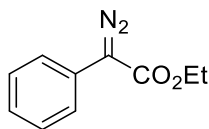
4.8 General Method 1 for Hydrazone Oxidation

A suspension of hydrazone (0.26 mmol), TEMPO (10 mol %), and laccase (33 mg, 350 U) in pH 8.0 phosphate buffer (3.5 mL) and ⁿBuOH (200 μ L) was stirred at 30 °C for 4 h. The reaction mixture was added to water (10 mL) and extracted with ethyl acetate (3 $\times$ 10 mL). The organic extracts were combined, washed with brine (10 mL), dried over MgSO₄ and filtered. The solvent was removed *in vacuo*, to afford a residue that was purified *via* column chromatography, using the eluent specified to give the desired diazo compound.

4.9 General Method 2 for Hydrazone Oxidation

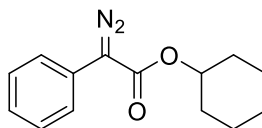
A solution of hydrazone (0.26 mmol), NCS (45 mg, 0.34 mmol), and potassium carbonate (36 mg, 0.26 mmol) in ethanol for 4 h. The solvent was removed *in vacuo*, to afford a residue that was purified *via* column chromatography, using the eluent specified to give the desired diazo compound.

Ethyl 2-diazo-2-phenylacetate 304



Following general method 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (1:99) (50 mg, quantitative yield) or laccase general method 1 for hydrazone oxidation (42 mg, quantitative yield), eluting with ethyl acetate and light petroleum (1:99): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2982, 2080, 1698, 1597, 1498, 1447, 1370, 1286, 1149, 1048; ^1H (300 MHz, CDCl_3): δ 7.5-7.42 (2H, m, ArH), 7.39-7.30 (2H, m, ArH), 7.18-7.11 (1H, m, ArH), 4.30 (2H, q, J 7.1, CH_2), 1.32 (3H, t, J 7.1, CH_3); ^{13}C (75 MHz, CDCl_3) δ 164.6 (C), 128.6 (CH), 125.4 (C), 125.4 (CH), 123.6 (CH), 60.6 (CH_2), 14.2 (CH_3). The signal due to CN_2 was not observed. The data were in agreement with the literature.^{55a}

Cyclohexyl 2-diazo-2-phenylacetate 334

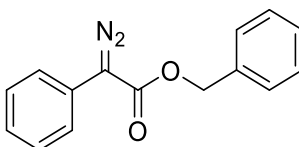


Following general method 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 44 mg, 81 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2934, 2858, 2079, 1694, 1598, 1498, 1374, 1334, 1239, 1164; ^1H (400 MHz, CDCl_3): δ 7.52-7.46 (2H, m, ArH), 7.43-7.33 (2H, m, ArH), 7.21-7.14 (1H, m, ArH), 4.99 (1H, tt, J 7.8, 3.8, CH), 1.98-1.84 (2H, m, CH_2), 1.81-1.68 (2H, m, CH_2), 1.59-1.25 (6H, m, CH_2); ^{13}C (100 MHz, CDCl_3) δ 164.9 (C), 129.0 (CH), 126.0 (C), 125.8 (CH), 124.1 (CH), 73.4

(CH), 31.9 (CH₂), 25.5 (CH₂), 23.7 (CH₂). The signal due to CN₂ was not observed.

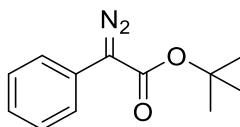
The data were in agreement with the literature.^{55a}

Benzyl 2-diazo-2-phenylacetate 335



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (1:99) (orange oil, 66 mg, quant.), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 43 mg, 77 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2082, 1697, 1496, 1345, 1285, 1241, 1146; ¹H (400 MHz, CDCl₃): δ 7.55-7.46 (2H, m, ArH), 7.45-7.30 (7H, m, ArH), 7.23-7.15 (1H, m, ArH), 5.33 (2H, s, CH₂); ¹³C (100 MHz, CDCl₃) δ 165.0 (C), 135.9 (C), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 126.0 (CH), 125.4 (C), 124.0 (CH), 66.5 (CH₂). The signal due to CN₂ was not observed. The data were in agreement with the literature.¹²⁸

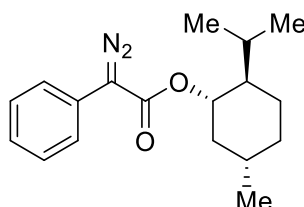
tert-Butyl 2-diazo-2-phenylacetate 336



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 48 mg, quant.), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 46 mg, 96 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2796, 2078, 1696, 1497, 1452, 1367, 1287, 1140, 1007; ¹H (400 MHz, CDCl₃): 7.51-7.43 (2H, m, ArH), 7.41-7.32 (2H, m, ArH), 7.20-7.12

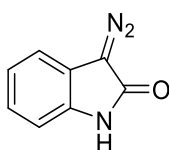
(1H, m, ArH), 1.96 (9H, s, CH₃); ¹³C (100 MHz, CDCl₃): δ 164.7 (C), 129.0 (CH), 126.3 (C), 125.7 (CH), 124.1 (CH), 82.2 (C), 28.5 (CH₃). The signal due to CN₂ was not observed. The data were in agreement with the literature.¹²⁹

(1S*,2R*,5S*)-2-isopropyl-5-methylcyclohexyl 2-diazo-2-phenylacetate 337



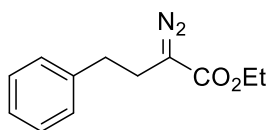
Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 79 mg, quant.), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95) (orange oil, 41 mg, 62 %): IR (ν_{max}/cm⁻¹): 2954, 2080, 1696, 1575, 1451, 1333, 1240, 1163, 1096; ¹H (400 MHz, CDCl₃): δ 7.55 – 7.45 (2H, m, ArH), 7.43 – 7.33 (2H, m, ArH), 7.21 – 7.12 (1H, m, ArH), 4.88 (1H, td, *J* 10.8, 4.4, CH), 2.19 – 2.05 (1H, m, CH), 1.96-1.88 (1H, m, CH), 1.78 – 1.64 (2H, m, CH₂), 1.48 – 1.39 (1H, m, CH), 1.20 – 1.03 (2H, m, CH₂), 0.99 – 0.88 (7H, m, CH₃, CH), 0.81 (3H, d, *J* 7.0, CH₃); ¹³C (100 MHz, CDCl₃): δ 165.0 (C), 129.0 (CH), 126.0 (C), 125.8 (CH), 124.1 (CH), 75.2 (CH), 47.3 (CH), 41.5 (CH₂), 34.4 (CH₂), 31.6 (CH), 26.7 (CH), 23.8 (CH₂), 22.2 (CH₃), 20.9 (CH₃), 16.7 (CH₃). The signal due to CN₂ was not observed. The data were in agreement with the literature.¹³⁰

3-Diazoindolin-2-one 338



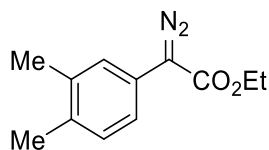
Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (3:7 to 1:1 gradient) (orange oil, 33 mg, 94 %): m.p. 138-140 °C (decomposition). Found MNa^+ 182.0327. $C_8H_5N_3ONa$ requires 182.0330. IR (ν_{max}/cm^{-1}): 3120, 2081, 1675, 1594, 1410, 1332, 1209, 1056; ^1H (400 MHz, $CDCl_3$): δ 9.62 (1H, s, NH), 7.20-7.12 (2H, m, ArH), 7.10-7.01 (2H, m, ArH); ^{13}C (100 MHz, $CDCl_3$) δ 169.6 (C), 132.1 (C), 125.7 (CH), 122.3 (CH), 118.4 (CH), 117.4 (CH), 111.0 (C). The signal due to CN_2 was not observed. The data were in agreement with the literature.^{55a}

Ethyl 2-diazo-4-phenylbutanoate 339



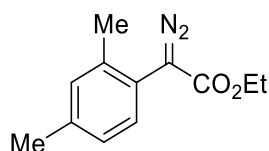
Following general procedure 2 for hydrazone oxidation. Yellow oil (42 mg, 74 %): IR (ν_{max}/cm^{-1}): 2981, 2080, 1685, 1497, 1392, 1309, 1169, 1073; ^1H (400 MHz, $CDCl_3$): δ 7.30 (2H, tt, J 7.0, 1.1, ArH), 7.25 – 7.18 (3H, m, ArH), 4.22 (2H, q, J 7.1, CH_2), 2.84 (2H, t, J 7.5, CH_2), 2.60 (2H, t, J 7.5, CH_2), 1.27 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 140.3 (C), 128.71 (CH) 128.65 (CH), 126.6 (CH), 60.9 (CH_2), 34.1 (CH_2), 25.5 (CH_2), 14.7 (CH_3). The data were in agreement with the literature.^{55a}

Ethyl 2-diazo-2-(3,4-dimethylphenyl)acetate 341



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95). Orange oil (57 mg, quant.): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2978, 2076, 1699, 1505, 1447, 1368, 1290, 1191, 1056; ^1H (400 MHz, CDCl_3): δ 7.26-7.24 (1H, m, ArH), 7.21 (1H, d, J 8.0, ArH), 7.15 (1H, d, J 8.0, ArH), 4.33 (2H, q, J 7.1, CH_2), 2.27 (3H, s, CH_3), 2.25 (3H, s, CH_3), 1.34 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 165.7 (C), 137.4 (C), 134.5 (C), 130.3 (CH), 125.5 (CH), 122.7 (C), 121.9 (CH), 61.0 (CH_2), 20.1 (CH_3), 19.4 (CH_3), 14.6 (CH_3). The signal due to CN_2 was not observed. The data were in agreement with the literature.¹³¹

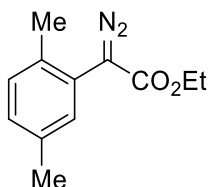
Ethyl 2-diazo-2-(2,4-dimethylphenyl)acetate 342



Following general procedure 2 for hydrazone oxidation, eluting with diethyl ether and pentanes (2:8) (yellow oil, 42 mg, 72 %), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (95:5) (yellow oil, 44 mg, 92 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2916, 2083, 1822, 1700, 1612, 1446, 1320, 1230, 1176, 1153, 1093, 1021; ^1H (400 MHz, CDCl_3): δ 7.27 (1H, d, J 7.5, ArH), 7.12 – 7.02 (2H, m, ArH), 4.29 (2H, q, J 7.1, CH_2), 2.33 (3H, s, CH_3), 2.27 (3H, s, CH_3), 1.31 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 175.4 (C), 139.0 (C), 137.8 (C), 131.6 (CH), 131.0 (CH).

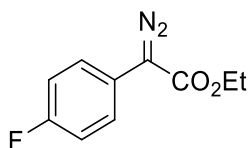
(CH), 127.3 (CH), 121.3 (C), 61.2 (CH₂), 21.3 (CH₃), 20.0 (CH₃), 14.7 (CH₃). The signal due to CN₂ was not observed. The data were in agreement with the literature.^{55a}

Ethyl 2-diazo-2-(2,5-dimethylphenyl)acetate 343



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95). Yellow oil (54 mg, 95 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2979, 2079, 1699, 1573, 1446, 1367, 1287, 1202, 1126; ¹H (400 MHz, CDCl₃): δ 7.23 – 7.19 (1H, m, ArH), 7.15 (1H, d, *J* 7.8, ArH), 7.08 (1H, dd, *J* 7.8, 1.8, ArH), 4.31 (2H, q, *J* 7.1, CH₂), 2.34 (3H, s, CH₃), 2.27 (3H, s, CH₃), 1.33 (3H, t, *J* 7.1, CH₃); ¹³C (100 MHz, CDCl₃): δ 166.3 (C), 136.1 (C), 134.7 (C), 131.4 (CH), 130.8 (CH), 129.8 (CH), 124.1 (C), 61.2 (CH₂), 21.0 (CH₃) 19.6 (CH₃), 14.7 (CH₃). The signal due to CN₂ was not observed. The data were in agreement with the literature.⁵¹

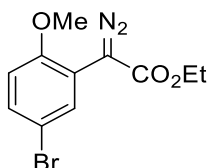
Ethyl 2-diazo-2-(4-fluorophenyl)acetate 344



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (1:9) (orange oil, 55 mg, quant.), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and pentanes (5:95) (orange oil, 40 mg, 87 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2985, 2082, 1698, 1510, 1417, 1371, 1287, 1150, 1041; ¹H (400 MHz, CDCl₃) δ 7.52 – 7.36 (2H, m, ArH), 7.15 – 6.96 (2H, m, ArH), 4.33 (2H, q, *J* 7.1,

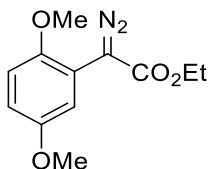
CH_2), 1.34 (3H, t, J 7.1, CH_2). ^{13}C (100 MHz, CDCl_3) δ 165.4 (C), 161.1 (d, J^{CF} 250, C), 126.0 (d, J^{CF} 7.9, CH), 121.5 (d, J^{CF} 3.4, C), 116.1 (d, J^{CF} 22, CH), 61.2 (CH_2), 14.6 (CH_3). The data were in agreement with the literature.¹³¹

Ethyl 2-(5-bromo-2-methoxyphenyl)-2-diazoacetate 345



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (2:8) (yellow oil, 65 mg, 83 %), or general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (1:9) (yellow oil, 46 mg, 70 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2939, 2099, 1685, 1492, 1458, 1403, 1367, 1287, 1179, 1140, 1117, 1020; ^1H (400 MHz, CDCl_3) δ 7.73 (1H, d, J 2.5, ArH), 7.32 (1H, dd, J 8.8, 2.5, ArH), 6.75 (1H, d, J 8.8, ArH), 4.30 (2H, q, J 7.1, CH_2), 3.83 (3H, s, OCH_3), 1.32 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 165.8 (C), 154.4 (C), 132.2 (CH), 130.9 (CH), 116.2 (C), 113.6 (C), 112.5 (CH), 61.2 (CH_2), 56.0 (OCH_3), 14.6 (CH_3). The signal due to CN_2 was not observed. The data were in agreement with the literature.¹³²

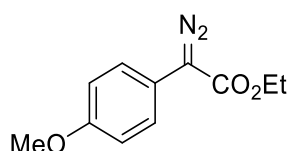
Ethyl 2-diazo-2-(2,5-dimethoxyphenyl)acetate 346



Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (0:1 to 5:95 gradient) (yellow oil, 66 mg, quant.), or general procedure 1 for hydrazone oxidation: IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2937, 2092, 1694, 1501, 1446, 1390, 1335,

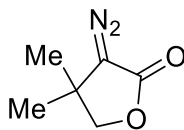
1222, 1170, 1041; ^1H (400 MHz, CDCl_3) δ 7.21 (1H, d, J 2.8, ArH), 6.86 – 6.76 (2H, m, ArH), 4.31 (2H, q, J 7.1, CH_2), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 1.34 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3) δ 166.3 (C), 154.1 (C), 149.7 (C), 115.0 (C), 114.8 (CH), 113.9 (CH), 112.2 (CH), 61.0 (CH_2), 56.3 (OCH_3), 55.9 (OCH_3), 14.7 (CH_3). The signal due to CN_2 was not observed. The data were in agreement with the literature.⁵¹

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate 347



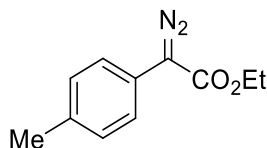
Following general procedure 2 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (1:9) (orange oil, 58 mg, quant.), or with general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and pentanes (5:95) (orange oil, 82 %): (IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2078, 1750, 1695, 1608, 1511, 1369, 1341, 1243, 1152; ^1H (400 MHz, CDCl_3): δ 7.41 – 7.36 (2H, m, ArH), 6.98 – 6.88 (2H, m, ArH), 4.32 (2H, q, J 7.1, CH_2), 3.80 (3H, s, CH_3), 1.33 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 165.9 (C), 158.1 (C), 126.1 (CH), 117.1 (C), 114.7 (CH), 61.0 (CH_2), 55.5 (CH_3), 14.6 (CH_3). The data were in agreement with the literature.¹³³

3-Diazo-4,4-dimethyldihydrofuran-2(3H)-one 348



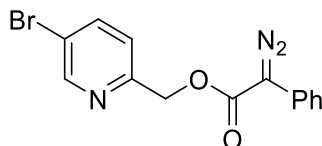
Following general procedure 2 for hydrazone oxidation. Yellow oil (30 mg, 83 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2968, 2089, 1789, 1729, 1463, 1345, 1180, 1051; ^1H (400 MHz, CDCl_3): 4.06 (2H, s, CH_2), 1.42 (6H, s, CH_3); ^{13}C (100 MHz, CDCl_3): 169.3 (C), δ 78.7 (CH_2), 39.0 (C), 26.1 (CH_3). The data were in agreement with the literature.^{55a}

Ethyl 2-diazo-2-(p-tolyl)acetate 354



Following laccase general procedure 1 for hydrazone oxidation, eluting with ethyl acetate and light petroleum (5:95). Orange oil (39 mg, 87 %): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 2981, 2079, 1738, 1568, 1513, 1445, 1369, 1284, 1194, 1095; ^1H (400 MHz, CDCl_3): δ 7.41 – 7.32 (2H, m, ArH), 7.23 – 7.16 (2H, m, ArH), 4.33 (2H, q, J 7.1, CH_2), 2.34 (3H, s, CH_3), 1.34 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 165.6 (C), 135.8 (C), 129.8 (CH), 124.3 (CH), 122.4 (C), 61.1 (CH_2), 21.1 (CH_3), 14.6 (CH_3).

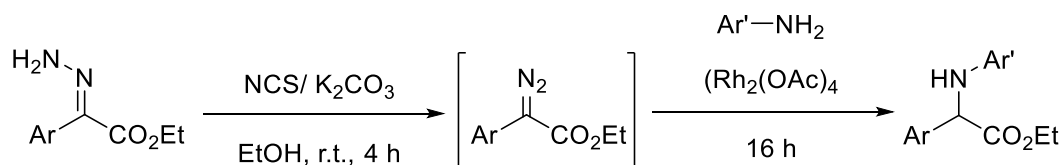
(5-bromopyridin-2-yl)methyl 2-diazo-2-phenylacetate 363



Following general procedure 2, with **pyridin-2-ylmethyl (Z)-2-hydrazineylidene-2-phenylacetate 362A** (20 mg, 0.06 mmol), NCS (11 mg, 0.08 mmol) and K_2CO_3 (8

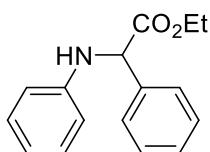
mg, 0.06 mmol) in ethanol (1 mL), eluting with ethyl acetate and light petroleum (1:9). Yellow oil (20 mg, Quant.): IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3041, 2095, 1688, 1573, 1469, 1348, 1308, 1264, 1194, 1076; ^1H (400 MHz, CDCl_3): δ 8.66 (1H, dd, J 2.4, 0.8, *ArH*), 7.84 (1H, dd, J 8.3, 2.4, *ArH*), 7.55 – 7.44 (2H, m, *ArH*), 7.42 – 7.35 (2H, m, *ArH*), 7.29 (1H, dd, J 8.3, 0.8, *ArH*), 7.24 – 7.14 (1H, m, *ArH*), 5.37 (2H, s, CH_2); ^{13}C (100 MHz, CDCl_3): δ 164.8 (C), 154.5 (C), 150.7 (CH), 139.6 (CH), 129.2 (CH), 126.2 (CH), 125.2 (C), 124.2 (CH), 123.1 (CH), 120.1 (C), 66.5 (CH_2). The data were in agreement with the literature.³⁰

4.10 General Method for Preparation of Amines



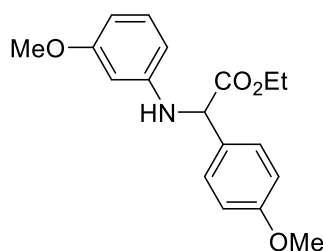
A solution of (*E*)-hydrazone (0.26 mmol), NCS (38 mg, 0.29 mmol) and K₂CO₃ (36 mg, 0.26 mmol) in ethanol (4 mL) was stirred at room temperature for 4 h. A solution of Rh₂(OAc)₄ (11 mg, 0.026 mmol) and the required aniline (0.78 mmol) in ethanol (1 mL) was added in one portion, and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed *in vacuo*, and the residue purified by column chromatography to give the desired amine.

Ethyl 2-phenyl-2-(phenylamino)acetate 349



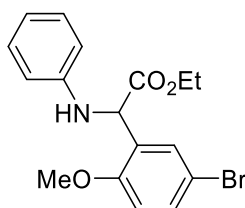
Following general method for preparation of amines, eluting with ethyl acetate and light petroleum (5:95). Pale yellow solid (53 mg, 80 %): M.p. 70-74 °C; Found MH⁺ 256.1338. C₁₆H₁₈NO₂ requires 256.1388; IR (ν_{max}/cm⁻¹): 3395, 2902, 1721, 1602, 1505, 1453, 1364, 1251, 1191, 1157, 1118, 1072; ¹H (400 MHz, CDCl₃): δ 7.57 – 7.44 (2H, m, ArH), 7.39 – 7.27 (3H, m, ArH), 7.19 – 7.04 (2H, m, ArH), 6.70 (1H, tt, *J* 7.3, 1.1, ArH), 6.62 – 6.46 (2H, m, ArH), 5.07 (1H, s, CH), 4.96 (1H, s *br.*, NH), 4.29-4.20 (1H, m, CH_ACH_B), 4.19-4.10 (1H, m, CH_ACH_B), 1.22 (3H, t, *J* 7.1, CH₃); ¹³C (75 MHz, CDCl₃): δ 171.7 (C), 145.9 (C), 137.6 (C), 129.1 (CH), 128.7 (CH), 128.1 (CH), 127.1 (CH), 117.9 (CH), 113.3 (CH), 61.7 (CH₂), 60.7 (CH), 13.9 (CH₃). The data were in agreement with the literature.⁷⁸

Ethyl 2-(4-methoxyphenyl)-2-((3-methoxyphenyl)amino)acetate 350



Following general method for preparation of amines. Yellow oil (80 mg, 98 %): Found MNa^+ 338.1370. $\text{C}_{18}\text{H}_{21}\text{NO}_4\text{Na}^+$ requires 338.1368; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3392, 2934, 1729, 1608, 1508, 1368, 1208, 1161, 1027; ^1H (400 MHz, CDCl_3): δ 7.43 – 7.36 (2H, m, ArH), 7.03 (1H, t, J 8.1, ArH), 6.93 – 6.82 (2H, m, ArH), 6.26 (1H, ddd, J 8.1, 2.3, 0.8, ArH), 6.18 (1H, ddd, J 8.1, 2.3, 0.8, ArH), 6.11 (1H, t, J 2.3, ArH), 4.99 (1H, s, CH), 4.93 (1H, s br., NH), 4.23 (1H, dq, J 10.8, 7.1, CH_AHB), 4.13 (1H, dq, J 10.7, 7.1, CH_AHB), 3.79 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 1.22 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 172.1 (C), 160.8 (C), 159.6 (C), 147.5 (C), 130.1 (CH), 129.7 (C), 128.4 (CH), 114.3 (CH), 106.5 (CH), 103.3 (CH), 99.6 (CH), 61.9 (CH_2), 60.2 (CH), 55.4 (OCH_3), 55.1 (OCH_3), 14.1 (CH_3).

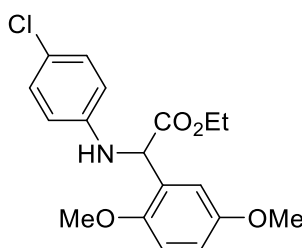
Ethyl 2-(5-bromo-2-methoxyphenyl)-2-(p-tolylamino)acetate 351



Following general method for preparation of amines. Red oil (90 mg, 92 %): Found MH^+ 378.0707. $\text{C}_{18}\text{H}_{21}\text{BrNO}_3^+$ requires 378.0705; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3393, 2971, 1730, 1650, 1589, 1484, 1402, 1281, 1183, 1024; ^1H (400 MHz, CDCl_3): δ 7.48 (1H, d, J 2.5, ArH), 7.35 (1H, dd, J 8.7, 2.5, ArH), 6.95 (2H, d, J 8.4, ArH), 6.79 (1H, d, J 8.7, ArH), 6.53 (1H, d, J 8.4, ArH), 5.42 (1H, s, CH), 4.26 – 4.17 (1H, m, CH_AHB), 4.17 –

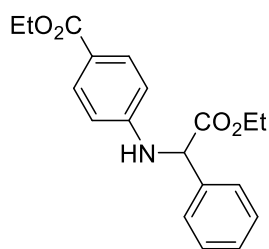
4.09 (1H, m, $\text{CH}_\text{A}\text{H}_\text{B}$), 3.89 (3H, s, OCH_3), 2.21 (3H, s, CH_3), 1.20 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 171.9 (C), 156.5 (C), 143.9 (C), 132.1 (CH), 130.9 (CH), 129.8 (CH), 129.1 (C), 127.6 (C), 113.7 (CH), 113.4 (C), 113.0 (CH), 61.8 (CH_2), 56.1 (OCH_3), 54.9 (CH), 20.5 (CH_3), 14.2 (CH_3).

Ethyl 2-((4-chlorophenyl)amino)-2-(2,5-dimethoxyphenyl)acetate 352



Following general method for preparation of amines. Pale yellow oil (65 mg, 84 %): Found $\text{MNa}^+ \text{C}_{18}\text{H}_{20}\text{ClNO}_4\text{Na}^+$ requires 372.0979; IR ($\nu_{\text{max}}/\text{cm}^{-1}$): 3391, 3012, 1935, 1723, 1600, 1426, 1318, 1254, 1175, 1048, 1023; ^1H (400 MHz, CDCl_3): δ 7.10 – 7.01 (2H, m, ArH), 6.89 (1H, d, J 3.0, ArH), 6.86 (1H, d, J 8.9, ArH), 6.79 (1H, dd, J 8.9, 3.0, ArH), 6.60 – 6.48 (2H, m, ArH), 4.27 – 4.17 (1H, m, $\text{CH}_\text{A}\text{CH}_\text{B}$), 4.17 – 4.10 (1H, m, $\text{CH}_\text{A}\text{CH}_\text{B}$), 3.87 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 1.19 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, CDCl_3): δ 172.0 (C), 154.0 (C), 151.6 (C), 145.0 (C), 129.1 (CH), 127.3 (C), 122.7 (C), 114.7 (CH), 114.1 (CH), 113.9 (CH), 112.6 (CH), 61.8 (CH_2), 56.6 (CH), 55.8 (OCH_3), 54.8 (OCH_3), 14.2 (CH_3).

Ethyl 4-((2-ethoxy-2-oxo-1-phenylethyl)amino)benzoate 353



Following general method for preparation of amines. Red solid (65 mg, 76 %): M.p. 112-114 °C; Found MH^+ 328.1550. $C_{19}H_{22}NO_4^+$ requires 328.1549; IR (ν_{max}/cm^{-1}): 3394, 2982, 1725, 1608, 1529, 1454, 1390, 1277, 1170, 1108; ^1H (400 MHz, $CDCl_3$): δ 7.85 – 7.79 (2H, m, ArH), 7.50 – 7.44 (2H, m, ArH), 7.40 – 7.29 (3H, m, ArH), 6.72 – 6.33 (2H, m, ArH), 5.45 (1H, s br., NH), 5.11 (1H, s, CH), 4.32 – 4.21 (3H, m, CH_2 , CH_AH_B), 4.14 (1H, dq, J 10.8, 7.1, CH_AH_B), 1.33 (3H, t, J 7.1, CH_3), 1.22 (3H, t, J 7.1, CH_3); ^{13}C (100 MHz, $CDCl_3$): δ 171.3 (C), 166.8 (C), 149.6 (C), 137.0 (C), 131.5 (CH), 129.1 (CH), 128.6 (CH), 127.2 (CH), 119.7 (C), 112.4 (CH), 62.3 (CH_2), 60.4 (CH_2), 60.2 (CH), 14.5 (CH_3), 14.1 (CH_3).

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