

Investigating the chemistry of pyridinium ylides



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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 has been fully acknowledged in the text.

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Dr. James Dowden

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Abstract

This thesis describes investigation into catalytic formation of pyridinium ylides from diazo compounds and their subsequent reactivity. In particular, cycloaddition reactions with electrophilic alkenes are performed to generate tetrahydroindolizines that can be transformed into indolizidines by reduction. Pyridinium ylides have been shown to be very reactive intermediates that are able to generate complex molecules with excellent yield and diastereoselectivity.

The introduction section provides a background on the chemistry of pyridinium ylides. This section also reports on development in the field of 1,3-dipolar cycloaddition chemistry of pyridinium ylides. A background to the generation of the pyridinium ylides by *in situ* decomposition of diazo compounds with transition metal catalysts was described.

The results and discussion section is divided into three sections. Section one describes metal-catalysed decomposition of diazo compounds to produce pyridinium ylides *in situ*. Performing this reaction in the presence of dipolarophiles gives tetrahydroindolizine cycloadducts in good yield with excellent diastereoselectivity. Subsequent reduction of the 1,2-dihydropyridine moiety component of the resulting cycloadducts is also demonstrated. Crystal structures of some of the resulting indolizidine products were valuable for assigning relative stereochemistry.

Section two describes attempts towards an asymmetric (3+2) dipolar cycloaddition, using pyridinium ylides produced by the *in-situ* decomposition of diazo compounds with either chiral transition metal

catalysts or achiral catalysts in the presence of chiral Brønsted acids. We started our investigation by exploring how acids with various pKa's e.g. camphorsulfonic acid, benzoic acid and p-nitro benzoic acid influenced the reaction between pyridine and diazo compounds.

Finally, section three describes attempts to develop new multicomponent catalytic reactions with mono and di-substituted diazo compounds to access structurally complex pyridinium salts *via in situ* C-alkylation of catalytically generated pyridinium ylides.

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List of abbreviations

4-ABSA	4-acetamidobenzenesulfonyl azide
BOX	Bisoxazoline
BH	Brønsted acid
BINOL	1,1'-Bi-2-naphthol
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDBNP	Didodecylbinaphtholphosphate
DEPT	distortionless enhancement by polarization transfer
DMAD	dimethyl acetylenedicarboxylate
DMSO	Dimethylsulfoxide
DOSP	dodecylbenzenesulfonyl)prolinate
E1cB	Elimination Unimolecular Conjugate Base
e.e.	enantiomeric excess
ESI	electrospray ionisation
EWG	electron-withdrawing group
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra-red
LUMO	lowest unoccupied molecular orbital
MEPY	methyl 2-pyrrolidone carboxylate
MEOX	methyl 2-oxazolidone carboxylate

MeCN	acetonitrile
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
MVK	Methyl vinyl ketone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Py	Pyridine
SM	starting material
THF	Tetrahydrofuran
TsNIK	potassium <i>N</i> -iodo <i>p</i> -toluenesulfonamide
TsN ₃	Tosyl azide
TLC	Thin layer chromatography
TPP	Tetraphenylporphyrin
Ts	<i>p</i> -toluenesulfonyl
UV	ultra-violet

Introduction

1.Introduction

Pyridines are widespread heterocycles found in pharmaceuticals, and materials science (Figure 1).¹

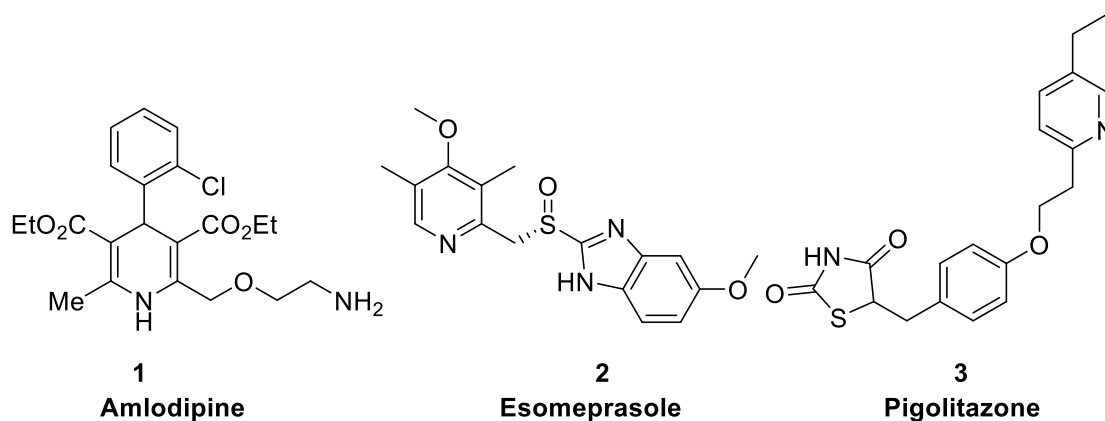


Figure 1. Examples of commercialized pyridine or dihydropyridine derivatives.

The chemistry to functionalise pyridine remains an important challenge.² For example, pyridine is poorly reactive for aromatic electrophilic substitution due to the deactivating nature of (electronegative) nitrogen which destabilises the positively charged intermediates (Figure 2).

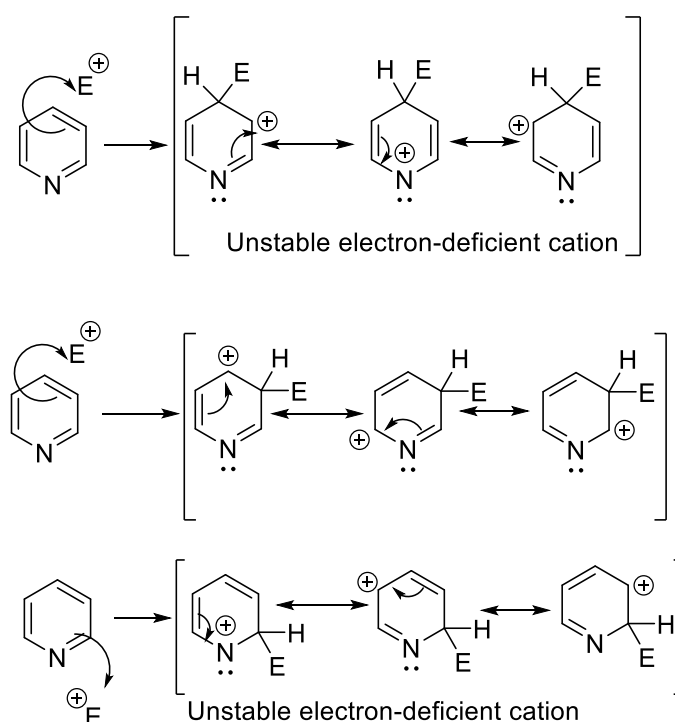


Figure 2. Possible electrophelic substitution on pyridine ring

The lone pair on nitrogen is not associated with the aromaticity and is the most nucleophilic part of pyridine molecules, consequently modifications leading to pyridinium salts are common. The resulting positively charged pyridinium species is much more electrophilic than pyridine itself and can also be deprotonated, providing more opportunity for functionalisation (Figure 3).²⁻³

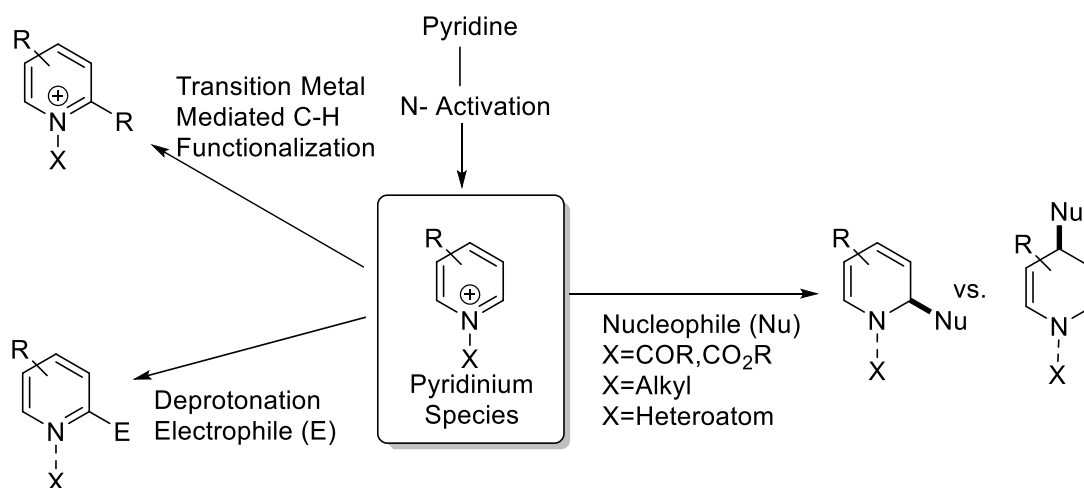


Figure 3. Functionlization of N-activated pyridinium species

Alkylation of pyridine results in *N*-alkylpyridinium salts where, typically, the leaving group features as the counterion (Figure 4). the Dowden group are particularly interested in the chemistry of pyridinium ylides which arise from treatment with a base, deprotonation occurring at the exocyclic position adjacent to the pyridinium nitrogen.⁴

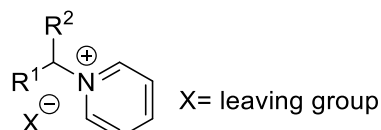


Figure 4. General structure of pyridinium salts

1.1 Pyridinium ylides

In general, ylides can be viewed as species in which a positively charged heteroatom is connected to a carbon atom possessing an unshared pair of electrons. These reactive intermediates are known to undergo synthetically useful transformations. Pyridinium ylides are classified as nitrogen ylides with a pyridinium moiety (pyridine, quinoline, isoquinoline etc.) as the

cationic part, represented by the general structure **4** (Figure 5).⁵ These compounds present exciting characteristics due to their enhanced stability compared to pyridine ring, and their potential application to a wide-range of reactions, including 1,3-dipolarcycloaddition,⁶⁻⁸ Michael additions,⁹⁻¹⁰ or cyclopropanation¹¹ depending on the nature of the reacting species.

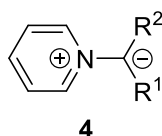
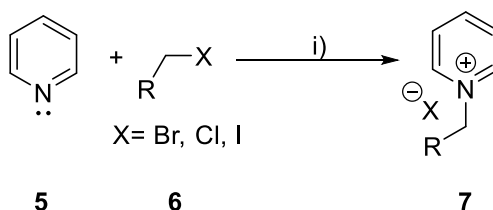


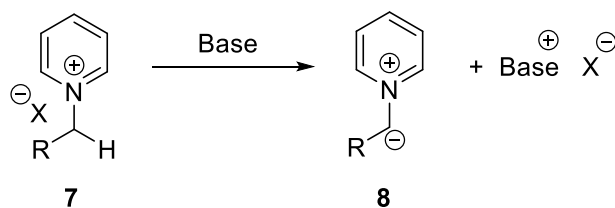
Figure 5. General structure of pyridinium ylide

In general, pyridinium ylides can be generated from *N*-alkyl pyridinium salts. Pyridinium salts can be synthesized by alkylation reactions between pyridine **5** and primary electrophiles (alkyl halide) **6** (Scheme 1). In many cases, pyridinium salts bearing the leaving group as counterion precipitate from the reaction mixture.¹²



Scheme 1. Reagents and conditions: i) EtOAc, 12 hr.

Subsequently, pyridinium ylides **8** can be easily generated through deprotonation of pyridinium salts **7** *in situ* using a suitable base (Scheme 2).



Scheme 2. Process of deprotonation to form pyridinium ylides

In 1993, Bordwell *et al.* measured the pK_a of eight *N*-substituted pyridinium salts in DMSO.¹³ The measured pK_a of the methylene proton was found to range between 10.7 and 24.9, depending on the ylide stabilization group (R) (Figure 6). An alternative investigation found that the pK_a of the *N*-methylene group of a pyridinium salt bearing a benzoyl ylide stabilising group ($\text{R}=\text{COPh}$) to be 9.7 in water.¹⁴

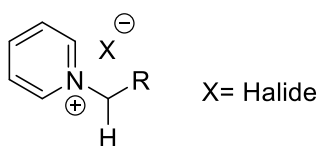


Figure 6

Table 1- pK_a of pyridinium methylene protons in DMSO

R	pK_a
CN	16.5
COMe	11.8
COPh	10.7
CO ₂ Et	14.1
CONEt ₂	24.9
Ph	20.5
SPh	17.7

These pK_a values mean that pyridinium salts can be easily deprotonated using mild bases. For example, triethylamine with the (pK_a (Et_3NH^+) = 9 in DMSO and 10.8 in H_2O) is often used to produce pyridinium ylides *in situ* for cycloaddition reactions,¹⁴ presumably an equilibrium between pyridinium salt and ylide, is sufficient for the cycloaddition to proceed. It is worth observing here that pyridinium ylide formation is accompanied by a salt composed of the protonated base and the counteranion that was initially present in the pyridinium salt.

Some kinetic studies on the formation and reactions of pyridinium ylides have been carried out by Mayer. The rates of these reactions was described by equation 1.¹⁵

$$\text{Log } k_2 (20^\circ\text{C}) = {}_{SN} (N+E) \rightarrow (\text{equation 1})$$

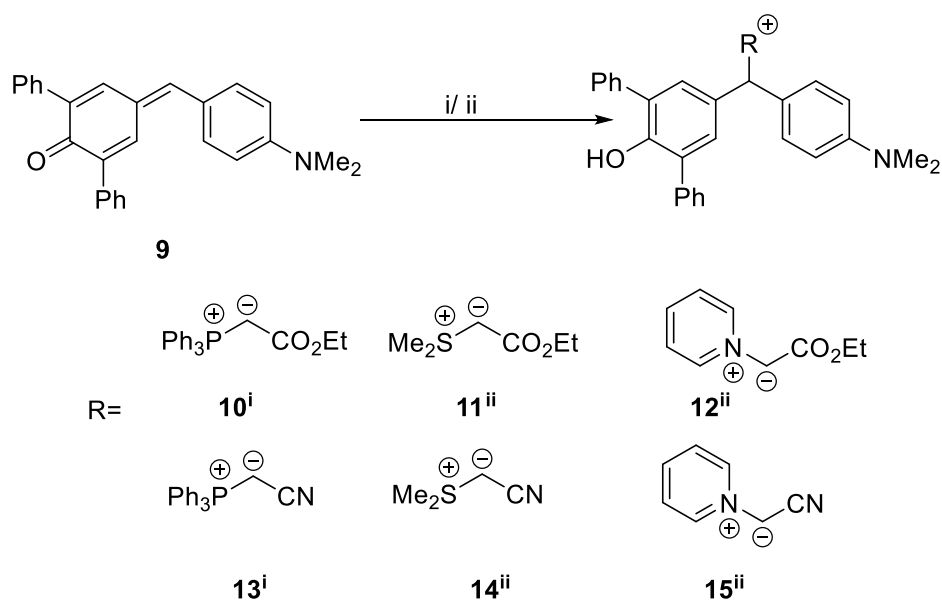
where: k = rate constant for reaction (2nd order)

SN = nucleophile-specific sensitivity parameter

N = nucleophilicity parameter

E = electrophilicity parameter

Mayr *et al* has also compared the rate constant and nucleophilicity parameters for pyridinium ylides with other types of ylides using eq.1 (Table 2).¹⁵⁻¹⁷



Scheme 3. Reagents and conditions - i) CH_2Cl_2 , 20 °C; ii) DMSO, 20 °C.

Table 2. rate constant and nucleophilicity parameters for pyridinium ylides with other types of ylides

Ylide	Log K_2	N
10	-0.71	12.79
11	1.49	15.85
12	4.95	26.71
13	-0.82	12.29
14	1.67	16.23
15	5.37	25.94

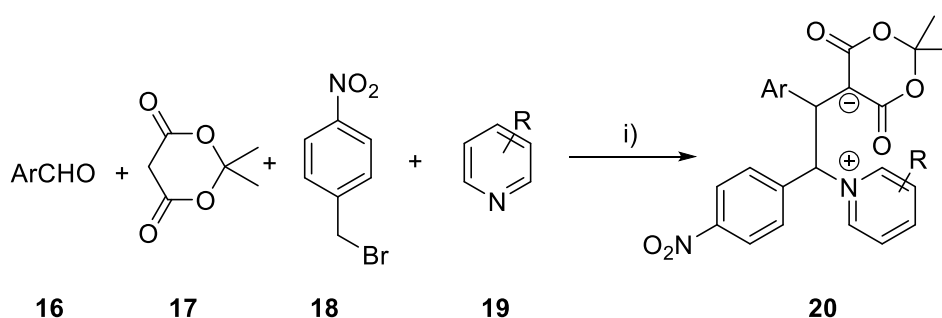
These results display that pyridinium ylides are significantly more nucleophilic than the corresponding triphenylphosphonium and sulfonium ylides. For example, pyridinium ylide **12** is more reactive than the corresponding Wittig-type phosphonium ylide **10**.

1.1.1 Reactions of pyridinium ylides

Ever since their first description in 1935 by Kröhnke,¹⁸ pyridinium ylides have been used for a diversity of different transformations, including 1,4-conjugate addition, cyclopropanation and cycloaddition, where the reaction outcome seems to be influenced by the nature of the reagents. Examples of pyridinium ylide reactivity are discussed here.

1.1.1.1 1,4-conjugate addition

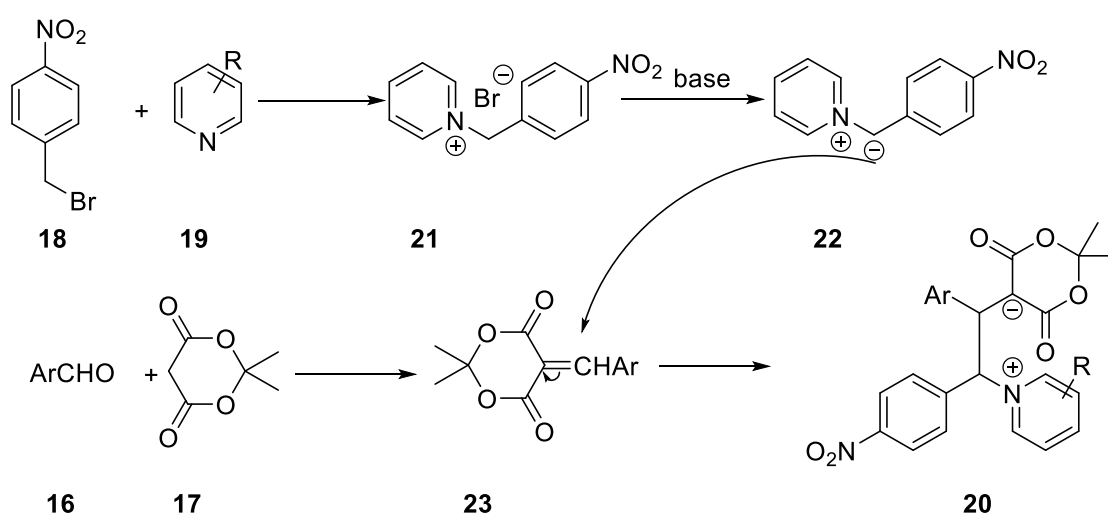
In 2010, Yan *et al.* produced stable betaine **20** products from reactions of a mixture of benzaldehyde **16**, Meldrum's acid **17**, 4-nitrobenzyl bromide **18**, and an excess pyridine **19** in acetonitrile (Scheme 4).¹⁹



Scheme 4. Reagents and conditions: *i)* Et₃N, CH₃CN, rt, 3-5 h. R = H; Ar = Ph, 4-BrC₆H₄, 4-ClC₆H₄, 4-CH₃C₆H₄, 4-CH₃OC₆H₄, 4-EtC₆H₄, 4-*i*-PrC₆H₄, 3-CH₃C₆H₄, 3-ClC₆H₄, 3-NO₂C₆H₄.

4-Nitrobenzylpyridinium salt **21** was formed *in situ* from the substitution reaction of 4-nitrobenzyl bromide **18** with pyridine **19**, deprotonation of the resulting salt **21** and subsequent conjugate addition of the resulting pyridinium ylide **22** to the benzylidene **23**, arising from Knoevenagel condensation of aromatic aldehyde **16** with Meldrum's acid **17** (Scheme 5)

resulting in the zwitterionic product **20**. Notably, Yan *et al.* did not state any observation of cycloaddition arising from intramolecular addition to the pyridinium ring. This may be due to the strongly withdrawing groups stabilising the betaine product, or their steric influence also. Additional examples of pyridinium ylides that undergo conjugate addition with alkenes to produce stable betaines have been described by Yan and Srivastava and co-workers.²⁰⁻²¹ Again, each of the products feature a strongly stabilising group such as Meldrum's acid.

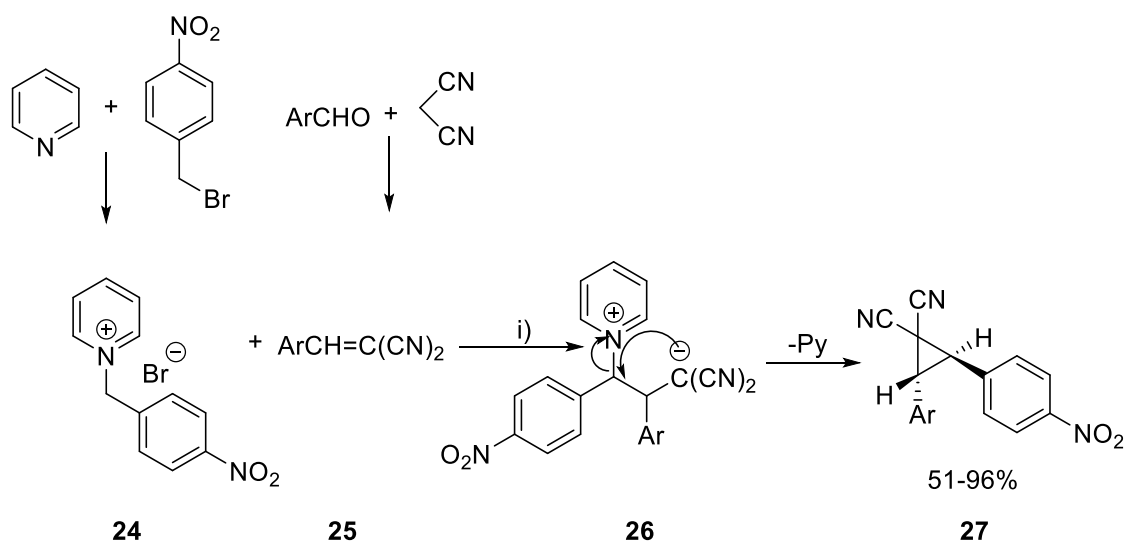


Scheme 5- Proposed Mechanism for production of **20**

1.1.1.2 Cyclopropanation

In 2009, Yan *et al.* studied using of *N*-phenacyl pyridinium ylide in the preparation of polysubstituted cyclopropane **27**.²² A stoichiometric one-pot three component reaction using 4-nitrobenzyl pyridinium bromide **24**, effected cyclopropanation of arylidenemalononitrile **25**.²² Deprotonation of

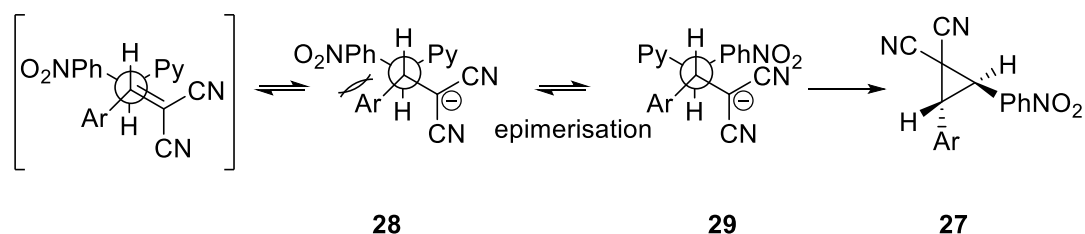
N-4-nitrobenzyl pyridinium bromide **24** using triethylamine gave a pyridinium ylide that underwent 1,4-conjugate addition with a various arylidenemalononitriles **25** to give zwitterionic intermediates **26**, which then eliminated pyridine to produce the cyclopropanes **27** (Scheme 6).



Scheme 6- Reagents and conditions: i) Et₃N, CH₂Cl₂, r.t., 4-12 h.

The observed relative stereochemistry was rationalised by presuming that the ylide would attack in an *anti*-periplanar fashion, with respect to the arrangement of the interacting π -bonds. Yan predicts that a *trans* configuration of the bulky aryl and *p*-nitrophenyl group would predominate so as to reduce *gauche* interactions. However, the resulting *cis* intermediate **28** experiences severe steric repulsion between the bulky aryl group and the *p*-nitrophenyl group, therefore cyclopropane formation is an unfavoured process. The zwitterionic intermediate likely has a moderately long lifetime, while the presence of the malonitrile stabilising groups can mediate epimerisation at the carbon in between the pyridinium and bulky aryl groups. The resulting *trans* intermediate **29** suffers no strong steric

repulsions and ring closing/elimination of the pyridine can take place (Scheme 7) to make the cyclopropane product.

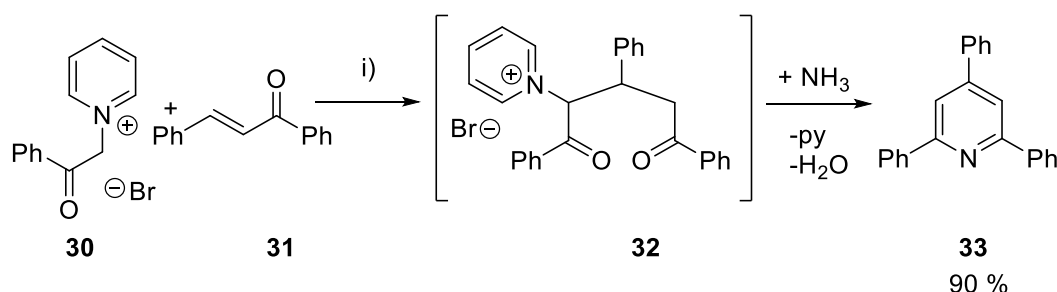


Scheme 7 - Proposed mechanism for the stereoselectivity in the cyclopropanation reaction

When this result is compared with cycloaddition reaction, this observation of an alternate reaction mechanism should not be ignored. Though the pK_a at the malonitrile position may favour cyclopropanation in this circumstance, this reaction path has the potential to compete when attempting (3+2) cycloadditions of pyridinium ylides.

1.1.1.3 Kröhnke pyridine synthesis

In 1962, Kröhnke *et al.* reported, under acidic conditions, the production of substituted pyridines through reaction between pyridinium salts and Michael acceptors, such as chalcone (Scheme 8).²³



Scheme 8 - Reagents and conditions: i) NH_4OAc , $AcOH$, reflux, 1 h

Dicarbonyl intermediate **32** was generated through acid mediated 1,4-conjugate addition of pyridinium salt **30** on *trans*-chalcone **31**. This species then underwent cyclisation in the presence of ammonium acetate with the elimination of pyridine, to produce the tri-substituted pyridine **33**. In this reaction, pyridine acts as a leaving group it may be that elimination of pyridine could occur when examining cycloadditions in this project.

1.2 1,3-Dipolar cycloaddition reactions of pyridinium ylides

1,3-Dipolar cycloadditions are a very effective method of producing sp³-rich heterocyclic frameworks. The ability to rapidly produce molecular complexity from rather simple starting materials using this reaction has long been attractive to synthetic chemists. Whilst there are many different 1,3-dipoles, we are interested in the use of pyridinium ylides **34** (Figure 7).

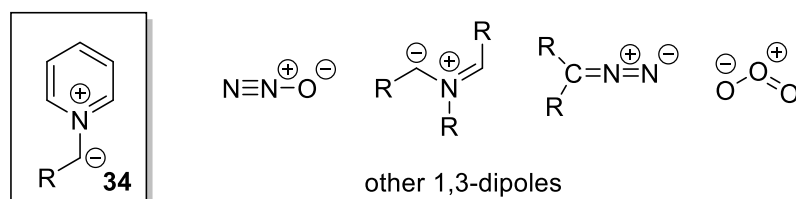
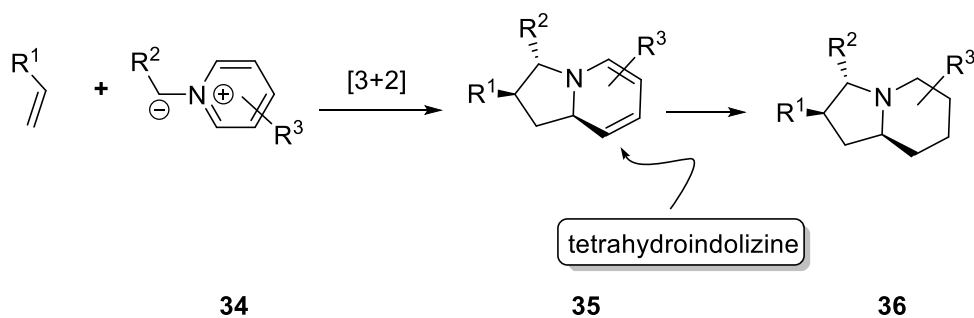


Figure 7. Other 1,3-dipoles including pyridinium ylide

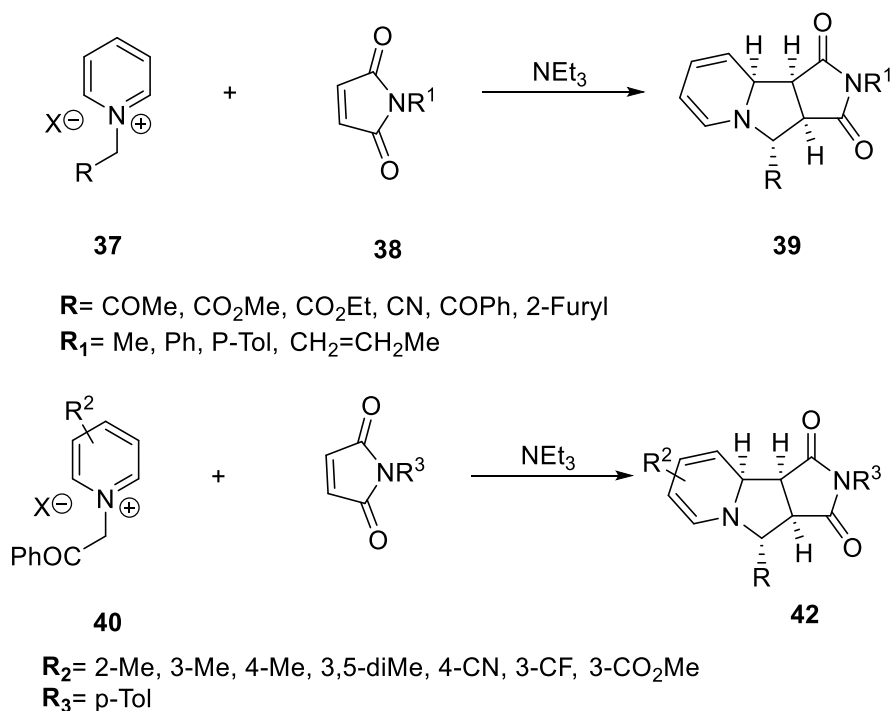
As well as up to 4 new stereocenters, the resulting cycloadducts **35** feature a tetrahydroindolizine moiety **35**, which can be additionally functionalised to afford complex indolizidines **36** (Scheme 9).



Scheme 9

Indolizidines are found in many biologically active alkaloids, as well as many pharmaceutical drugs.²⁴⁻²⁵ Consequently, the development of the rapid synthesis of a 'drug-like' core with predictable regio and diastereoselectivity would be of important value. There are a few examples in the literature that describe the synthesis of tetrahydroindolizines *via* (3+2) cycloadditions of pyridinium ylides. This limitation of investigation may be related to the instability of 1,2-dihydropyridine ring. These examples of tetrahydroindolizines synthesis are described in this section.

During the 1980s, Tsuge *et al.* presented cycloaddition reactions with pyridinium ylides (Scheme 10). Their work was initiated with unsubstituted pyridinium ylides generated from pyridinium salts **37** that were reacted with simple olefins **38** to produce 1,2-dihydropyridine **39**. Those cycloadducts were reported to decompose in 24 hours or upon purification but they were stable enough to be characterized by ¹H NMR spectroscopy.¹⁴ Later, substitution of the pyridinium ring **40** was examined in these reactions. 3-Me, 3-CF₃ and 3-CO₂Me substituted pyridinium ylides were found to give a mixture of products originating from addition to either the C-2 or C-6 position of the pyridinium ylides.¹⁴



Scheme 10. Reagents and conditions: CHCl_3 , CH_2Cl_2 or DMSO , r.t., 78-100%

Various terms used to describe stereochemical outcomes from 1,3-dipolar cycloaddition reactions of pyridinium ylides are described. The stereochemistry in the resultant cycloadducts are determined by the relative orientation of the dipolarophile and ylide in the transition state. The necessary terms to describe the orientations is discussed in the following sections (Sections 1.2.1 and 1.2.2)

1.2.1 *Endo* vs. *exo*

There are two probable orientations for the dipolarophile in the transition state during the cycloaddition reaction, named *endo* and *exo*. These descriptions are based upon the relative positions of the units of unsaturation (in the pyridinium ylide and in dipolarophile) (Figure 8). In an

endo transition state the unit of unsaturation is in closest proximity, whereas in an *exo* transition state, the units of unsaturation are further away.²⁶

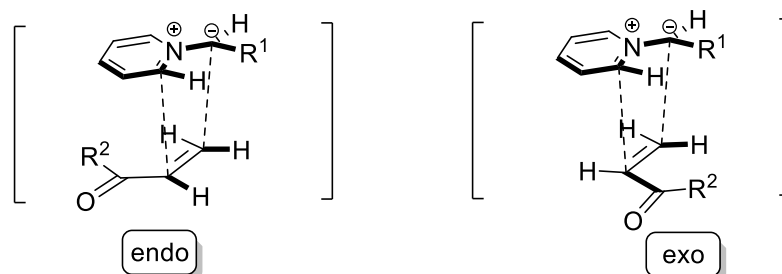


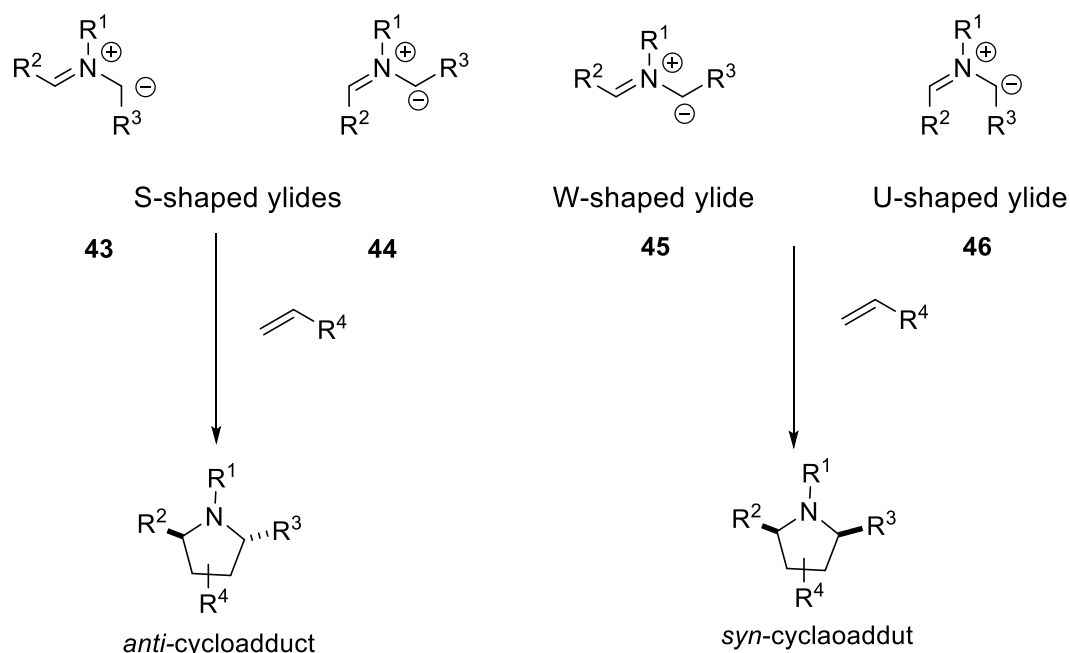
Figure 8. Diagram of *endo* and *exo* transition states

Secondary orbital interactions of the π conjugation system of the pyridinium ring lower the energy of the *endo* transition state, therefore, without any unfavourable steric interactions the *endo* transition state should be the favoured pathway generating *endo* cycloadduct. The relative stereochemistry of other centres in the final product arises from the ylide shape in the transition state.

1.2.2 Ylide shape

Pyridinium ylides are closely related to azomethine ylides and therefore terms used to describe azomethine ylide shape may also be the same when describing the shape of pyridinium ylides in the transition state. Azomethine ylides have four possible types of ylide geometry in the transition state; 2 types of S-shaped ylide **43**, **44**, a W-shaped ylide **45** and a U-shaped ylide **46** (Scheme 11). In a review, Coldham *et al.* described intramolecular cycloadditions reaction of azomethine ylides and observed a general preference for S-shaped ylides, based on the examples inspected.²⁷ No

exact clarification for the preference of the S-shaped ylide was given, though, steric or conformational effects may have an important influence on the ylide shape.



Scheme 11. Azomethine ylide shape

The *S* **43-44** conformations form the *anti*-cycloadduct with the respect to R¹ and R² and *W* **45** and *U* **46** conformations form the *syn* cycloadduct.

For pyridinium ylides, only two shapes are possible, S-shaped ylides **47** and W-shaped ylides **48**, because of the restrictions of the pyridinium ring (Figure 9).

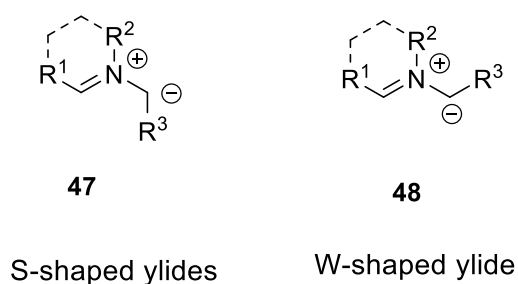
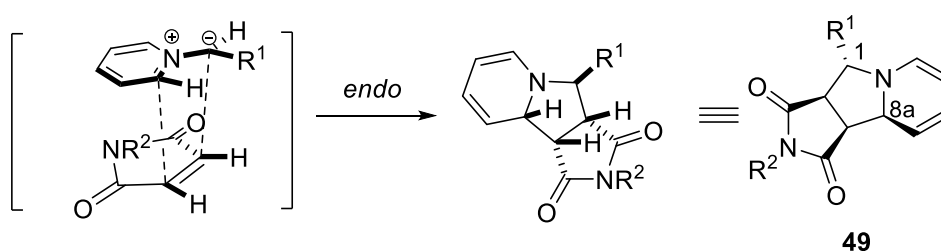


Figure 9. Possible ylide shape for pyridinium ylides

Ylide shape affects the stereochemistry of the ylide stabilising group (R^1 , Scheme 12) noticed in the product, with the favoured shape determined by the nature of the ylide stabilising group.

The relative stereochemistry of the cycloadducts was determined based on the coupling constants obtained from the ^1H NMR data and rationalised as arising from an *endo* transition state and an *S*-shaped ylide as justified by Tsuge (Scheme 12).²⁸



Scheme 12. Rationale for observed stereochemistry

The *endo* pathway is favoured because of the secondary interactions between the carbonyls and the π -system on the pyridinium ring. Once partial bonds have begun to form, the relative stereochemistry of the ylide stabilisation group (R^1) is eventually determined by the shape of the *anti* (*W*) and *syn* (*S*) shaped ylides (Figure 10).²⁷

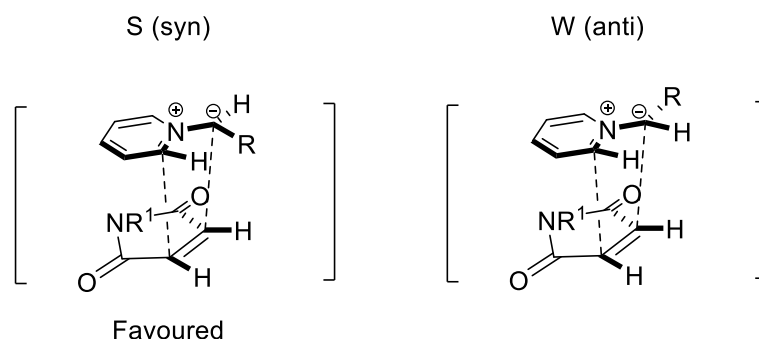


Figure 10. Possible ylide geometries in the transition state

Tsuge observed that the *S*-shaped ylide was favourable and reasoned that its stabilisation arose from proximal stabilisation of the two charges *via* an extended 1,5-dipole (Figure 11).²⁸

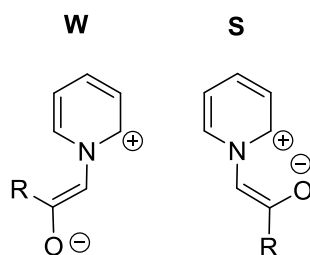
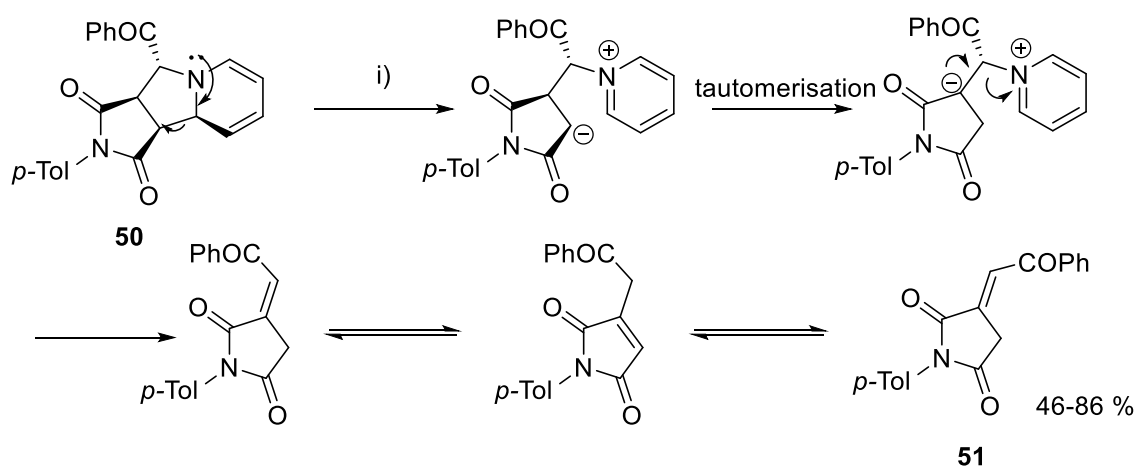


Figure 11. Preference of *S*-shaped ylide²⁸

More generally it has been observed that if the ylide stabilising group is a resonance stabilising group such as a carbonyl, then the *S* ylide product is favoured, while for non-resonance stabilised groups the *W* is preferred.²⁸ One explanation for this observation may be to reduce unfavourable dipole interactions in the transition state.²⁸

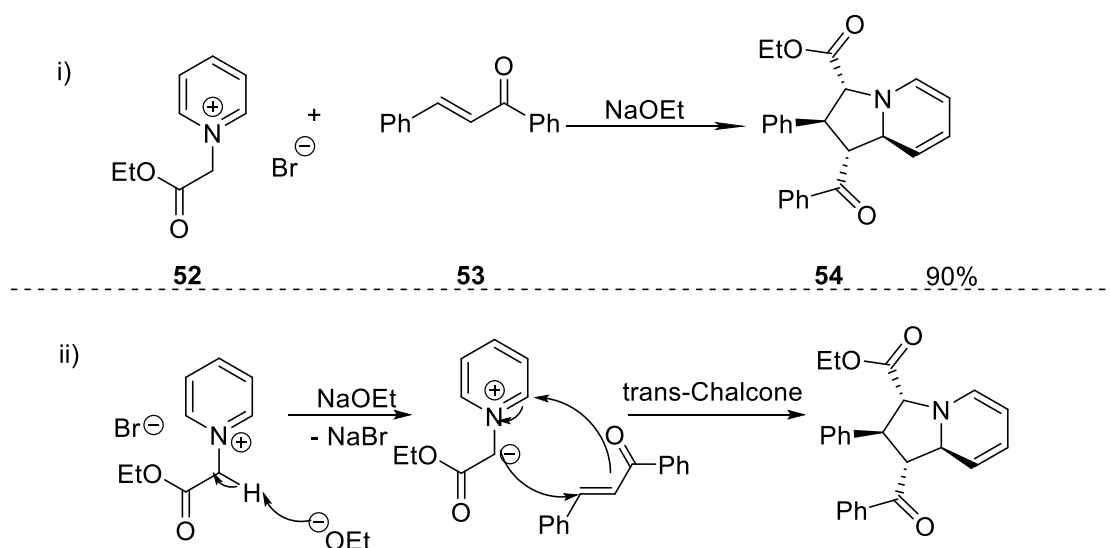
During this investigation on the cycloaddition reaction, Tsuge *et al.* also noticed that it is possible for the cycloadducts to undergo other conversions. for example, he described a fragmentation pathway for maleimide derived cycloadduct **50**.²⁹



Scheme 13. Reagents and conditions: i) CH_2Cl_2 or CHCl_3 , silica gel, rt.

The compound **51** was observed when the cycloadduct **50** was purified using silica gel, apparently arising from re-aromatisation and elimination of pyridine (Scheme 13). This observation confirms the instability of the 1,2-dihydropyridine cycloadducts, implying that care should be taken throughout purification of the cycloadduct.

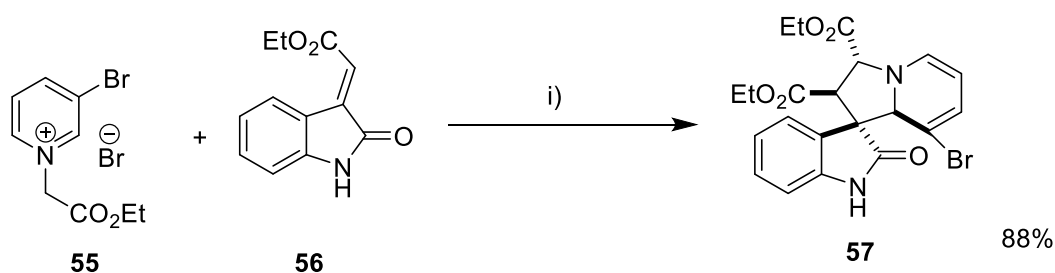
In 1981, Katritzky *et al.* reported effective cycloaddition between pyridinium ylides and chalcones leading to various tetrahydroindolizidines in high yield (Scheme 14).³⁰



Scheme 14. Reagents and conditions: i) EtOH, NaOEt, 90%; ii) Mechanism of 1,3-dipolar cycloaddition

In this case, an *endo* product **54** based on the coupling constants measured between protons corresponding to ring junction 8a and the 2-position adjacent to phenylacyl 3 was claimed (Scheme 14).³⁰

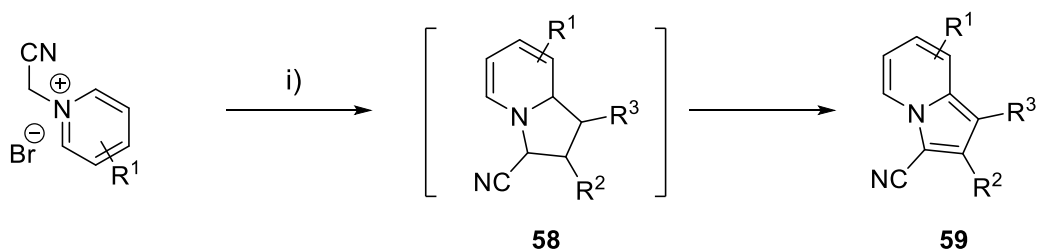
Recently, an example from the Dowden group of a (3+2) cycloaddition between a pyridinium ylide and a 3-alkylidene oxindole **56** produced cycloadduct **57** in high yield as a single diastereoisomer (Scheme 15).³¹



Scheme 15 - Reagents and conditions -i) Et₃N, CH₂Cl₂, 20 °C, 2 hr.

The stability of these cycloadducts depends significantly on the substituents on the dihydropyridine ring, electron withdrawing groups appear to stabilise the resulted cycloadducts.

There have been a number of studies to generate indolizines. Typically, pyridinium ylides can undergo cycloaddition reaction with electron deficient alkynes or alkenes, leading to indolizines after aromatisation of dihydroindolizine intermediates (**58**, Scheme 16).³²

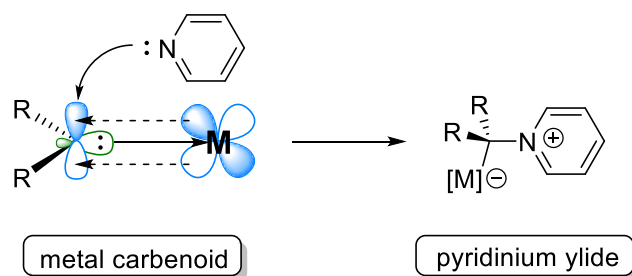


Scheme 16 - Reagents and conditions: i) substituted alkene, pyridine, MnO₂, DMF, 90 °C

Although, indolizines are very important,³³⁻³⁶ this aromatisation of the cycloadducts destroys the stereochemical information accrued through the cycloaddition reaction.

1.3 Generation of pyridinium ylides from metal carbenoids

Reaction of metal carbenoids with pyridines offer an alternative route to directly produce pyridinium ylides.³⁷⁻³⁹ In this case, ylide formation happens through attack of the nitrogen lone pair into the empty p-orbital of a metal carbenoid (Scheme 17).



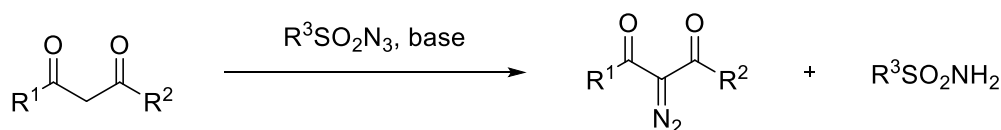
Scheme 17- Trapping of a singlet carbene with pyridine

Metal carbenoids can be generated *in situ* from transition metal-catalysed decomposition of diazo compounds. This method of pyridinium ylide generation offers many benefits over formation from pyridinium salts, such as accomplishing the catalytic reaction in one pot without added base. Metal carbenoids are highly reactive species able to undergo an enormous range of different reactions, consequently selectivity may be an issue when designing new transformations. The synthesis of diazo compounds and the reactivity of metal carbenoids are briefly discussed below.

1.3.1 Synthesis of diazo compounds

Diazo compounds are valuable and versatile synthetic intermediates and their rich chemistry has attracted much attention since the first synthesis of ethyl diazoacetate by Curtius in 1883.⁴⁰ One of their key features is the generation of carbenes or metal carbenoids which present reactive intermediates that undergo a wide range of useful reactions.⁴¹⁻⁴⁵ Diazo compounds themselves may be accessed from low-cost precursors. With conservation of the diazo moiety, they also react as 1,3-dipoles in cycloaddition reactions to give heterocycles.⁴⁶⁻⁴⁷ A wide diversity of procedures for the preparation of diazo compounds has been described and a selection of the most common approaches is described below.⁴⁸

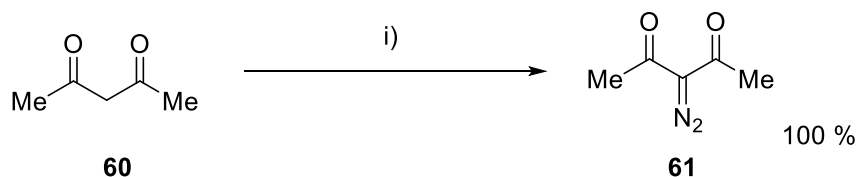
1.3.1.1 Regitz-diazo transfer



Scheme 18- The Regitz-diazo transfer reaction

The Regitz-diazo transfer method classically applies to activated carbonyl C-H compounds, for example 1,3-diketones, 1,3-diesters and 1,3-ketoesters, along with base and a sulfonyl azide, such as TsN₃ (*p*-toluenesulfonyl azide) or 4-ABSA (4-acetamidobenzenesulfonyl azide), acting as diazo transfer reagent.

For example, Regitz-diazo transfer was utilised for the synthesis of 3-diazopentane-2,4-dione **61** from pentane-2,4-dione **60** (Scheme 19) using 4-ABSA as the sulfonyl azide transfer reagent.⁴⁸

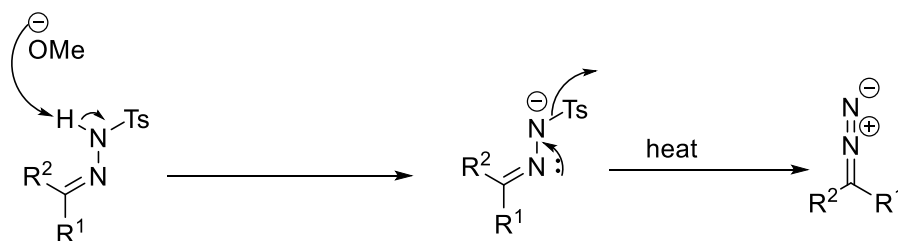


Scheme 19 - Results and conditions: i) 4-ABSA, Et₃N, MeCN, rt, 1 h

1.3.1.2 Bamford-Stevens reaction

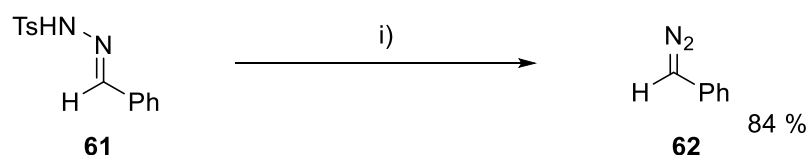
The Bamford-Stevens reaction is considered a general method for the preparation of a wide range of diazo compounds through condensation of ketones or aldehydes with tosyl hydrazine. The resulting tosyl hydrazone is

then deprotonated with base (NaOMe), frequently a sodium alkoxide, and then heated to 50-70 °C to produce the diazo compound *via* pyrolytic decomposition of the deprotonated tosyl hydrazone (Scheme 20).⁴⁹



Scheme 20. The Bamford-Stevens reaction

For example, phenyldiazomethane **62** may be produced from tosylhydrazone **61** *via* this method (Scheme 21).

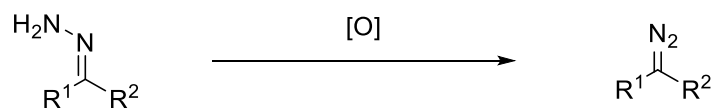


Scheme 21 - Reagents and conditions: i) NaOMe, MeOH, heat

Unfortunately, it was found that this method is generally unsuitable to produce diazo compounds with low thermal stability such as diazoalkanes.

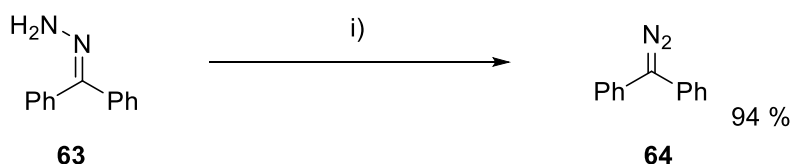
1.3.1.3 Oxidation of hydrazones

Generally, diazo compounds can be generated from oxidizing hydrazones using an external oxidant (Scheme 22). The most widely used methods for oxidation of hydrazones use toxic metal reagents, such as (HgO, MnO₂, Pb(OAc)₄ and Ag₂O), despite their suitability of some protocols for lab-scale preparations, these methods do not offer acceptable circumstances in terms of waste production and/or toxicity.



Scheme 22 - Oxidation of hydrazones

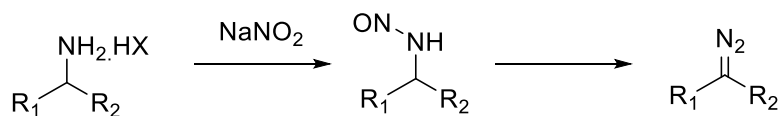
Recently, Moody *et al.* described a synthesis of varied range of diazo compounds without using toxic reagents by the oxidation of hydrazones **62** using TsNIK (potassium *N*-iodo-*p*-toluenesulfonamide) (Scheme 23).⁵⁰ This method has one benefit that high temperatures are not required for oxidation to take place, permitting the synthesis of diazo compounds with low thermal stability, such as diazo alkanes.



Scheme 23- Reagents and conditions: i) TsNIK, THF/KOH (aq), rt

1.3.1.4 Diazotisation

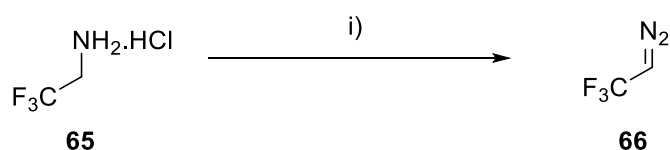
Diazotisation is frequently used for preparation of diazo compounds from aliphatic amines using a nitrosating agent under acidic conditions (Scheme 24).



Scheme 24 - Diazotisation method

For this reaction, sodium nitrite is the most common reagent. Generally, an amine salt is dissolved in aqueous media, followed by addition of the

nitrosating agent. The active reagent, nitrous acid (HNO_2), is formed *in situ* and performs the diazotisation.

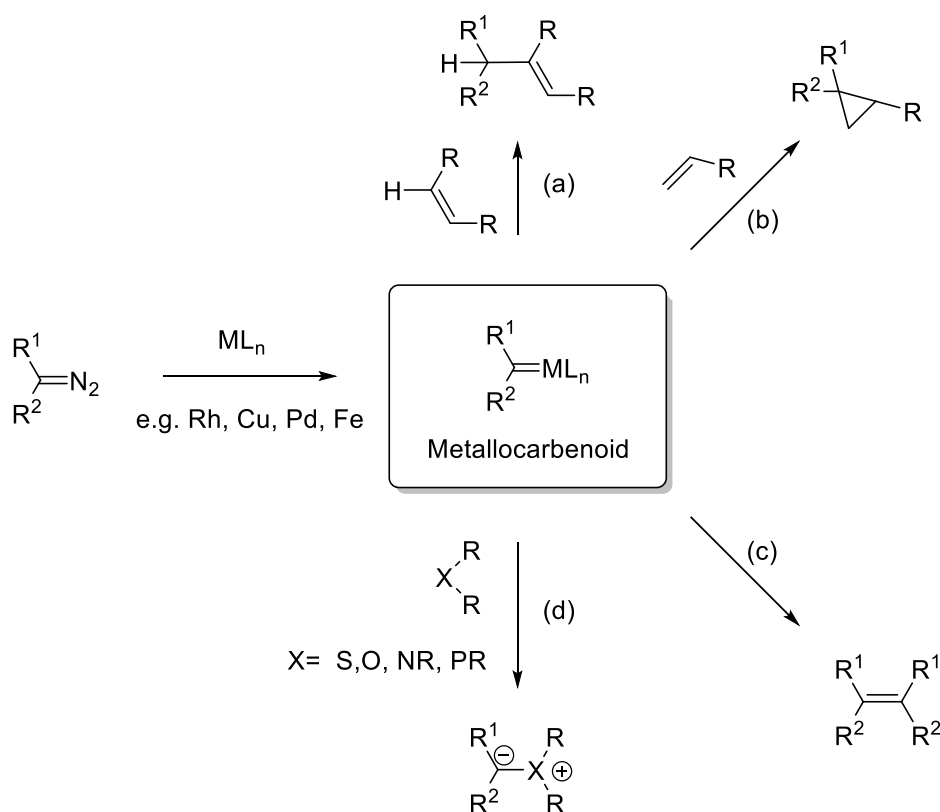


Scheme 25 - Reagents and conditions: i) NaNO_2 , H_2O , r.t, 2 h

For example, trifluorodiazooethane **66** may be produced from the hydrochloride salt of 2,2,2-trifluoroethylamine **65** using sodium nitrite in water (Scheme 25).⁵¹ The diazotisation method is cheap; but it is restricted to amines bearing an additional group (CO_2Et , CF_3 , and NO_2) on the α -carbon. Consequently, this method cannot form electron-rich diazo compounds. Other methods not discussed here include base-mediated decomposition of nitrosamides and the Forster reaction.⁵²⁻⁵³

In summary, there is a variety of methods allowing to produce diazo compounds (electron-rich and electron-poor). Usually, reagents for these processes are cheap and commercially available, or easy to access.

1.3.2 Reactivity of metal carbenoids



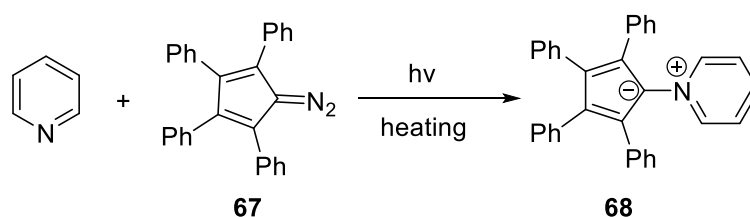
Scheme 26- Generation and reactivity of metal carbenoids: (a) C-H insertion; (b) Cyclopropanation; (c) Coupling; (d) Ylide formation

Metal carbenoids may be generated by transition metal catalysed decomposition of diazo compounds. Common catalysts for this pathway include rhodium,⁵⁴ copper,⁵⁵ palladium and iron complexes.⁵⁶⁻⁵⁷ Once metal carbenoids are formed, they undergo a wide range of reactions such as C-H insertion (a),⁵⁸ cyclopropanation (b),⁵⁹ coupling reactions (c)⁴² and ylide formation (d) (Scheme 26).⁶⁰ These and other studies show that the reactivity of the metal carbenoid may be controlled by selection of both metal and ligand. For this project, the emphasis will be on pyridinium ylide formation *via* trapping of metal carbenoids with pyridines.

1.4 Generation of pyridinium ylides from carbenes and carbenoids

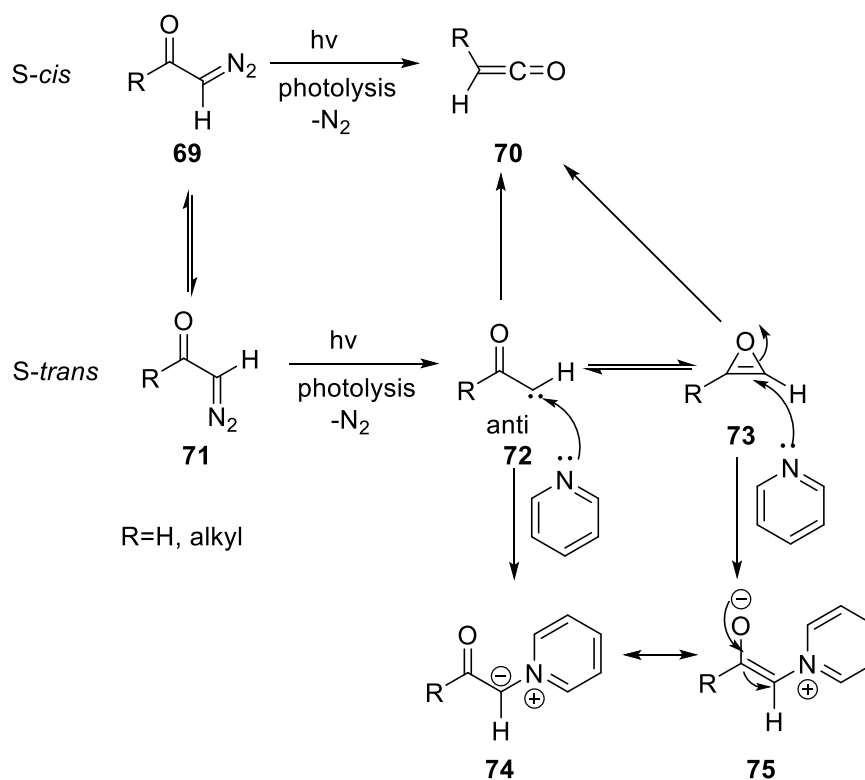
Several examples dealing with the preparation of pyridinium ylides have been reported in the literature. Some of these methods for generating pyridinium ylides involve thermal or photochemical methods.^{39, 61-64}

As early as 1960, pyridinium tetraphenylcyclopentadienylide **68** was produced by heating of diazo compound **67** in refluxing pyridine. Subsequent addition of water precipitated the purple ylide in nearly quantitative yield (Scheme 27).^{62-63, 65}



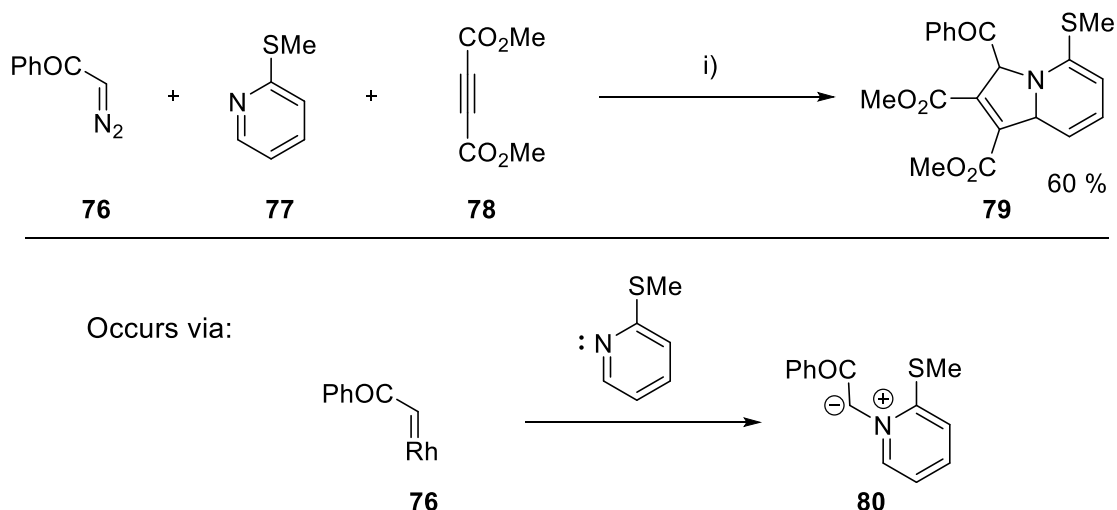
Scheme 27. Thermolysis formation of pyridinium ylide

Photochemical decomposition of α -diazoketones in the presence of pyridine also leads to the formation of pyridinium ylides (Scheme 28).⁶⁶



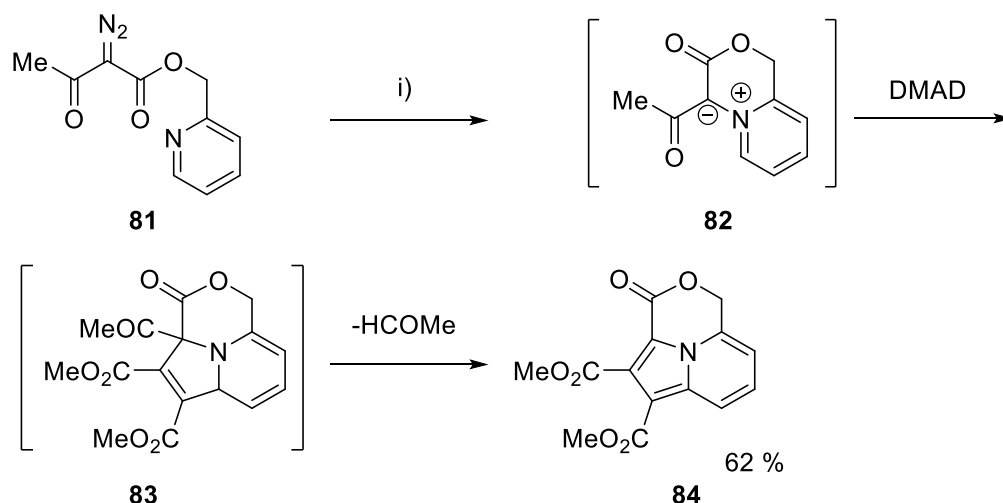
Scheme 28. Photolysis formation of pyridinium ylide

In 1993, Padwa *et al.* described a rhodium (II) octanoate catalysed reaction of α -diazoacetophenone **76** in the presence of 2-(methylthio)pyridine **77** and dimethyl acetylenedicarboxylate (DMAD) **78**.³⁷ This was followed by nucleophilic attack of the pyridine nitrogen lone pair on to the electrophilic α -keto carbenoid **76**, the formed pyridinium ylide **80** subsequently underwent a cycloaddition reaction with DMAD **78** to produce thiomethyl cycloadduct **79** in 60% yield (Scheme 29).



Scheme 29- Reagents and conditions: i) $\text{Rh}_2(\text{oct})_4$ (1 %), CH_2Cl_2 , rt, 2 h

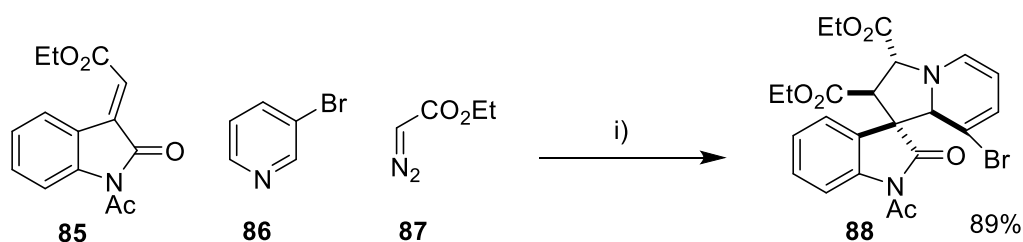
Padwa *et al.* explains that the placement of the thiomethyl group on the pyridine ring was the key for enhanced ylide formation because of the improved nucleophilicity at the pyridine nitrogen. However, Padwa and colleagues did report the formation of a small range of pyridinium ylides through intramolecular trapping of rhodium carbenoids with tethered pyridines.³⁷ In Scheme 30, rhodium (II) acetate catalysed decomposition of α -diazo- β -ketoester **81**, followed by intramolecular trapping of the resulting metal carbenoid with the tethered pyridine gave pyridinium ylide **82** *in situ*. Subsequent cycloaddition between the ylide **82** and DMAD forms cycloadduct **83**, which was then able to undergo deacetylation and oxidation to give indolizine **84** in 62% yield.



Scheme 30. Reagents and conditions: *i)* $Rh_2(OAc)_4$ (1 %), DMAD, CH_2Cl_2

These outcomes are extremely important to this project as they prove that pyridinium ylides can be successfully generated directly from the pyridine through trapping of metal carbenoids, and then used in 1,3-dipolar cycloadditions.

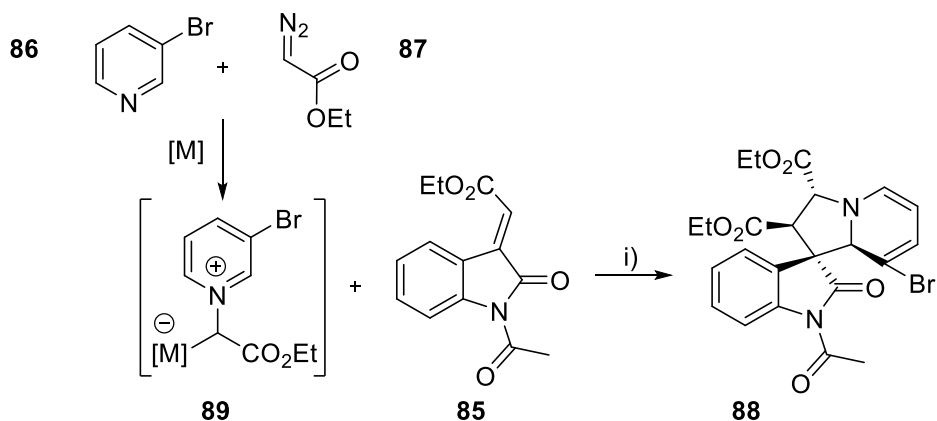
During my research, a new methodology was established in Dowden group to perform 1,3-dipolar cycloadditions *via* the *in situ* generation of pyridinium ylides from diazo compounds (Scheme 31).



Scheme 31 - Reagents and conditions - *i)* $Fe(PPP)Cl$ (1 mol%), toluene, 20 °C, 4 hr.

This methodology described the synthesis of pyridinium ylides **89** *in situ* from $Fe(PPP)Cl$ catalysed decomposition of ethyldiazoacetate **87** with pyridine.⁶⁷ subsequent reaction of pyridinium ylide with oxindole **85** to

produce cycloadduct **88** (Scheme 32), most of which could be isolated as the tetrahydroindolizine, such as **88**.⁶⁷



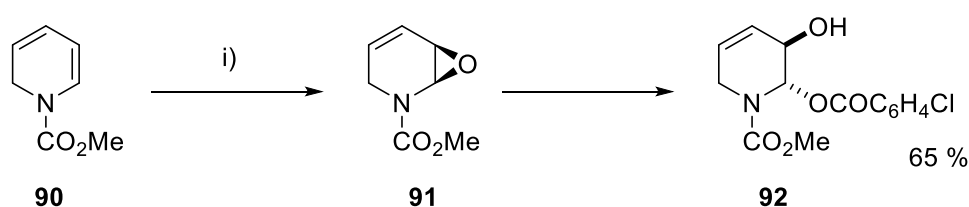
Scheme 32 - Reagents and conditions: i) Fe(TPP)Cl (1 mol%), toluene, 20 °C, 4 hr.

If the metal complex remains associated with the pyridinium ylide then there may be scope for ligands attached to it to directly influence the reaction mechanism.

In this project, the goal was to access 'drug-like' indolizidines. Generally, every tetrahydroindolizine cycloadduct comprises a 1,2-dihydropyridine that may be used for further functionalisation. As stated previously, Tsuge *et al.* described that their cycloadducts were unstable to purification *via* column chromatography.¹⁴ Consequently, modification of the dihydropyridine ring may help to stabilise the cycloadducts or introduce additional functionality to the indolizidine core. For example, global reduction of the dihydropyridine ring provides an easy route to access saturated indolizidines.

1.5 Modification of the dihydropyridine ring

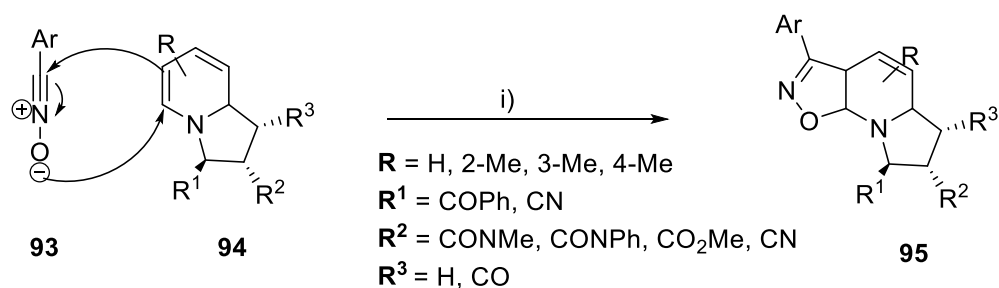
The 1,2-dihydropyridines produced through the cycloaddition reaction, feature both an alkene and an electron-rich enamine; the difference in reactivity between these two alkenes offers the prospect of selective functionalisation that may be used to introduce opportunities for additional diversification. Lavilla reported in a review a diversity of 1,2-dihydropyridine functionalisations that included epoxidations (Scheme 33).⁶⁸



Scheme 33 - Reagents and conditions: i) *m*-CPBA, CH₂Cl₂, rt

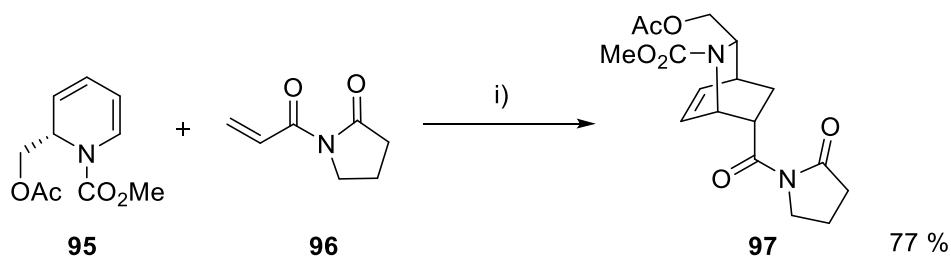
The selective epoxidation of 1,2-dihydropyridine **90** using *m*-CPBA produces an epoxide **91** that subsequently undergoes ring-opening with the *meta*-chlorobenzoic acid by-product to produce alcohol **92** (Scheme 33).

Interestingly, Tsuge *et al.* also demonstrated a (3+2) cycloaddition reaction that offers another means of modifying the more electron-rich enamine alkene. He investigated more derivation of their products *via* subsequent reaction of cycloadduct **94** with *N*-oxide 1,3 dipoles **93** (Scheme 34).⁶⁹ This second reaction is a (3+2) cycloaddition reaction that offers another means of modifying the more electron-rich enamine alkene.



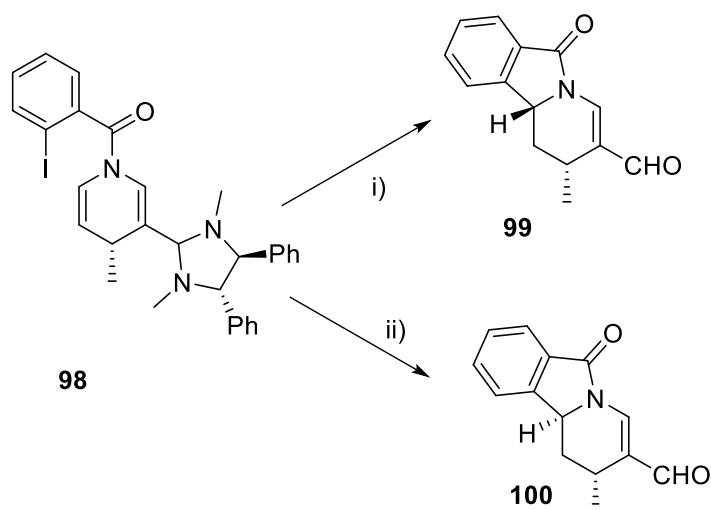
Scheme 34. Reagents and conditions: i) CH_2Cl_2 , r.t., 45-97%

Lavilla also stated the reaction between 1,2-dihydropyridine **95** and dienophile **96** to produce azabicyclic compound **97** via a Lewis acid catalysed Diels-Alder cycloaddition (Scheme 35).⁶⁸



Scheme 35. Reagents and conditions: i) AlCl_3 , CH_2Cl_2 , rt

In 2001, Mangeney *et al.* studied intramolecular Heck reactions of chiral 1-(o-iodobenzoyl)-1,4-dihydropyridines **98**. He observed that the stereoselectivity of the reaction outcome is reliant on the reaction conditions, therefore the use of a reductive protocol produces (after removal of the chiral auxiliary) tetrahydropyridine **99** (together with the enantiomer of **100**, in a 7 : 3 ratio), while standard conditions lead to **100** (Scheme 36).⁷⁰

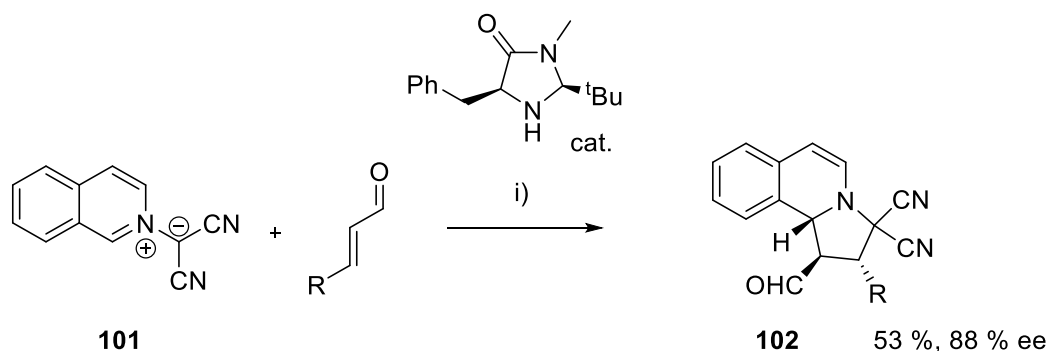


Scheme 36. Reagents and conditions: i, a) $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$, piperidine, HCO_2H , b) HCl 5%- Et_2O (35% overall, together with *ent*-100); ii, a) $\text{Pd}(\text{OAc})_2$, AcOK , DMF , b) HCl 5%- Et_2O , c) H_2 , Pd/C (38% overall).

This varied pattern of reactions that are possible with 1,2-dihydropyridine offers a platform for an additional modification possibly toward complex drug-like structures. Study of the 1,2-dihydropyridine reactivity will similarly be imperative in terms of the production of associated natural products and their analogues.

1.6 Asymmetric cycloaddition of pyridinium salts

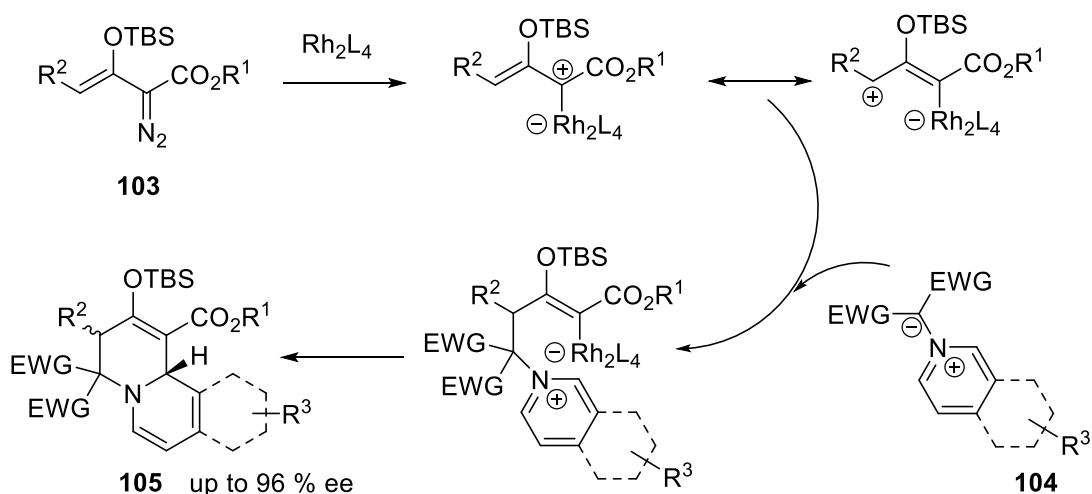
Recently, Reyes *et al.* reported an organocatalytic enantioselective (3+2) cycloaddition reactions of azomethine ylides (Scheme 37). Phthalizinium methylides **101** and Isoquinolium were confirmed as efficient reagents to participate in chiral iminium catalysed (3+2) cycloaddition reactions to generate asymmetric induction of cycloadduct **102**.⁷¹



Scheme 37. Reagents and conditions: i) THF, -30°C

So far, there is no corresponding enantioselective cycloaddition reactions of pyridinium ylides reported, so, we are very interested to explore suitable asymmetric methods such as organocatalysts, and chiral metal catalysis. Analogous asymmetric cycloadditions are outlined below.

Doyle *et al.* recently described the asymmetric synthesis of related quinolizidines **105** through a chiral dirhodium (II) carboxylate-catalysed de-aromatising formal (3+3) cycloaddition of isoquinolinium/pyridinium ylides **104** with enol diazoacetates **103** (Scheme 38).⁷² In this example stable pyridinium ylides are used in the reaction but they are not produced by trapping of metal carbenoids with pyridines in this example.



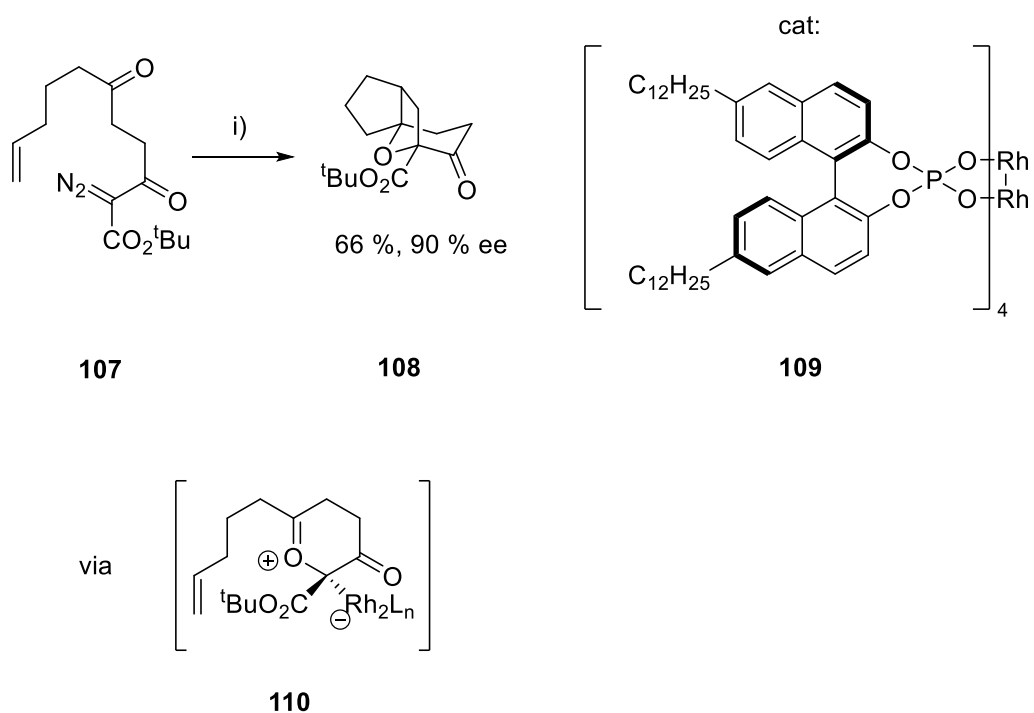
Scheme 38. Doyle's chiral dirhodium(II) carboxylate-catalysed de-aromatising formal (3+3)-cycloaddition of isoquinolinium/pyridinium ylides with enol diazoacetates.

In this reaction, the dirhodium (II) catalyst **106** presumably remains sufficiently associated with the reaction intermediates to affect the stereochemical outcome of the reaction.

There is also a possibility to achieve stereoselective cycloadditions of oxonium ylides. Oxonium ylides may be accessed *in situ* by trapping of metal carbenoids with carbonyl substituents, in a similar way to the formation of pyridinium ylides. The resulting oxonium ylides are effective 1,3-dipoles and undergo cycloadditions with alkenes.

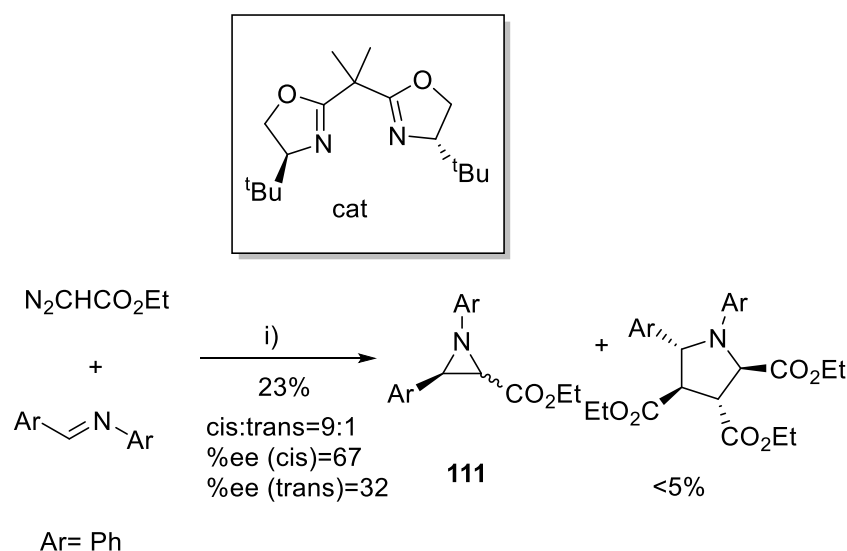
Scheme 39 illustrates the intramolecular cycloaddition reaction of an oxonium ylide **110**. Oxonium ylide **110** was produced from the reaction of α -diazo-

β -ketoester **107** with chiral $(\text{Rh}_2(R\text{-DDBNP})_4)$ catalyst **109**.⁷³ High enantioselectivity was accomplished in this reaction.⁷³



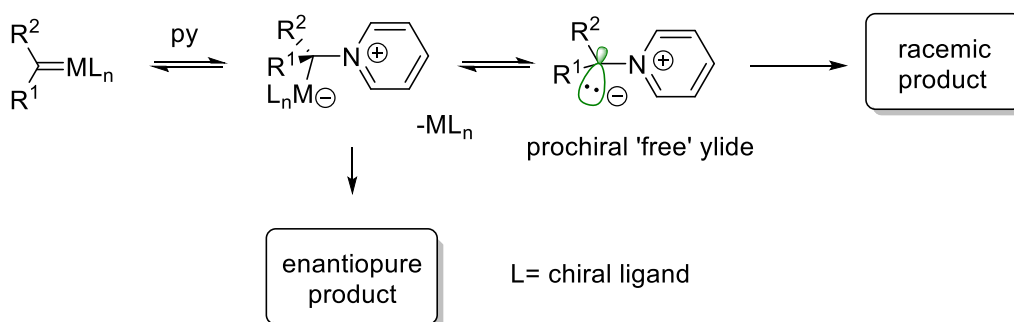
Scheme 39. Reagents and conditions: i) cat. (1 %), hexane, $-15\text{ }^\circ\text{C}$

In this example, the asymmetric conversion could have arisen from the free ylide after dissociation of the metal but before configurational inversion at the onium centre.⁷³ Jacobsen *et al.* reported formation of aziridine **111** with asymmetric induction up to 67% ee from benzylideneimines and ethyl diazoacetate catalyzed by chiral copper(I) bisoxazoline complexes (Scheme 40).⁷⁴



Scheme 40. Reagents and conditions: i) $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$, cat, CH_2Cl_2

According to these examples, chiral metal complexes are sometimes able to affect the stereochemical result of a cycloaddition reaction of oxonium ylides. These observations suggest that the chiral catalyst remains sufficiently associated with the ylide to accomplish asymmetric induction. If, following dissociation of the catalyst, the free ylide is achiral, then enantioselective formation of the product would be highly unlikely (Scheme 41).⁷⁵ One of the main aims of our project examine whether chiral metal catalysts, used for the generation of pyridinium ylides from diazo compounds, are able to achieve asymmetric induction to the cycloaddition reactions.

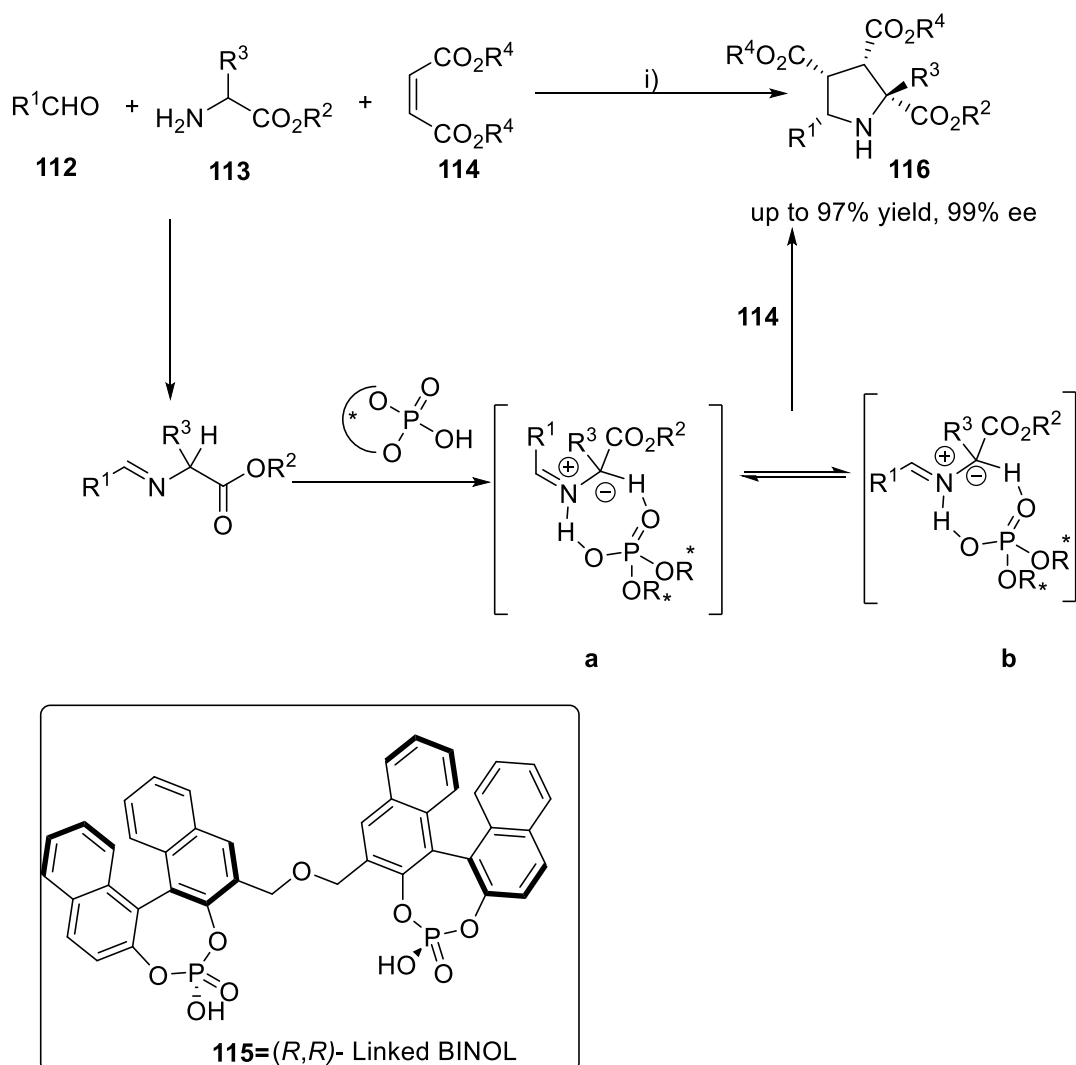


Scheme 41. Possible reactive species for metal carbenoid derived pyridinium

1.7 Brønsted acid and bifunctional catalysts in asymmetric cycloaddition

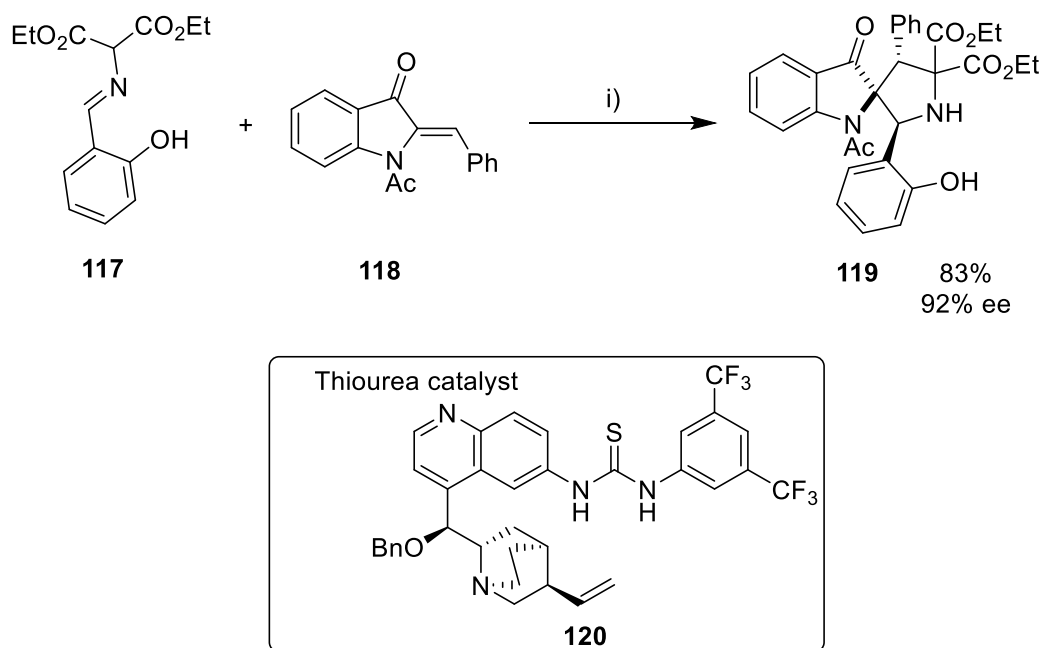
There is an alternative pathway to obtain asymmetric induction which is chiral activation of electrophile using bifunctional catalysts such as thiourea, squaramide or chiral phosphonic acids. Such bifunctional organocatalysts are gaining momentum for asymmetric transformations and have shown remarkably good results in diverse reaction types.

Gong *et al.* envisioned that chiral Brønsted acids (BH) are theoretically able to form a chiral azomethine ylide dipole **a** or **b** with an azomethine compound that would undergo an enantioselective 1,3-dipolar cycloaddition with dipolarophiles (Scheme 42).⁷⁶ They performed a Brønsted-acid-catalyzed asymmetric three-component 1,3-dipolar cycloaddition of aldehydes **112**, amino esters **113**, and maleates **114**, yielding multisubstituted pyrrolidines **116**. Strikingly, a bisphosphoric acid BINOL derivative **115**,⁷⁷ was the most promising catalyst and provided an almost quantitative yield and excellent enantioselectivity.



Scheme 42. Reagents and conditions: i) (R,R)-linked BINOL (10 mol%), CH_2Cl_2 , rt.

Recently, Xu *et al.* described the synthesis of spirocyclic indoxyls through (3+2) dipolar cycloadditions of azomethine ylides with high enantiomeric excess.⁷⁸ This work was achieved using imines as the 1,3-dipolar component to produce a range of spirocyclic pyrrolidines in high yield and enantiomeric excess using a thiourea catalyst **120** (Scheme 43). In this reaction order, deprotonation *via* the quinuclidine combined with activation of the imine through hydrogen bonding to the thiourea **120** makes the 1,3-dipole, which accomplishes the (3+2) dipolar cycloaddition.



Scheme 43. Reagents and conditions - *i)* cat. (10 mol%), DCE, 20 °C.

Encouragingly, these two examples provide an interesting pathway to accelerate chiral reactions by lowering the LUMO of electrophiles *via* the use of the bifunctional catalyst (such as squaramide and thiourea catalysts) in order to promote the enantioselective reaction. In these examples, there is an activation of the imine *via* hydrogen bond which is simply not possible with pyridinium ylides.

1.8 Aims and objectives

The main goal of the project was to explore the reactivity of pyridinium ylides in 1,3-dipolar cycloadditions, and to investigate subsequent reactions of the 1,2-dihydropyridine ring with the aim of forming stable indolizidine products that have the potential to possess interesting biological activity. We are particularly inspired to develop a cycloaddition strategy that may provide rapid access to valuable natural product derived structures.

In order to accomplish this, a number of contributing aims need to be met.

1.8.1 Synthesis of pyridinium salts

The first step in this project to reach the general aim will be the synthesis of a diversity pyridinium salts. Pyridinium salts will be produced through alkylation reactions between substituted pyridines and primary electrophiles. Substituted pyridinium salts will be examined for use in cycloaddition reactions.

1.8.2 Generation of pyridinium ylides from metal carbenoids

As previously mentioned, this routine of pyridinium ylide formation may allow the reaction to be achieved in one pot, base-free and catalytically. As a consequence, *in situ* trapping of metal carbenoids with substituted pyridines will be examined. Effect of metal and ligand on selectivity and yield will be detected. This possible methodology could provide an effective method to accumulate 'drug-like' indolizidine scaffolds. Furthermore, investigating whether use of chiral metal catalysts can lead to asymmetric cycloaddition and offer access to chiral indolizidine scaffolds is another aim of this project.

1.8.3 Modification of dihydropyridine ring

In this project, I was particularly interested in global reduction of the cycloadducts, leading to indolizine products. I was also interested in exploiting the enamine reactivity displayed by the 1,2-dihydropyridine featured with the cycloadducts. The development of this chemistry offers incorporation of varied indolizidine substituents.

1.8.4 Asymmetric cycloadditions of pyridinium ylides

At first, the formation of pyridinium ylides from diazo compounds using various transition metal catalysts will be investigated. Subsequently, the influence of chiral ligands on these catalytic reactions will be examined to see whether asymmetric (3+2) dipolar cycloaddition can be achieved. The metals that accomplish the desired cycloaddition will be followed up by decorating them with chiral ligands to see whether they are able to influence the stereochemical outcome of the reaction.

1.8.5 Alkylation of pyridinium ylides

The reactivity of pyridinium ylides has been utilised in cycloaddition reactions in the literature, however, they may offer much scope in their reactivity outside of cycloadditions. Because of the high nucleophilicity of such species, it may be possible to use them in alkylation reactions with electrophiles. If it is possible to alkylate pyridinium ylides, this may offer an attractive path to access valuable products that may possess biological activity.

Results and Discussion

Numbering of atoms within molecules

Numbering conventions that will be used in this results and discussion section in order to describe positions of interest on key molecules are described below (Figure 12).

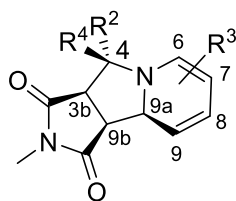
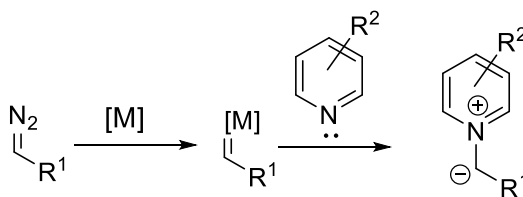


Figure 12 - Positions on the indolizidine ring¹³

2. Results and discussion

This results and discussion section is separated into 3 sections. The first section will study the metal-catalysed *in situ* formation of pyridinium ylides from diazo compounds (Scheme 44) and performing this reaction in the presence of alkene dipolarophiles to give tetrahydroindolizines. Subsequent modification of the 1,2-dihydropyridine moiety in the resulting cycloadducts is also discussed. Eventually, valued indolizidine core structures may be accessed efficiently through cycloaddition of pyridinium ylides with dipolarophiles and subsequent modification of the dihydropyridine ring.



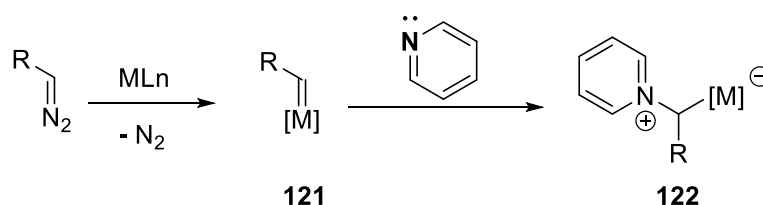
Scheme 44. Generation of pyridinium ylide

The second section describes the examination of an asymmetric (3+2) dipolar cycloaddition, using pyridinium ylides generated by the *in situ* decomposition of diazo compounds with transition metal catalysts bifunctional catalysts.

Finally, section three describes attempts to alkylate pyridinium ylide produced *in situ* from the decomposition of diazo compounds.

2.1 Catalytic production of pyridinium ylides from diazo compounds

As we mentioned previously, pyridinium ylides **122** may be generated by trapping of metal carbenoids **121** with pyridines (Scheme 45).³⁷⁻³⁹



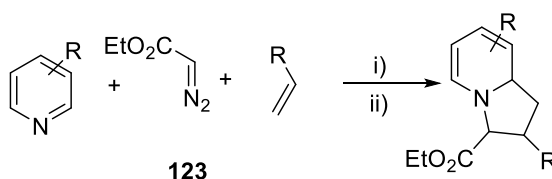
Scheme 45. Generation of pyridinium ylide from metal carbenoids

Metal carbenoids may be produced *in situ* from transition metal-catalysed decomposition of diazo compounds.³⁷ Recently, the Dowden group

developed a new methodology for performing 1,3-dipolar cycloadditions, in which pyridinium ylides are generated *via* metal catalysed decomposition of diazo compounds.⁶⁷ Initial investigations of (3+2) cycloaddition reactions using diazo compound precursors are discussed below.

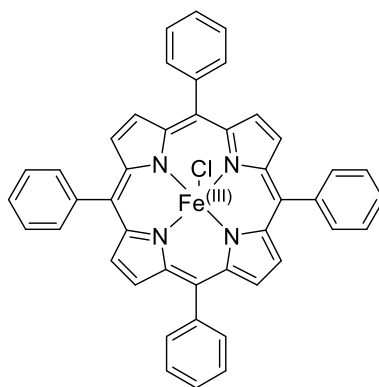
2.2 Maleimide cycloadducts

Methods previously developed within the Dowden group were used as a starting point for these studies. Specifically, these conditions involved dropwise addition of ethyl diazoacetate (EDA) **123**, *via* syringe pump to a solution of other reagents in an appropriate solvent (Scheme 46).⁶⁷



Scheme 46. Reagents and conditions: i) CH_2Cl_2 or toluene, $\text{Fe}(\text{TPP})\text{Cl}$ (1 mol%), ii) CH_2Cl_2 , $(\text{MeCN})_4\text{CuPF}_6$.

The iron-porphyrin complex, $\text{Fe}(\text{TPP})\text{Cl}$ **124** (Figure 13), was an efficient catalyst for transformations of EDA in toluene or CH_2Cl_2 at loadings of 1 mol%. Alternatively, $[(\text{MeCN})_4\text{CuPF}_6]$ at 5 mol% loading in dichloromethane was also found to be a good catalyst for these reactions and was uniquely effective for transformations involving donor acceptor diazo esters.

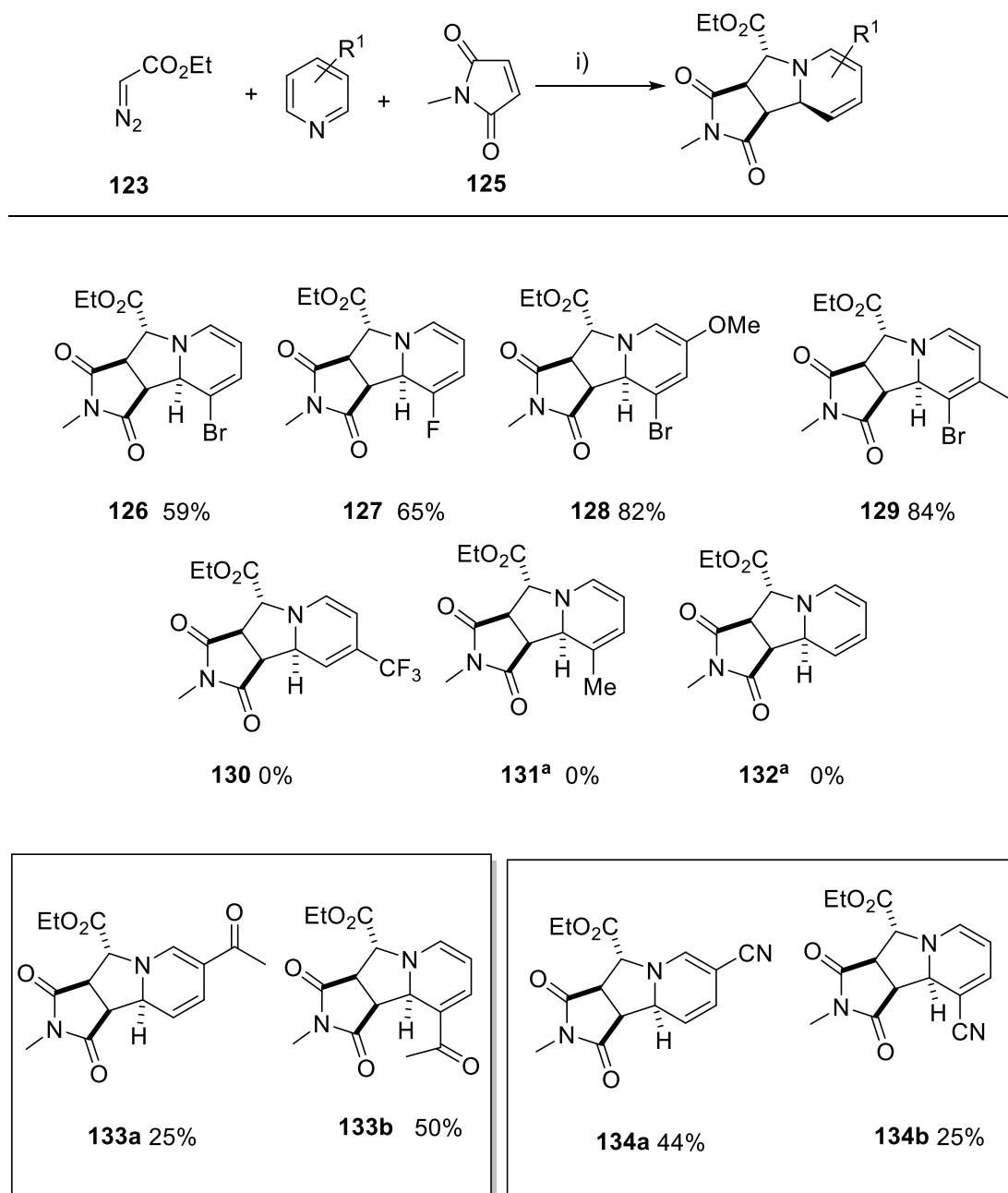


124

Figure 10 - Structure of *Fe(TPP)Cl*

Initially, we sought to investigate cycloaddition reactions of *N*-methylmaleimide **125** using these catalytic conditions to give products that resembled cycloadducts generated by base-promoted reaction conditions originally reported by Tsuge and co-workers.

The first reactions attempted combined ethyl diazoacetate **123**, and a small variety of pyridines bearing a substitution at either the 3- or 4-position under our standard reaction conditions *Fe(TPP)Cl* **124** (1 mol %), toluene or CH_2Cl_2 , at room temperature. These reactions gave cycloadduct products in moderate to good yield (25-84%) and as single diastereoisomers (Scheme 47).



Scheme 47. Reagents and conditions: i) $\text{Fe}(\text{PPP})\text{Cl}$ (1 mol %), toluene or CH_2Cl_2 , r.t., 5 h
^a= After purification via column chromatography

Both 3-bromopyridine and 3-fluoropyridine gave the cycloadducts respectively as single diastereoisomers in good yields of 59% (**126**) and 65% (**127**) respectively. In each case, the product arising from regioselective cyclisation at the C-2 position of the pyridinium ring was obtained as the sole product. This effect may be due to rings with donor

substituents would be expected to be less reactive and therefore have more product-like transition states than rings with acceptor substituents (product stability).⁷⁹ Unfortunately, we were not able to isolate **131** and **132** from reaction of 3-methylpyridine and pyridine respectively due to instability of these cycloadducts.

By contrast, reactions involving pyridines bearing a resonance withdrawing substituent in the 3-position produced cycloadducts (**133a**, **133b**, **134a**, **134b**) as a mixture of regioisomers originating from cyclisation at either the C-2 or C-6 position of the pyridinium ylides (Figure 14) that could be separated by column chromatography on silica gel. 3-Acetylpyridine, for example, gave products corresponding to cyclisation at the C-6 position (**133a**, 25%) as well as the C-2 position (**133b**, 50%), whereas 3-cyanopyridine gave the corresponding adducts in 44% (**134a** C6) and 25% (**134b** C2) respectively. Unfortunately, the reaction was attempted using 4-trifluoromethylpyridine, but it was not possible to isolate **130** from this reaction mixture.

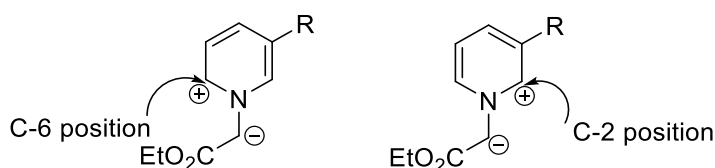


Figure 14. C-6 Vs C-2 position⁷⁹

Reaction of di-substituted pyridines 5-bromo-3-methoxypyridine and 3-bromo-4-methylpyridine was successful, giving good yields of the corresponding cycloadducts (**128**, 82%) and (**129**, 84%) respectively. The

regiochemistry of the cycloadduct **128** is consistent with the 3-bromo cycloadduct **129** (Figure 15), as confirmed through ^{13}C NMR of the two compounds.

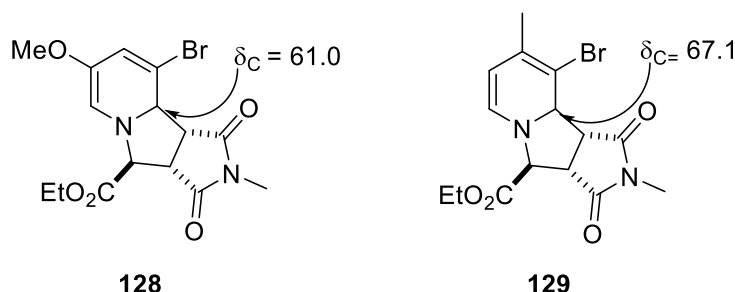


Figure 15. Illustration of key ^{13}C comparison between **128** and **129**

Typically, the regiochemistry of the cycloadducts could be assigned by examining the coupling pattern arising from the alkene protons associated with the 1,2-dihydropyridine. The relative shift of the singlet in the ^1H NMR spectrum of the cycloadducts was especially diagnostic. For example, the 3-fluoro cycloadduct **127** this arises from an aliphatic methane signal ($\delta_{\text{H}} = 4.7$) equivalent to the proton at 9a (C-2). The singlet observed in the ^1H NMR spectrum of adducts arising from addition at C-6 pyridinium intermediate, such as **134a** arising from 3-cyanopyridine, corresponds to an alkenyl proton at the 6 (C-6) position at a more downfield position ($\delta_{\text{H}} = 7.3$) (Figure 16).

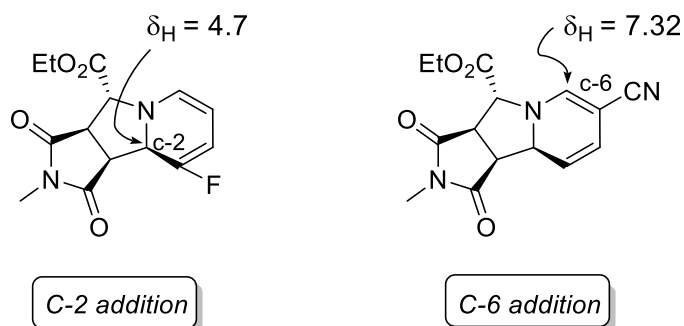


Figure 16. Comparison of C-2 addition versus C-6 addition

Ultimately, the position of cyclisation and relative stereochemistry of the cycloadduct **126** were confirmed using X-ray crystallography (Figure 17).

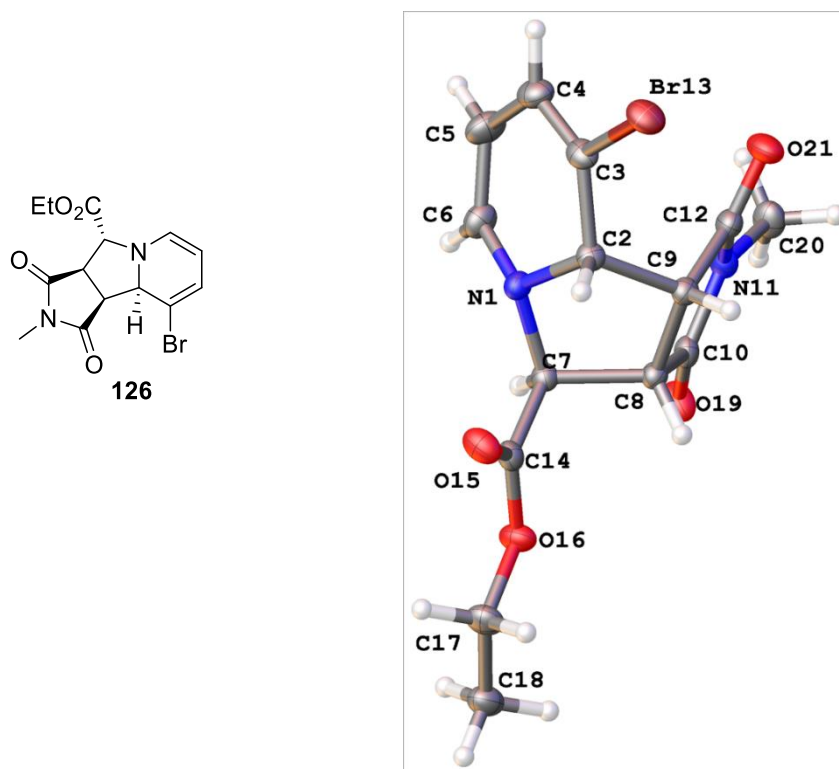
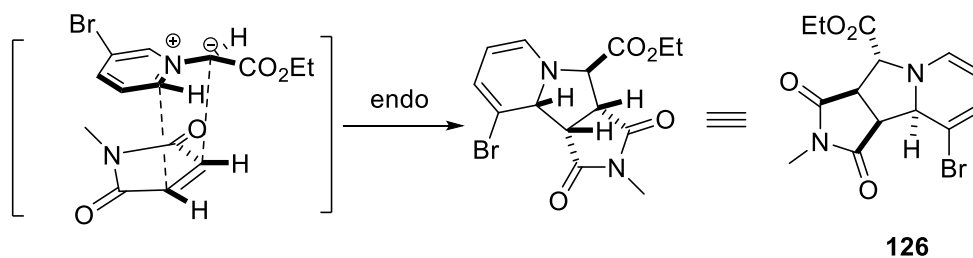


Figure 17. X-ray crystal structure for compound **126**

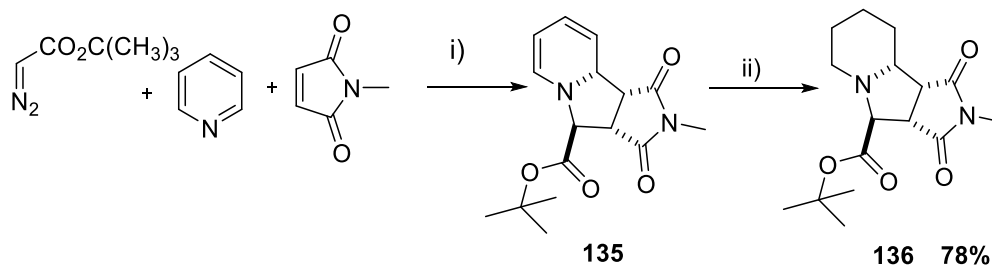
The observed stereochemistry was rationalised to arise from an *endo* transition state and an S-shaped ylide, which is in keeping with observations of similar cycloaddition reactions in our group and others. It is apparent that positive interactions between the maleimide carbonyls and the pyridinium ring favour the *endo* pathway. Once partial bonds have begun to form, the relative stereochemistry of the ylide stabilisation group (CO₂Et) is translated into the product. The preference for an S-shaped ylide is thought to arise from minimising repulsion of carbonyl dipoles of the ylide and maleimide in the transition state (Scheme 48).



Scheme 48 – Rationale for observed stereochemistry

The relative stereochemistry of each previous cycloadducts was determined using ^1H NOESY analysis. Attempting the cycloaddition reaction with unsubstituted pyridine gave cycloadducts that were too unstable for isolation. In this case, reduction of the tetrahydroindolizine using Raney Nickel $\text{\textcircled{R}}$ in a hydrogen atmosphere gave the more stable indolizidines **136** in a good yield (Scheme 49). This indolizine product was also crystalline and could be characterised and the relative stereochemistry confirmed by X-Ray crystallography (Figure 18).

This structure revealed the same diastereoselectivity of an 'endo' type transition state and an *S*-shaped ylide of the reduced cycloadduct **135** was observed (Scheme 49).



Scheme 49. Reagents and conditions: i) $\text{Fe}(\text{TPP})\text{Cl}$ (1 mol %), toluene, r.t., 5 h; ii) Raney Nickel $\text{\textcircled{R}}$, H_2 , EtOH, r.t., 16 h.

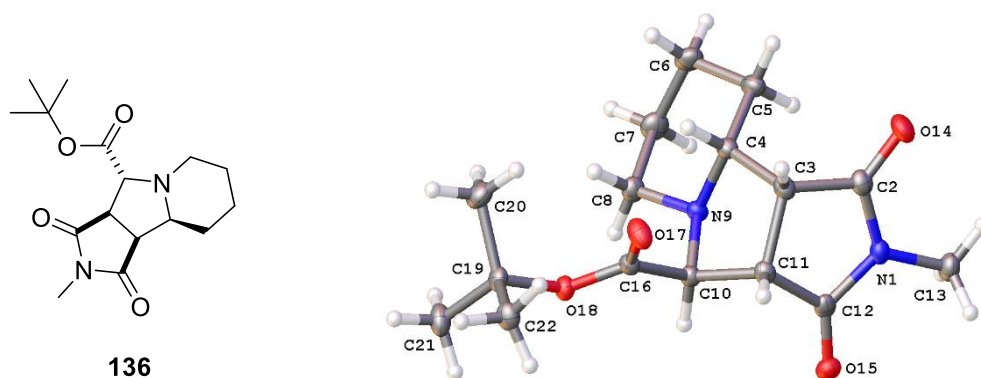
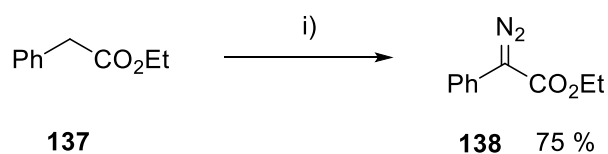


Figure 18. X-ray crystal structure of compound **131**

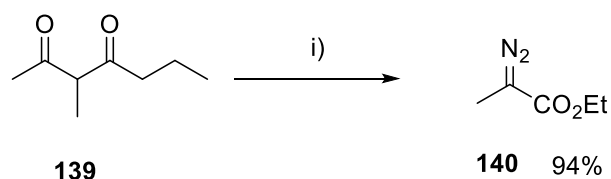
2.3 Synthesis of di-substituted diazo compounds

To broaden the substrate scope of this reaction, a small selection of diazo compounds was synthesised. Ethyl diazophenylacetate **138** was prepared according to literature procedure.⁸⁰ Briefly, ethyl 2-phenylacetate **137** and tosyl azide were combined with DBU in acetonitrile at room temperature to yield the desired diazo compound **138** in 75% yield (Scheme 50).



Scheme 50. Reagents and conditions: i) TsN₃ (1.2 equiv.), DBU (1.5 equiv.), acetonitrile, rt, 16 h.

Ethyl 2-diazopropanoate **140** was prepared from a related literature procedure,⁸¹ thus ethyl-2-methylacetoacetate **139** was combined with tosyl azide and sodium hydride in diethylether at room temperature to give the corresponding diazo product in 94% yield (Scheme 51).

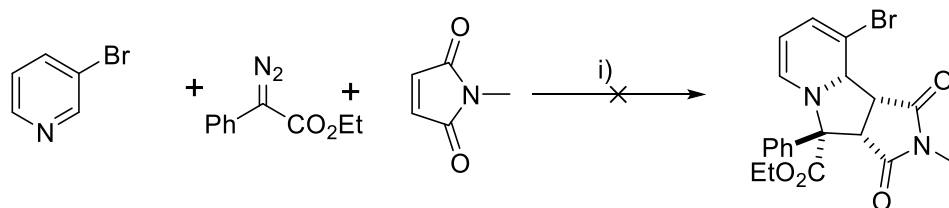


Scheme 51. Reagents and conditions: i) TsN_3 (1.16 equiv.), NaH (1.9 equiv.), dry diethyl ether, rt, 16 h.

These diazo compounds bear two substituents and allow us to further study how changes in electronics affects reaction with the metal catalyst and any subsequent cycloaddition reaction.

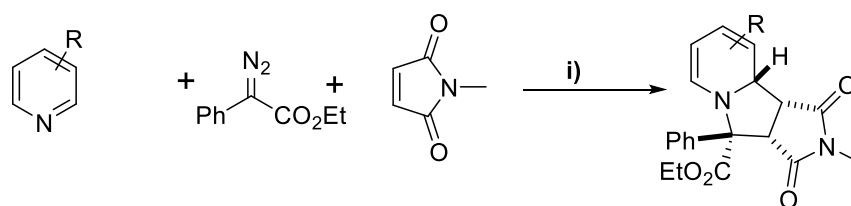
2.4 Disubstituted diazo cycloadduct

With the synthesised diazo compounds in hand, we began examining the use of diazo compounds bearing two substituents, such as ethyl diazophenylacetate **138**. Early investigations with $\text{Fe}(\text{TPP})\text{Cl}$ **118** in toluene failed to produce the cycloadduct and only starting material was returned from the reaction mixture (Scheme 52). It generally seems that $\text{Fe}(\text{TPP})\text{Cl}$ is a poor catalyst for the decomposition of ethyl diazophenylacetate.

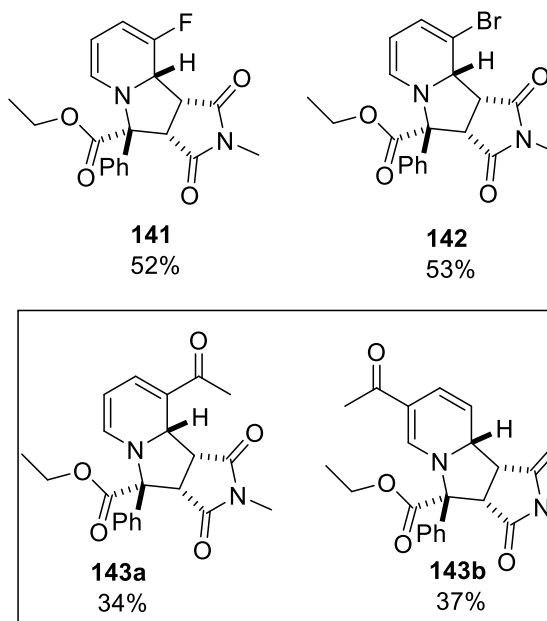


Scheme 52. Reagents and conditions: i) $\text{Fe}(\text{TPP})\text{Cl}$ (1 mol %), toluene, r.t., 5 h.

We have previously found $[(\text{MeCN})_4\text{CuPF}_6]$ to be an effective catalyst for transformation of donor-acceptor diazo compounds.⁸² Pleasingly, use of this catalyst in CH_2Cl_2 gave the desired cycloadducts as single diastereoisomers in good to moderate yield (Scheme 53).



R= F, Br, COCH₃



Scheme 53. Reagents and conditions: i) [(MeCN)₄CuPF₆] (5 mol %), CH₂Cl₂, r.t., 5 h

Specifically, both 3-fluoropyridine and 3-bromopyridine gave the cycloadducts **141** and **142** in 52 and 53% yield respectively as a single diastereoisomer. As observed earlier, pyridines bearing a resonance stabilising substituent in the 3-position produced cycloadducts **143** as a mixture of regioisomers originating from cyclisation at either the C-2 or C-6 position of the pyridinium ylides that, for these examples, could be separated by column chromatography on silica gel. 3-Acetylpyridine, gave products corresponding to cyclisation at the C-6 position (**143b**, 37%) as well as the C-2 position (**143a**, 34%).

The relative stereochemistry of the cycloadduct **142** was confirmed using ^1H NOESY analysis, which revealed a correlation between 3 protons of the newly formed ring (9a, 9b) and a proton corresponding to ring junction 8a (Figure 18).

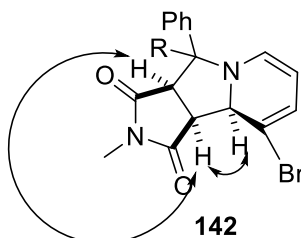
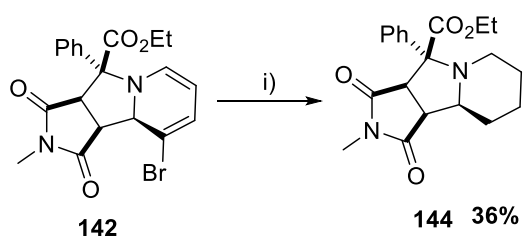


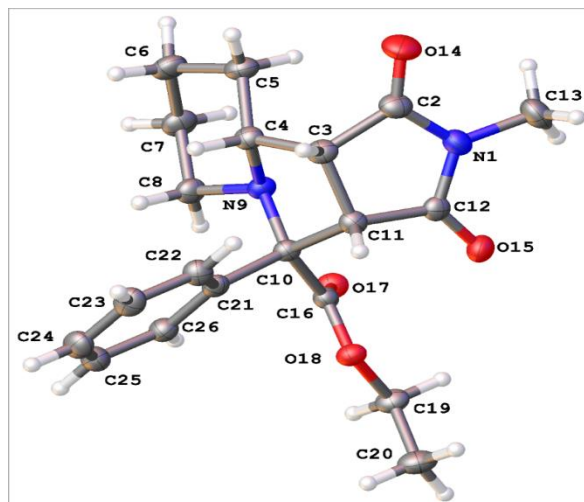
Figure 18. Illustration showing key NOESY interactions for compound **142**

Reduction of the tetrahydroindolizine using Raney Nickel $\text{\textcircled{R}}$ in a hydrogen atmosphere gave the more stable indolizidines **144** in a good yield (Scheme 54). This indolizine product was also crystalline and the relative stereochemistry was confirmed by X-Ray crystallography (Figure 19).

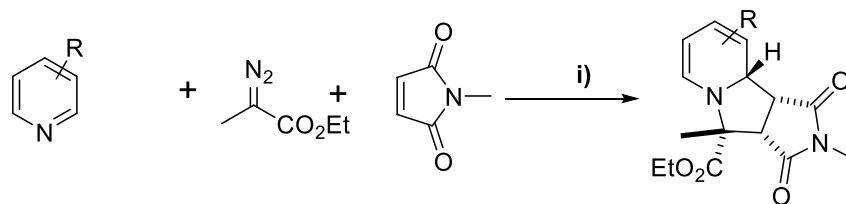


Scheme 54. Reagents and conditions: i) Raney Nickel, H_2 , EtOAc, r.t., 16 h.

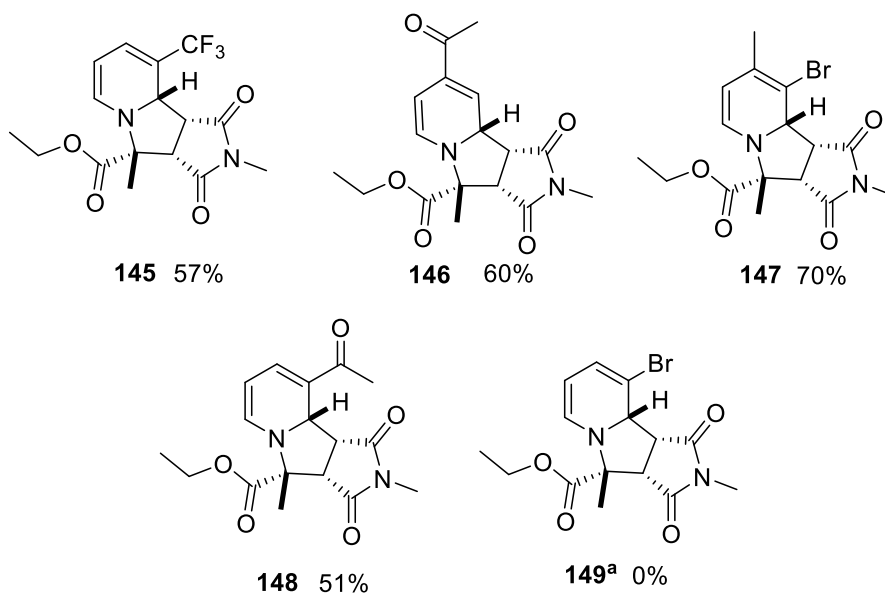
The most notable aspect here is that the ylide-derived ester group is on the same face as the imide derived from maleimide, whereas it is on the opposite face for EDA derived cycloadducts (Figure 19). Presumably, the steric influence of the phenyl group is greater than the repulsion arising from the carbonyls in this example.



Further investigation focussed on reaction of ethyl 2-diazopropanoate **140** and a small variety of substituted pyridines bearing electron-withdrawing and donating groups in the cycloaddition reactions under our standard reaction conditions (Scheme 55).



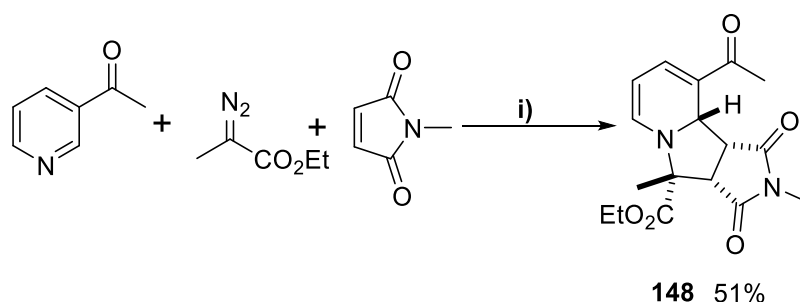
R = CF₃, Br, COCH₃



Scheme 55. Reagents and conditions: i) [(MeCN)₄ CuPF₆] (5 mol %), CH₂Cl₂, r.t., 5 h
^a= after purification using column chromatography

we were generally able to access maleimide cycloadducts in a good to moderate yield (Scheme 55). Cycloadducts derived from 3-trifluoromethylpyridine **145** and 4-acetylpyridine **146** were isolated as a single distereoisomers in good yields of 57% and 60% respectively. Unfortunately, reaction involving 3-bromopyridine produced cycloadduct **149** which was unstable and characterisation proved difficult. As observed earlier, the reaction of 3-acetylpyridine produced cycloadducts **148** as a mixture of regioisomers [1.2:1] originating from cyclisation at either the C-2 or C-6 position of the pyridinium ylides were obtained as observed in the crude ¹H NMR spectrum. For this example, unfortunately, we were unable

to separate both cycloadducts from the crude mixture but could separate one of these cycloadduct **148** by column chromatography on silica gel (Scheme 56). Reaction of di-substituted pyridine 3-bromo-4-methyl pyridine did however produce cycloadduct **147** in a good yield 70%. These were the first examples of cycloaddition reactions involving ethyl 2-diazopropanoate **140** observed within the group, it is exciting to observe that there are not side reactions of these potentially reactive donor-acceptor diazo compounds with broad implications for the potential utility of this multicomponent reaction.



Scheme 56. Reagents and conditions i) $[(\text{MeCN})_4\text{CuPF}_6]$ (5 mol %), CH_2Cl_2 , r.t., 5h.

The relative stereochemistry of the cycloadduct **143** was determined by analysis of the ^1H NOESY spectrum and confirmed to have the same relative orientation as that observed the cycloadduct **142** arising from ethyl diazophenylacetate **138**, the ylide derived ester is on the same face as the imide, presumably because the methyl group has the greater steric influence on the ylide shape in the transition state. Again, the relative stereochemistry of previous cycloadducts was determined using ^1H NOESY analysis.

Again, Initial ^1H NOESY analysis of the reduced cycloadduct **150** revealed a correlation between protons corresponding to methyl group at the 1-position and the proton at the 5-position adjacent to the nitrogen of the indolizine ring. Furthermore, ^1H NOESY data revealed an interaction between methyl group at 1 position and the proton at 2 positions adjacent to the quaternary carbon carrying (methyl and ester groups). Much like the reduced cycloadduct **142** arising from ethyl diazophenylacetate **138**, the ylide derived ester is on the same face as the imide, presumably because the methyl group has a greater steric influence on the ylide shape in the transition state (Figure 20).

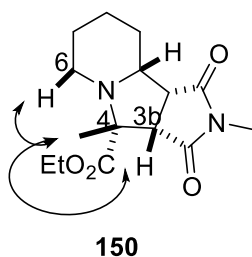
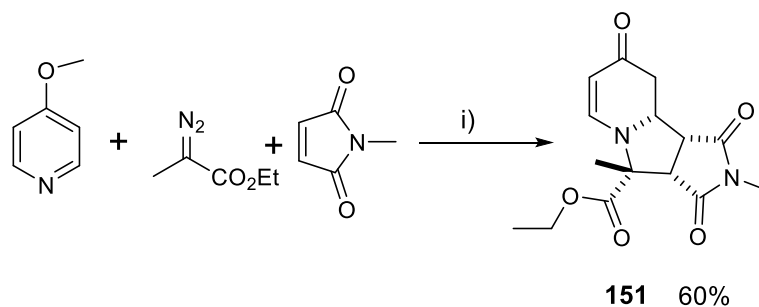


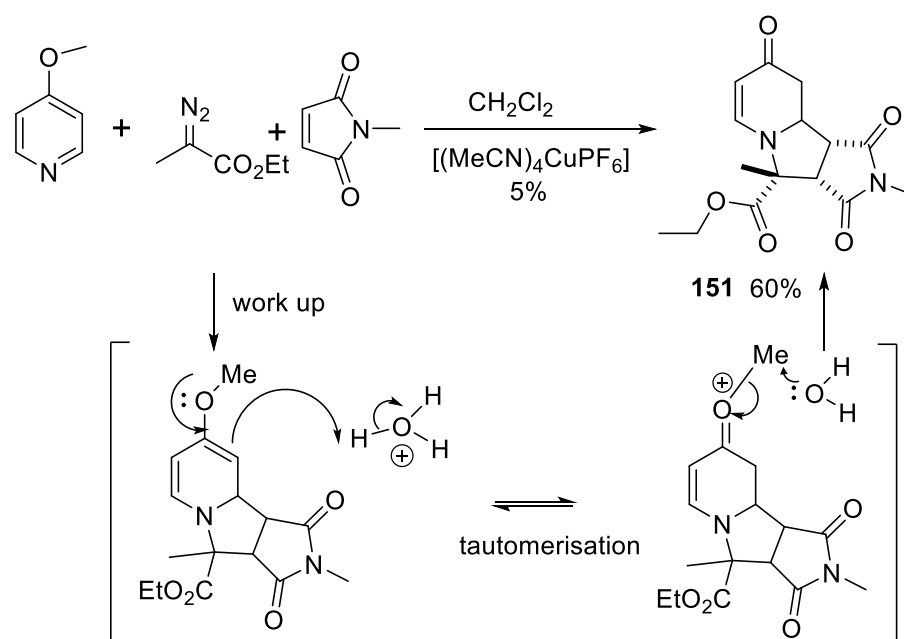
Figure 20. Illustration showing key NOESY interactions for compound **150**

Interestingly, during our investigation using ethyl 2-diazopropanoate **140** with 4-methoxypyridine and *N*-methyl maleimide, another product was observed. When trying to produce 1,2-dihydropyridine cycloadduct, the 2,3-dihydro-4-pyridone product **151** was the only product isolated from the reaction in a good yield (60%) (Scheme 57).



Scheme 57. Reagents and conditions: i) $[(\text{MeCN})_4\text{CuPF}_6]$ (5 mol %), CH_2Cl_2 , r.t., 5 h

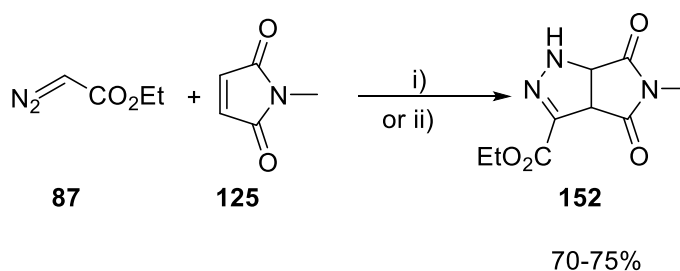
Presumably this product arises from protonation of the initial tetrahydroindolizidine intermediate and hydrolysis of the resulting oxonium intermediate (Scheme 58). The resulting 2,3-dihydro-4-pyridone products **151** are more stable than 1,2-dihydropyridines, and offer several points for potential derivatization.



Scheme 58 Proposed mechanism for the reaction

2.4.1 Cycloaddition of the diazo compound

We did investigate alternative catalysts for this multicomponent cycloaddition reaction and during these studies, we noticed another reaction product **152**, specifically, this arises from direct cycloaddition of ethyldiazoacetate **87** and *N*-methylmaleimide **125** (Scheme 59). This cycloadduct was observed when $\text{Rh}_2(\text{OAc})_4$ or $\text{Rh}_2(\text{S-DOPS})_4$ were used as a catalyst for the reaction, but was not present in reaction mixtures involving $\text{Fe}(\text{TPP})\text{Cl}$ as catalyst.



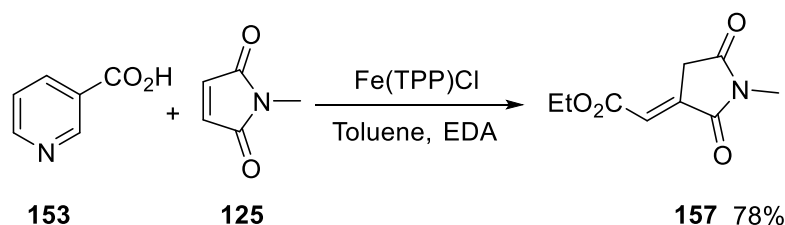
Scheme 59. Reagents and conditions: i) $\text{Rh}_2(\text{OAc})_4$ (1 mol%), CH_2Cl_2 , rt, 4 hr, ii) $\text{Rh}_2(\text{S-DOPS})_4$ (1 mol %), CH_2Cl_2 , rt, 4 hr

These results suggest that the 1,3-dipolar cycloaddition of the diazo compound to the *N*-methylmaleimide proceeds at a much faster rate than the rhodium catalysed loss of nitrogen from the starting diazo compound in this case.

These observations show that the reaction outcome is dependent upon choice of metal and ligand and suggests that these two aspects have an important impact on the pyridinium ylide formation.

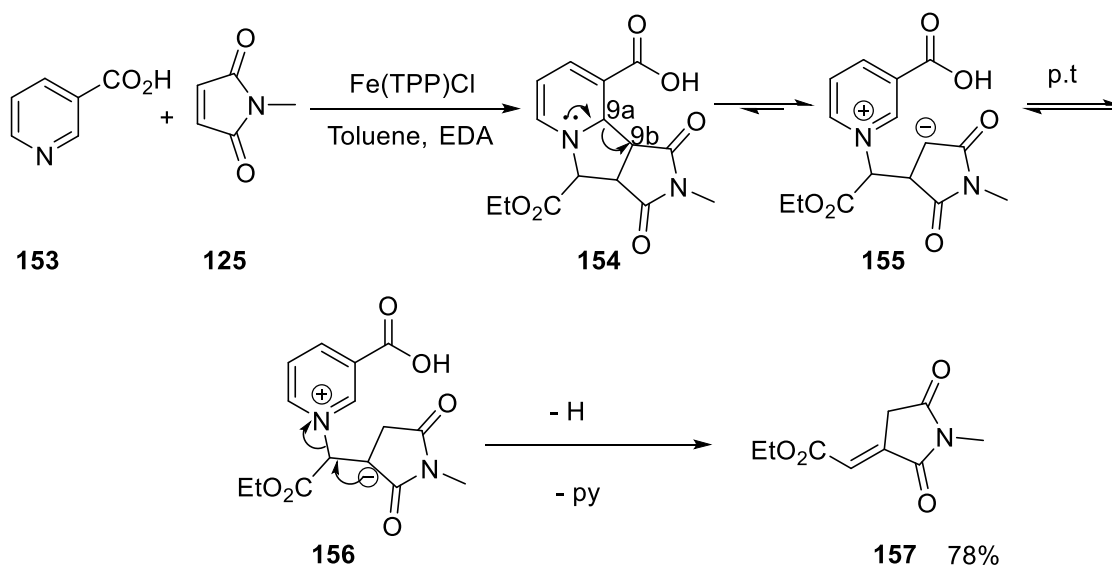
2.4.2 Alternative reaction outcomes (elimination)

Throughout our investigation of cycloadditions with *N*-methylmaleimide, a further alternative product was detected, when trying the cycloaddition between nicotinic acid **153**, *N*-methyl maleimide **125** and ethyldiazoacetate in toluene with Fe(TPP)Cl. Although the cycloadduct **154** was observed in the crude mixture by ¹H-NMR spectroscopy, attempts to purify this material by column chromatography gave the product of pyridine elimination, **157** was the sole product 78% (Scheme 60).



Scheme 60. Formation of the elimination product **157**

The formation of **157** can be rationalized by the mechanism shown in (Scheme 61). Cleavage of the weak bond between position 9a and 9b in tetrahydroindolizine **154** produces a betaine **155**, subsequent tautomerisation and elimination leads to the *E*- α,β -unsaturated alkene **157**.



Scheme 61. Proposed mechanism for formation of **157**

The *E* geometry of **157** was confirmed by the comparison of chemical shifts of the 4-methylene doublet (3.69 ppm) and 6-olefin triplet (6.82 ppm) with those of Methyl (*E*)-2-(2,4-dioxo-3-(*p*-tolyl)cyclopentylidene)acetate **158**⁸³ (the 4-methylene doublet at 3.80 ppm and two 6-olefin triplets at 6.86 (Figure 21).

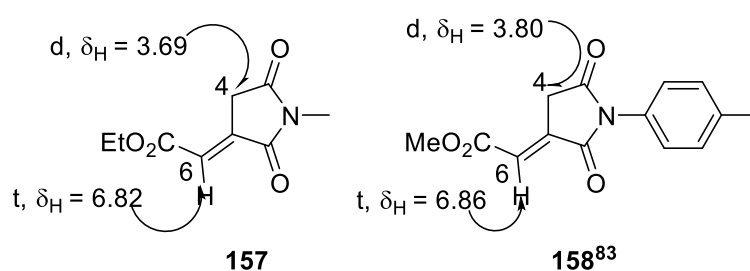


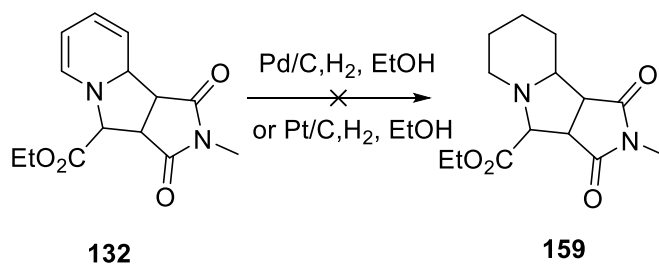
Figure 21. Comparison between **157** and **158**

2.5 Modification of 1,2-dihydropyridine

One of the aims of our project was to develop a system for modification of the dihydropyridine ring because some of the tetrahydroindolizine products were unstable to purification by column chromatography.¹⁴ Both an alkene

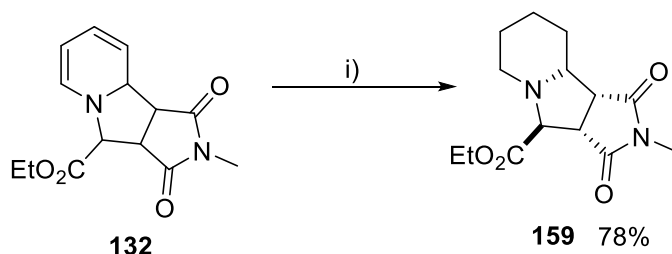
and an electron rich enamine exist within the 1,2-dihydropyridine ring which present opportunities for additional diversification reactions. The first objective was to examine some reduction methods that can be used to access indolizidines.

Several reducing agents such as Raney® nickel, Ni, Pd/C and Pt/C were examined with this goal in mind. Our first attempts to reduce cycloadduct **132** too unstable for purification by column chromatography using Pd/C and Pt/C with ethanol as a solvent, ultimately failed to generate clean indolizidine product (Scheme 62).

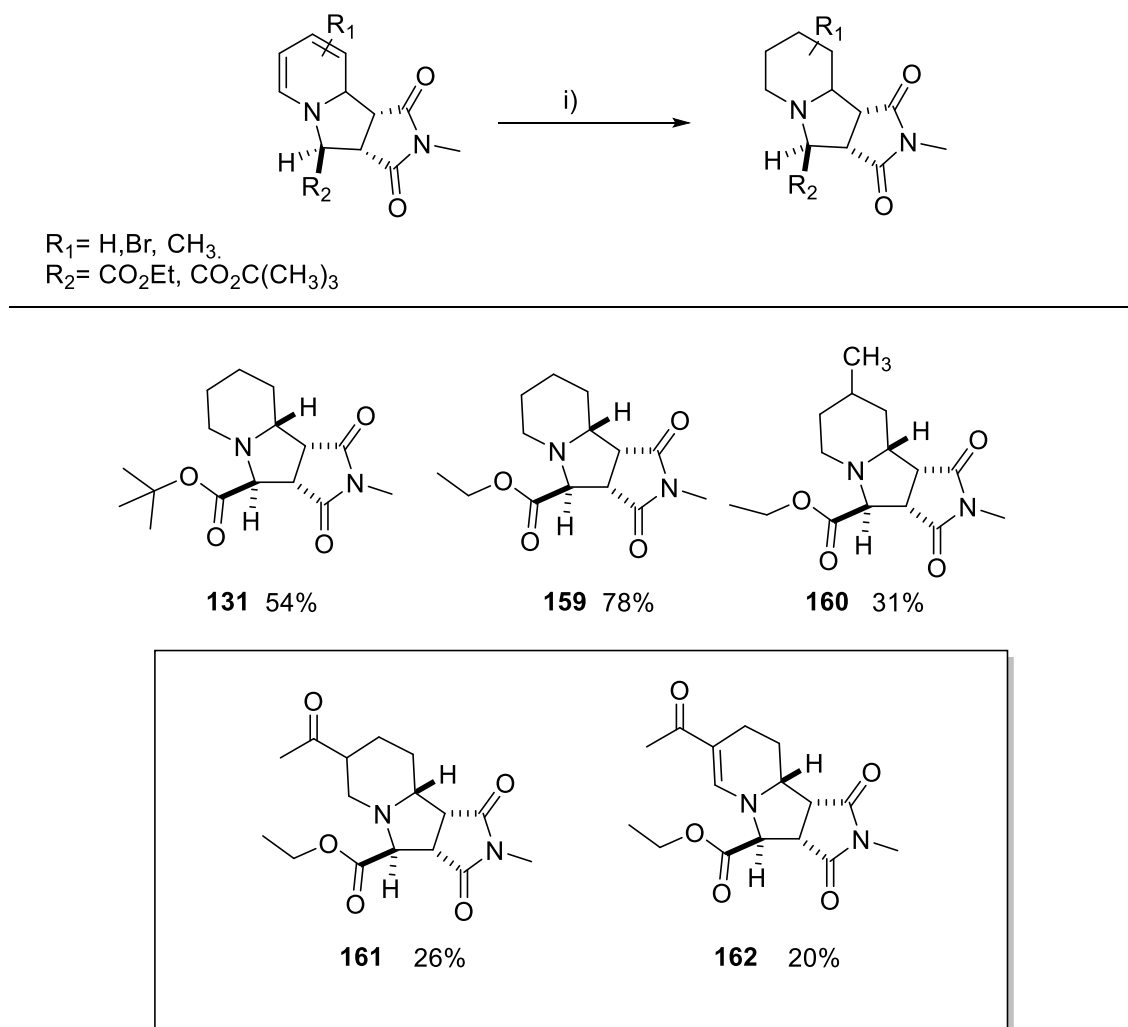


Scheme 62. Unsuccessful attempts to reduce cycloadduct **132**

Fortunately, reduction of the same cycloadduct **132** using Raney® nickel in ethanol as a solvent was successful and gave the product shown in (Scheme 63).



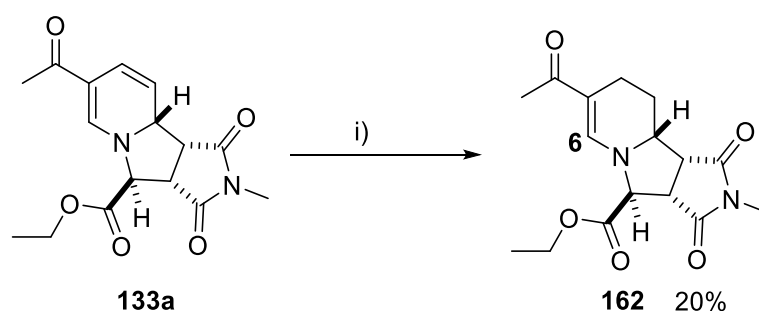
Scheme 63. Reagents and conditions: i) Raney/Ni (10 mol%), H₂, EtOH, rt, 16h



Scheme 64. Reagents and conditions: i) Raney/ Ni (10 mol%), H_2 , EtOH or EtOAc, rt, 16h

With the previous result in hand, reduction was carried out using a selection of our dihydropyridine cycloadducts under the same conditions. Consequently, we could access a range of reduced cycloadducts in moderate to good yield. Reduction of the cycloadduct **127a** arising from reaction with 3-acetylpyridine with Raney ® Nickel/ H_2 under these conditions gave a mixture of the fully reduced piperidine **161** in 26% and partially reduced enone **162** in 20% yield (Scheme 64). Analysis of ^1H NMR data of **162** revealed a singlet ($\delta_{\text{H}} = 7.38$) linked to the enamine proton at the 6 position (Scheme 65). In addition to this, analysis of ^{13}C DEPT spectra

revealed three $-\text{CH}_2$ signals in the reduced molecule, one from the ethyl ester group ($\delta_{\text{C}} = 62.58$) and the other two from the adjoining secondary carbons on the tetrahydropyridine ring ($\delta_{\text{C}} = 24.04, 20.15$). Interestingly, this information indicates that the alkene functionality was reduced, instead of the enamine functionality. This can be due to conjugation of the enamine with the ketone functionality.



Scheme 65. Reagents and conditions: Raney/Ni (10 mol%), H_2 , EtOH, rt, 16h

The relative stereochemistry of methyl group of the isolated product **160** was difficult to assign by ^1H NOESY analysis.

Thus far, investigations into the effect of Raney nickel on the reduction of 1,2-dihydropyridine ring was limited to cycloadducts bearing one substituent arising from the pyridinium ylide stabilising group. We therefore, set out to examine some other cycloadducts e.g. **150** derived from donor-acceptor diazo compounds (Figure 22).

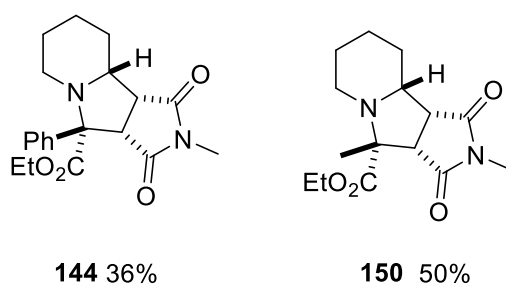
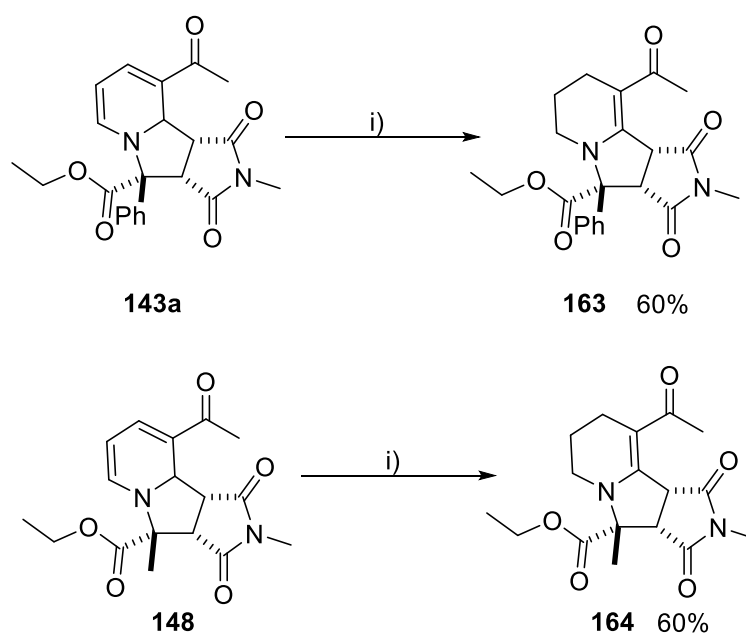


Figure 22. Reduced disubstituted cycloadducts

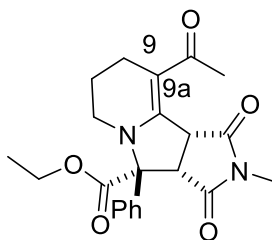
Our investigation towards the reduction of disubstituted cycloadducts was successful using the same reaction conditions (Raney ® Nickel/ H_2). Moreover, mass spectrometry revealed mass ion peaks ($m/z=397.1774$, 335.1608) for the corresponding partial reduction of the 3-acetylpyridine derived cycloadducts **143a** and **148** observed of the products **163** and **164**, each obtained in 60% yield (Scheme 66).



Scheme 66. Reagents and conditions: *Ra/Ni* (10 mol%), H_2 , EtOH, rt, 16h

Interestingly, these products **163** and **164** appear to be the result of the alkene apparently migrating to the ring junction (1,5-shift). These structures were assigned due to an absence of -CH signals corresponding to the (9a) and (9) position in ^1H NMR spectra and the presence of 3 adjacent methylene signals as confirmed through HMBC correlations (Figure 23). Further to this, analysis of ^{13}C DEPT spectra revealed four $-CH_2$ signals in the molecule arising from the ethyl ester ($\delta_c = 62.2$) and three adjacent

secondary carbons on the tetrahydropyridine ring ($\delta_c = 41.6, 23.6, 21.2$) in addition to the extra quaternary signals belong to the 9 and 9a positions.

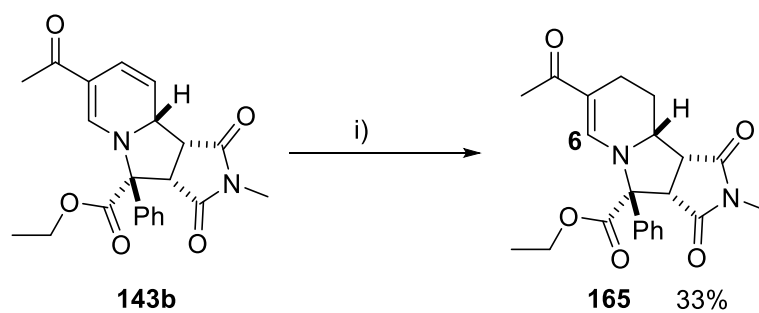


163

Figure 23. Partially reduced cycloadducts **163**

Similar spectroscopic results were obtained for indolizidine **164**. These structures have not been observed previously within the group but unfortunately, limited project time prevented any follow up studies on their transformation here.

Reduction of the cycloadduct **143b** arising from reaction with 3-acetylpyridine with Raney ® Nickel/ H_2 under these conditions gave also a mixture of partially reduced enone **165** in 33% yield. Analysis of ^1H NMR data of **165** revealed a singlet ($\delta_H = 7.85$) linked to the enamine proton at the 6 position (Scheme 67). In addition to this, analysis of ^{13}C DEPT spectra revealed three $-CH_2$ signals in the reduced molecule, one from the ethyl ester group ($\delta_c = 62.7$) and the other two from the adjoining secondary carbons on the tetrahydropyridine ring ($\delta_c = 24, 20.4$). Interestingly, this information indicates that the alkene functionality was reduced, instead of the enamine functionality. This can be due to conjugation of the enamine with the ketone functionality.

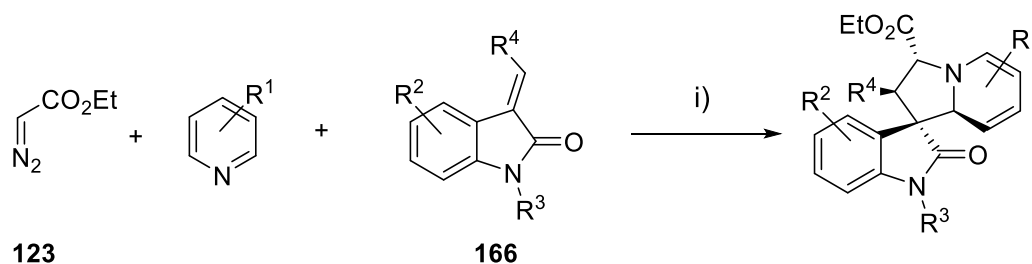


Scheme 67. Reagents and conditions: Raney/Ni (10 mol%), H_2 , EtOH, rt, 16h

In summary, reduction of the tetrahydroindolizine products with Raney Nickel proved to be a successful method to give simple access to stable indolizidines in good to moderate yield. The presence of carbonyl functionality attached to the 1,2-dihydropyridine tends to give enones which are more resistance to reduction under these conditions however.

2.6 Initial investigation towards an asymmetric cycloaddition

Dowden group developed a novel catalytic method to achieve 1,3-dipolar cycloadditions through the formation of pyridinium ylides *in situ* from diazo compounds (Scheme 68).



Scheme 68. Reagents and conditions: i) Fe(TPP)Cl (1 mol %), toluene, rt

Diazo compounds can decompose *via* transition metal catalysts to provide metallocarbenoids. Pyridine can be added to the metallocarbenoids to afford the ylide that may or may not be associated or bound to the metal (Figure 24).

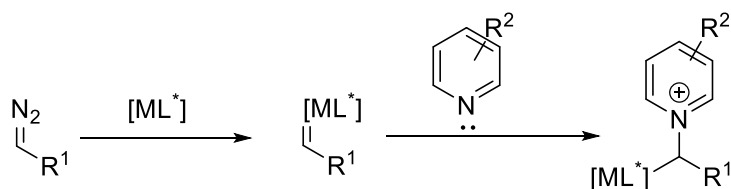
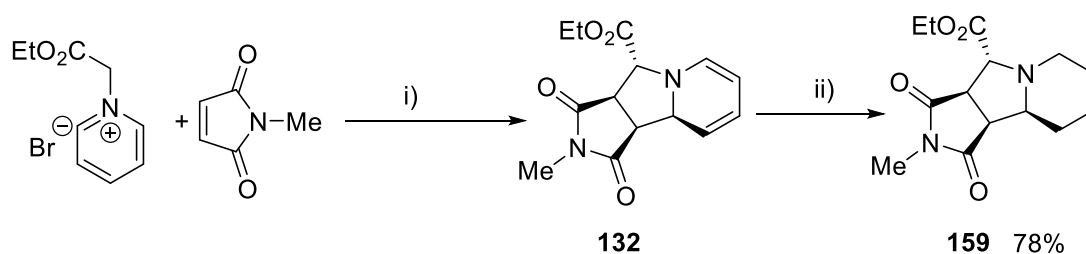


Figure 24. Formation of pyridinium ylide from diazo compounds

Thus far, developing enantioselective cycloadditions of pyridinium ylides remains a significant challenge with no relevant methods in the literature. A key goal at this stage of our research was therefore to investigate whether enantioselective cycloaddition of pyridinium ylides can be achieved, perhaps by using chiral ligands attached to the metal catalysts. Achieving this goal

will require organisation of the transition state to effectively block one face of the ylide.

The most convenient technique for measuring enantioselectivity is by HPLC of the reaction products using a chiral stationary phase. Our initial investigations therefore started with the goal of achieving separation of a racemic cycloaddition product. Unfortunately, attempts to separate the racemic maleimide derived cycloadduct **132** by chiral HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (95:5 v/v) were not successful. Based on our experience of handling tetrahydroindolizines in general, it was perceived that the 1,2-dihydropyridine ring was too unstable to the chromatography conditions. Modification of the dihydropyridine to obtain a more stable racemic product may serve our purposes. As previously reported, we carried out reduction of the maleimide cycloadduct **132** using Raney [®] nickel (Scheme 69). These racemic indolizidines could indeed be separated by chiral HPLC: Chiralcel AD-H; mobile phase, hexane/2-propanol (95:5 v/v) (Figure 25) and this allowed us to set about investigating whether chiral ligands could be introduced to the cycloaddition reactions.

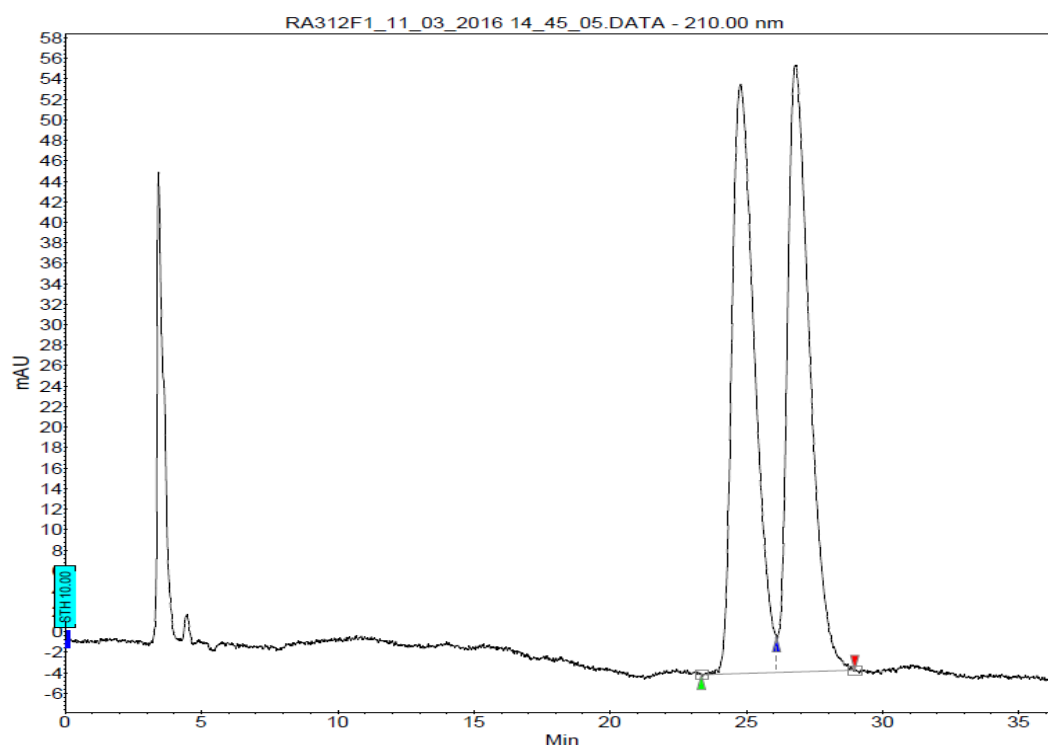


Scheme 69. Reagents and conditions: i) Et_3N , CH_2Cl_2 , 4 h, rt, ii) Raney Ni, H_2 , EtOAc , 16 h

Chromatogram : RA312F1_11_03_2016 14_45_05_channel4

System : HPLC
Chiralpak AD-H + guard
95:5 Hexane:IPA
1 ml/min

Acquired : 11/03/2016 14:46:22
Processed : 11/03/2016 15:30:51
Printed : 11/03/2016 15:31:19

**Peak results :**

Index	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.78	49.54	57.6	55.1	49.544
2	UNKNOWN	26.80	50.46	59.2	56.2	50.456
Total			100.00	116.7	111.3	100.000

Figure 25. HPLC analysis for racemic product of **159**

When the cycloaddition reaction was performed using the diazo materials the reaction continued in nearly identical yield to that obtained by deprotonation of the pyridinium salt. Both base mediated and catalytically cycloaddition reaction could form racemic cycloadducts. Also, we could separate the enantiomers by chiral HPLC and so a catalyst screen was achieved (Table 3).

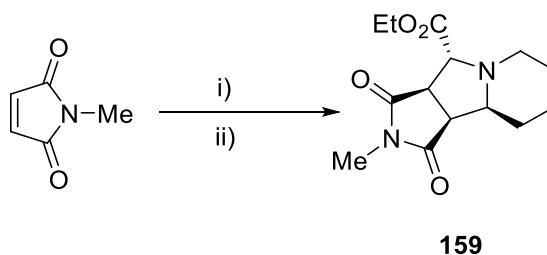


Table 3 – *Reagents and conditions:* i) pyridine (0.23 mmol), ethyldiazoacetate (0.23 mmol in 120 μ L solvent), catalyst, *N*-methylmaleimide (0.15 mmol), solvent (2 mL), ii) H_2 /Raney Nickel, EtOAc. a) Chiral Lewis acid catalysts were pre-formed *in situ* by stirring ligand and metal salt (entry 2 and 4) for several hours at room temperature, followed by addition of the remaining reagents.

Entry	Loading (%)	Yield (%)	e.e. %
1	1	68	0
2	20	50	0
3	2.5	89	0
4	20	55	0
5	1	50	0
6	1	51	0
7	1	0	---
8	1	0	---

Catalyst for the entries (1-8) shown in Fig 26.

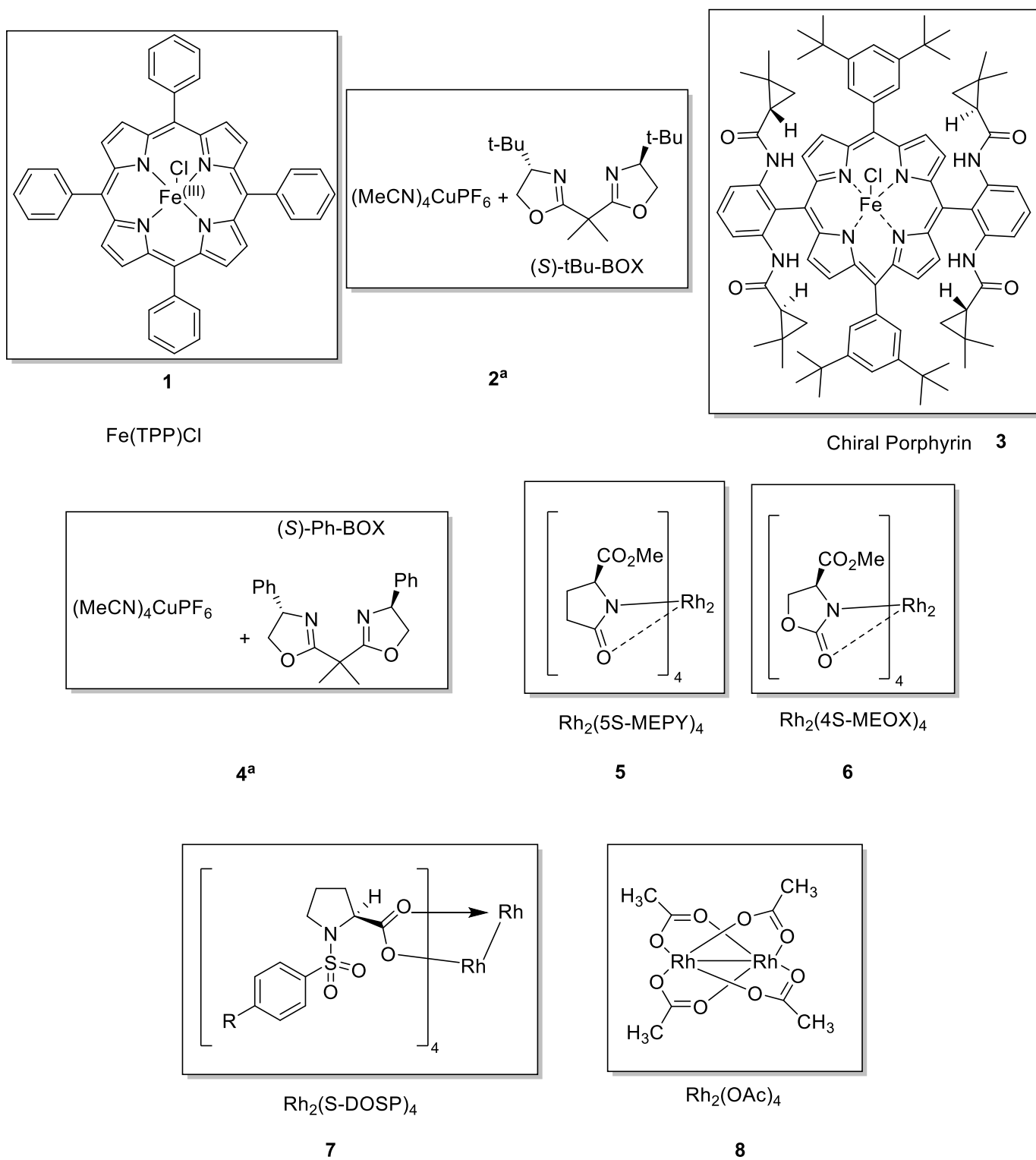
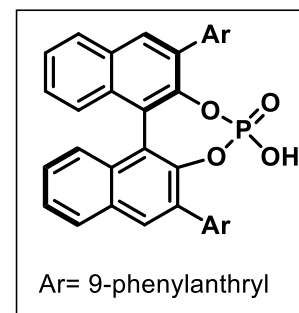
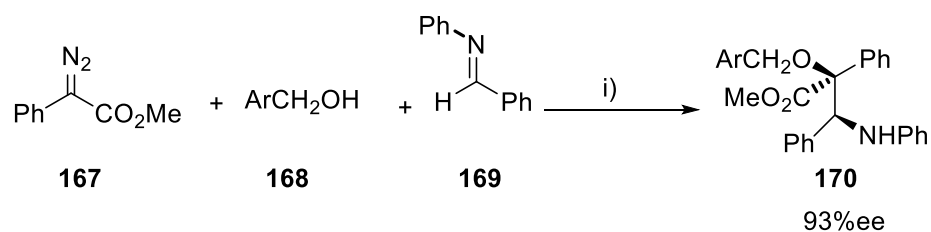


Figure 26. Examples of chiral ligands and metal salts

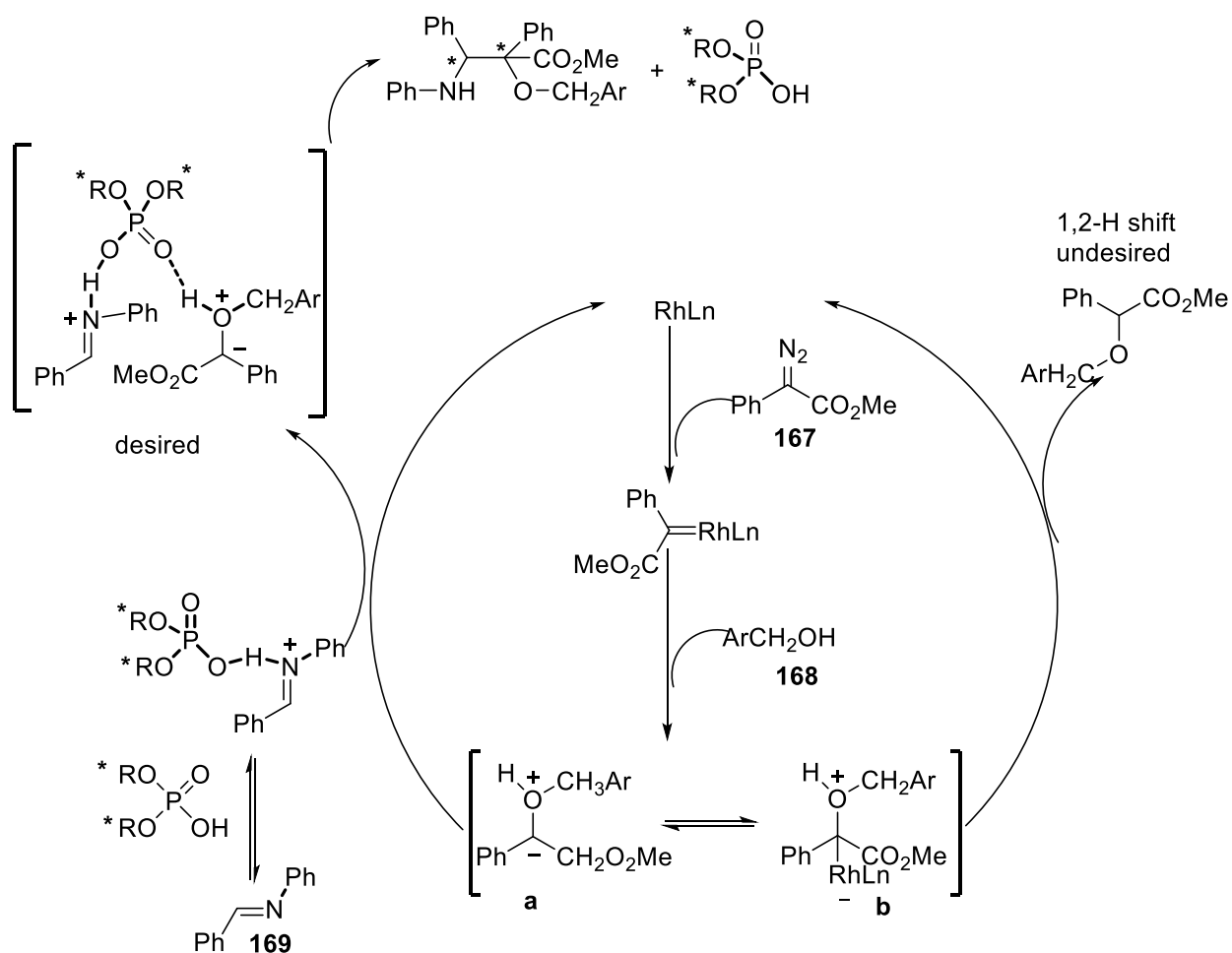
The purpose for choosing these specific ligand types was due to their use in asymmetric cycloadditions of associated azomethine ylides and Diels-Alder cycloadditions.⁸⁴⁻⁸⁵ Additionally, these ligands were commercially available.

Entries 2 and 4; along with (Entry 3) and Doyle's catalysts (Entries 5 and 6) all successfully produced the desired cycloadduct **159** in yields ranging from 50-89% while (Entries 7 and 8) as catalysts were unsuccessful to produce the cycloadducts. However, analysis of each of these reaction products by chiral HPLC revealed two peaks corresponding with the original racemic sample. Any of these catalysts were unsuccessful to induce any enantioselectivity in the outcome of the reaction as confirmed by chiral HPLC.

These results were not encouraging and might suggest that there is little transfer of information between catalyst and pyridinium ylide. Rather than continue to explore more catalysts, I decided to explore the idea of placing the chiral information on the electrophile. This concept has been successfully applied for related reactions, such as O-H insertion reactions. For example, Hu *et al* has developed a catalytic and enantioselective reaction three-component reaction of aryl diazoacetates **167**, alcohols **168**, and imines **169**. In these reactions, the racemic metallocarbenoid is intercepted by the alcohol leading to an oxonium ylide, which subsequently undergoes enantioselective addition to an activated by a chiral Brønsted acid (Scheme 70).⁸⁶



Scheme 70. Reagents and conditions: i) $\text{Rh}_2(\text{OAc})_4$ (2 mol%), chiral Brønsted acid, CH_2Cl_2 , 0°C



Scheme 71 - Proposed reaction mechanism

This mode of chiral activation of electrophiles requires the following sequence to occur for our purposes. First, the diazo compound must form the metallocarbenoid species **171**, presumably this become the most electrophilic species in the reaction mixture. Subsequent addition of pyridine generates the racemic ylide **172**. We know that these are very potent nucleophiles ¹⁵⁻¹⁷ and thus, once formed, can be expected to outcompete pyridine for subsequent reaction with electrophiles (Figure 27).

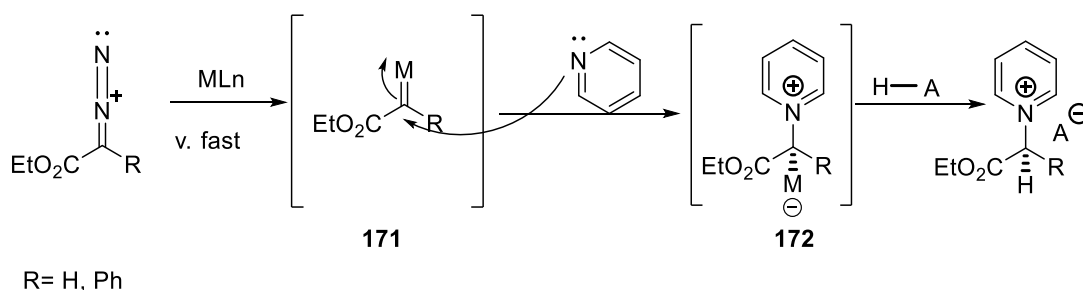


Figure 27. Expected pathways if we used acid in our reaction

It is possible to accelerate enantioselective reactions by lowering the LUMO of electrophiles in the presence of a chiral Brønsted or Lewis acid.

There is a potential competing pathway for diazo compounds, which proceeds *via* protonation of the diazonium ylide to give a highly electrophilic diazonium species that would be expected to alkylate the conjugate base *via* a classical caged intermediate (Figure 28). Clearly, the degree to which this occurs will depend upon how easy it is to protonate the diazocompound and consequently, the Brønsted acid and solvent conditions. We set out to examine the extent to which the classical alkylation pathway would compete

with the catalytic pathway by comparing the yield of the same reaction mixtures in the presence of catalysed with those where it was absent.

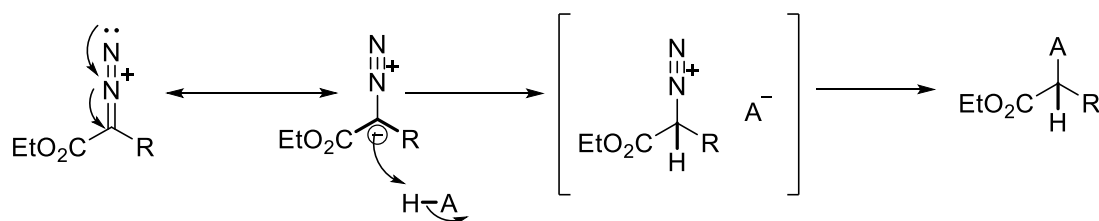


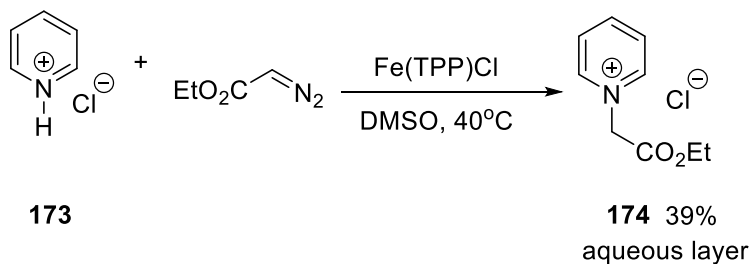
Figure 28. Protonation of diazonium ylide

Our investigation started by exploring how acids with various pKa's influenced the reaction between pyridine and diazo compounds. Pyridinium.HCl **173** was this first species to be investigated but the only solvent that it would dissolve in was DMSO. Classical alkylation was observed to occur when EDA was added to this mixture, resulting in a modest 32% yield of pyridinium salt **174**, which was isolated from the aqueous layer upon work up of the reaction mixture. These conditions were repeated in the presence of 1 mol% Fe(TPP)Cl but the amount of pyridinium salt formed from the diazo compound was the same. This suggests that under these strongly acidic conditions classical ('non-catalysed') alkylation is the only reaction that takes place (Scheme 72).

non-catalysed



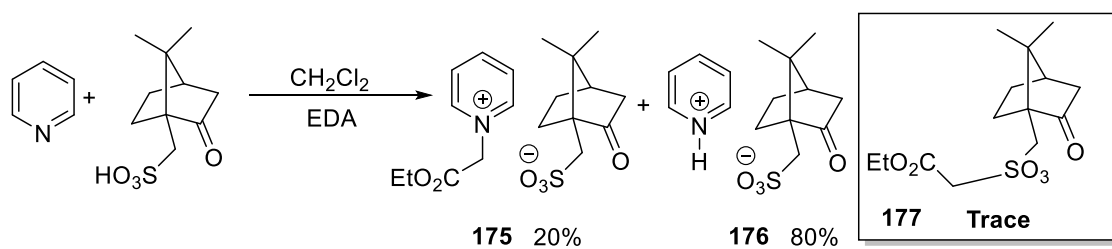
catalysed



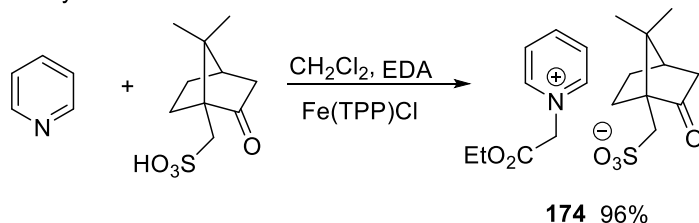
Scheme 72. Classical alkylation of pyridine under acidic condition

Next investigation was the addition of camphorsulfonic acid to pyridine, this time in dichloromethane. This mixture gave a much lower yield of alkylated pyridine **175** (the yield was inferred from relative integration of methylene related to pyridinium salt in the ^1H NMR spectra of the aqueous layer). We also recovered a trace of sulfonic ester **177** from the organic layer along with starting material. In contrast, in the presence of catalyst a substantial yield of the alkylated pyridine **174** was recovered (96%). This suggests that under the right conditions the catalyst can affect alkylation, presumably the diazocompound is first converted to the metallocarbenoid and subsequently the ylide is then protonated under the influence of the catalyst (Scheme 73).

Non-catalysed



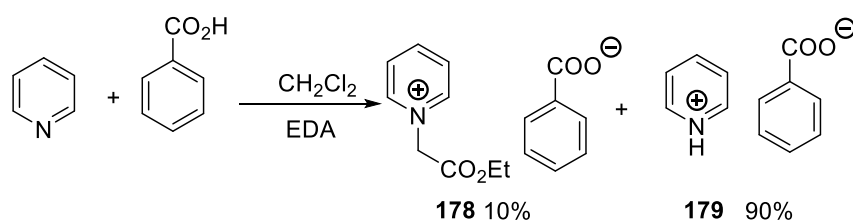
Catalysed



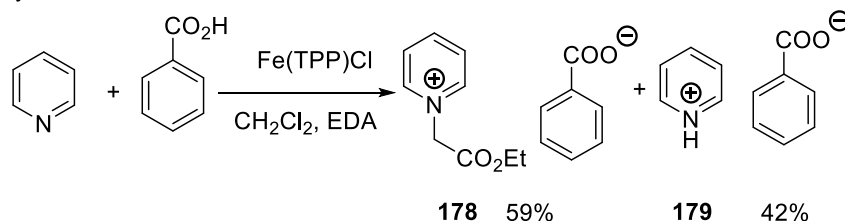
Scheme 73. Alkylation of pyridine in the presence of camphor sulfonic acid

This type of experiment was repeated by replacing camphor sulfonic acid with other acids. A much lower yield of alkylated pyridine was observed when benzoic acid was used in the control reaction, a corresponding higher yield of the starting material was isolated. This contrasts with the observation made in the presence of the catalyst, where alkylated pyridine predominates (Scheme 74).

Non-catalysed

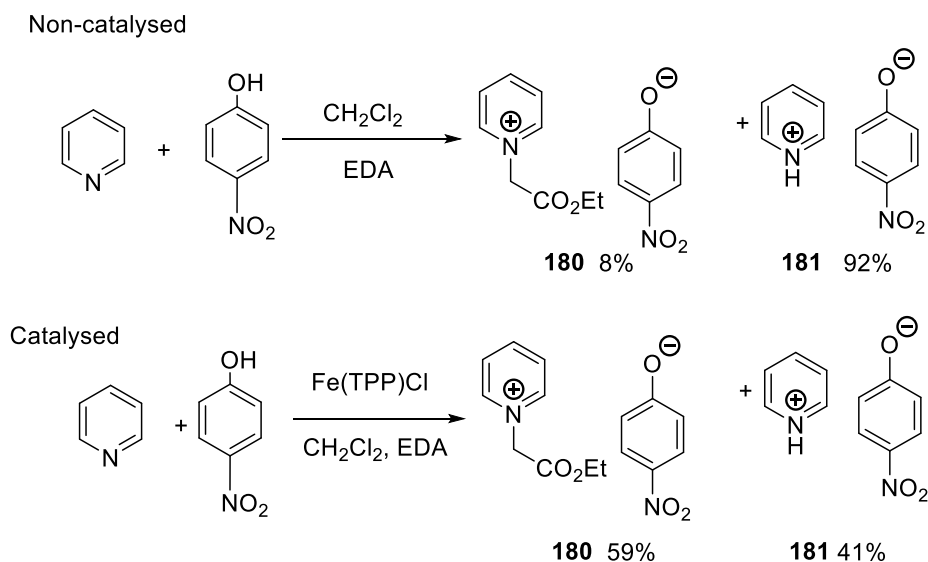


Catalysed



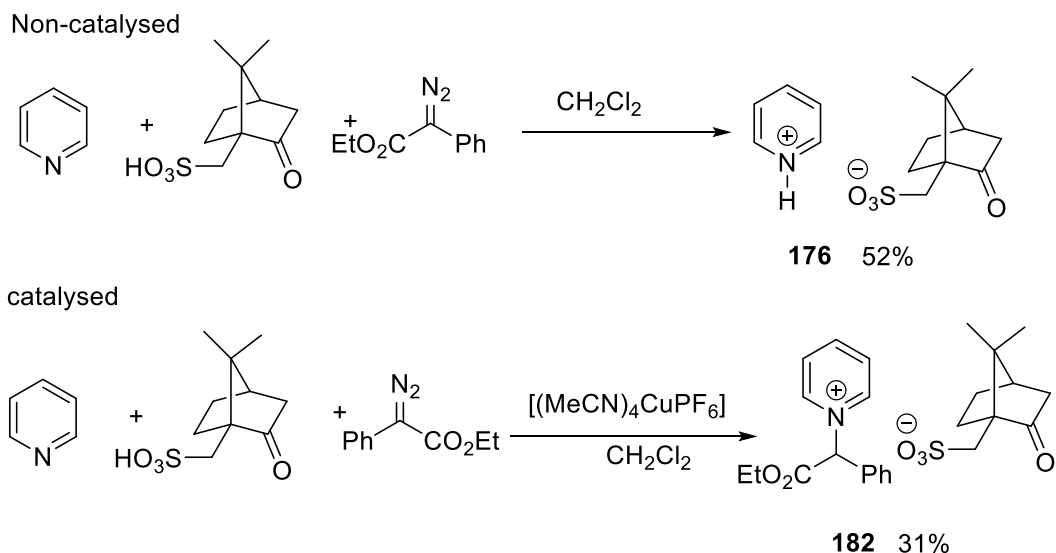
Scheme 75. Non-catalysed vs catalysed reaction with benzoic acid

A similar result was obtained when 4-nitrophenol was used (Scheme 75). In summary, experiments with weak acids in dichloromethane gave higher yields of alkylated pyridinium salts from catalysed, rather than the non-catalysed reactions.



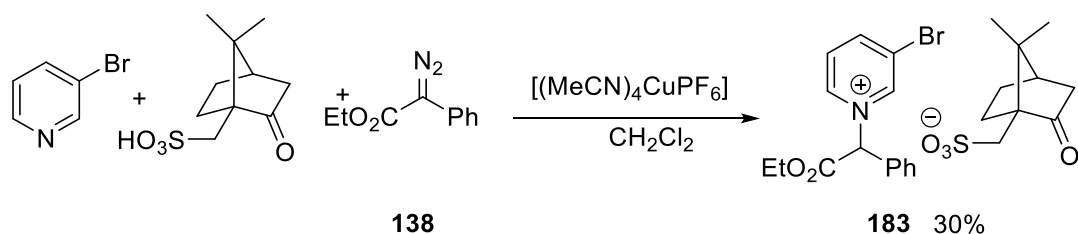
Scheme 75. Non-catalysed vs catalysed reaction with 4-nitrophenol

Interestingly, the same pattern was noticed for the branched diazo compounds. this time we used $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ as catalyst in keeping with our earlier observations that $\text{Fe}(\text{TPP})\text{Cl}$ was not able to transform these diazo compounds. Notably, the product pyridinium salts have a chiral centre and enantioselective protonation could occur in principle. We did not observe alkylation of pyridine in the non-catalysed reaction mixture (Scheme 76). By contrast, only the alkylated pyridine **182** was obtained in the presence of catalyst although the yield was quite low (31%).



Scheme 76. Non-catalysed vs catalysed reaction with di-substituted diazo compound

Another reaction was carried out using 3-bromopyridine with disubstituted diazo compound **138** under the catalytic conditions which gave the pyridinium salt **183** in low yield (Scheme 77). Crystalline material was obtained from this product; interestingly, the resulting crystal structure showed that the counter ion of this crystal structure was PF_6 rather than camphorsulfonate (Figure 29). Presumably this counterion originates from the catalyst in this instance.



Scheme 77. Alkylation of 3-bromopyridine with di-substituted diazo compound.

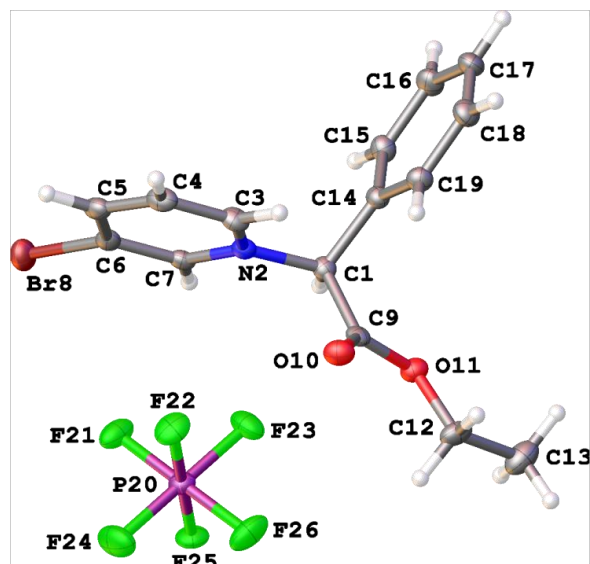
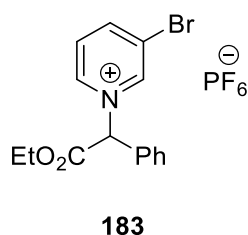
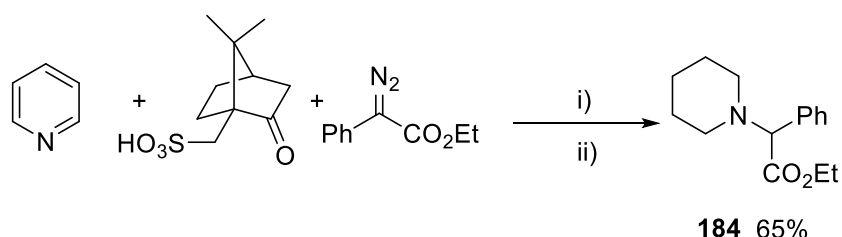


Figure 29. X-Ray crystal structure of **183**

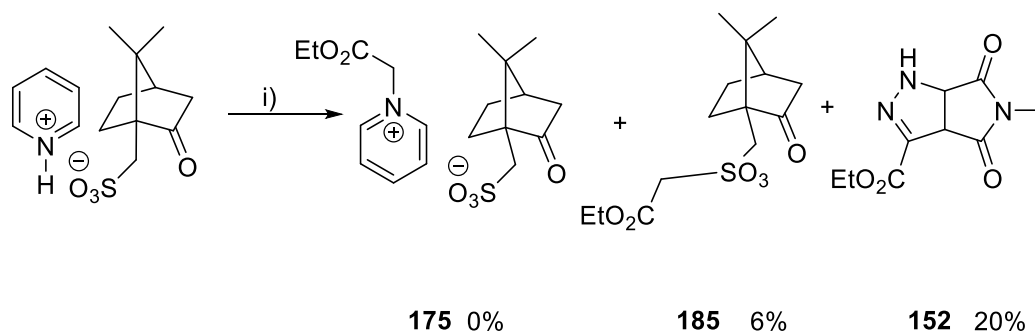
So, from this point, we sought to reduce the alkylated pyridine derived from camphorsulfonic acid and check whether any asymmetric induction occurred using chiral HPLC. Unfortunately, no stereochemical induction was observed in the product **184** (Scheme 78).



Scheme 78. Reagents and conditions: i) $[(\text{MeCN})_4\text{CuPF}_6]$, CH_2Cl_2 ; ii) Raney Ni/ H_2 , EtOH.

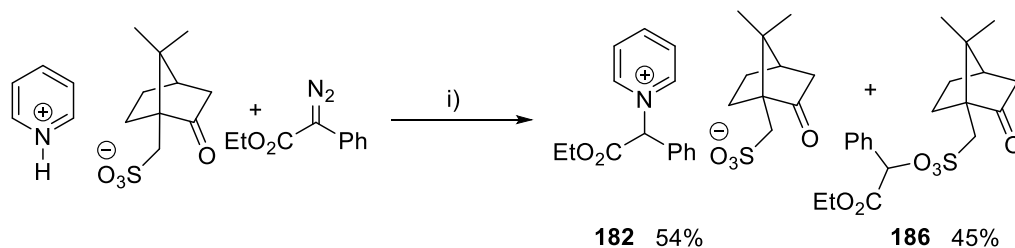
Next, we attempted to carry out the cycloaddition reaction of ethyldiazoacetate and *N*-methylmaleimide with $\text{Fe}(\text{TPP})\text{Cl}$ in CH_2Cl_2 , in the presence of pyridinium camphor sulfonate with the aim of seeing whether protonation or nucleophilic addition would predominate. According to ^1H NMR and mass spectrometry analysis of the crude reaction mixture, the

formation of the pyridinium ylide was observed in addition to alkylated of camphorsulfonic acid **185** and the product of direct cycloaddition of EDA with maleimide. Unfortunately, we were unable to purify the pyridinium salt **175** using column chromatography. However, we could obtain a small amount of alkylated camphorsulfonic acid **185** (6%) and the product **152** of direct cycloaddition of EDA with maleimide (20%) after purification *via* column chromatography (Scheme 79).



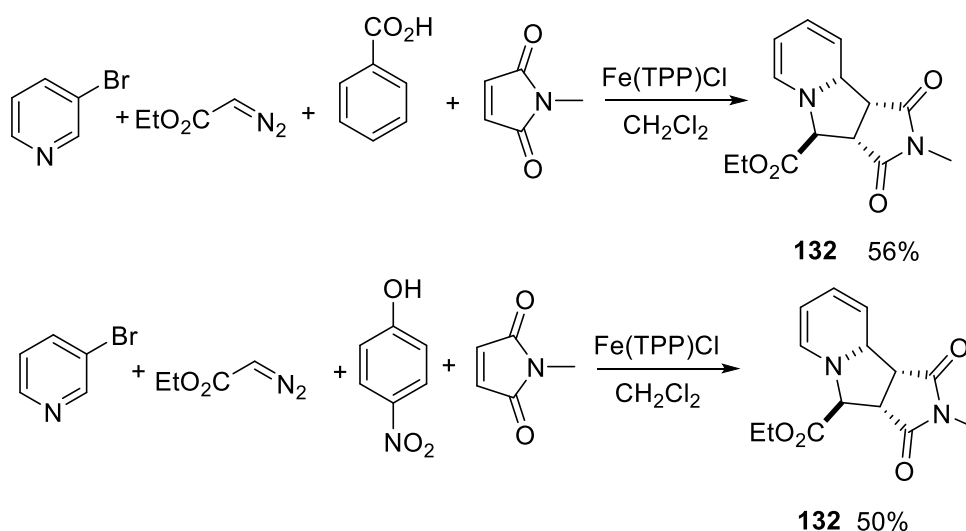
Scheme 79. Reagents and conditions: i) *N*-methylmaleimide, EDA, Fe(PPP)Cl (1 mol%), CH₂Cl₂, 5 hr.

A similar reaction was carried out with ethyl diazophenylacetate **123**. Crude ¹H NMR spectroscopy of the crude reaction mixture (after aqueous work-up) suggested a mixture of alkylation of the camphorsulfonic acid or pyridine but no cycloadduct was observed (Scheme 80). This result might suggest that the pyridinium ylide, if formed catalytically, undergoes protonation before it can undergo cycloaddition.



Scheme 80. Reagents and conditions: i) *N*-methylmaleimide, $(\text{MeCN})_4\text{CuPF}_6$, CH_2Cl_2 , 5 hr.

Interestingly, our desired cycloadduct was obtained when we used weak acids such as benzoic acid and *p*-nitrophenol (Scheme 81).

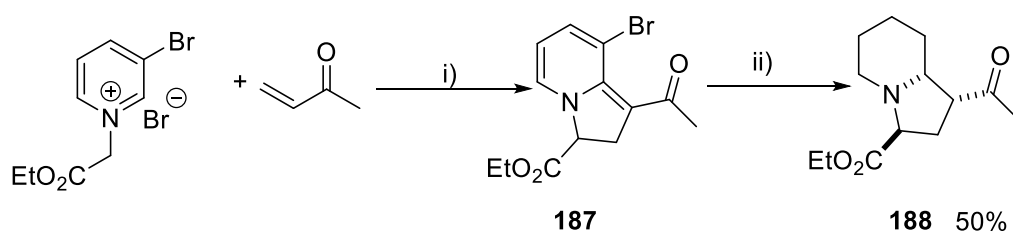


Scheme 81. Cycloaddition reaction in the presence of weak acids

With these results in hand, we begin our investigation to check the influence of chiral Brønsted acid on the outcomes of our reaction.

As mentioned previously, our attempts to produce enantioselective maleimide cycloadduct were unsuccessful, it was decided to investigate an alternative substrate that has been used more widely for asymmetric synthesis, specifically methylvinylketone.

From this reported cycloaddition, we decided to see if this dipolarophile could be subject to reactions with pyridinium ylides. Therefore, investigations into the use of methylvinylketone in our cycloaddition reaction began, the cycloaddition was attempted with 3-bromopyridine derived salt in dichloromethane with triethylamine base. We could notice the 1,2-dihydropyridine peaks of the corresponding cycloadduct **187** in the crude by ^1H NMR spectroscopy. Subsequent *in situ* reduction of the 1,2-dihydropyridine ring using Raney® nickel and hydrogen gave the indolizidine **188** in 50% overall yield (Scheme 82). This reduction step was required to give molecules that were stable to chiral HPLC. This method of chromatography gave two peaks by chiral HPLC, which were assumed to be the indolizidine enantiomers (Figure 30).



Scheme 82. Reagents and conditions i) Et_3N , CH_2Cl_2 , rt; ii) Raney Ni, H_2 , EtOH .

Chromatogram : Rtest1_channel4

System : HPLC
Chiralpak AD-H + guard
95:5 Hexane:IPA
1 ml/min

Acquired : 30/09/2016 12:15:51
Processed : 30/09/2016 12:57:47
Printed : 30/09/2016 12:58:16

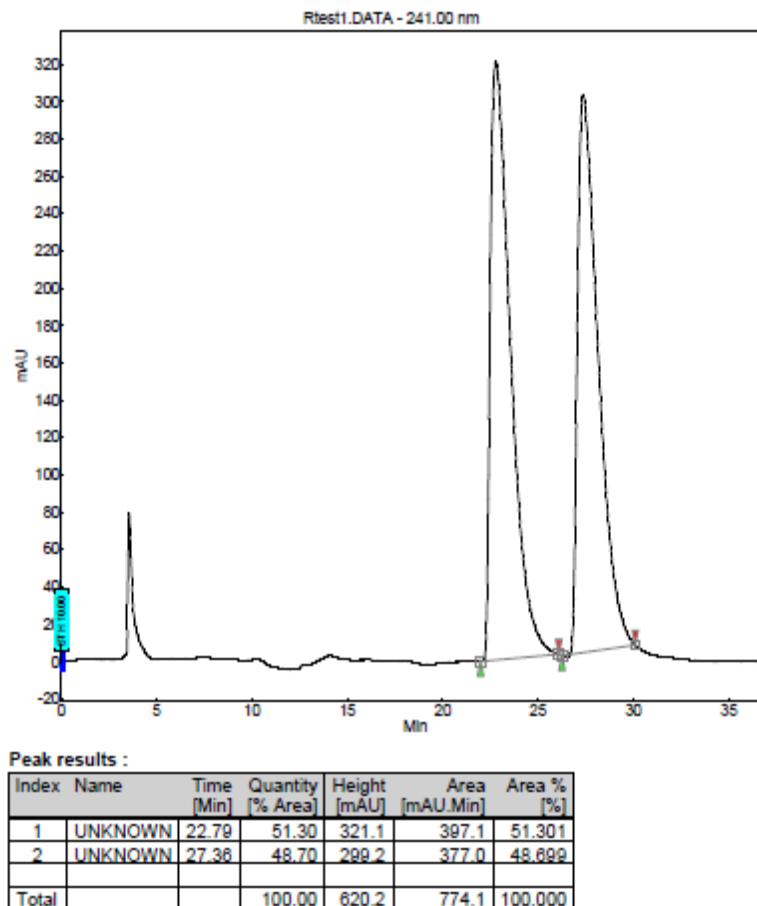


Figure 30. HPLC analysis for a racemic product of **188**

In order to further increase the scope of the investigation towards the asymmetric cycloaddition of pyridinium ylides, a small selection of bifunctional catalysts **189-191** was gifted for use in asymmetric cycloaddition⁸⁷ (Figure 31). A common feature of these catalysts is that they bear both a H-bonding group (thiourea or squaramide) and basic/nucleophilic moiety (primary, secondary or tertiary amine), and may act cooperatively to activate one or both of the nucleophile and electrophile

within the chiral environment of the catalyst to promote enantioselective reactions.

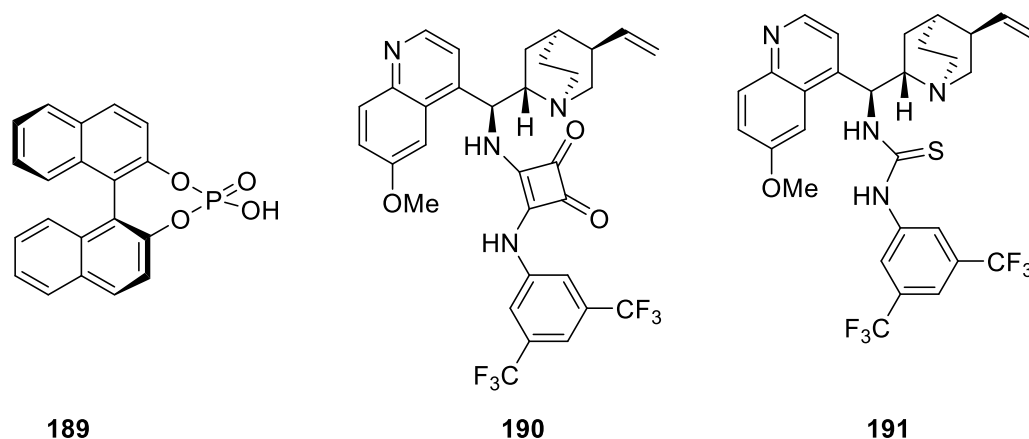
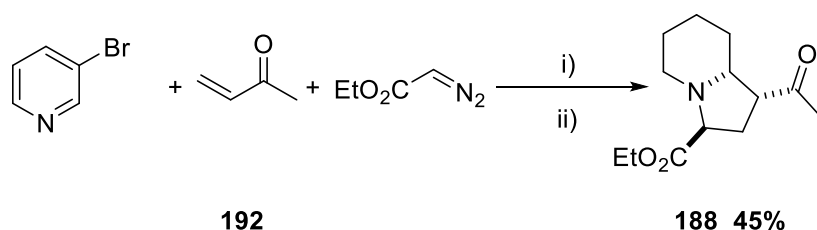


Figure 31. Examples of bifunctional catalysts used in our investigation.

With this new combination (methyl vinyl ketone **192**, the bifunctional catalysts, pyridine, ethyl diazoacetate and Fe(TPP)Cl) in hand, our initial attempts towards our goal began (Scheme 83).



Scheme 83. Reagents and conditions i) Fe(TPP)Cl 1 mol%, bifunctional catalyst (**189**, **190**, **191**), CH₂Cl₂, rt; ii) Raney Ni, H₂, EtOH.

Cycloadduct was produced in almost the same yield to that obtained by deprotonation of the pyridinium salt. Again, the presumed indolizidine enantiomers were separated by chiral HPLC (Chiralcel AD-H; mobile phase, hexane/2-propanol (9.5:0.5 v/v); flow rate, 1 ml/min) and thus a bifunctional catalyst screen was performed (Table 4).

Table 4

Entry	Catalyst	Loading (%)	Yield (%)	e.e
1	189	10	45	0
2	190	10	55	20
3	191	10	50	40

Entry 1 (phosphoric acid **189**) failed to induce any enantioselectivity to the reaction outcomes. The cycloaddition reaction with combination of Fe(TPP)Cl and squaramide **190** (entry 2) and thiourea **191** (entry 3) appeared to give chiral indolizine ring with low enantioselectivity.

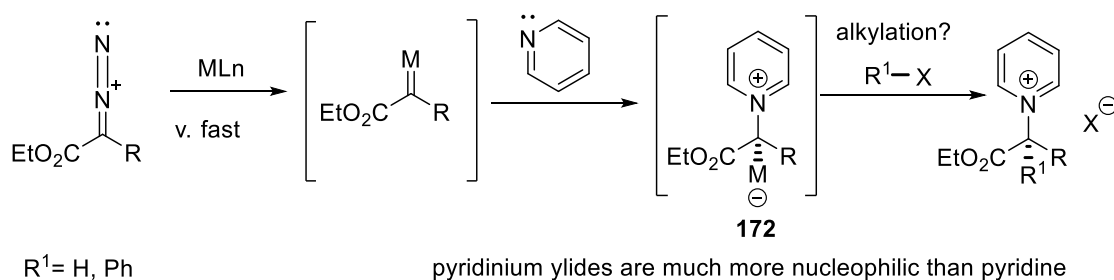
Unfortunately, time constraints prevented further investigation of these enantioselective reactions with more of the bifunctional catalysts within this project but will be studied in future.

2.7 Alkylation of pyridinium ylides

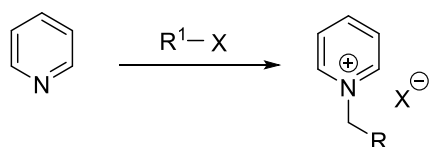
Our investigations, suggest that conditions can be found where catalytic formation of metal carbene is the fastest, which is then rapidly followed by the addition of pyridine to give pyridinium ylide. Generally, pyridinium ylides are among the most potent nucleophiles known.¹⁴⁻¹⁷ Because of the high nucleophilicity of such species, it may be possible to use them in alkylation reactions with appropriate electrophiles. We are interested in extending the range of electrophiles that can be used. Several potential competing pathways may feature in such experiments. Mayr has carried out numerous studies that have provided a combined scale that allows the reactivity of various molecules to be compared, as mentioned previously. There are potential side reactions that may complicate such a reaction. One may consider direct *N*-alkylation of pyridine, but comparison of the

nucleophilicity for pyridines, as reported by Mayer (e.g. dimethylaminopyridine $N \sim 15$ in DMSO)⁸⁸ (Scheme 84), with pyridinium ylide corresponding to **172** ($N \sim 26$ in DMSO)¹⁵ is many times more nucleophilic. It is also possible to consider direct alkylation of the diazonium ylide, but these are likely to be among the least nucleophilic species in the reaction mixture (EDA, $N \sim 5$ in CH_2Cl_2)⁸⁹ (Scheme 84).

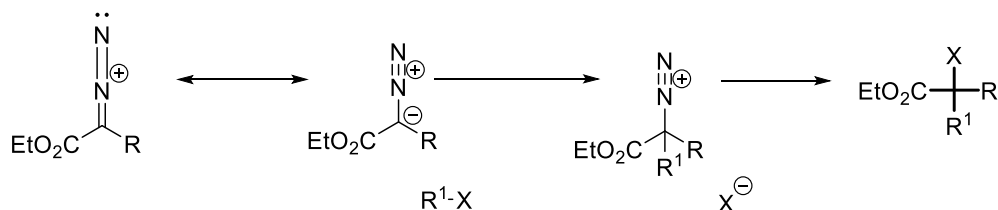
Proposed catalytic pathway



Competing pathway: pyridine alkylation



diazo alkylation pathway



Scheme 84. Possible pathways during alkylation of pyridinium ylide

If it is possible to alkylate pyridinium ylides, this may offer an attractive path towards quaternary centres next to substituted amines. An example of such a structure is AZD9164 **192**, a novel muscarinic M3 antagonist developed by AstraZeneca, and other analogues (Figure 32).⁹⁰ This may be followed by the formation of the alkylated pyridinium ylide, reduction to the piperidine would be required.

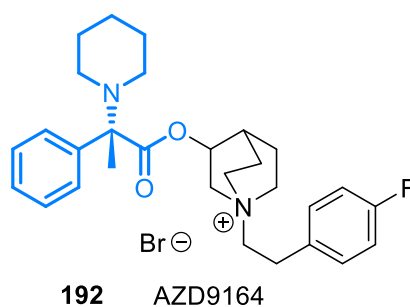
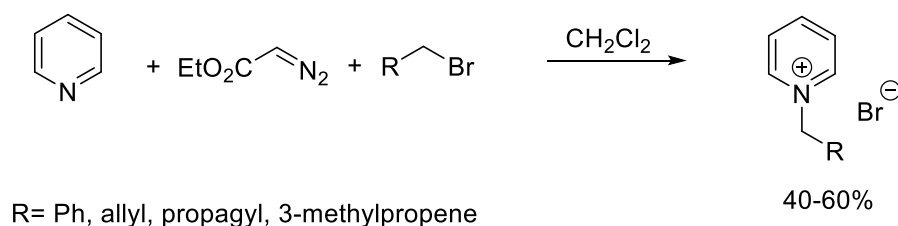


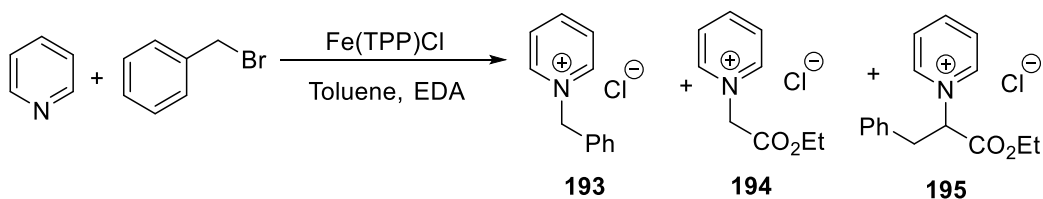
Figure 32 Structure of AZD9164

We began our investigation towards the alkylation of pyridinium ylides by setting up control non-catalysed reactions without using the catalyst. Not surprisingly, we only observed the result of direct *N*-alkylation of pyridine (Scheme 85).



Scheme 85. Control reaction without the catalyst

We subsequently investigated the equivalent reaction by the addition of ethyldiazoacetate dropwise *via* syringe pump to a mixture of pyridine and Fe(TPP)Cl (1%) in toluene, benzyl bromide was added after the addition of diazo compound was finished. From this reaction, we obtained a mixture of the product of direct alkylation of the pyridine **193**, alkylation of the pyridine with diazo compound **194** and small amount of the alkylation of the pyridinium salt presumed to arise from the ylide **195** (Scheme 86).



Scheme 86. Alkylation of pyridinium ylide

This information was observed and confirmed by analysis of the crude reaction mixture by ^1H NMR spectroscopy and comparison of the relative integration of peaks uniquely corresponding to each product. ^1H NMR spectroscopy data revealed a doublet of doublets ($\delta_{\text{H}} = 6.14$) corresponding to α -proton at position 7, in addition to double of doublet ($\delta_{\text{H}} = 3.93$) and double of doublet ($\delta_{\text{H}} = 3.66$) corresponding to diastereotopic of methylene group (position 8) adjacent to the α -proton (position 7) in the alkylated pyridinium salt **195** (Figure 33).

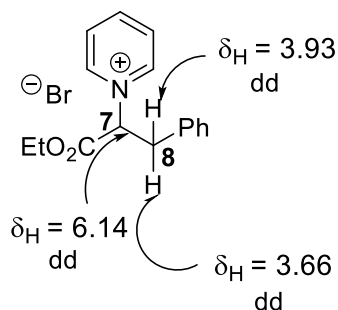
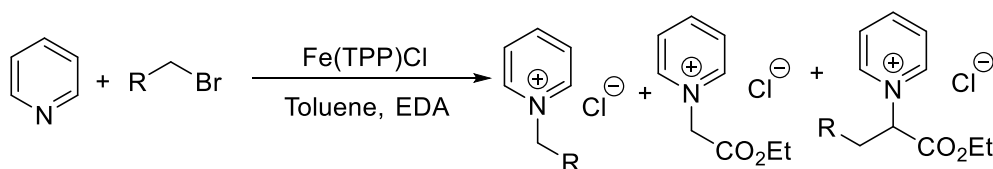


Figure 33. ^1H NMR data for alkylated Pyridinium salt **195**

Unfortunately, separation of these compounds was an issue as all three products were salts and too polar to separate by conventional gel chromatography.

A small selection of alkylation reagents was examined under the same reaction conditions, the same mixture of products was observed (Scheme 87).



R= allyl, propargyl, 2-methyl propene

Scheme 87. Alkylation of pyridinium ylide.

Bluham *et al.* described a separation method to isolate quaternary ammonium and pyridinium compounds using sodium bromide NaBr as a modifier, which allowed separation by conventional chromatography using a saturated solution of methanolic NaBr solution (12% w/v) as eluent.⁹¹

We could separate alkylated pyridinium salts **195**, **196**, **197** and **198** from their respective reaction component using the modifier NaBr method (Figure 34).

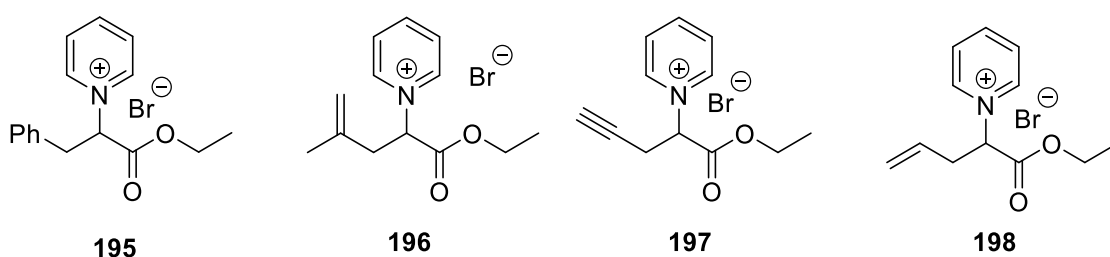
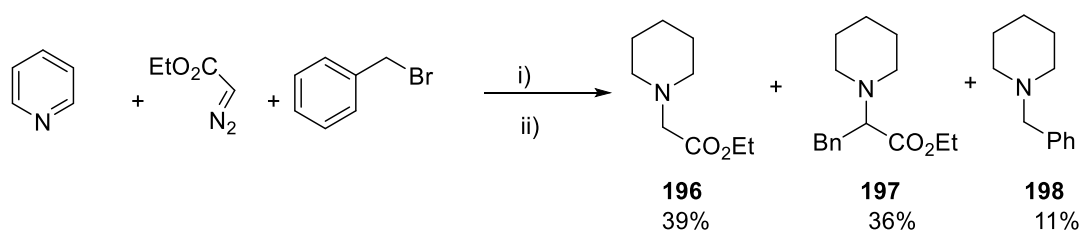


Figure 34. Successful separation of alkylated pyridinium salts.

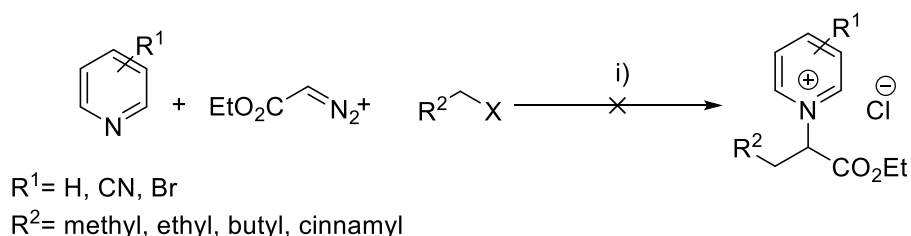
Unfortunately, we could not remove sodium bromide from these salts after chromatography, so we couldn't get the overall yield by mass. Ultimately, we wanted a preparative method. Instead we decided to carry out reduction of the mixture of the three pyridinium salts (Scheme 88). In this way, we

could isolate alkylated piperidine **196** in 39% resulting overall yield, arising from the alkylation of the pyridine from the diazo compound. The next most abundant fraction piperidine **197** in 36%, arising from alkylation of pyridine with EDA. The *N*-benzylpiperidine was obtained in just 11% yield as the product of competing direct *N*-alkylation of pyridine. Together these results indicate that ylide formation is the predominant pathway in this reaction.



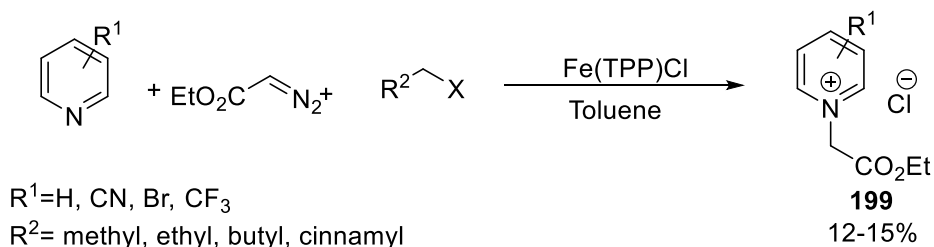
Scheme 88. Reagents and conditions i) *Fe*(TPP)*Cl*, CH₂Cl₂; ii) Raney Ni/H₂, EtOH.

With these results in hand, we sought to extend the range of the electrophile and substituted pyridine may produce our desired product (alkylated pyridinium ylide). Therefore, our attempt began (Scheme 89).



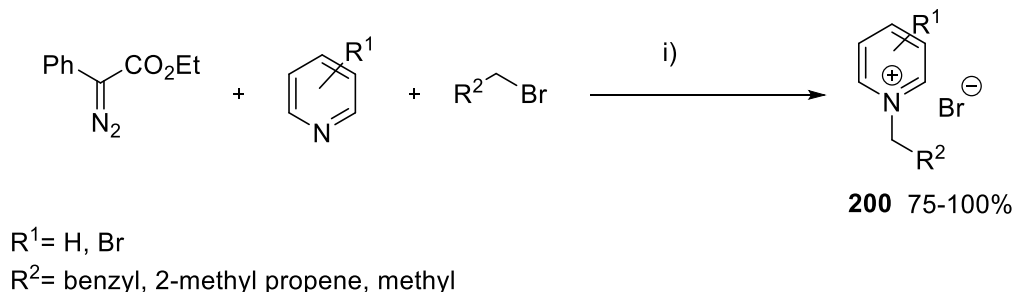
Scheme 89. Reagents and conditions i) *Fe*(TPP)*Cl* (1 mol%), toluene.

However, these attempts proved unsuccessful in generating the desired alkylation product. Instead only the pyridinium salt **199** formed from diazo alkylation of the pyridine were obtained (Scheme 90).



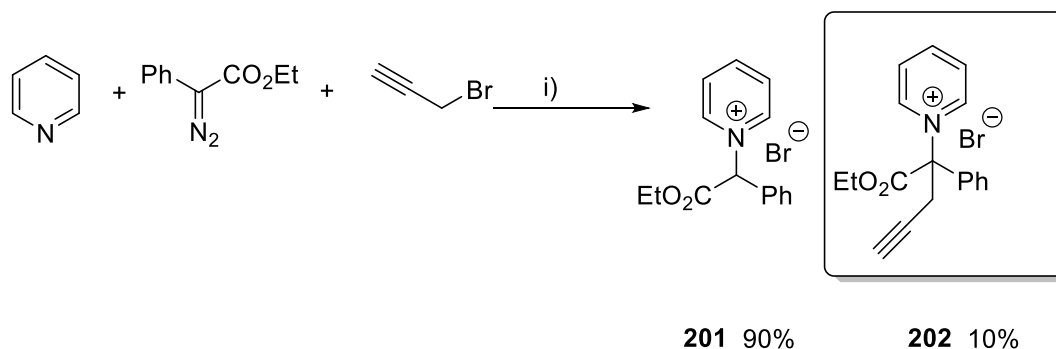
Scheme 90. *Pyridinium salt formation*

Equivalent reactions using the disubstituted diazo compound **138** were also investigated in the presence of various alkylation reagents (scheme 91). We were interested in this route because it would allow access to more structurally complex pyridinium salt. Unfortunately, our attempts to access these salts were unsuccessful because it seems that the reaction of the pyridine with the alkylation reagent is faster than the formation of pyridinium ylide from metal carbenoid.



Scheme 91. *Reagents and conditions i) [(MeCN)₄CuPF₆], CH₂Cl₂.*

When propargyl bromide was used as an alkylation reagent formation of a relatively small amount of desired compound **202** occurred. This was observed by mass spectrometry of the crude mixture which revealed a mass ion peak ($m/z = 280.1331$, $I\% = 20$) for the corresponding pyridinium ylide **202**. Also, the pyridinium salt peaks of the corresponding product **202** were apparent in the crude ^1H NMR (Scheme 92).

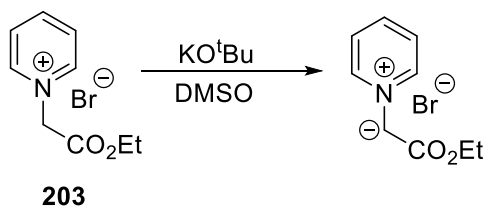


Scheme 92. Reagents and conditions i) [(MeCN)₄CuPF₆], CH₂Cl₂

Our investigation of this route was very limited due a lack of time. We have identified some reaction conditions that appear to proceed *via* the pyridinium ylide and subsequent C-alkylation but the results are not always consistent at present. There is some potential for such as route toward highly substituted pyridinium salts and piperidines. Consequently, further investigation in this area is justified.

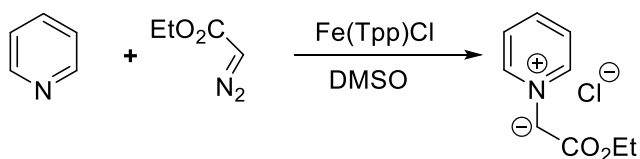
2.8 Spectroscopic investigation.

As mentioned before Mayr *et al.* confirmed the formation of pyridinium ylides by UV-vis spectra ($\lambda_{\text{max}} = 425\text{-}453\text{ nm}$).¹⁵ We also investigated the same method as a reference to monitor the free ylide formation from the deprotonation of pyridinium salt **203** by using KO^tBu as a base in DMSO as a solvent (Scheme 93). We noticed that the ylide began to form after the addition a portion of KO^tBu in DMSO. (see appendix for the UV-vis spectra for pyridinium ylide formation using base)



Scheme 93. Formation of pyridinium ylide using a base

In order to ensure that the pyridinium ylide was formed catalytically, we decided to use UV-vis analysis to monitor the reaction of pyridine with EDA in the presence of Fe(TPP)Cl as a catalyst in DMSO as a solvent (Scheme 94) using the same concentration in the above reaction. Fortunately, we noticed an increase of the absorbance of pyridinium ylide after the addition of EDA. (see appendix for the UV-vis spectra for pyridinium ylide formation metal catalyst).

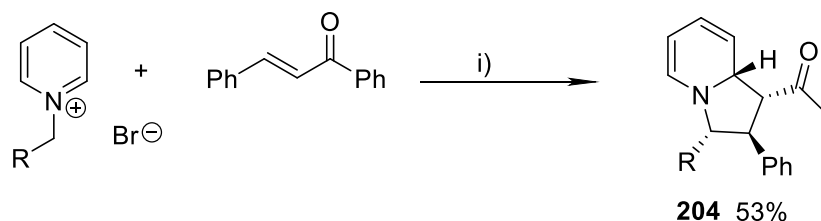


Scheme 94. Formation of the ylide catalytically

2.9 Summary and future work

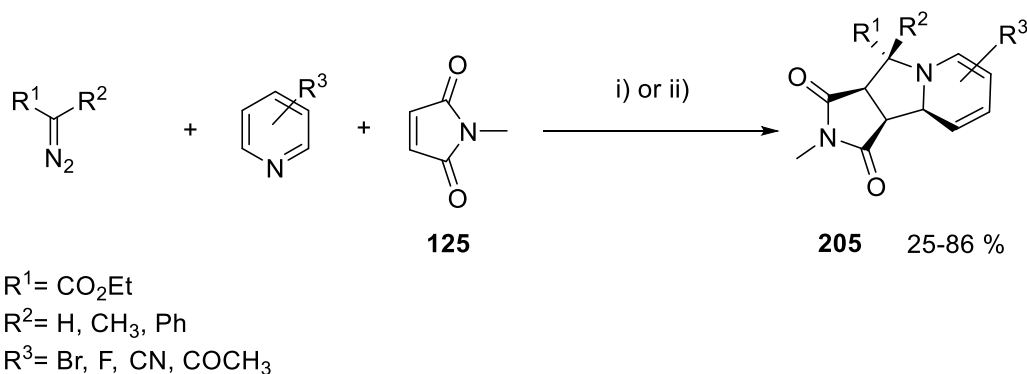
In this project, we were interested in exploring the reactivity of pyridinium ylides in different reactions. Firstly, highly reactive pyridinium ylides have been shown to undergo cycloaddition reactions with electrophilic alkenes to generate tetrahydroindolizines, featuring a 1,2-dihydropyridine with excellent diastereoselectivity.

Pyridinium ylides may be produced *in situ* through deprotonation of pyridinium salts and then undergo cycloaddition reaction with chalcones to generate chalcone cycloadduct **204** in moderate yield (Scheme 95). Unfortunately, some of the chalcone cycloadducts were unstable under purification techniques.



Scheme 95. Reagents and conditions: i) dry CH₃CN, *t*-BuOK, 4 hr.

Metal-catalysed decomposition of diazo compounds to produce pyridinium ylides *in situ* has also been established. Accomplishment of this reaction in the presence of dipolarophile **117**, gives tetrahydroindolizines **205** in good yield (Scheme 96) with excellent diastereoselectivity.



Scheme 96. Reagents and conditions: i) Fe(TPP)Cl (1 mol %), toluene or CH₂Cl₂, rt; ii) [(MeCN)₄CuPF₆] (5 mol %), CH₂Cl₂, rt.

As the results show, we have established a highly-efficient path towards a variety of tetrahydroindolizines using metal catalysis. This multi-component reaction seems to be general and offers much scope for variation of the ylide functionality and choice of dipolarophile.

Also, manipulation of the 1,2-dihydropyridine has been achieved using Raney ® nickel and hydrogen, leading to indolizidines. The development of this chemistry offers a potentially valuable route to indolizidines.

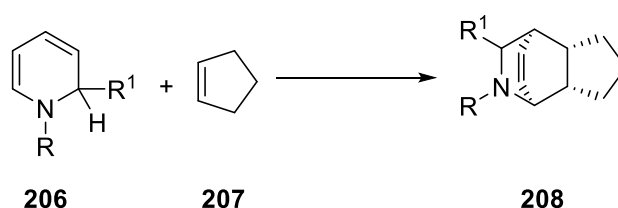
Unfortunately, initial attempts at asymmetric cycloadditions of pyridinium ylide by adding chiral Lewis acids to the catalytic mixture were unsuccessful. Several catalysts could generate the desired cycloadduct, however, none were successful in imparting enantioselectivity into the reaction outcome.

During these studies, we carried out interesting comparative studies that appeared to suggest that under the right conditions it is possible to effect catalytic formation of the pyridinium ylide in the presence of mild acids. This suggests that chiral Brønsted acids that activate the electrophile may be compatible with this mode of reaction. Preliminary investigation of several different bifunctional co-catalysts used in the cycloaddition reaction under our catalytic conditions were investigated. Cycloadducts were synthesised under these reactions conditions, and a low enantiomeric excess was measured following reduction. These modest results seem to encourage further investigation in future. Finally, we were able to identify conditions for *in situ* C-alkylation of catalytically generated pyridinium ylides. At present, these products are obtained as part of a mixture that includes the product arising from non-catalysed pyridine *N*-alkylation alongside the protonated form of the pyridinium ylide. We found a literature method that allowed separation of pyridinium salts using sodium bromide NaBr as a modifier that allowed separation by conventional chromatography on silica gel.⁹¹ Unfortunately, removal of the sodium bromide from the

target products was difficult, thus we have used *in situ* reduction as a means to obtain stable piperdines.

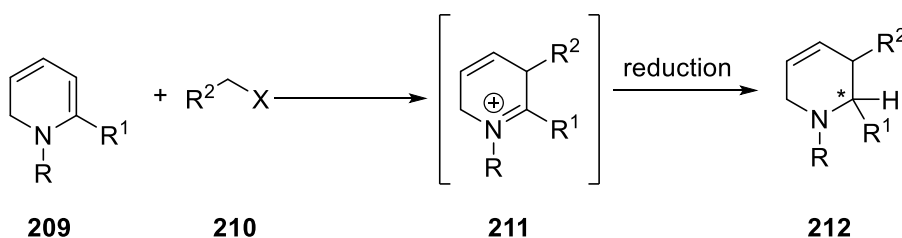
Future work

Development of the substrate scope for the cycloaddition reaction to expand the range of dipolarophiles and ylide substituents is necessary for the generation of libraries of indolizidines. That this motif is commonly found in medicinal alkaloids justifies this endeavour. Subsequent dihydropyridine modification needs more detailed investigation in future as this would extend the range of molecules that can be accessed in further functionalisation using, for example, Diels-Alder cycloaddition (Scheme 97).



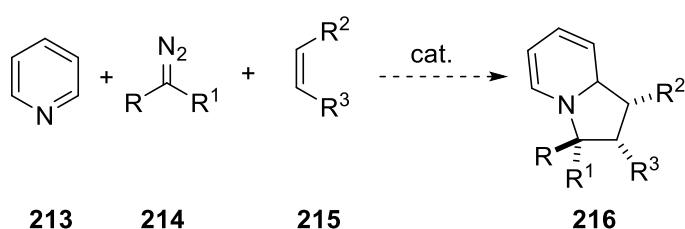
Scheme 97. Possible Diels-Alder reaction of dihydropyridine ring.

or alkylation/reduction sequences (Scheme 98).



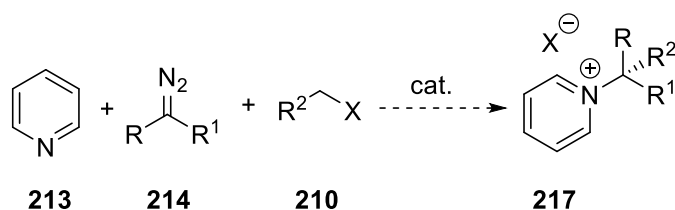
Scheme 98. Possible alkylation/reduction sequence of dihydropyridine ring.

Here, we described a multicomponent reaction that produces highly functionalized pyridinium ylides. These reactions include the catalytic generation of pyridinium ylides *via* metal carbenoid and *in situ* alkylation with alkylation reagent. This highly efficient route generates nitrogen as the only by-product. Further work is required to extend the range of di-substituted diazo compound and check their influence on the outcome of the cycloaddition reaction (Scheme 99).



Scheme 99. Extend the range of di-substituted diazo compound and dipolarophile.

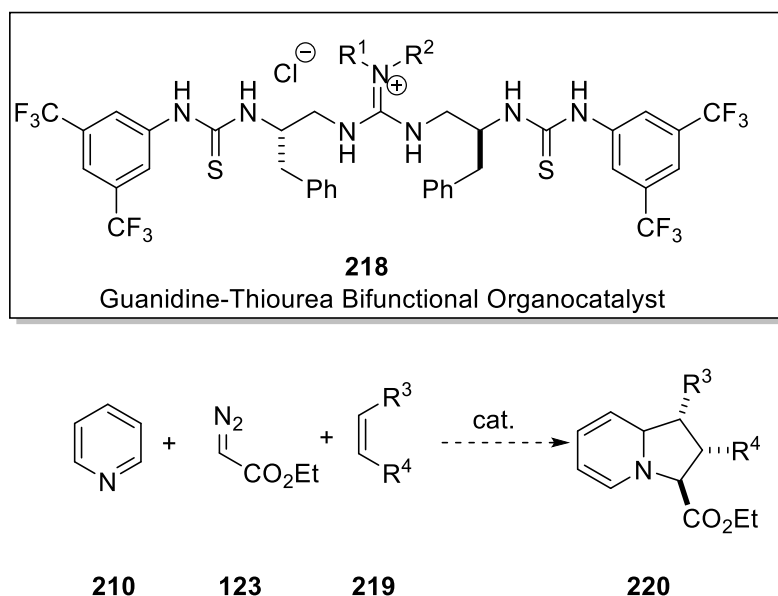
Also, developing a method for the *in situ* alkylation of pyridinium ylide to control the reaction conditions is required in order to allow access to more structurally complex pyridinium salt. If it is possible to control this catalysed reaction in future, this may offer an attractive path towards quaternary centres next to substituted amines (Scheme 100).



Scheme 100. Development of the alkylation method

Further work is also required for the development of an asymmetric methodology for (3+2) dipolar cycloadditions. Methods involving activation

of electrophiles by lowering their LUMO may be the most amenable. Chiral Brønsted acid catalysts (**218**)⁹² and different dipolarophile to obtain asymmetric induction the cycloadducts (Scheme 101).



Scheme 101. Development of the cycloaddition reaction with potential chiral Brønsted acid catalyst **218**

Experimental

3. Experimental

3.1 General

Reagents were obtained from commercial sources and used as received.

Anhydrous THF was obtained by distillation from sodium/benzophenone, under dry nitrogen. Anhydrous dichloromethane was obtained by distillation from CaH_2 , under dry nitrogen. Anhydrous Et_2O and toluene were obtained via filtration from a dry nitrogen pressurised, basic, activated 58 Å aluminium column. Ethyl diazoacetate and *tert*-butyl diazoacetate were purchased from Sigma-Aldrich chemical company.

Reactions requiring anhydrous conditions were conducted in an inert atmosphere of dry argon in flame-dried apparatus.

When conditions state reaction was performed at room temperature, this represents the ambient temperature in the laboratory which typically ranged from 18-22 °C.

Thin Layer Chromatography (TLC) was performed using Merck aluminium foil backed plates, pre-coated with silica gel 60 F₂₅₄. Visualisation carried out via U.V. fluorescence quenching (λ max = 254 nm) or staining with potassium permanganate solution, followed by heating. Flash column chromatography was performed using ICN Silica 32-73, 60 Å.

Melting points were measured on a Bibby™ Stuart Scientific SMP3 melting point apparatus. Melting points are recorded to the nearest °C and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR or Brüker Avatar 320 FTIR spectrometer as dilute solutions, in spectroscopic grade chloroform. Absorption maxima (λ max) of major, significant peaks are reported in wavenumbers (cm^{-1}), quoted to the nearest integral wavenumber.

^1H Nuclear magnetic resonance spectra were recorded on either a Brüker AV400 (400 MHz), Brüker AV(III)400 (400 MHz), Brüker DPX400 (400 MHz), Brüker AV(III)500 (500 MHz) or Brüker DPX300 (300 MHz) spectrometer at ambient temperature. Proton magnetic resonance chemical shifts (δ_{H}) recorded in parts per million (ppm), are referenced relative to residual solvent peak, and recorded to two decimal places. Coupling constants (J), are reported to the nearest 0.1 Hz. Multiplicity of each signal is designated using a combination of the following abbreviations; s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), tt (triplet of triplet), m (multiplet) and br (broad). Carbon magnetic resonance chemical shifts (δ_{C}), recorded in ppm, were referenced relative to the residual solvent peak and are recorded to one decimal place. Multiplicities were determined by DEPT analysis.

Mass spectra were recorded on a Brüker MicroTOF (ESI) mass spectrometer. All mass spectrometry data are high resolution.

Synthesis of pyridinium salts

General Procedure (A) for preparation of pyridinium salts:

Corresponding alkylation reagent (1 equiv.) and (substituted or non-substituted) pyridine (1 equiv.) in dry ethyl acetate (5mL/g), were stirred overnight under argon at room temperature. The resulting precipitate was filtered and washed with diethyl ether and purified by recrystallisation from ethanol, if required.

General Procedure (B) for preparation of pyridinium salts:

General procedure A was followed, but reaction was refluxed for 3 days. The resulting precipitant was filtered and purified by recrystallisation from ethanol.

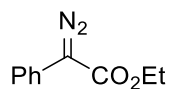
General procedure for separation a mixture of pyridinium salts:

For thin layer chromatography, a silica gel TLC plate was immersed in a methanolic NaBr solution (6% w/v). Absorption time must be about five minutes. Then, the plate was removed and allowed to dry in air, as remaining methanol may change R_f values. Once dry, the plate was ready for use. This system works well enough to separate a mixture up to 4 pyridinium salts using a mobile phase of 1:9 methanol/dichloromethane (v/v). For most pyridinium salts compounds, a methanol/dichloromethane solvent system worked well. All TLC plates were visualized using UV light.

For flash chromatography, columns are dry-packed with ICN Silica 32-73, 60 Å silica gel, and a saturated methanolic NaBr solution (12% w/v) was passed through the column. The volume vital to cover the silica gel column with enough NaBr is about 75 ml per 20 g silica gel. Bromide was detected by spotting the eluant onto TLC plates with subsequent visualization using a silver nitrate stain.⁹¹ The column was left to dry for several minutes to remove additional methanolic NaBr solution. Approximately 1-2 column volumes of the selected mobile phase (as determined by TLC) was then passed through the column to remove air from the immobile phase.

3.2 Synthesis of diazo compounds

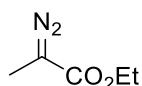
Ethyl 3-diazo-3-phenylpropanoate (138) ⁸⁰



At room temperature, a solution of 1,8-diazabicyclo- [5.4.0]-undec-7-ene (DBU) in anhydrous CH₃CN was added dropwise to a solution of ethyl phenyl acetate and p-toluenesulfonyl azide (TsN₃) in anhydrous CH₃CN. Then the reaction mixture was stirred at room temperature for 15 hours. After water was added, the resulting mixture was extracted with diethyl ether. The combined organic layer was washed with brine and dried over anhydrous MgSO₄. After the removal of the solvent under reduced pressure, the residual was purified by a silica gel column chromatography with petroleum ether /ethyl acetate (1:9) as the eluent to give orange oil (600 mg, 75%); IRsol (CHCl₃,cm⁻¹) 2984, 2089 , 1698, 1247, 1172; δ_H (300 MHz; CDCl₃) 7.51 (2H, app d, J= 7.5 Hz, ArH), 7.44-7.37 (2H, app t, J=7.5 Hz, ArH),

7.18- 7.12 (1H, m, ArH), 4.36 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 1.37 (3H, t, $J = 7.1$ Hz, CH_2CH_3); δ_{C} (100 MHz; CDCl_3) 165.3 (C), 128.9 (CH), 125.7 (CH), 125.6 (C), 123.9 (CH), 60.9 (CH_2), 14.5 (CH_3); m/z (HRMS-ESI+) 213.0645 (M^+ requires $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2\text{Na}^+$ 213.63), the signal due to CN_2 was not observed. The data are consistent with the literature.⁸⁰

Ethyl 2-diazopropanoate (140) ⁸¹

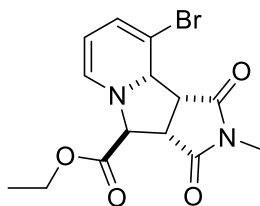


To a stirred suspension of NaH (338 mg, 60% in oil, 8.46 mmol) in dry diethyl ether (15 mL), at room temperature, a solution of ethyl 2-methyl-3-oxobutanoate (627 mg, 4.35 mmol) in diethyl ether (5 mL) was added dropwise over a period of 5 min. The reaction mixture was cooled to 0°C and tosyl azide (1.00 g, 5.08 mmol) was added dropwise over 5 mins. The reaction mixture was diluted with diethyl ether (10 mL), stirred for 16 hr. The resulting precipitate was filtered and the filtrate extracted with water (20 mL), the organic phase was dried over sodium sulphate and the solvent removed under reduced pressure to give a yellow solution (520 mg, 94%) (2:1, dichloromethane: petroleum); V_{max} (CHCl_3)/ cm^{-1} 2934, 2079, 1680, 1246, 1173; δ_{H} (300 MHz; CDCl_3) 4.23 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 1.97 (3H, s, CH_3), 1.28 (3H, t, $J = 7.1$ Hz, CH_2CH_3); δ_{C} (100 MHz; CDCl_3) 174.8 (C), 60.7 (CH_2), 14.5 (CH_3), 8.4 (CH_3); m/z (HRMS-ESI+) 204.0898 (M^+

requires $C_5H_8N_2O_2^+$ 128.0586), the signal due to CN_2 was not observed. The data are consistent with the literature.

3.3 Synthesis of cycloadducts via metal catalyzed decomposition of diazo compound

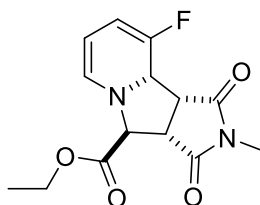
Ethyl (3a*S,4*S**,9b*R**)-9-bromo-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (126)** ⁸²



3-bromopyridine (0.14 ml, 1.42 mmol), N-methyl maleimide (158 mg, 1.42 mmol) and Fe(TPP)Cl (10.0 mg, 0.01 mmol) were stirred in dry toluene (3 ml) under argon at room temperature. Ethyldiazoacetate (224 μ L, 2.13 mmol in 200 μ L dry toluene) was then added dropwise using syringe pump over 2 h, followed by stirring for an additional 2 h. Solvent was removed in *vacuo* and the crude product purified by column chromatography on silica gel using (3:2 petrol/ethyl acetate) as an eluent. The product was crystallised from a mixture of solvents to give crystals suitable for X-ray analysis. Yellow solid 56%. m.p. 60-63°C, Lit: 56-58°C;⁸² IR_{sol} (CHCl₃, cm⁻¹) 3156, 2942, 2905, 1595, 1561, 1437, 1286, 1257; NMR δ_H (400 MHz, Acetone-d₆) 6.3 (1H, d, *J* = 6.4 Hz, NCH=CH-CH), 6.2 (1H, dd, *J* = 7.3, 0.7 Hz, NCH=CH-CH), 4.77-4.75 (1H, m, N-CH-C(Br)), 4.74 (1H, app. s,

N-CH(CO₂Et), 4.57 (1H, dd, *J* = 7.3, 6.4 Hz, NCH=CH-CH), 4.23 (2H, q, *J*=7.2 Hz, CH₂CH₃), 3.72 (1H, dd, *J* = 7.6, 1.2 Hz, N-CH(CO₂Et)-CH), 3.63 (1H, app. t, *J* = 7.6 Hz, N-CH-CH-CO), 2.80 (3H, s, NCH₃) , 1.29 (3H, t, *J*=7.2 Hz, CH₂CH₃); NMR δ_C (100 MHz, Acetone-d₆) 176.6 (C), 175.4 (C), 168.9 (C) , 134.4 (CH), 126.7 (CH), 108.8 (C), 95.1 (CH), 69.2 (CH), 65.9 (CH), 61.6 (CH₂), 50.4 (CH), 45.8 (CH), 24.5 (CH₃), 13.6 (CH₃); *m/z* (HRMS-ESI+) 355.0144 (M+H requires C₁₄H₁₆⁷⁹BrN₂O₄⁺ 355.0293), 357.0263 (M+H C₁₄H₁₆⁸¹BrN₂O₄⁺ requires 357.0273). See appendix for X-Ray crystallography data.

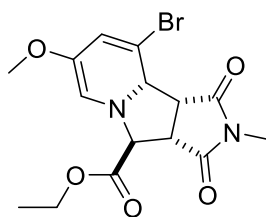
Ethyl (3aS*,4S*,9bR*)-9-fluoro-2-methyl-1,3-dioxo-2, 3, 3a, 4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (127)



3-Fluoro pyridine (0.18 ml, 2.06 mmol), *N*-methylmaleimide (67.0 mg, 0.68 mmol) and Fe(TPP)Cl (5.00 mg, 6.00 μmole) were stirred in dry toluene (3 mL) under argon at room temperature. Ethyldiazo acetate (108 μL, 1.03 mmol in 200 μL dry toluene) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (2:1 petrol/acetone) as an eluent to give the desired product as a brown oil (130 mg, 65%) ;IR_{sol} (CHCl₃,cm⁻¹) 3156, 2942, 2905, 1595,

1561, 1437, 1286, 1257; NMR δ_{H} (400 MHz, Acetone- d_6) 5.98 (1H, d, $J=7.3$ Hz, $\text{NCH}=\text{CH}-\text{CH}$), 5.66-5.59 (1H, m, $\text{NCH}=\text{CH}-\text{CH}$), 4.78- 4.76 (1H, m, $\text{NCH}(\text{CO}_2\text{Et})$), 4.73 (1H, d, $J = 7.6$ Hz, $\text{N}-\text{CH}-\text{CF}$), 4.54-4.49(1H, m, $\text{NCH}=\text{CH}-\text{CH}$), 4.2(2H, q, $J=7.2$ Hz, CH_2CH_3), 3.75(1H, d, $J=7.6$ Hz, $\text{N}-\text{CH}(\text{CO}_2\text{Et})-\text{CH}$), 3.6 (1H, app t, $J= 7.6$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 2.8 (3H, s, NCH_3) , 1.29 (3H, t, $J=7.2$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, Acetone- d_6) 176.3 (C), 174.3 (C), 169.1 (C) , 151.2 (d, $J^{\text{C-F}}= 256$ Hz, C), 131.1 (d, $J^{\text{C-F}}= 3.9$ Hz, CH), 101.9 (d, $J^{\text{C-F}}= 15.3$ Hz, CH), 92.3 (d, $J^{\text{C-F}}= 5.2$ Hz, CH), 69.1 (d, $J^{\text{C-F}}= 2.6$ Hz, CH), 60.1 (CH_2), 59.9 (d, $J^{\text{C-F}}= 36.4$ Hz, CH), 50.8 (d, $J^{\text{C-F}}= 4.3$ Hz, CH), 46.8 (CH), 24.5 (CH_3), 13.6 (CH_3); m/z (HRMS-ESI+) 295.1042 (M+H requires $\text{C}_{14}\text{H}_{16}\text{FN}_2\text{O}_4^+$ 295.1094).

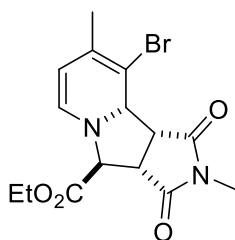
Ethyl (3aS*,4S*,9bR*)-9-bromo-7-methoxy-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (128) ⁸²



3-bromo-5-methoxypyridine(238mg,1.26mmol),*N*-methylmaleimide (140 mg, 1.26 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyldiazoacetate (160 μL , 1.51 mmol in 200 μL dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product

purified by column chromatography on silica gel using (2:1 ethyl acetate/petroleum ether) as an eluent to give the desired product as light brown gum (403 mg, 82%); IRsol (CHCl_3 , cm^{-1}) 2941, 1789, 1699, 1585, 1502, 1433, 1336, 1287, 1124; NMR δ_{H} (400 MHz, Acetone- d_6) 6.07 (1H, app d, $J=1.2$ Hz, $\text{NCH}=\text{C}(\text{OCH}_3)-\text{CH}$), 5.23 (1H, d, $J=1.2$ Hz, $\text{NCH}=\text{C}(\text{OCH}_3)-\text{CH}$), 4.74 (1H, br s, $\text{NCH}(\text{CO}_2\text{Et})$), 4.41 (1H, d, $J=7.7$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CH}-\text{CH}(\text{CO}_2\text{Et})$), 4.22 (2H, q, $J=7.2$ Hz, CH_2CH_3), 3.74 (1H, d, $J=7.7$ Hz, $\text{N}-\text{CH}(\text{CO}_2\text{Et})-\text{CH}$), 3.71 (3H, s, $\text{NCH}=\text{C}(\text{OCH}_3)$), 3.55 (1H, app t, $J=7.7$ Hz, $\text{NCH}-\text{CH}-\text{CO}$), 2.81 (3H, s, NCH_3), 1.28 (3H, t, $J=7.2$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, Acetone- d_6) 176.3 (C), 175.6 (C), 169.2 (C), 150.0 (C), 116.0 (C), 127.7 (CH), 97.8 (CH), 70.1 (CH), 61.0 (CH), 61.5 (CH_2), 54.8 (CH_3), 50.6 (CH), 47.3 (CH), 25.2 (CH_3), 13.8 (CH_3); m/z (HRMS-ESI+) 385.0221 ($\text{M}+\text{H}$ requires $\text{C}_{15}\text{H}_{18}^{79}\text{BrN}_2\text{O}_5^+$ 385.0394), 387.0287 ($\text{M}+\text{H}$ $\text{C}_{15}\text{H}_{18}^{81}\text{BrN}_2\text{O}_5^+$ requires 387.0373).

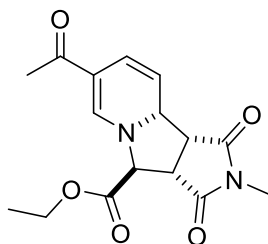
Ethyl (3aS*,4S*,9bR*)-9-bromo-2,8-dimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (129)



3-bromo-4-methylpyridine (172 mg, 1.00 mmol), *N*-methylmaleimide (111 mg, 1.00 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl diazo acetate (171 μL , 1.50 mmol in 200 μL dry dichloromethane) was then added

dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 acetone /petroleum ether) as an eluent to give the desired product as a brown oil (310 mg, 84%); IRsol (CHCl₃,cm⁻¹) 3066, 2938, 1736, 1269, 1029, 647; NMR δ_H (400 MHz, CDCl₃) 5.86 (1H, d, *J*=7.3 Hz, NCH=CH-C(CH₃)), 4.67 (1H, dd, *J*=7.6, 0.8 Hz, N-CH-C-Br), 4.61 (1H, d, *J*=7.3 Hz NCH=CH-C(CH₃)), 4.57 (1H, br. s, N-CH(CO₂Et)), 4.22 (2H, q, *J*=7.2 Hz, CH₂CH₃), 3.65 (1H, dd, *J*=7.6, 1.1 Hz, N-CH(CO₂Et)-CH), 3.53 (1H, app t, *J*=7.6 Hz, N-CH-CH-CO), 2.85 (3H, s, NCH₃), 1.84 (3H, s, N-CH=CH-C(CH₃)) 1.32 (3H, t, *J*=7.2 Hz, CH₂CH₃); NMR δ_C (100 MHz, CDCl₃) 176.6 (C), 174.3 (C), 168.7 (C), 133.6 (CH), 131.9 (C), 106.7 (C), 100.8 (CH), 70.0 (CH), 67.1 (CH), 62.3 (CH₂), 49.8 (CH), 45.8 (CH), 25.84 (CH₃), 20.6 (CH₃), 14.1 (CH₃); *m/z* (HRMS-ESI+) 369.0355 (M+H requires C₁₅H₁₈⁷⁹BrN₂O₄⁺ 369.0444), 371.0424 (M+H C₁₅H₁₈⁸¹BrN₂O₄⁺ requires 371.0424).

Ethyl (3a*S,4*S**,9b*R**)-7-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (133a) and Ethyl (3a*S**,4*S**,9b*R**)-9-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (133b)**



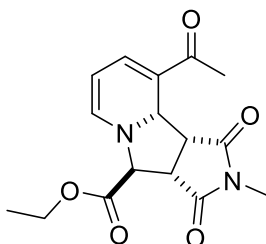
3-acetyl pyridine (0.14 ml, 1.26 mmol), *N*-methylmaleimide (140 mg, 1.26 mmol) and Fe(TPP)Cl (7 mg, 0.01 mmol) were stirred in dry dichloromethane (4 mL) under argon at room temperature. Ethyl diazoacetate (200 μ , 1.89 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (1:1 acetone/petroleum ether) as an eluent to give two fractions:

Fraction one

As a brown oil (100mg, 25%); IRsol (CHCl₃,cm⁻¹) 2985, 1782, 1702, 1434, 1227, 1019, 749; NMR δ_H (400 MHz, CDCl₃) 7.32(1H, br. s, NCH=C((CO)CH₃), 6.58(1H, ddd, *J*=10.3, 2.3, 1.4 Hz, NCH-CH-CH-C((COCH₃)), 5.56-5.47(1H,m,N-CH-CH-CH-C((COCH₃)), 4.88(1H, dt, *J*=8.0, 2.1 Hz, NCH-CH-CO), 4.66(1H, br. s, NCH (CO₂Et)), 4.31(2H, q, *J*=7.1 Hz, CH₂CH₃), 3.70(1H, d, *J*=8.0 Hz, N-CH(CO₂Et)), 3.57(1H, app t, *J*=8.0 Hz, N-CH-CH-CO), 2.99(3H, s, NCH₃) , 2.18(3H, N-CHC(COCH₃)),

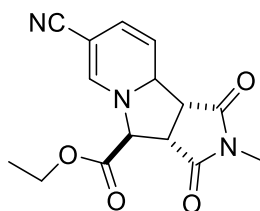
1.36(3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 192.0 (C), 176.0 (C), 174.4 (C), 168.1 (C), 142.6 (CH), 121.9 (CH), 111.3 (CH), 110.9 (C), 66.2 (CH), 62.9 (CH_2), 59.0 (CH), 49.3 (CH), 45.6 (CH), 25.5 (CH_3), 24.4 (CH_3), 14.1 (CH_3); m/z (HRMS-ESI+) 319.1304 (M+H requires $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_5$ + 319.1288).

Fraction two



As a brown oil (226 mg, 50%) IRsol (CHCl_3 , cm^{-1}) 2982, 1781, 1697, 1432, 1285, 1205, 1018, 726; NMR δ_{H} (400 MHz, CDCl_3) 6.95 (1H, app dd, $J=6.6, 0.6$ Hz, $\text{NCH}=\text{CH}-\text{CH}$), 6.34 (1H, dd, $J=6.6, 0.7$ Hz, $\text{NCH}=\text{CH}-\text{CH}$), 5.00 (1H, d, $J=7.5$ Hz, $\text{N}-\text{CH}-\text{C}(\text{COCH}_3)$), 4.76 (1H, app t, $J=6.6$ Hz, $\text{NCH}=\text{CH}-\text{CH}$), 4.6 (1H, br s, $\text{N}-\text{CH}(\text{CO}_2\text{Et})$), 4.21 (2H, q, $J=7.1$ Hz, CH_2CH_3), 3.74 (1H, app t, $J=7.5$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 3.64 (1H, dd, $J=7.5, 1.1$ Hz, $\text{N}-\text{CH}(\text{CO}_2\text{Et})-\text{CH}$), 2.87 (3H, s, $\text{N}-\text{CH}_3$), 2.34 (3H, $\text{N}-\text{CH}-\text{C}(\text{COCH}_3)$), 1.32 (3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 195.7 (C), 176.7 (C), 174.7 (C), 168.3 (C), 140.9 (CH), 135.0 (CH), 123.9 (C), 94.2 (CH), 69.0 (CH), 62.2 (CH_2), 58.7 (CH), 49.5 (CH), 45.2 (CH), 25.3 (CH_3), 24.3 (CH_3), 14.1 (CH_3); m/z (HRMS-ESI+) 341.1120 (M+Na requires $\text{C}_{16}\text{H}_{18}\text{N}_2\text{NaO}_5$ + 341.1113).

Ethyl (3aS*,4S*,9bR*)-7-cyano-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (134a) and Ethyl (3aS*,4S*,9bR*)-9-cyano-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (134b)



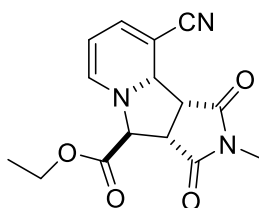
3-cyanopyridine (104 mg, 1.00 mmol), *N*-methylmaleimide (111 mg, 1.00 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) were stirred in dry toluene (5 mL) under argon at room temperature. Ethyl diazoacetate (158 μ L, 1.50 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (1:1.5 acetone/petroleum ether) as an eluent to give two fractions:

Fraction one

As a yellow oil (138 mg, 25%); IRsol (CHCl₃, cm⁻¹) 2984, 2254, 1715, 1380, 1254, 1174, 795; NMR δ_H (400 MHz, Acetone-*d*₆) 7.32(1H, br s, N-CH=C(CN)), 5.89(1H, ddd, *J* = 10.2, 2.2, 1.4 Hz, NCH=C(CN)-CH), 5.52–5.46 (1H, m, N-CH-CH), 4.91(1H, app dt, *J* = 8.0, 2.2 Hz, NCH-CH-CO), 4.87 (1H, br s, NCH (CO₂Et)), 4.26(2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.80(1H, dd, *J* = 8.0, 1.3 Hz, N-CH(CO₂Et)-CH), 3.73(1H, app.t, *J* = 8.0 Hz, N-CH-CH-CO), 2.91(3H, s, N-CH₃), 1.3(3H, t, *J*=7.1 Hz, CH₂CH₃); NMR δ_C (100

MHz, Acetone- d_6) 176.0 (C), 174.7 (C), 168.6 (C) , 144.8 (CH), 120.9 (CH), 119.3 (C), 112.5 (CH), 79.3 (C), 65.3 (CH), 62 (CH₂), 58.2 (CH), 49.3 (CH), 45.9 (CH), 24.4 (CH₃), 13.4 (CH₃); m/z (HRMS-ESI+) 324.0960 (M+Na requires C₁₅H₁₅N₃ NaO₄+ 324.0955).

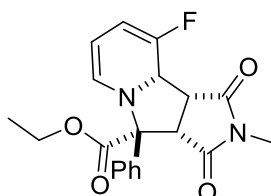
Fraction two



As a brown oil (100mg, 25%); IRsol (CHCl₃, cm⁻¹) 2990, 2210, 1716, 1436, 1378, 1288, 1128; NMR δ_H (400 MHz, Acetone- d_6) 6.70 (1H, dt, J = 6.4, 0.9 Hz, NCH=CH-CH), 6.60 (1H, app dd, J = 7.1, 0.9 Hz, NCH=CH-CH), 4.9 (1H, d, J =7.1 Hz, N-CH-CH-CO), 4.82 (1H, d, J = 1.3 Hz, N-CH(CO₂Et), 4.72 (1H, dd, J = 7.1, 6.4 Hz, N-CH=CH-CH), 4.25 (2H, q, J = 7.1 Hz, CH₂CH₃), 3.76 (1H, dd, J = 7.8, 1.3 Hz, N-CH(CO₂Et)-CH), 3.67 (1H, app t, J = 7.8 Hz, N-CH-CH-CO), 2.86 (3H, s, N-CH₃), 1.30 (3H, t, J = 7.1 Hz, CH₂CH₃) ; NMR δ_C (100 MHz, Acetone- d_6) 175.9 (C), 174.2 (C), 168.5 (C) , 140.5 (CH), 138.7 (CH), 118.3 (C), 95.1 (C), 93.4 (CH), 67.8 (CH), 61.8 (CH₂), 59 (CH), 50.5 (CH), 45 (CH), 24.5 (CH₃), 13.4 (CH₃); m/z (HRMS-ESI+) 324.0957 (M+Na requires C₁₅H₁₅N₃ NaO₄+ 324.0955).

3.4 Disubstituted diazo cycloadducts

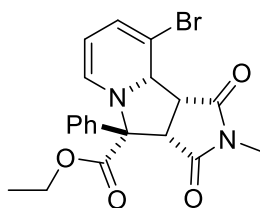
Ethyl (3a*S**,4*S**,9b*R**)-9-fluoro-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (141)



3-Fluoropyridine (0.07 ml, 0.90 mmol), *N*-methylmaleimide (66.0 mg, 0.60 mmol) and [(MeCN)₄CuPF₆] (5.60 mg, 15 μmol) were stirred in dry CH₂Cl₂ (3 mL) under argon at room temperature. Phenyl ethyldiazoacetate (85.5 mg, 0.45 mmol in 200 μL dry CH₂Cl₂) was then added dropwise by syringe pump over 2 hrs, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 ethyl acetate/petrol) as an eluent to give the desired product as a yellow oil (60 mg, 52%); IRsol (CHCl₃, cm⁻¹) 3007, 1707, 1599, 1384, 1324, 1249; NMR δ_H (400 MHz, Acetone-*d*₆) 7.59-7.5(2H, m, *ArH*), 7.5-7.38(3H, m, *ArH*) 6.72(1H, d, *J*=7.4 Hz, NCH=CH-CH), 5.62(1H, dd, *J*=12.9, 6.4 Hz, NCH=CH-CH), 4.68-4.66(1H, m, NCH=CH-CH), 4.41(1H, d, *J*=7.2 Hz, N-C(Ph)(CO₂Et)-CH), 4.31-4.29 (1H, m, N-CH-CH-CO), 4.25(2H, q, *J*= 7.2 Hz, CH₂CH₃), 3.61(1H, app t, *J*= 7.2 Hz, N-CH-CH-CO), 2.85(3H, s, NCH₃), 1.19(3H, t, *J*=7.2 Hz, CH₂CH₃); NMR δ_C (100 MHz, Acetone-*d*₆) 175.1 (C), 174 (C), 167.9 (C), 160.3 (d, *J*^{C-F}= 254 Hz, C), 152.7 (C), 137.7 (C), 128.6 (CH), 128.3 (d, *J*^{C-F}= 4.2 Hz, CH), 127 (CH), 123.3 (CH), 101.9 (d, *J*^{C-F}= 14.6 Hz, CH), 92.7 (d, *J*^{C-F}= 4.9 Hz, CH), 61.6 (CH₂), 58.9 (d, *J*^{C-F}=35.8 Hz, CH), 52 (CH), 49.6 (d, *J*^{C-F}= 4.1

Hz, CH), 24.5 (CH₃), 13.17 (CH₃) ; *m/z* (HRMS-ESI+) 393.2221 (M+Na requires C₂₀H₁₉N₂O₄FNa⁺ 393.2218).

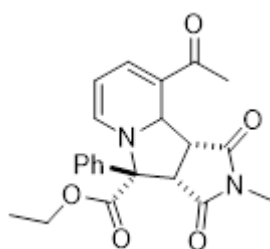
Ethyl (3a*S,4*S**,9b*R**)-9-bromo-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (142)**



3-Bromopyridine (0.10 ml, 0.93 mmol), *N*-methylmaleimide (70.0 mg, 0.63 mmol) and [(MeCN)₄CuPF₆] (5.60 mg, 15.0 μmol) were stirred in dry CH₂Cl₂ (3 mL) under argon at room temperature. Phenylethyldiazoacetate (120 mg, 0.63 mmol in 200 μL dry CH₂Cl₂) was then added dropwise by syringe pump over 2 hrs, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (1:1 ethyl acetate/petrol) as an eluent to give the desired product as an orange solid (130 mg, 53%), 60-64 °C; IR_{sol} (CHCl₃, cm⁻¹) 2988, 2890, 2254, 1705, 1562; NMR δ_H (400 MHz, Acetone-*d*₆) 7.62-7.60(2H, m, Ar*H*), 7.50-7.40(3H, m, Ar*H*), 7.01(1H, d, *J*=7.5 Hz, NCH=CH-CH), 6.31(1H, d, *J*= 6.4 Hz, NCH=CH-CH), 4.68(1H, dd, *J*= 7.5, 6.4 Hz NCH=CH-CH), 4.38-4.37(1H, m, N-C((Ph)(CO₂Et))-CH), 4.36-4.34(1H, m, N-CH-CH-CO), 4.17(2H, q, *J*=7.2 Hz, CH₂CH₃), 3.62 (1H, app t, *J*= 7.1 Hz, N-CH-CH-CO), 2.83 (3H, s, NCH₃) , 1.19 (3H, t, *J*=7.2 Hz, CH₂CH₃); δ_C (100 MHz; Acetone-*d*₆) 175.0 (C), 173.7 (C), 167.7 (C), 148.1 (C), 137.7 (C), 128.7 (CH), 127.9 (CH), 126.7 (CH), 118.0 (CH), 109.1

(CH), 95.0 (CH), 76.1 (C), 64.7 (CH), 61.6 (CH₂), 50.7 (CH), 50.1 (CH), 24.5 (CH₃), 13.1(CH₃); *m/z*(HRMS-ESI+)453.0425(M+Nrequires C₂₀H₁₉⁷⁹BrN₂O₄Na⁺453.0426), 455.0413 (M+Na C₂₀H₁₉⁸¹BrN₂O₄Na⁺ requires 455.0405).

Ethyl(3a*S,4*S**,9b*R**)-7-acetyl-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (143a) and Ethyl (3a*S**,4*S**,9b*R**)-9-acetyl-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (143b)**

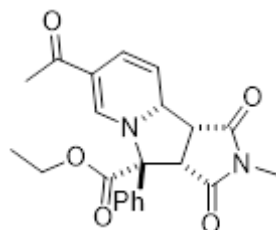


3-acetylpyridine (87.0 μ L, 0.78 mmol), *N*-methylmaleimide (88.0 mg, 0.78 mmol) and (MeCN)₄CuPF₆ (15.0 mg, 0.04 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazo-2-phenylacetate (150 mg, 0.78 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (3:1 acetone /petroleum ether) as an eluent to give two fractions:

Fraction one

As a colourless solid (90 mg, 34%); m.p. 118-120°C; IRsol (CHCl₃,cm⁻¹) 3027, 2926, 2256, 1715, 1458, 907, 757; NMR δ_H (400 MHz, CDCl₃) 7.53-7.45 (2H,m, *ArH*), 7.47-7.32 (3H, m, *ArH*), 7.26 (1H, dd, *J*=7.2, 0.9 Hz, *NCH=CHCH*), 6.95 (1H, dt, *J*= 6.4, 0.9 Hz, *NCH=CHCH*), 4.92-4.81 (2H, m, *NCH=CHCH*, *NCH-C(COCH₃)*), 4.29-4.15 (2H, m, *CH₂CH₃*), 4.01 (1H, d, *J* = 7.6 Hz, *N-C((CO₂Et)(Ph))-CH*), 3.85 (1H, app t, *J* = 7.6 Hz, *NCH-CH-CO*), 2.92 (3H, s, *NCH₃*), 2.33 (3H, s, *C(COCH₃)*), 1.24 (3 H, t, *J* = 7.1 Hz, *CH₂CH₃*); NMR δ_C (100 MHz, CDCl₃) 195.7 (C), 175.5 (C), 175.2 (C), 174.7 (C), 168.4 (C), 139.4 (CH), 136.7 (C), 134.8 (CH), 128.9 (CH), 128.7 (CH), 126.9 (CH), 124.8 (C), 93.7 (CH), 62.4 (CH₂), 58.7 (CH), 51.7 (CH), 48.7 (CH), 25.2 (CH₃), 24.3 (CH₃), 13.7 (CH₃); *m/z* (HRMS-ESI⁺) 395.1608 (*M*+H requires C₂₂H₂₃N₂O₅⁺ 395.1601).

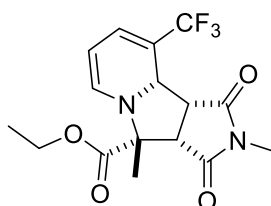
Fraction two



As an orange oil (100 mg, 37%); IRsol (CHCl₃,cm⁻¹) 3005, 1735, 1715, 1602, 1376, 1255, 1177; NMR δ_H (400 MHz, CDCl₃) 8.14(1H, br s, *NCH-C(COCH₃)*), 7.62 – 7.27(5H, m, *ArH*), 6.65(1H, ddd, *J* = 10.3, 2.4, 1.5 Hz, *N-CH-CH-CH-C(COCH₃)*), 5.57(1H, ddd, *J* = 10.3, 2.1, 0.9 Hz, *NCH-CH-CH-C(COCH₃)*), 4.60(1H, dt, *J* = 8.2, 2.1 Hz, *NCH-CHCH*), 4.38-4.24(1H, m, *J* = 10.8, 7.2 Hz, *CH₂CH₃*), 4.06(1H, d, *J* = 8.2 Hz, *N-C((CO₂Et)(Ph))-CH*), 3.40(1H, app t, *J* = 8.2 Hz, *NCH-CH-CO*), 3.03(3H, s, *NCH₃*), 2.25 (3H, s,

C(COCH₃), 1.29(3H, t, *J* = 7.2 Hz, CH₂CH₃); NMR δ_c (100 MHz, CDCl₃) 192.4 (C), 174.4 (C), 174.2 (C), 167.6 (C), 143.4 (CH), 135.3 (C), 129.1 (CH), 128.9 (CH), 127.0 (CH), 122.0 (CH), 112.1 (C), 111.2 (CH), 73.9 (C), 62.8 (CH₂), 58.5 (CH), 52.8 (CH), 47.3 (CH), 30.9 (CH₃), 25.4 (CH₃), 13.8 (CH₃); *m/z* (HRMS-ESI+) 395.1608 (M+H requires C₂₂H₂₃N₂O₅+ 395.1601).

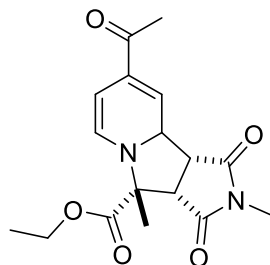
Ethyl (3a*S,4*R**,9b*R**)-2,4-dimethyl-1,3-dioxo-9-(trifluoromethyl)-2, 3, 3a, 4, 9a, 9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (145)**



3-(trifluoromethyl)pyridine(66.0mg,0.45 mmol),*N*-methyl maleimide (66.0 mg, 0.60 mmol) and (MeCN)₄CuPF₆ (5.58 mg, 0.01 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazopropanoate (57.0 mg, 0.45 mmol in 200 μL dry dichloromethane) was then added dropwise via syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (2:1 acetone/petroleum ether) as an eluent to give the desired product as an orange oil (120 mg, 57%); IRsol (CHCl₃,cm⁻¹) 3104, 2950, 1697, 1103,

939, 825, 753; NMR δ_{H} (400 MHz, CDCl_3) 6.81(1H, br.s, $\text{NCH}=\text{CH}-\text{CH}$), 6.07-6.03 (1H, m, $\text{NCH}=\text{CH}$), 5.69(1H, dd, $J=9.3, 1.3$ Hz, $\text{NCH}=\text{CH}$), 4.5(1H, d, $J=8.0$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 4.26(2H, q, $J=7.1$ Hz, CH_2CH_3), 3.83 (1H, d, $J=8.0$ Hz, $\text{N}-\text{C}((\text{CH}_3)(\text{CO}_2\text{Et}))- \text{CH}$), 3.40(1H, app t, $J=8.0$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 3.01(3H, s, NCH_3), 1.77(3H, s, $\text{N}-\text{C}((\text{CH}_3)(\text{CO}_2\text{Et})))$ 1.32(3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) , 175.0 (C), 174.5 (C), 171.2 (C) , 131.5 (q, $J^{\text{C-F}}= 31$ Hz, C), 124.8 (q, $J^{\text{C-F}}= 267$ Hz, C), 120.1 (q, $J^{\text{C-F}}= 6.5$ Hz, CH), 119.7 (CH), 112.9 (CH), 68.1 (C), 62.7 (CH_2), 58.8 (CH), 48.2 (CH), 46.6 (CH), 25.2 (CH_3), 18.6 (CH_3), 14.1 (CH_3); IRsol ($\text{CHCl}_3, \text{cm}^{-1}$); m/z (HRMS-ESI+) 359.1214 ($\text{M}+\text{H}$ requires $\text{C}_{16}\text{H}_{18}\text{F}_3\text{N}_2\text{O}_4^+$ 359.1218).

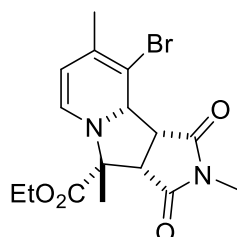
Ethyl (3aS*,4R*,9bR*)-8-acetyl-2,4-dimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (146)



4-acetylpyridine (54.0 mg, 0.45 mmol), N-methylmaleimide (67.0 mg, 0.60 mmol) and $(\text{MeCN})_4\text{CuPF}_6$ (6.00 mg, 0.01 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazopropanoate (58.0 mg, 0.45 mmol in 200 μL dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (2:1 ethyl

acetate/petroleum ether) as an eluent to give the desired product as a brown oil (120 mg, 70%); IRsol (CHCl_3 , cm^{-1}) 3066, 2034, 1715, 1557, 1434, 1288; NMR δ_{H} (400 MHz, CDCl_3) 6.58-6.52(1H, m, $\text{NCH}=\text{CH}-\text{C}(\text{COCH}_3)$), 6.43(1H, d, $J=7.8$ Hz, $\text{N-CH-CH}=\text{C}(\text{COCH}_3)$), 5.56(1H, dd, $J=7.7, 1.8$ Hz, $\text{N-CH}=\text{CH}-\text{C}(\text{COCH}_3)$), 4.53(1H, dd, $J=7.8, 2.6$ Hz, $\text{N-CH-CH}=\text{C}(\text{COCH}_3)$), 4.25(2H, q, $J=7.1$ Hz, CH_2CH_3), 3.82(1H, d, $J=7.8$ Hz, $\text{N-C}((\text{CH}_3)(\text{CO}_2\text{Et}))-CH$), 3.41(1H, app t, $J=7.8$ Hz, N-CH-CH-CO), 3.01(3H, s, NCH_3), 2.35(3H, s, $\text{CO}(\text{CH}_3)$), 1.64(3H, s, $\text{N-C}((\text{CH}_3)(\text{CO}_2\text{Et})))$, 1.32(3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 196.2 (C), 175.8 (C), 174.9 (C), 171.4 (C), 136.4 (C), 131.4 (CH), 121.0 (CH), 96.3 (CH), 67.5 (C), 62.6 (CH_2), 59.2 (CH), 48.8 (CH), 45.9 (CH), 25.33 (CH_3), 25.4 (CH_3), 18.7 (CH_3), 14.3 (CH_3); m/z (HRMS-ESI+) 333.1460 ($\text{M}+\text{H}$ requires $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_5$ + 333.1445).

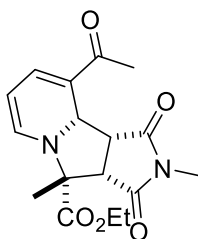
Ethyl(3aS*,4R*,9bR*)-9-bromo-2,4,8-trimethyl-1,3-dioxo-2, 3, 3a, 4,9a,9b-hexahydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate (147)



3-bromo-4-methyl pyridine (77.0 mg, 0.45 mmol), N-methyl maleimide (66.0 mg, 0.60 mmol) and $(\text{MeCN})_4\text{CuPF}_6$ (5.58 mg, 0.01 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazopropanoate(57.0 mg, 0.45 mmol in 200 μL dry dichloromethane) was then added dropwise *via* syringe pump over 2 h,

followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 ethyl acetate/petroleum ether) as an eluent to give the desired product as a brown oil (120 mg, 70%); IRsol (CHCl_3 , cm^{-1}) 3066, 2938, 1736, 1269, 1029, 647; NMR δ_{H} (400 MHz, CDCl_3) 6.17(1H, d, $J=7.4$ Hz, $\text{NCH}=\text{CH}-\text{C}(\text{CH}_3)$), 4.75-4.46(2H, m, $\text{NCH}=\text{CH}-\text{C}(\text{CH}_3)$, $\text{N}-\text{CH}-\text{C}(\text{Br})$), 4.26(2H, q, $J=7.1$ Hz, CH_2CH_3), 3.82(1H, d, $J=7.6$ Hz, $\text{N}-\text{C}((\text{CH}_3)(\text{CO}_2\text{Et}))-\text{CH}$), 3.54(1H, dd, $J=7.6, 6.4$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 2.92(3H, s, NCH_3), 2.06(3H, s, $\text{C}(\text{CH}_3)$), 1.66(3H, s, $\text{N}-\text{C}(\text{CH}_3)(\text{CO}_2\text{Et})$), 1.32(3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 174.9 (C), 174.3 (C), 172 (C), 132.3 (C), 127.5 (CH), 126.5 (C), 98.9 (CH), 67.1 (C), 62.6 (CH_2), 61.3 (CH), 52.4 (CH), 49.6 (CH), 24.9 (CH_3), 20.7 (CH_3), 19.2 (CH_3), 14.1 (CH_3); m/z (HRMS-ESI+) 383.0560 ($\text{M}+\text{H}$ requires $\text{C}_{16}\text{H}_{20}^{79}\text{BrN}_2\text{O}_4^+$ 383.0548), 385.0585 ($\text{M}+\text{H}$ $\text{C}_{16}\text{H}_{20}^{81}\text{BrN}_2\text{O}_4^+$ requires 385.0585).

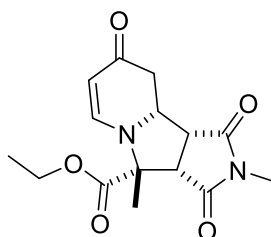
Ethyl (3aS*,4R*,9bR*)-9-acetyl-2,4-dimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (148)



3-acetylpyridine (79.0 mg, 0.65 mmol), *N*-methylmaleimide (72.0 mg, 0.65 mmol) and $(\text{MeCN})_4\text{CuPF}_6$ (11.0 mg, 0.03 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-

diazopropanoate (100 mg, 0.78 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 acetone /petroleum ether) as an eluent to give the desired product as an orange oil (110 mg, 51%); IRsol (CHCl_3 , cm^{-1}) 3070, 1740, 1438, 1376, 1248, 1166; NMR δ_{H} (500 MHz, CDCl_3) 6.92(1H, d, J = 6.4 Hz, $\text{NCH}=\text{CHCH}$), 6.58-6.55 (1H, m, $\text{NCH}=\text{CH}-\text{CH}$), 4.86(1H, d, J =6.7 Hz, $\text{NCH}-\text{C}(\text{COCH}_3)$), 4.80(1H, app. t, J = 6.4 Hz, $\text{NCH}=\text{CH}-\text{CH}$), 4.36-4.20(2H, m, CH_2CH_3), 4.00-3.95 (1H, m, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 3.84(1H, d, J = 7.9 Hz, $\text{N}-\text{C}((\text{CO}_2\text{Et})(\text{CH}_3))-\text{CH}$), 2.90(3H, s, NCH_3), 2.35(3H, s, $\text{C}(\text{COCH}_3)$), 1.67(3H, s, $\text{N}-\text{C}((\text{CO}_2\text{Et})(\text{CH}_3))$), 1.31(3H, t, J = 7.2 Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 195.7 (C), 175.0 (C), 174.9 (C), 171.6 (C), 136.2 (CH), 135.1 (CH), 93.7 (CH), 62.9 (CH_2), 60.0 (CH), 48.0 (CH), 47.0 (CH), 20.9 (CH_3), 25.1 (CH_3), 18.7 (CH_3), 13.9 (CH_3); m/z (HRMS-ESI+) 333.1449 ($\text{M}+\text{H}$ requires $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_5^+$ 333.1445).

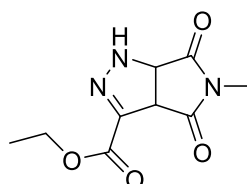
Ethyl (3aS*,4R*,9bR*)-2, 4-dimethyl-1,3,8-trioxo-2,3,3a,4,8,9,9a,9b-octahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (151)



4-methoxypyridine (71.0 mg, 0.65 mmol), *N*-methylmaleimide (72.0 mg, 0.65 mmol) and $(\text{MeCN})_4\text{CuPF}_6$ (11.0 mg, 0.05 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-

diazopropanoate (100 mg, 0.78 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 acetone/petroleum ether) as an eluent to give orange oil (120 mg, 60%); IRsol ($\text{CHCl}_3, \text{cm}^{-1}$) 2991, 1726, 1583, 1440, 1289, 1130, 907; NMR δ_{H} (300 MHz, CDCl_3) 7.21(1H, d, $J=7.9$ Hz, $\text{NCH}=\text{CH}-\text{CO}$), 5.22(1H, dd, $J=7.9, 1.0$ Hz, $\text{NCH}=\text{CH}-\text{CO}$), 4.23(2H, q, $J=7.1$ Hz, CH_2CH_3), 3.96-3.86(2H, m, $\text{N}-\text{CH}-\text{CH}_2$), $\text{N}-\text{C}((\text{CH}_3)(\text{CO}_2\text{Et}))-\text{CH}$, 3.40(1H, app t, $J=8.3$ Hz, $\text{N}-\text{CH}-\text{CH}-\text{CO}$), 3.03(3H, s, NCH_3), 2.77(1H, ddd, $J=16.5, 4.3, 1.2$ Hz, $\text{N}-\text{CH}-\text{CH}_a\text{H}_b-\text{CO}$), 2.42(1H, app.t, $J=16.5$ Hz, $\text{N}-\text{CH}-\text{CH}_a\text{H}_b-\text{CO}$), 1.72(3H, s, $\text{N}-\text{C}((\text{CH}_3)(\text{CO}_2\text{Et}))$), 1.30(3H, t, $J=7.1$ Hz, CH_2CH_3); NMR δ_{C} (100 MHz, CDCl_3) 192.4 (C), 174.2 (C), 174 (C), 170.9 (C), 147.7 (CH), 103.2 (CH), 69.3 (C), 62.9 (CH_2), 59.7 (CH), 50.6 (CH), 45.3 (CH), 39.5 (CH_2), 25.2 (CH_3), 19.1 (CH_3), 14.2 (CH_3); m/z (HRMS-ESI+) 307.1296 ($\text{M}+\text{H}$ requires $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_5+$ 307.1288).

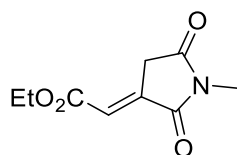
Ethyl 5-methyl-4,6-dioxo-3,3a,4,5,6,6a-hexahydro pyrrolo [3,4-c] pyrazole-3-carboxylate (152)



Pyridin-1-ium((1*R**,4*R**)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methanesulfonate, *N*-methylmaleimide (97.0 mg, 0.87 mmol) and Fe(TPP)Cl (6.30 mg, 0.01 mmol) were stirred in dry dichloromethane (3

mL) under argon at room temperature. Ethyl diazoacetate (139 μ L, 1.31 mmol in 200 μ L dry dichloromethane) was then added dropwise via syringe pump over 2 hr, followed by stirring for an additional 2 hrs. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (2:1 ethyl acetate /petroleum ether) as an eluent to give the desired product as yellow solid (60 mg, 30%); M.p. 138-140 $^{\circ}$ C; IRsol (CHCl_3 , cm^{-1}) 1725, 1428, 1382, 1190, 750; ^1H NMR (400 MHz, Acetone- d_6) δ 8.63 (1H, br.s, $\text{NH-N}=\text{CH}(\text{CO}_2\text{Et})$), 5.07-5.04 (1H, m, N-CH-CH-CO), 4.64-4.61 (1H, m, N-CH-CH-CO), 4.27 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 2.93 (3H, s, N-CH_3), 1.32 (3H, t, $J = 7.1$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, Acetone- d_6) δ 174.2 (C), 172.5 (C), 160.8 (C), 135.0 (C), 64.9 (CH), 60.3 (CH_2), 52.0 (CH), 24.3 (CH_3), 13.6 (CH_3); m/z (HRMS-ESI+) 248.0636 (M^+Na requires $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_4\text{Na}^+$ 248.0642).

Ethyl 2-(1-methyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl) acetate (157) ²⁹

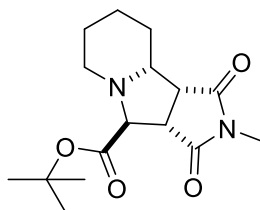


Nicotinic acid (74.0 mg, 0.60 mmole), N-methylmaleimide (44.0 mg, 0.4 mmol) and Fe(TPP)Cl (3.00 mg, 4 μ mol) were stirred in dry toluene (3 mL) under argon at room temperature. Ethyldiazoacetate (68.0 μ L, 0.60 mmol in 150 μ L dry toluene) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 h. Solvent was removed *in vacuo* and the crude product purified by column chromatography on silica gel using (1:1 petrol/acetone) as an eluent to give a yellow oil (70 mg, 78%);

IRsol (CHCl₃,cm⁻¹) 3076, 2991, 1780, 1689, 1213, 1145, 785; NMR δ_H (400 MHz, CDCl₃): 6.82 (1H, t, *J*=2.6 Hz, C=CH-C(CO₂Et)), 4.28 (2H, q, *J*=7.2 Hz, CH₂CH₃), 3.69 (2H, d, *J*= 2.6 Hz, CH₂-C=CH-(CO₂Et)), 3.12 (3H, s, N-CH₃), 1.35 (3H, t, *J*=7.2 Hz, CH₂CH₃) ; NMR δ_C (100 MHz, CDCl₃) : 173.5 (C), 169.0 (C), 164.8 (C), 140.0 (C), 122.3 (CH), 61.4 (CH₂), 34.3 (CH₂), 25.0 (CH₃), 14.1 (CH₃); IRsol (CHCl₃,cm⁻¹); *m/z* (HRMS-ESI+) 220.0583 (M+Na requires C₉H₁₁N₁NaO₄+ 220.0580).

3.5 Modification of 1,2-dihydropyridine

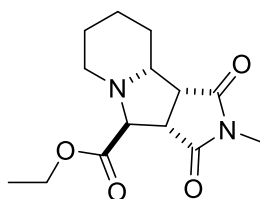
***tert*-Butyl (3a*S,4S*,9bR*)-2-methyl-1,3-dioxodecahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (131)**



tert-Butyl-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo [3,4-*a*] indolizine-4-carboxylate (150 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethanol (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give dark brown oil that was purified *via* column chromatography on silica gel using (2:1; petrol:acetone) as an eluent to give the desired product as a pale red solid, the product was crystallised from a mixture of solvents to give crystals suitable for X-ray analysis (70.0 mg, 54%) ; m.p.67-70°C; IR_{sol} (CHCl₃,cm⁻¹) 2982, 2859, 1701, 1438, 1153; NMR δ_H (400 MHz, CDCl₃)

3.85 (1H, br s, $\text{NCH}(\text{CO}_2\text{C}(\text{CH}_3)_3)$), 3.32(1H, d, $J=7.9$ Hz, $\text{N-CH-CH-CH-CH}(\text{CO}_2\text{C}(\text{CH}_3)_3)$), 3.35(1H, dd, $J=12.0, 7.9$ Hz, N-CH-CH-CO), 3.11(1H, ddd, $J=11.0, 7.9, 2.52$ Hz, N-CH-CH_2), 2.98-2.95(1H, m, $\text{N-CH}_a\text{H}_b\text{-CH}_2$), 2.88 (3H, s, NCH_3), 2.44(1H, td, $J=11.5, 2.9$ Hz, $\text{N-CH}_a\text{H}_b\text{-CH}_2$), 1.93-1.90(1H, m, $\text{N-CH-CH}_a\text{H}_b$), 1.76-1.73(1H, m, $\text{NCH-CH}_2\text{CH}_a\text{H}_b$), 1.57-1.55 (1H, m, $\text{N-CH}_2\text{CH}_a\text{H}_b\text{CH}_2$), 1.51(9H, s, $\text{C}(\text{CH}_3)_3$), 1.42-1.29(1H, m, $\text{N-CH}_2\text{CH}_a\text{H}_b\text{CH}_2$), 1.23-1.11(1H, m, $\text{N-CH-CH}_2\text{CH}_a\text{H}_b$), 1.06-1.0(1H, m, $\text{NCHCH}_a\text{H}_b\text{CH}_2$); NMR δ_{C} (100 MHz, CDCl_3) 178 (C), 176.8 (C), 169.3 (C), 82.1 (C), 69.3 (CH), 60.4 (CH), 49.7 (CH_2), 48.6 (CH), 47.7 (CH), 28.9 (CH_2), 28.2 (CH_3), 25.1 (CH_2), 24.9 (CH_3), 24.1 (CH_2) ; IR_{sol} (CDCl_3 , cm^{-1}) 2859, 2982, 1701, 1438, 1153; m/z (HRMS-ESI+) 309.1817 (M+H requires $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4^+$ 309.1814). See appendix for X-Ray crystallography data.

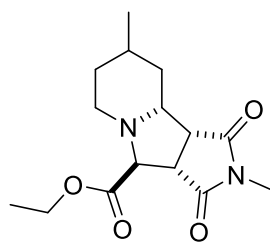
Ethyl (3aS*,4S*,9bR*)-2-methyl-1,3-dioxodecahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (159)



Ethyl-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a] indolizine-4-carboxylate (316 mg) and Raney ® Ni (~ 100 mg) were dissolved in ethanol (10 ml and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give dark brown oil that was purified *via* column chromatography (2:1; petrol: acetone) as eluent to give the product as a brown oil using (192 mg,

78%); IR_{sol} (CHCl₃, cm⁻¹) 2984, 2859, 1701, 1461, 1130; NMR δ_H (400 MHz, Acetone -d₆), 4.20(2H, q, *J*=7.2 Hz, CH₂CH₃), 3.96(1H, br s, NCH(CO₂Et)), 3.32(1H, d, *J*=7.9 Hz, N-CH(CO₂Et)-CH), 3.35(1H, dd, *J*= 8.2, 7.9 Hz, NCH-CH-CO), 3.08(1H, ddd, *J*= 11.3, 8.2, 2.6 Hz, N-CH-CH₂), 2.96-2.7(1H, m, NCH_aH_bCH₂), 2.88(3H, s, NCH₃), 2.37(1H, td, *J*=11.4, 2.9 Hz, NCH_aH_b-CH₂), 1.94-1.83(1H, m, NCH-CH_aH_b), 1.76-1.61(1H, m, NCH-CH₂CH_aH_b), 1.57-1.5(1H, m, NCH₂CH_aH_b), 1.39-1.31(1H, m, NCH₂CH_aH_b), 1.29(3H, t, *J*= 7.2 Hz, CH₂CH₃), 1.26-1.17(1H, m, NCH-CH₂CH_aH_b), 1.06-1.00(1H, m, NCHCH_aH_bCH₂); NMR δ_C (100 MHz, Acetone -d₆) 177.8 (C), 176.6 (C), 169.9 (C), 68.8 (CH), 61.1 (CH), 60.7 (CH₂), 48.5 (CH₂), 47.6 (CH), 47.3 (CH), 28.8 (CH₂), 27.4 (CH₂), 24.9 (CH₃), 24 (CH₂), 14.3(CH₃); *m/z* (HRMS-ESI+) 281.1495 (M+H requires C₁₄H₂₁N₂O₄⁺ 281.1496).

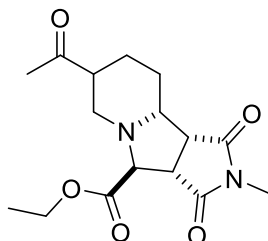
Ethyl (3a*S,4*S**,9b*R**)-2,8-dimethyl-1,3-dioxodecahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (160)**



Ethyl(3a*S**,4*R**,9b*R**)-9-bromo-2,4,8-trimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (120 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethanol (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give colourless oil that was purified

via column chromatography on silica gel using (2:1, acetone: petrol) as an eluent to give the desired product as a colourless oil (30.0 mg, 31%); IRsol ($\text{CHCl}_3, \text{cm}^{-1}$) 2930, 2870, 1777, 1698, 1433, 1285, 1195, 1169; NMR δ_{H} (400 MHz, Acetone- d_6) 4.20 (2H, q, $J=7.2$ Hz, CH_2CH_3), 3.96 (1H, br s, $\text{NCH}(\text{CO}_2\text{Et})$), 3.46-3.36 (1H, m, $\text{NCH}(\text{CO}_2\text{Et})\text{CH}$), 3.40-3.20 (1H, m, N-CH-CH-CO), 3.14 (1H, ddd, $J=11.1, 8.4, 2.7$ Hz, $\text{N-CH-CH}_2\text{-CH}(\text{CH}_3)$), 3.01-2.77 (1H, m, $\text{NCH}_a\text{H}_b\text{CH}_2$), 2.88 (3H, s, NCH_3), 2.45-2.33 (1H, m, $\text{NCH}_a\text{H}_b\text{-CH}_2$), 2.01-1.86 (1H, m, $\text{NCH-CH}_a\text{H}_b\text{-CH}(\text{CH}_3)$), 1.64-1.53 (1H, m, $\text{N-CH}_2\text{-CH}_a\text{H}_b$), 1.47-1.32 (1H, m, $\text{N-CH}_2\text{-CH}_2\text{-CH}(\text{CH}_3)$), 1.28 (3H, t, $J=7.2$ Hz, CH_2CH_3), 1.19-0.99 (1H, m, $\text{NCH}_2\text{CH}_a\text{H}_b$), 0.93 (3H, d, $J=6.5$ Hz, $\text{NCH}_2\text{CH}_2\text{-CH}(\text{CH}_3)$), 0.72 (1H, dt, $J=12.8, 11.5$ Hz, $\text{N-CH-CH}_a\text{H}_b$); NMR δ_{C} (100 MHz, Acetone- d_6) 177.5 (C), 176.0 (C), 169.8 (C), 66.3 (CH), 60.2 (CH), 60.1 (CH_2), 47.9 (CH), 47.4 (CH), 47.3 (CH_2), 37.3 (CH_2), 33.7 (CH_2), 31.1 (CH), 24 (CH_3), 21.3 (CH_3), 13.8 (CH_3); m/z (HRMS-ESI+) 295.1658 ($\text{M}+\text{H}$ requires $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_4+$ 295.1652).

Ethyl (3a*S,4*S**,9b*R**)-7-acetyl-2-methyl-1,3-dioxodecahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (161) and Ethyl (3a*S**,4*S**,9b*R**)-7-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,8,9,9a,9b-octahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (162)**



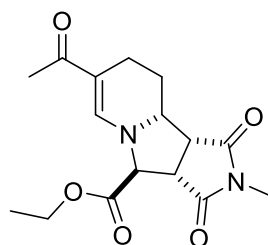
Ethyl(3a*S**,4*S**,9b*R**)-9-acetyl-2-methyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (90 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethanol (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give colourless oil that was purified *via* column chromatography on silica gel using (1:1, acetone: petrol) as an eluent to give two fractions:

Fraction one

As an orange oil (10.0 mg, 20%); IRsol (CHCl₃,cm⁻¹) 2989, 1773, 1698, 1434, 1381, 1283; NMR δ_H (400 MHz, CDCl₃) 4.24 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 4.12 (1H, app s, NCH-(CO₂Et), 3.55 (1H, app dt, *J* = 11.9, 2.1 Hz, NCH_aH_b-CH(COCH₃)), 3.50-3.27 (2H,m, NCH-CH-CO), 3.26-2.85 (2H, m, N-CH-CH_aH_b), 2.96 (3H, s, N-CH₃), 2.67 (1H, dd, *J* = 11.9, 3.7 Hz, NCH_aH_b-CH(COCH₃)), 2.42-2.37 (1H, m, NCH₂-CH(COCH₃)), 2.13 (3H, s, NCH₂-CH(COCH₃)), 1.99-1.85 (1H, m, NCH₂-CH(COCH₃)-CH_aH_b), 1.54-1.34 (1H,

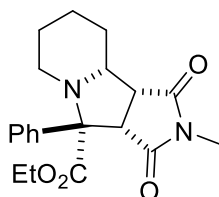
m, NCH₂-CH(COCH₃)-CH_aH_b), 1.35 (3H, t, *J*=7.1 Hz, CH₂CH₃), 1.24-1.13 (1H, m, N-CH-CH_aH_b-CH₂); NMR δ_C (100 MHz, CDCl₃) 208.7 (C), 177.5 (C), 176.0 (C), 169.7 (C), 66.6 (CH), 61.0 (CH₂), 60.6 (CH), 49.4 (CH₂), 47.5 (CH), 47.4 (CH), 46.5 (CH), 27.7 (CH₃), 25.6 (CH₂), 25.0 (CH₃), 24.5 (CH₂), 14.4 (CH₃); *m/z* (HRMS-ESI+) 323.1614 (M+H requires C₁₆H₂₃N₂ O₅⁺ 323.1601).

Fraction two



As a colourless oil (10.0 mg, 20%); IRsol (CHCl₃, cm⁻¹) 2937, 1735, 1699, 1586, 1234, 727; NMR δ_H (400 MHz, CDCl₃) 7.38 (1H, d, *J*= 1.6 Hz, NCH=C ((CO) CH₃), 4.60 (1H, br s, NCH-(CO₂Et), 4.28 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.78 (1H, ddd, *J* = 12.1, 8.5, 3.2 Hz, NCH-CH₂-CH₂), 3.70 (1H, dd, *J* = 8.5, 1.1 Hz, N-CH(CO₂Et)-CH), 3.52 (1H, app t, *J* = 8.5 Hz, NCH-CH-CO), 3.01 (3H, s, NCH₃), 2.68 (1H, ddd, *J*=17, 5.1, 1.9 Hz, N-CH-CH₂-CH_aH_b), 2.39 (1H, dddd, *J* = 13.4, 5.3, 3.2, 1.9 Hz, N-CH-CH_aH_b-CH₂), 2.27-2.11 (1H, m, N-CH-CH₂-CH_aH_b), 2.18 (3H, s, C((CO)CH₃), 1.33 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 1.29-1.14 (1H, m, N-CH-CH_aH_b-CH₂). NMR δ_C (100 MHz, CDCl₃) 194.3 (C), 176.3 (C), 174.5 (C), 169.1 (C), 143.2 (CH), 112.5 (C), 65.0 (CH), 62.5 (CH₂), 56.6 (CH), 47.9 (CH), 46.7 (CH), 25.4 (CH₃), 24.0 (CH₂), 23.9 (CH₃), 20.1 (CH₂), 14.2 (CH₃); *m/z* (HRMS-ESI+) 321.1458 (M+H requires C₁₆H₂₁N₂ O₅⁺ 321.1457).

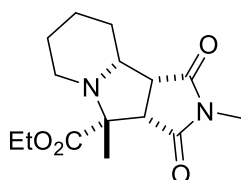
Ethyl (3a*S,4*S**,9b*R**)-2-methyl-1,3-dioxo-4-phenyldecahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (144)**



Ethyl(3a*S**,4*S**,9b*R**)-9-bromo-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate [3,4-*a*] indolizine-4-carboxylate (250 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethyl acetate (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give colorless oil that was purified *via* column chromatography on silica gel using (3:1, ether: petrol) as an eluent to give the desired product as a pale yellow solid (90.0 mg, 36%) The product was crystallised from a mixture of solvents to give appearance crystals suitable for X-ray analysis; m.p. 173-175 °C; IR_{sol} (CHCl₃,cm⁻¹) 2981, 1742, 1704, 1466, 1295, 1049; NMR δ_H (500 MHz, CDCl₃) 7.47-7.29 (3H, m, Ar*H*), 7.07-7.01 (2H, m, Ar*H*), 4.32 (2H, q, *J*=7.2 Hz, CH₂CH₃), 3.81 (1H, d, *J*= 7.8 Hz, N-C((Ph)(CO₂Et)-CH), 3.46 (1H, dd, *J*=9.1, 7.8 Hz, N-CH-CH-CO), 3.42-3.31 (1H, m, NCH_aH_bCH₂), 3.04 (3H, s, NCH₃), 2.34 (1H, ddd, *J*=11.5, 9.1, 2.7 Hz, N-CH-CH₂), 2.04-1.95 (1H, m, NCH-CH₂CH_aH_b), 1.76-1.68 (1H, m, NCH-CH_aH_b), 1.64-1.44 (3H, m, NCH_aH_b-CH₂CH₂), 1.26 (3H, t, *J*= 7.2 Hz, CH₂CH₃), 1.25-1.13 (1H, m, NCH-CH₂-CH_aH_b), 0.94 (1H, qt, *J*= 13.0, 3.9 Hz, NCH-CH_aH_bCH₂); NMR δ_C (100 MHz, CDCl₃) 176.0 (C), 175.8 (C), 172 (C), 133.3 (C), 127.9 (CH), 127.2 (CH), 126.8 (CH), 75.8 (C), 61.3 (CH₂), 59.7 (CH), 51.6 (CH), 48.0

(CH₂), 47.2 (CH), 29.0 (CH₂), 25.2 (CH₃), 24.6 (CH₂), 24.0 (CH₂), 13.9 (CH₃); *m/z* (HRMS-ESI+) 357.1808 (M+H requires C₂₀H₂₅N₂O₄⁺ 357.1814). See appendix for X-Ray crystallography data.

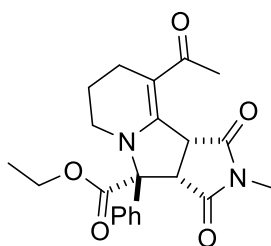
Ethyl (3a*S,4*R**,9b*R**)-2,4-dimethyl-1,3-dioxodecahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (150)**



Ethyl(3a*R**,4*R**,9b*S**)-9-bromo-2,4-dimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (200 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethanol (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give colourless oil that was purified *via* column chromatography on silica gel using (3:1, ether: petrol) as an eluent to give the desired product as an orange oil (80.0 mg, 50%); IRsol (CHCl₃, cm⁻¹) 2945, 1773, 1384, 1139, 1104, 1046; ¹H NMR (400 MHz, CDCl₃) δ 4.20 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.44 (1H, d, *J* = 8.0 Hz, N-C((CH₃)(CO₂Et))-CH), 3.25 (1H, app t, *J* = 8.0 Hz, N-CH-CH-CO), 3.05-2.99 (1H, m, N-CH_aH_b-CH₂), 3.00 (3H, s, N-CH₃), 2.76 (1H, ddd, *J* = 11.0, 8.0, 2.7 Hz, N-CH-CH₂), 2.13 – 2.08 (1H, m, N-CH_aH_b-CH₂), 2.07 – 2.01 (1H, m, N-CH-CH_aH_b), 1.83-1.79 (1H, m, N-CH₂-CH₂-CH_aH_b), 1.71–1.54 (2H, m, N-CH₂-CH₂), 1.49 (3H, s, N-C((CH₃)(CO₂Et))), 1.31 (3H, t, *J* = 7.1 Hz, CH₂CH₃),

1.22 – 1.19 (1H, m, N-CH₂-CH₂-CH_aH_b), 1.17 – 1.07 (1H, m, N-CH-CH_aH_b);
 NMR δ_C (100 MHz, CDCl₃) 176.6 (C), 176.3 (C), 170.9 (C), 69.5 (C), 61.1 (CH), 60.8 (CH₂), 50.2 (CH), 47.2 (CH), 46.6 (CH₂), 29.1 (CH₂), 25.4 (CH₂), 24.8 (CH₃), 24.3 (CH₂), 18.4 (CH₃), 14.5 (CH₃); *m/z* (HRMS-ESI+) 295.1648 (M+H requires C₁₅H₂₃N₂O₄+ 295.1652).

Ethyl(3a*S,4*S**,9b*R**)-9-acetyl-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,6,7,8,9b-octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (163) and Ethyl (3a*S**,4*S**,9b*R**)-7-acetyl-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,8,9,9a,9b-octahydro-1*H*-pyrrolo[3,4-*a*] indolizine-4-carboxylate (165)**

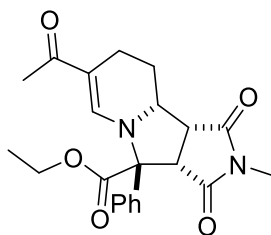


Ethyl(3a*S**,4*S**,9b*R**)-9-acetyl-2-methyl-1,3-dioxo-4-phenyl-2,3,3a,4,6,7,8,9b-octahydro-1*H*-pyrrolo[3,4-*a*]indolizine-4-carboxylate (250 mg) and Raney ® Nickel (~ 100 mg) were dissolved in ethanol (10 mL) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give colourless oil that was purified *via* column chromatography on silica gel using (2:1, acetone: petrol) as an eluent to give two fractions:

Fraction one

As a colourless oil (151 mg, 60%); IRsol (CHCl_3 , cm^{-1}) 3074, 2293, 1722, 1434, 1280, 1134; NMR δ_{H} (400 MHz, CDCl_3) 7.48 – 7.36 (5H, m, ArH), 5.54 (1H, d, $J=9.5$ Hz, N-C((Ph)(CO₂Et))-CH), 4.29 – 4.11 (2H, m, CH₂CH₃), 3.54 (1H, d, $J = 9.5$ Hz, N-C-CH-CH-CO), 3.1 (1H, ddd, $J = 11.4, 6.9, 4.0$ Hz, N-CH_aH_b-CH₂), 3.04-2.94 (4H, m, N-CH₃, N-CH_aH_b-CH₂), 2.69-2.57 (1H, m, N-CH₂-CH₂-CH_aH_b), 2.42 (1H, ddd, $J=15.8, 8.3, 5.3$ Hz, N-CH₂-CH₂-CH_aH_b), 2.30 (3H, s, N-C=C(COCH₃)), 2.03 – 1.81 (2H, m, N-CH₂-CH₂), 1.24 (3H, t, $J = 7.1$ Hz, CH₂CH₃); NMR δ_{C} (100 MHz, CDCl_3) 197.1 (C), 174.1 (C), 172.7 (C), 168.8 (C), 148.5 (C), 138.9 (C), 128.8 (CH), 128.3 (CH), 126.3 (CH), 105 (C), 77.5 (C), 62.6 (CH₂), 54.4 (CH), 49.1 (CH), 43.4 (CH₂), 28.45 (CH₃), 25.44 (CH₃), 23.7 (CH₂), 21.1 (CH₂), 14.1 (CH₃); m/z (HRMS-ESI+) 397.1774 (M^+H requires C₂₂H₂₅N₂O₅+ 397.1758).

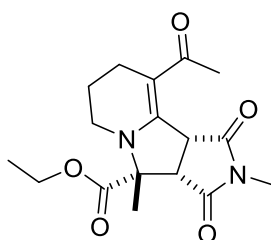
Fraction two



as a yellow oil (83 mg, 33%); IRsol (CHCl_3 , cm^{-1}) 3044, 2939, 1709, 1597, 1384, 1296; NMR δ_{H} (400 MHz, CDCl_3) 7.85 (1H, br s, N-CH-C(COCH₃)), 7.51 – 7.34 (5H, m, ArH), 4.10 – 4.27 (2H, m, CH₂CH₃), 4.00 (1H, d, $J = 8.0$ Hz, N-C((Ph)(CO₂Et))-CH), 3.60 (1H, ddd, $J = 12.0, 9.0, 2.9$ Hz, N-CH-CH₂), 3.40 (1H, app. t, $J = 9.0$ Hz, N-CH-CH-CO), 3.04 (3H, s, N-CH₃), 2.70 (1H, ddd, $J = 17.1, 4.9, 1.7$ Hz, N-CH-CH₂-CH_aH_b), 2.41 (1H, ddd, $J = 16.8, 6.9, 4.0$ Hz, N-CH-CH_aH_b), 2.22 (3H, s, N-CH-C(COCH₃)), 2.20- 2.14 (1H,

m, N-CH-CH₂-CH_aH_b), 1.58 – 1.40 (1H, m, N-CH-CH_aH_b), 1.30 (3H, J= 7.1 Hz, CH₂CH₃); NMR δ_C (100 MHz, CDCl₃) 195.1 (C), 174.7 (C), 174.1 (C), 168.5 (C), 143.6 (CH), 138 (C), 129 (CH), 128.7 (CH), 126.2 (CH), 113.4 (C), 74.7 (C), 62.7 (CH₂), 56.9 (CH), 55.3 (CH), 45.7 (CH), 25.3 (CH₃), 24.2 (CH₃), 24.0 (CH₂), 20.4 (CH₂), 13.8 (CH₃); *m/z* (HRMS-ESI+) 397.1774 (M⁺H requires C₂₂H₂₅N₂O₅+ 397.1758).

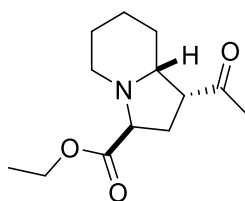
Ethyl(3aS*,4R*,9bR*)-9-acetyl-2,4-dimethyl-1,3-dioxo-2,3,3a,4,6,7,8,9b-octahydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate (164)



Ethyl(3aS*,4R*,9bR*)-9-acetyl-2,4-dimethyl-1,3-dioxo-2,3,3a,4,9a,9b-hexahydro-1H-pyrrolo[3,4-a]indolizine-4-carboxylate (100 mg) and Raney Ni (~ 100 mg) were dissolved in ethanol (10 mL) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give colourless oil that was purified *via* column chromatography on silica gel using (2:1, acetone: petrol) as an eluent to give the desired product as a colourless oil (60.0 mg, 60%); IRsol (CHCl₃, cm⁻¹) 2852, 1782, 1656, 1435, 1287; NMR δ_H (400 MHz, CDCl₃) 5.53 (1H, d, J = 8.8 Hz, N-C((CH₃)(CO₂Et)-CH), 4.23-4.1(2H, m, CH₂CH₃), 3.58 (1H, d, J=8.8 Hz, N-C-CH-CO), 3.13 (1H, ddd, J = 11.7, 5.9, 4.1 Hz, N-CH_aH_b-

CH₂), 2.99 (3H, s, N-CH₃), 3.06–2.85 (1H, m, N-CH_aH_b-CH₂), 2.57–2.34 (2H, m, N-CH₂-CH₂-CH₂), 2.26 (3H, s, COCH₃), 1.97 – 1.81 (2H, m, N-CH₂-CH₂), 1.46 (3H, s, N-C((CH₃)CO₂Et)), 1.39–1.20 (3H, t, J=7.2 Hz, CH₂CH₃); NMR δ_C (100 MHz, CDCl₃) 196.1 (C), 174.1 (C), 173.6 (C), 171.4 (C), 149.4 (C), 104.4 (C), 69.4 (C), 62.2 (CH₂), 48.8 (CH), 48.5 (CH), 41.68 (CH₂), 28.7 (CH₃), 25.3 (CH₃), 23.6 (CH₂), 21.2 (CH₂), 18.1 (CH₃), 14.2 (CH₃); *m/z* (HRMS-ESI+) 335.1608 (M+H requires C₁₇H₂₃N₂O₅ 335.1601).

Ethyl(1*R,3*S**,8*aR**)-1-acetyloctahydroindolizine-3-carboxylate (188)**

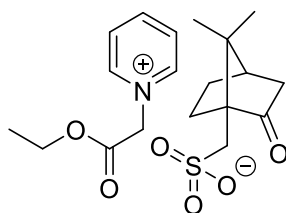


Ethyl 2-acetyl-8-bromo-1,2,3, 8*a*-tetrahydroindolizine-3-carboxylate (350 mg) and Raney® Ni (~ 100 mg) were dissolved in ethanol (10 ml) and stirred for 4 hours. The atmosphere was replaced with hydrogen. The mixture of reaction was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated in vacuo to give yellow oil that was purified *via* column chromatography on silica gel using (2:1, ethyl acetate: petrol) as an eluent to give the desired product as a colourless oil (134 mg, 50 %); IR_{sol} (CHCl₃, cm⁻¹) 2936, 2853, 1729, 1437, 1159, 1025; NMR δ_H (400 MHz, CDCl₃) 4.30 (2H, q, J=7.2 Hz, CH₂CH₃), 3.27–3.16 (1H, m, , N-CH_aH_b-CH₂), 3.03 (1H, dd, J = 9.2, 8.1 Hz, N-CH-(CO₂Et)), 2.87 (1H, ddd, J=10.7, 9.7, 3.8 Hz, N-CH-CH-(COCH₃)), 2.32–2.21 (1H, m, N-CH-(CO₂Et)-CH_aH_b), 2.20 (3H, s, COCH₃), 2.19–2.10 (2H, m, N-CH-(CO₂Et)-CH_aH_b, N-

CH-CH (COCH₃)), 2.01 (1H, td, *J*=3.8, 10.7 Hz, N-CH_aH_b-CH₂), 1.91-1.83 (1H, m, N-CH-CH_aH_b), 1.82-1.72 (1H, m, N-CH-CH_aH_b), 1.68- 1.55 (2H, m, N-CH₂CH₂), 1.52-1.38 (1H, m, N-CH₂-CH₂-CH_aH_b), 1.29 (3H, t, *J* = 7.2 Hz, CH₂CH₃), 1.28-1.20 (1H, m, N-CH₂-CH₂-CH_aH_b); NMR δ_C (100 MHz, CDCl₃) 208.8 (C), 172.5 (C), 66.8 (CH), 65.5 (CH), 60.8 (CH₂), 54.9 (CH), 52.2 (CH₂), 30.4 (CH₃), 30.4 (CH₂), 30.2 (CH₂), 24.8 (CH₂), 23.8 (CH₂), 14.2 (CH₃); *m/z* (HRMS-ESI+) 240.1590 (M+H requires C₁₃H₂₂NO₃+ 240.1594).

3.6 Reaction of pyridine with acid

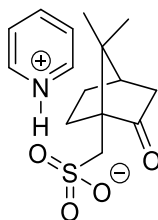
1-(2-Ethoxy-2-oxoethyl) pyridin-1-ium((1*R**,4*R**)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl)methane sulfonate (175)



Pyridine (0.12 mL, 1.50 mmol), camphor sulfonic acid (348 mg, 1.50 mmol) and Fe(PPP)Cl (10.5 mg, 0.02 mmol) was stirred in dichloromethane (3 mL) under argon at room temperature. Ethyl diazoacetate (158 μL, 1.50 mmol in 200 μL dichloromethane) was then added dropwise *via* syringe pump over 2 h, The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3x15 mL). The water layer was separated and evaporated to give the desired product as a yellow oil (585mg, 96%); IR (CHCl₃,cm⁻¹) 3054, 2959, 1742, 1635, 1376, 1272, 1168; δ_H (400 MHz, MeOD) 9.05- 8.98 (2H,m, *ArH*), 8.73 (1H, app tt, *J* = 7.8, 1.4 Hz, *ArH*), 8.22 (2H, dd, *J*

= 7.8, 6.8 Hz, *ArH*), 5.51 (2H, s, N-CH₂-(CO₂Et)), 4.35 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.69-3.24 (1H, m, CH₂(SO₃⁻)), 2.74 – 2.62 (1H, m, C-CH₂-CH_aH_b), 2.41–2.29 (1H, m, C-CO-CH_aH_b), 2.11-1.99 (2H, m, C-CH_aH_b-CH₂-CH(C(CH₃)₂)), 1.90 (1H, d, *J* = 18.4 Hz, C-(C=O)-CH_aH_b-CH(C(CH₃)₂)), 1.62 (1H, ddd, *J* = 13.7, 9.3, 4.4 Hz, C-CH₂-CH_aH_b), 1.49–1.41 (1H, m, C-CH_aH_b-CH₂), 1.35 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 1.14 (3H, s, CH₃), 0.87 (3H, s, CH₃); δ_C (100 MHz, MeOD) 216.8 (C), 165.9 (C), 146.6 (CH), 146.2 (CH), 127.8 (CH), 62.7 (CH₂), 58.1 (CH₂), 56.6 (CH₂), 56.9 (C), 47.5 (C), 42.6 (CH), 42.2 (CH₂), 26.39 (CH₂), 24.3 (CH₂), 19.0 (CH₃), 18.7 (CH₃); *m/z* (HRMS-ESI+) 166.0871 (M⁺ requires C₉H₁₂NO₂⁺ 166.0868).

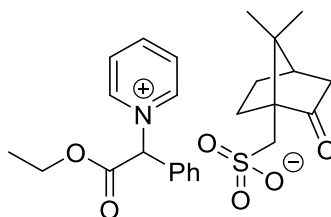
Pyridinium ((1*R, 4*R**)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methane sulfonate (176)**



Pyridine (346 mL, 4.31 mmol) was added to camphor sulfonic acid (1 g, 4.31 mmol) in dichloromethane (7 mL). The mixture of reaction was stirred for 4 hr. Solvent was removed in vacuo and we get our desired compound as white solid (1.27 g, 95%), M.p. 170-172°C; IR (CHCl₃, cm⁻¹) 2938, 1699, 1435, 1382, 1192; δ_H (400 MHz, MeOD) 8.95 (2H, app dt, *J* = 5.3, 1.5 Hz, *ArH*), 8.72 (1H, app tt, *J* = 7.9, 1.5 Hz, *ArH*), 8.22 – 8.13 (2H, m, *ArH*), 3.35 (1H, d, *J* = 14.8 Hz, CH_aH_b(SO₃⁻)), 2.81 (1H, d, *J* = 14.8 Hz, CH_aH_b(SO₃⁻)), 2.71–2.61 (1H, m, C-CH₂-CH_aH_b), 2.37 (1H, app ddd, *J* = 18,

4.9, 3.2 Hz, C-CO-CH_aH_b), 2.11-2.07 (1H, m, C-CO-CH₂-CH(C(CH₃)₂), 2.06-2.01 (1H, m, C-CH_aH_b-CH₂), 1.92 (1H, d, *J* = 18 Hz, C-CO-CH_aH_b), 1.70-1.61 (1H, m, C-CH₂-CH_aH_b), 1.44 (1H, ddd, *J* = 12.0, 9.4, 4.1 Hz, C-CH_aH_b-CH₂), 1.14 (3H, s, CH₃), 0.88 (3H, s, CH₃); δ_C (100 MHz, MeOD) δ 216.9 (C), 147.0 (CH), 141.5 (CH), 127.4 (CH), 58.1 (C), 47.7 (C), 46.9 (CH₂), 42.6 (CH), 42.2 (CH₂), 26.3 (CH₂), 24.3 (CH₂), 18.9 (CH₃), 18.3 (CH₃).

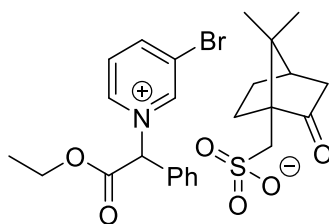
1-(2-Ethoxy-2-oxo-1-phenylethyl) pyridin-1-ium ((1*R, 4*R**)-7,7-dimethyl-2- oxobicyclo [2.2.1] heptan-1-yl) methane sulfonate (182)**



Pyridinium((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl) methane sulfonate (50.0 mg, 0.16 mmol) was stirred in dichloromethane (3 mL) with [(MeCN)₄CuPF₆] (3.00 mg, 0.01 mmol) under argon at room temperature. Ethyl 2-diazo-2-phenylacetate (30.0 mg, 0.16 mmol in 250 μL toluene) was then added dropwise *via* syringe pump over 2 h. The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3x15 mL). The water layer was separated and evaporated to give colourless oil (25 mg, 31%); IR (CHCl₃, cm⁻¹) 2984, 1951, 1723, 1391, 1370, 1334, 1211; δ_H (500 MHz, MeOD) 9.00-8.55 (2H, m, ArH), 8.62-8.25 (1H, m, ArH), 8.10-7.89 (2H, m, ArH), 7.68 – 7.29 (5H, m, ArH),

7.03 (1H, s, N-CH-((Ph)(CO₂Et))), 4.35 (2H, q, *J* = 7.1 Hz, CH₂CH₃), 3.02 (2H, br s, CH₂(SO₃⁻)), 2.74–2.62 (1H, m, C-CH₂-CH_aH_b), 2.35 (1H, br d, *J*=16.8 Hz, C-(C=O)-CH_aH_b), 2.14–2.09 (2H, m, C-CH_aH_b-CH₂-CH(C(CH₃)₂)), 1.92 (1H, d, *J* = 16.8 Hz, C-(C=O)-CH_aH_b), 1.73 - 1.60 (1H, m, C-CH₂-CH_aH_b), 1.46–1.36 (1H, m, C-CH_aH_b-CH₂), 1.29–1.19 (3H, t, *J*=7.1 Hz, CH₂CH₃), 1.10 (3H, s, CH₃), 0.87 (3H, s, CH₃); δ_C (100 MHz, MeOD) 217.7 (C), 208.3 (C), 166.8 (C), 147.0 (CH), 144.8 (CH), 131.2 (C), 130.6 (CH), 129.6 (CH), 129.2 (CH), 127.9 (CH), 74.5 (CH), 63.3 (CH₂), 59.0 (C), 43.4 (CH₂), 42.8 (CH), 29.2 (CH₂), 26.38 (CH₂), 24.2 (CH₂), 19.0 (CH₃), 18.7 (CH₃), 12.7 (CH₃); *m/z* (HRMS-ESI+) 242.1185 (M⁺ requires C₁₅H₁₆NO₂⁺ 242.1176).

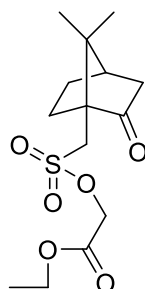
3-bromo-1-(2-ethoxy-2-oxo-1-phenyl ethyl) pyridin-1-ium ((1R*, 4R*)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methane sulfonate (183)



3-bromo pyridine (62.0 μL, 0.63 mmol), camphor sulfonic acid (146 mg, 0.63 mmol) and (MeCN)₄CuPF₆ (11.0 mg, 0.03 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazo-2-phenylacetate (120 mg, 0.63 mmol in 200 μL dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. The mixture of reaction was stirred for 16 hr. Solvent was

removed in vacuo and the crude product purified by addition of H₂O (3 mL) and dichloromethane (3*15 mL). The water layer was separated and evaporated to give the product as colourless solid (60 mg, 30%). The product was crystallised from a mixture of methanol, chloroform, ethanol, acetone and diethyl ether to give crystals suitable for X-ray analysis; M.p. 240-244°C; IRsol (CHCl₃, cm⁻¹) 3057, 1985, 1736, 1452, 1371, 1264, 1214, 675; δ_H (400 MHz, CDCl₃) 8.74 (1H, s, N-CH-C(Br)), 8.59 (1H, app.d, *J* = 8 Hz, N-CH=CH-CH), 8.12-7.91 (2H, m, N-CH=CH-CH), 7.59-7.33 (5H, m, ArH), 5.98 (1H, s, N-CH-((Ph)(CO₂Et))), 4.35 (2H, m, CH₂CH₃), 3.73 (1H, app dd, *J* = 17.4, 15.2 Hz, CH_aH_b(SO₃⁻)), 3.17 (1H, dd, *J* = 17.4, 15.2 Hz, CH_aH_b(SO₃⁻)), 2.53-2.45 (1H, m, C-CH₂-CH_aH_b-CH(C(CH₃)₂)), 2.40-2.30 (1H, m, C-(C=O)-CH_aH_b-CH(C(CH₃)₂)), 2.10-2.03 (1H, m, C-CH₂-CH₂-CH(C(CH₃)₂)), 2.06 (1H, m, C-CH_aH_b-CH₂-CH(C(CH₃)₂)), 1.96 (1H, dd, *J* = 18.5, 7.7 Hz, C-(C=O)-CH_aH_b-CH(C(CH₃)₂)), 1.70-1.61 (1H, m, C-CH₂-CH_aH_b-CH(C(CH₃)₂)), 1.50-1.40 (1H, m, C-CH_aH_b-CH₂-CH(C(CH₃)₂)), 1.27 (3H, t, *J* = 7.1 Hz, CH₂CH₃), 1.12 (3H, s, CH₃), 0.87 (3H, s, CH₃); δ_C (100 MHz, CDCl₃) 217.7 (C), 166.8 (C), 147.0 (CH), 144.8 (CH), 133.1 (C), 129.8 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 123.9 (C), 79.0 (CH), 78.9 (C), 62.3 (CH₂), 62.2 (C), 49.1 (CH₂), 42.8 (CH), 42.4 (CH₂), 26.9 (CH₂), 24.9 (CH₂), 19.8 (CH₃), 19.8 (CH₃), 13.9 (CH₃); *m/z* (HRMS-ESI+) 320.0299 (M+ C₁₅H₁₅NO₂⁷⁹Br⁺ requires 320.0281), 322.0278 (M+ C₁₅H₁₅NO₂⁸¹Br⁺ requires 322.0260).

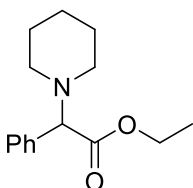
Ethyl 2-((((((1*R, 4*R**)-7, 7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methyl) sulfonyl) oxy) acetate (178)**



Pyridin-1-ium(((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methanesulfonate, N-methyl maleimide (97.0 mg, 0.87 mmol) and Fe(TPP)Cl (6.3 mg, 9.00 μ mol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl diazoacetate (139 μ L, 1.31 mmol in 200 μ L dry dichloromethane) was then added dropwise via syringe pump over 2 h, followed by stirring for an additional 2 hrs. Solvent was removed in vacuo and the crude product purified by column chromatography on silica gel using (2:1 ethyl acetate /petroleum ether) as an eluent to give the desired product as green solid (26 mg, 6%); M.p. 70-74 $^{\circ}$ C; IR (CHCl_3 , cm^{-1}) 2968, 1748, 1449, 1375, 1212, 1167; δ_{H} (400 MHz, CDCl_3) 4.79 (2H, s, $\text{SO}_3\text{-CH}_2\text{-(CO}_2\text{Et)}$), 4.29 (2H, q, $J = 7.1$ Hz, CH_2CH_3), 3.76 (1H, app d, $J = 15.1$ Hz, $\text{CH}_a\text{H}_b\text{-SO}_3\text{-CH}_2$), 3.26 (1H, app d, $J = 15.1$ Hz, $\text{CH}_a\text{H}_b\text{-SO}_3\text{-CH}_2$), 2.53– 2.45 (1H, m, $\text{C-CH}_2\text{-CH}_a\text{H}_b$), 2.41-2.3 (1H, m, $\text{C-(C=O)-CH}_a\text{H}_b$), 2.16- 2.12 (1H, m, $\text{C-CH}_a\text{H}_b\text{-CH}_2$), 2.11-2.03 (1H, m, $\text{C-CH}_2\text{-CH}_2\text{-CH(C(CH}_3)_2)$), 1.95 (1H, dd, $J = 18.5, 7.7$ Hz, $\text{C-(C=O)-CH}_a\text{H}_b$), 1.76 (1H, ddd, $J = 14.0, 9.4, 4.7$ Hz, $\text{CH}_2\text{-CH}_a\text{H}_b$), 1.47 (1H, ddd, $J = 13.1, 9.4, 4.0$ Hz, $\text{C-CH}_a\text{H}_b\text{-CH}_2$), 1.32 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 1.13 (3H, s, CH_3), 0.91 (3H, s, CH_3); δ_{C} (100 MHz, CDCl_3) 214.1 (C), 170.8 (C), 166.0 (C), 64.9 (CH_2), 61.9 (CH_2), 58.0 (C), 48.5 (CH_2), 42.8 (CH), 42.4 (CH_2), 26.9 (CH_2), 25.0 (CH_2),

19.7 (CH₃), 19.6 (CH₃), 14.0 (CH₃); *m/z* (HRMS-ESI+) 341.1042 (M⁺Na requires C₁₄H₂₂O₆SNa⁺ 341.1035).

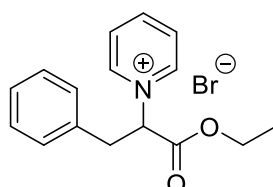
Ethyl 2-phenyl-2-(piperidin-1-yl) acetate (184) ⁹³



1-(2-ethoxy-2-oxo-1-phenylethyl) piperidin-1-ium((1*R**,4*R**)-7, 7-dimethyl-2-oxobicyclo [2.2.1] heptan-1-yl) methane sulfonate (100 mg) and Raney® nickel (~ 100 mg) were dissolved in ethanol (10 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give colourless oil that was purified *via* column chromatography on silica gel using (9:1, dichloromethane: ammonia saturated methanol) as an eluent to give the desired product as a colourless oil (50.0 mg, 65%); IR (CHCl₃, cm⁻¹) 3064, 2937, 1723, 1450, 1300; δ_H (400 MHz, CDCl₃) 7.50–7.42 (2H, m, *ArH*), 7.42–7.24 (3H, m, *ArH*), 4.32–4.18 (2H, m, CH₂CH₃), 3.64 (1H, s, N-CH-Ph), 2.53–2.33 (4H, m, CH₂-CH₂-N-CH₂-CH₂), 1.69–1.55 (4H, m, CH₂-CH₂-N-CH₂-CH₂), 1.51–1.40 (2H, m, N-CH₂-CH₂-CH₂), 1.25 (3H, t, *J* = 7.1 Hz, CH₂CH₃); δ_C (100 MHz, CDCl₃) 171.6 (C), 134.1 (C), 129.2 (CH), 128.4 (CH), 128.0 (CH), 75.0 (CH), 60.7 (CH₂), 52.3 (CH₂), 25.8 (CH₂), 24.3 (CH₂), 14.1 (CH₃); *m/z* (HRMS-ESI+) 248.1648 (M+H requires C₁₅H₂₂NO₂⁺ 248.1645).

3.7 Alkylation of pyridinium ylides

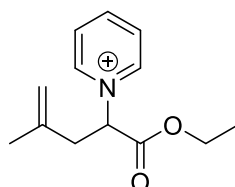
1-(1-ethoxy-1-oxo-3-phenylpropan-2-yl)pyridin-1-iumbromide (195)



Pyridine (0.20 mL, 2.35 mmol), benzyl bromide (0.33 mL, 2.78 mmol) and Fe(TPP)Cl (9.00 mg, 0.01 mmol) was stirred in toluene (3 mL) under argon at room temperature. Ethyl diazoacetate (400 μ L, 3.79 mmol in 250 μ L toluene) was then added dropwise via syringe pump over 2 h, The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3*15 mL). The water layer was separated and evaporated to give the crude product. The crude product was separated according the general method to separate the mixture of pyridinium salts to give white solid (173 mg with NaBr); IRsol (CHCl₃,cm⁻¹) 3028, 1724, 1495, 1465, 1442, 1342, 1273, 1215, 1184, 993; δ_{H} (400 MHz, CD₃OD) 9.18 (2H, app dt, J = 7.8, 1.8 Hz, ArH), 8.67 (1H, app tt, J = 7.8, 1.6 Hz, ArH), 8.18 – 8.08 (2H, m, ArH), 7.30 – 7.16 (5H, m, ArH), 6.27 (1H, app dd, J = 11.8, 5.3 Hz, N-CH-CH₂-Ph), 4.38 (2H, m, CH₂CH₃), 3.93 (1H, app dd, J = 14.6, 5.3 Hz, N-CH-CH_aH_bPh), 3.74 (1H, ddd, J = 14.6, 10.5, 2.8 Hz, N-CH-CH_aH_bPh), 1.34 (3H, t, J = 7.1 Hz, CH₂CH₃); δ_{C} (100 MHz, CD₃OD) 166.8 (C), 147.1 (CH), 145.1 (CH), 145.1 (CH), 133.9 (C), 128.7 (CH), 127.8 (CH), 127.4 (CH), 73.3

(CH), 63.2 (CH₂), 37.7 (CH₂), 13.0 (CH₃); *m/z* (HRMS-ESI+) 256.1344 (M⁺ requires C₁₆H₁₈NO₂⁺ 256.1332).

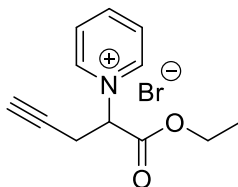
1-(1-Ethoxy-4- methyl-1- oxopent- 4- en-2-yl) pyridinium bromide (196)



Pyridine (0.10 mL, 1.26 mmol), 3-bromo-2- methyl propene (0.13 mL, 1.39 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) was stirred in toluene (3 mL) under argon at room temperature. Ethyldiazoacetate (200 μ L, 1.89 mmol in 250 μ L toluene) was then added dropwise via syringe pump over 2 h, followed by the addition of allyl bromide. The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3x15 mL). The water layer was separated and evaporated to give the crude product. The crude product was separated according the general method to separate the mixture of pyridinium salts to give a white solid (50.0 mg with NaBr); IR (CHCl₃,cm⁻¹) 3026, 1739, 1631, 1579, 1277; δ _H (400 MHz, CD₃OD) 9.32 (2H, app dt, *J* = 6.4, 1.3 Hz, *ArH*), 8.78 (1H, app tt, *J* = 7.8, 1.3 Hz, *ArH*), 8.31 – 8.23 (2H, m, *ArH*), 6.15 (1H, app. dd, *J* = 10.8, 5.4 Hz, N-CH-CH₂-C(CH₃)=CH₂), 4.78-4.68 (2H, m, N-CH-CH₂-C(CH₃)=CH₂), 4.44-4.27 (2H, m, CH₂CH₃), 3.29 (1H, dd, *J*= 4.0, 0.8 Hz, N-CH-CH_aH_b-C(CH₃)=CH₂), 3.27-3.17 (1H, m, N-CH-CH_aH_b-C(CH₃)=CH₂), 1.84 (3H, s, N-CH-CH₂-C(CH₃)=CH₂), 1.34 (3H, t, *J* = 7.1 Hz, CH₂CH₃); δ _C (100 MHz, CD₃OD) 165.7 (C), 145.8 (CH), 143.9 (CH), 137.2 (C), 126.68 (CH), 114.4 (CH₂), 68.8 (CH), 61.9 (CH₂), 38.5

(CH₂), 19.0 (CH₃), 11.6 (CH₃); *m/z* (HRMS-ESI+) 220.1333 (MH⁺ requires C₁₃H₁₈NO₂⁺ 220.1332).

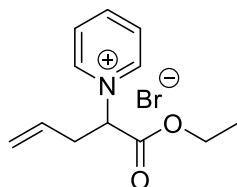
1-(1-ethoxy-1-oxopent-4-yn-2-yl)pyridin-1-iumbromide (197)



Pyridine (0.10 mL, 1.26 mmol), propargyl bromide (0.12 mL, 1.39 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) was stirred in toluene (3 mL) under argon at room temperature. Ethyl diazoacetate (200 μ L, 1.89 mmol in 250 μ L toluene) was then added dropwise *via* syringe pump over 2 h. The mixture of reaction was stirred for 16 hr. Solvent was removed *in vacuo* and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3*15 mL). The water layer was separated and evaporated to give the crude product. The crude product was separated according the general method C to separate the mixture of pyridinium salts to give pale yellow solid (700 mg with NaBr); IRsol (CHCl₃, cm⁻¹) 3200, 2114, 1868, 1743, 1344, 1281, 1178; δ_H (400 MHz, CD₃OD) 9.40 – 9.33 (2H, m, ArH), 8.87 (1H, app.tt, *J* = 7.8, 1.3 Hz, ArH), 8.39 – 8.28 (2H, m, ArH), 6.20 (1H, dd, *J* = 9.9, 4.5 Hz, N-CH-CH₂-C $\equiv$ CH), 4.38-4.27 (2H, m, CH₂CH₃), 3.61 (1H, ddd, *J* = 18.0, 9.9, 2.7 Hz, N-CH-CH_aH_b-C $\equiv$ CH), 3.46 (1H, ddd, *J* = 18.0, 4.5, 2.7 Hz, N-CH-CH_aH_b-C $\equiv$ CH), 2.63 (1H, t, *J* = 2.7 Hz, N-CH-CH₂-C $\equiv$ CH), 1.35 (3H, t, *J* = 7.1 Hz, CH₂CH₃); δ_C (100 MHz, CD₃OD) 165.7 (C), 147.7 (CH), 145.3 (CH), 128.1 (CH), 76.1 (CH), 74.3 (C), 70.3 (CH), 63.6

(CH₂), 22.2 (CH₂), 13.0 (CH₃); *m/z* (HRMS-ESI+) 205.1090 (M⁺ requires C₁₂H₁₅NO₂⁺ 205.1097).

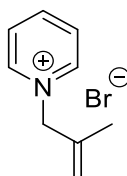
1-(1-ethoxy-1-oxopent-4-en-2-yl) pyridinium bromide (198)



Pyridine (0.10 mL, 1.26 mmol) and Fe(TPP)Cl (7.00 mg, 0.01 mmol) was stirred in toluene (3 mL) under argon at room temperature. Ethyl diazoacetate (200 μ L, 1.89 mmol in 250 μ L toluene) was then added dropwise via syringe pump over 2 h, followed by the addition of allyl bromide. The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (5 mL) and dichloromethane (3*15 mL). The water layer was separated and evaporated to give the crude product. The crude product was separated according the general method C to separate the mixture of pyridinium salts to give pale yellow solid (700 mg with NaBr); IR (CHCl₃,cm⁻¹) 3044, 1953, 1737, 1638, 1478, 1370, 1280, 1177; δ_{H} (400 MHz, DMSO-*d*₆) 9.28-9.05 (2H,m, Ar-*H*), 8.73 (1H, app tt, *J*= 7.8, 1.2 Hz, Ar-*H*), 8.37-8.11 (2H, m, Ar-*H*), 6.01 (1H, dd, *J* = 10.2, 5.4 Hz, N-CH-CH₂-CH=CH₂), 5.72 (1H, dddd, *J* = 17.1, 10.2, 8.5, 5.7 Hz,N-CH-CH₂-CH=CH₂), 5.2-5.1 (1H, m, N-CH-CH₂-CH=CH_aH_b), 5.06-5.00 (1H, m, N-CH-CH₂-CH=CH_aH_b), 4.4-4.26 (2H, m, CH₂CH₃), 3.24-3.03 (2H, m, N-CH-CH₂-CH=CH₂), 1.35 (3H, t, *J* = 7.1 Hz, CH₂CH₃) ; δ_{C} (100 MHz, DMSO-*d*₆) 167.5 (C), 147.8 (CH), 145.6 (CH), 131.8

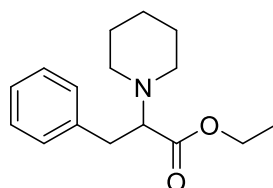
(CH), 128.4 (CH), 120.7 (CH₂), 70.9 (CH), 63.2 (CH₂), 36.1 (CH₂), 14.3 (CH₃) ; *m/z* (HRMS-ESI⁺) 206.1176 (M⁺ requires C₁₂H₁₆NO₂⁺ 206.1184).

1-(2-methyl allyl) pyridin-1-ium bromide (200)



Pyridine (35.0 μ L, 0.43 mmol), 3-bromo-2-methylpropene (66.0 μ L, 0.657 mmol) and (MeCN)₄CuPF₆ (7.00 mg, 0.02 mmol) were stirred in dry dichloromethane (3 mL) under argon at room temperature. Ethyl 2-diazo-2-phenylacetate (100 mg, 0.52 mmol in 200 μ L dry dichloromethane) was then added dropwise *via* syringe pump over 2 h, followed by stirring for an additional 2 hrs. The mixture of reaction was stirred for 16 hr. Solvent was removed in vacuo and the crude product purified by addition of H₂O (3 mL) and dichloromethane (3*10 mL). The water layer was separated and evaporated to give the product as colourless oil (112 mg, 100%); IRsol (CHCl₃, cm⁻¹) 2937, 1993, 1628, 1309, 1280, 304, 148; δ_H (400 MHz, CD₃OD) 9.1-9.08 (2H, m, ArH), 8.73 (1H, app t, *J* = 7.7 Hz, ArH), 8.24-8.22 (2H, m, ArH), 5.36 (2H, s, N-CH₂-C(CH₃)=CH₂), 5.26 (1H, br.s, N-CH₂-C(CH₃)=CH_aH_b), 5.04 (1H, br.s, N-CH₂-C(CH₃)=CH_aH_b), 1.82 (3H, s, N-CH₂-C(CH₃)=CH₂); δ_C (100 MHz, CD₃OD) 146.1 (CH), 144.9 (CH), 138.9 (C), 128.3 (CH), 116.9 (CH₂), 66.4 (CH₂), 18.5 (CH₃); *m/z* (HRMS-ESI⁺) 134.0962 (M⁺ requires C₉H₁₂N⁺ 134.0964).

Ethyl 3-phenyl-2-(piperidin-1-yl) propanoate (197)



1-(1-Ethoxy-1-oxo-3-phenylpropan-2-yl)pyridin-1-iumbromide (50.0 mg) and Raney® nickel (~ 100 mg) were dissolved in ethanol (10.0 ml) and stirred under argon. The atmosphere was replaced with hydrogen. The mixture was stirred for 16 hours and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give colourless oil that was purified *via* column chromatography on silica gel using (8:2, dichloromethane: ammonia saturated methanol) as an eluent to give the desired product as a colorless oil (26 mg, 51%); IRsol (CHCl₃, cm⁻¹) 2253, 1735, 1464, 1382, 1245, 1208; δ_{H} (400 MHz, CDCl₃) 7.35 – 7.23 (2H, m, ArH), 7.26 – 7.14 (3H, m, ArH), 4.12-4.03 (2H, m, CH₂CH₃), 3.41 (1H, dd, *J* = 9.8, 5.5 Hz, N-CH-(CO₂Et)), 3.09 (1H, dd, *J* = 13.2, 9.8 Hz, N-CH-CH_aH_bPh), 2.96 (1H, dd, *J* = 13.2, 5.5 Hz, N-CH-CH_aH_bPh), 2.70 (2H, m, CH₂-N-CH₂), 2.57 (2H, m, CH₂-N-CH₂), 1.68 – 1.16 (2H, m, CH₂-CH₂-N-CH₂-CH₂-CH₂), 1.58 (2H, m, *J* = 11.2, 5.6, 3 Hz, CH₂-CH₂-N-CH₂-CH₂-CH₂), 1.47 (2H, q, *J* = 5.6 Hz, CH₂-CH₂-N-CH₂-CH₂-CH₂), 1.15 (3H, t, *J* = 7.1 Hz, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.4 (C), 138.4 (C), 129.2 (CH), 128.2 (CH), 126.2 (CH), 70.3 (CH), 59.9 (CH₂), 51.0 (CH₂), 35.9 (CH₂), 26.4 (CH₂), 24.5 (CH₂), 14.3 (CH₃); *m/z* (HRMS-ESI+) 262.1810 (M+H requires C₁₆H₂₄NO₂⁺ 262.1802).

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Appendix

Appendix

General methods for synthesis of pyridinium salts

Various pyridinium salts with different substituent groups and with different *N*-alkyl groups were synthesized. Usually, the alkylation reactions of pyridine were achieved in ethyl acetate at 20 °C, or under reflux for pyridinium salts with electron-withdrawing groups. Figure 35 shows the pyridinium salts synthesized until now.

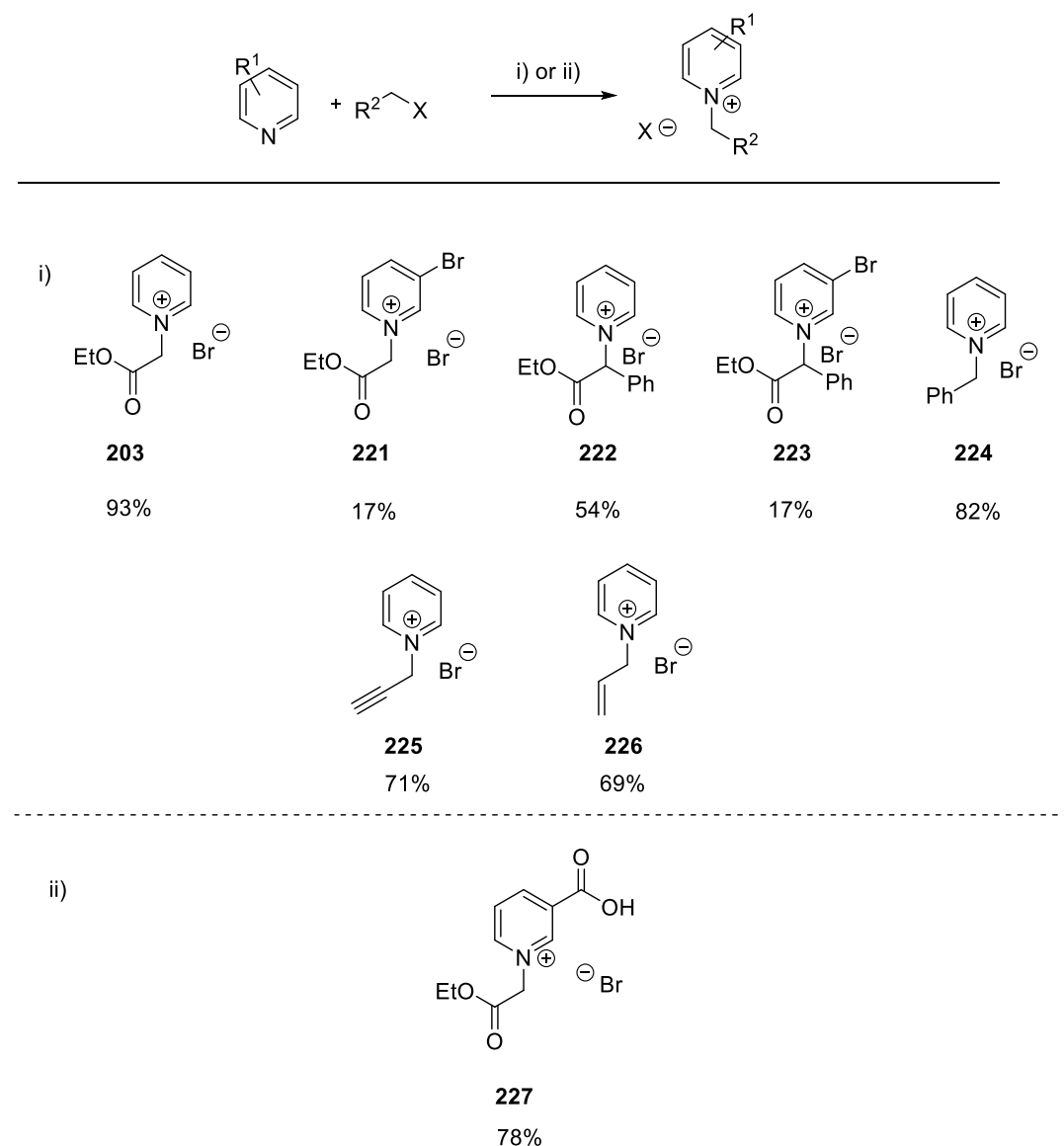
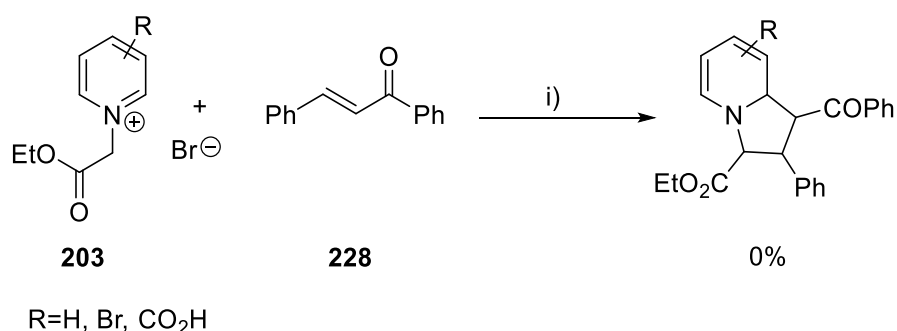


Figure 35. Reagents and conditions: i) EtOAc, 16 hr, r.t., ii) Reagents and conditions: EtOAc, 72 hr, reflux

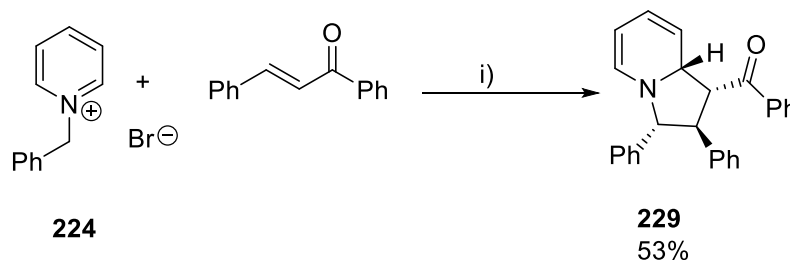
We wanted to examine the reactions of chalcone with pyridinium ylides. These gave a simple system to learn about these cycloaddition reactions. They are interesting because although studied by Katritzky in 1981, the variety of chalcone substrate that have been examined is limited.³⁰ Chalcones offer a route to low molecular weight indolizidine structures and are different to all of the other dipolarphiles studied within the group, which produce a spirocyclic products.

Pyridinium salt **203** was evaluated in the cycloaddition reaction with *E*-chalcone **228** in dichloromethane and triethylamine (Scheme 102). These convenient reaction conditions were previously developed in our group.³⁰ Unfortunately, these attempts lead to the formation of mainly cycloadducts according to ¹H NMR spectroscopy of the crude reaction mixtures. However, these cycloadducts were unstable and characterisation proved difficult. Generally, these cycloadducts could be observed by TLC during the reaction monitoring but not always after purification by column chromatography. This led to the hypothesis That cycloadducts appears to be unstable in the presence of silica gel.



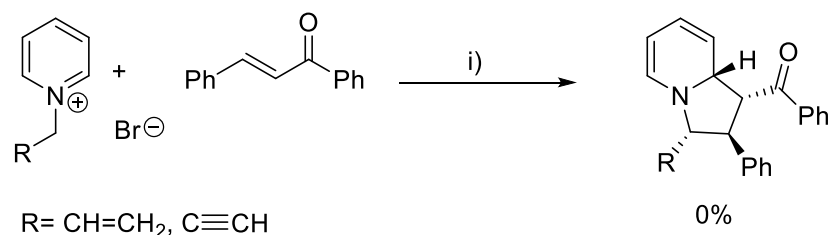
Scheme 102. Reagents and conditions: i) CH₂Cl₂, Et₃N, 20 °C, 4 h

During our investigation, we tried to use other solvents and bases with the range of pyridinium salts that we synthesised due to the poor solubility of some of our salts in the reaction solvent. So, the cycloaddition reaction between pyridinium salt **224** and chalcone with *t*-BuOK in CH₃CN was investigated first (Scheme 104). The assignment of the regiochemistry and stereochemistry was again based upon ¹H NMR techniques. Single diastereoisomer **229** was isolated in a moderate yield of 53% (Scheme 103).



Scheme 103. Reagents and conditions: i) dry CH₃CN, *t*-BuOK, 4 hr.

The separation of cycloadducts from both pyridinium salts with allyl and propargyl on the ylide stabilising group were unsuccessful. In these cases, the cycloadduct was the only product observed in the individual mass spectrum, also the cycloadduct peaks observed in the crude ¹H NMR but unfortunately, we were unable to isolate any product from these reactions (Scheme 104).



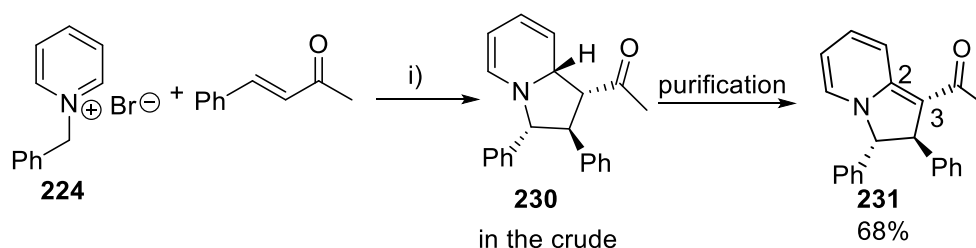
Scheme 104. Reagents and conditions: i) dry CH₃CN, *t*-BuOK, 4 hr.

It appears that these dihydropyridine cycloadducts decomposed upon work up and/or upon purification *via* column chromatography. Obtaining the material without chromatographic purification is an option to be studied, where reduction of dihydropyridine ring would increase the stability.

Alternative product

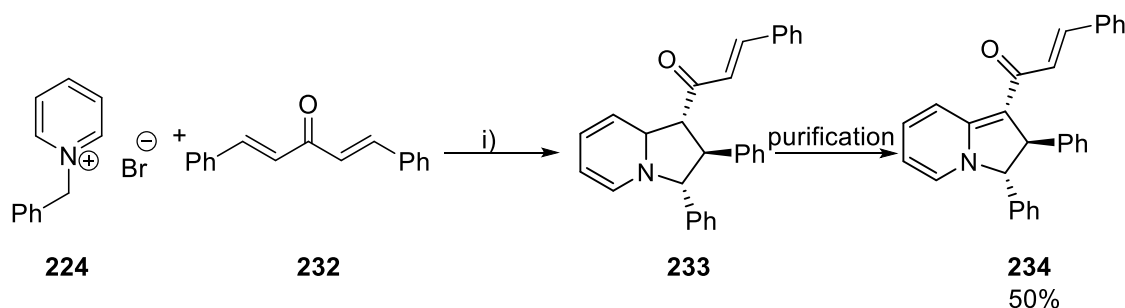
During our investigations, we observed alternative products from dihydropyridine cycloadducts, both of these products was obtained after the purification *via* column chromatography. The first compound was gained from the reaction between the pyridinium salt **224** and dibenzylidene acetone in the presence of dry CH₃CN and *t*BuOK. Analysis of the crude by the mass spectroscopy confirmed the presence of the cycloadduct product **230** (*m/z*=100%) which suggested this cycloadduct as the sole product. Analysis of this by NMR spectroscopy also seemed to confirm the presence of the cycloadduct. Unfortunately, purifying the product *via* silica gel afforded the oxidised molecule **231** as the sole product in good yield (68%). The ¹H NMR spectrum of the **231** did not show the expected dd signal corresponding to the proton in the C-2 position or the triplet signal that would correspond to the adjacent proton in the C-3 position of the cycloadduct **231** (Scheme 105). Further to this, the position of the double

bond was confirmed in the ^{13}C NMR spectrum which revealed two quaternary carbon signals in the alkene region, arising from the C-2 position ($\delta\text{C} = 154.2$) and the C-3 position ($\delta\text{C} = 119.3$).



Scheme 105. Reagents and conditions: i) dry CH_3CN , $t\text{-BuOK}$, 4 hr

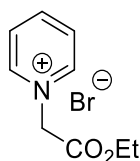
The same kind of product was observed for the reaction of dibenzal acetone **232** with pyridinium salt **224** (Scheme 106). Again, the expected cycloadduct **233** was observed in the crude but the oxidised product **234** was obtained following column chromatography in moderate yield (50%).



Scheme 106. Reagents and conditions: i) dry CH_3CN , $t\text{-BuOK}$, 4 hr

This reaction model was as a part of our training on how to deal with different reactions under different condition, for the purpose giving us more confidence in dealing with these reactions due to the lack of experience at that stage of project.

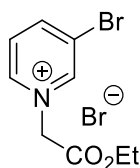
1-(2-Ethoxy-2-oxomethyl) pyridinium bromide (203)³⁰



Prepared according to general procedure A for preparation of pyridinium salts.

Colorless solid (14.5 g, 93%); m.p.138-142 °C, Lit: 135-137 °C;³⁰ IR_{Sol} (CHCl₃, cm⁻¹) 3010, 1748, 1600, 1449, 1318, 1020; NMR δ_H (400 MHz, D₂O) 8.88 - 8.81 (2H, m, ArH), 8.65 (1H, app tt, J=7.9, 1.4 Hz, ArH), 8.17-8.07 (2H, m, ArH), 5.57 (2H, s, CH₂CO₂Et), 4.30 (2H, q, J=7.2 Hz, CH₂CH₃), 1.26 (3H, t, J= 7.2 Hz, CH₂CH₃); NMR δ_C (100 MHz, D₂O) 167.2 (C), 147.8 (CH), 147.1 (CH), 128.2 (CH), 64.1 (CH₂), 61.0 (CH₂), 13.2 (CH₃); *m/z* (HRMS-ESI+) 166.0881 (M⁺ requires C₉H₁₂NO₂⁺ 166.0871).

3-Bromo-1-(2-ethoxy-2-oxomethyl) pyridinium bromide (221)⁸²

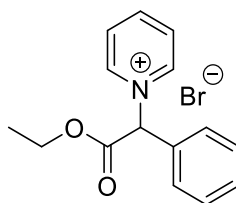


Prepared according to general procedure A for preparation of pyridinium salts.

Yellow solid (0.71 g, 17%); m.p.178-181 °C, Lit:177-179 °C;⁸² IR_{Sol} (CHCl₃, cm⁻¹) 2865, 1725, 1580,1471, 1463; NMR δ_H (300MHz, D₂O) 9.12 (1H, s, ArH), 8.87-8.81 (2H, m, ArH), 8.02 (1H, dd, J=8.4, 6.2 Hz, ArH), 5.52 (2H, s, CH₂), 4.27 (2H, q, J= 7.2 Hz, CH₂CH₃), 1.23 (3H, t, J=7.2 Hz, CH₂CH₃),

NMR δ_c (100 MHz, D₂O) 166.6 (C), 149.7 (CH), 147.0 (CH), 144.7 (CH), 128.6 (CH), 122.7 (C), 64.2 (CH₂), 61.0 (CH₂), 13.1 (CH₃); m/z (HRMS-ESI+) 243.9975 (M+ C₉H₁₁NO₂⁷⁹Br⁺ requires 243.9973), 245.9954 (M+ C₉H₁₁NO₂⁸¹Br⁺ requires 45.9952).

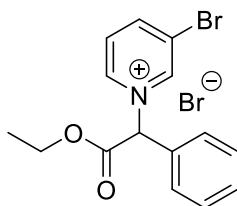
1-(2-ethoxy-2-oxo-1-phenylethyl)pyridin-1-ium bromide (222) ⁹⁴



Prepared according to general procedure A for preparation of pyridinium salts.

white powder (90.0 mg, 54%); M.p. 161-164°C, lit 161-162°C;⁹⁴ IRsol (CHCl₃, cm⁻¹); 3034, 2953, 1745, 1690, 1632, 1450, 1273; δ_H (400 MHz, MeOD) 9.05-8.88 (2H, m, *ArH*), 8.72 (1H, app t, $J = 7.7$ Hz, *ArH*), 8.19-7.85 (2H, m, *ArH*), 7.62-7.40 (5H, m, *ArH*), 7.16 (1H, s, NCH-(CO₂Et)), 4.44 (2H, q, $J = 7.2$ Hz, CH₂CH₃), 1.34 (3H, t, $J = 7.2$ Hz, CH₂CH₃); δ_c (100 MHz, CD₃OD) 166.6 (C), 147.1 (CH), 144.9 (CH), 131.2 (C), 130.7 (CH), 129.7 (CH), 129.2 (CH), 127.9 (CH), 74.6 (CH), 63.4 (CH₂), 12.8 (CH₃) m/z (HRMS-ESI+) 242.1183 (M+ requires C₁₅H₁₆NO₂+ 242.1176).

3-bromo-1-(2-ethoxy-2-oxo-1-phenylethyl)pyridin-1-iumbromide
(223)



Prepared according to general procedure A for preparation of pyridinium salts.

Hygroscopic colourless solid (49 mg, 17%); IRsol (CHCl₃, cm⁻¹); 3032, 2927, 1715, 1695, 1621, 1458, 1282, 687; ¹H NMR (400 MHz, CDCl₃) δ 8.70 (1H, app. d, *J*=2.4 Hz, N-CH-C-(Br)), 8.53 (1H, dd, *J* = 4.7, 1.4 Hz, N-CH=CH-CH), 7.82 (1H, ddd, *J* = 8.2, 2.4, 1.4 Hz, N-CH=CH-CH), 7.61 – 7.49 (2H, m, ArH), 7.44 – 7.27 (3H, m, ArH), 7.19 (1H, ddd, *J* = 8.2, 4.7, 0.8 Hz, N-CH-CH-CH), 5.36 (1H, s, N-CH(CO₂Et)), 4.33 (2H, *J*=7.1 Hz, CH₂CH₃), 1.34 (3H, t, *J*=7.1 Hz, CH₂CH₃); δ_C (100 MHz, CDCl₃) 168.2 (C), 151.0 (CH), 147.8 (CH), 138.6 (CH), 135.8 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 124.8 (CH), 120.9 (C), 62.5 (CH₂), 46.8 (CH), 13.9 (CH₃); *m/z* (HRMS-ESI+) 320.0294 (M⁺ requires C₁₅H₁₅⁷⁹BrNO⁺ 320.0281), 322.0274 (M⁺ C₁₅H₁₅⁸¹BrNO₂⁺ requires 322.0260).

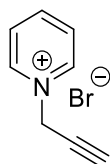
1-Benzylpyridin-1-ium bromide (224) ⁹⁵



Prepared according to general procedure A for preparation of pyridinium salts.

Colorless hygroscopic solid (13.0 g, 82%) ; IR_{Sol} (CHCl₃, cm⁻¹) 3071, 1537, 1475, 1294; δ_{H} (400 MHz, D₂O) 8.88-8.81 (2H, m, ArH), 8.49 (1H, app. tt, $J=7.84, 1.4$ Hz, ArH), 8.0-7.75 (2H, m, ArH), 7.45-7.40 (5H, m, ArH), 5.75 (2H, s, CH₂Ph); NMR δ_{C} (100 MHz, D₂O), 146.0 (CH), 144.2 (CH), 132.7 (C), 129.9 (CH), 129.9 (CH), 129.1 (CH), 128.3 (CH), 64.5 (CH₂); m/z (HRMS-ESI+) 170.0965 (M⁺ requires C₁₂H₁₂N⁺ 170.0969).

1-(Prop-2-yn-1-yl) pyridin-1-ium bromide (225) ⁹⁶

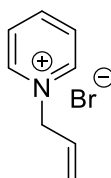


Prepared according to general procedure A for preparation of pyridinium salts.

Dark brown hygroscopic solid (9.00 g, 71%); IR_{Sol} (CHCl₃, cm⁻¹) 3303, 3052, 2255, 2128, 1484, 1036; δ_{H} (300 MHz, D₂O) 9.11-8.84 (2H, m, ArH), 8.56 (1H, app tt, $J=7.8, 1.4$ Hz, ArH), 8.21-7.91 (2H, m, ArH), 5.48 (2H, d, $J=2.6$ Hz, CH₂-C≡CH), 3.23 (1H, t, $J=2.6$ Hz, C≡CH); NMR δ_{C} (100 MHz,

D₂O), 146.6 (CH), 143.9 (CH), 128.2 (CH), 80.2 (C), 73.5 (CH), 50.6 (CH₂); *m/z* (HRMS-ESI+) 118.0602 (M⁺ requires C₈H₈N⁺ 118.0656).

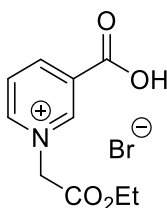
1-Allylpyridin-1-ium bromide (226) ⁹⁷



Prepared according to general procedure A for preparation of pyridinium salts.

Brown hygroscopic solid (8.80 g, 70%); IR_{Sol} (CHCl₃, cm⁻¹) 3078, 3050, 1631, 1486, 1160, 1026; δ_H (300 MHz, D₂O) 8.86-8.76 (2H, m, Hz, ArH), 8.53 (1H, app tt, *J*=7.8, 1.4 Hz, ArH), 8.04 (2H, app t, *J*=7.8 Hz, ArH), 6.11 (1H, ddt, *J*=16.7, 10.4, 6.4 Hz, CH=CH₂), 5.51 (1H, d, *J*= 16.7 Hz, CH=CH_aH_b), 5.48 (1H, d, *J*= 10.4 Hz, CH=CH_aH_b), 5.19 (2H, app. dt, *J*= 6.4, 1.3 Hz, CH₂CH); NMR δ_C (100 MHz, D₂O), 146.9 (CH), 144.2 (CH), 129.9 (CH), 128.2 (CH), 123.0 (CH₂), 63.4 (CH₂); *m/z* (HRMS-ESI+) 120.0761 (M⁺ requires C₈H₁₀N⁺ 120.0808).

3-Carboxy-1-(2-ethoxy-2-oxoethyl) pyridin-1-ium bromide(227) ⁹⁸



General procedure B for preparation of pyridinium salts was followed to give the desired product as colorless solid (4.00 g, 78%); m.p.156-159 °C Lit: m.p. 160-162 °C; 160-162 °C ⁹⁸; IR_{Sol} (CHCl₃ , cm⁻¹) 3007, 2914, 1748, 1484, 1373, 1242, 1036; NMR δ_H (300 MHz, D₂O) 9.27 (1H, s, ArH) , 8.99 (1H, d, J= 8.1 Hz, ArH), 8.91 (1H, d, J=6.22 Hz, ArH), 8.61 (1H, dd, J=8.1, 6.22 Hz, ArH), 5.57 (2H, s, CH₂(CO₂Et)) , 4.25 (2H, q, J= 7.1 Hz, CH₂CH₃), 1.21 (3H, t, J= 7.1 Hz, CH₂CH₃); NMR δ_C (100 MHz, D₂O) 166.9 (C), 165.1 (C), 147.7 (CH), 147 (CH), 146.8 (CH) , 133.8 (C), 128.1 (CH) , 64.3 (CH₂) ,61 (CH₂),13.1 (CH₃); *m/z* (HRMS-ESI+) 210.0763 (M⁺ requires C₁₀H₁₂NO₄⁺ 210.0766).

Synthesis of chalcone cycloadducts

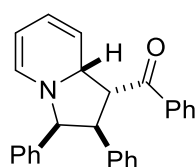
General procedure for preparation of chalcone cycloadducts from pyridinium salts.

Base (2 equiv.) was added to substituted and unsubstituted pyridinium salts (2 equiv.) in dry solvent (3 ml), under argon and the mixture stirred at room temperature for 5 mins, followed by addition of α, β-unsaturated carbonyls (1 equiv.). Water was then added and the organic layer separated, washed with water (2x), dried over Na₂SO₄, filtered and

evaporated. The products were then purified *via* flash chromatography on silica gel or recrystallisation.

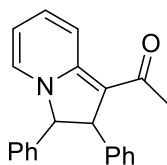
(2, 3-Diphenyl-1, 2, 3, 8a-tetrahydroindolizin-1-yl) (Phenyl)

methanone (229) ⁹⁹



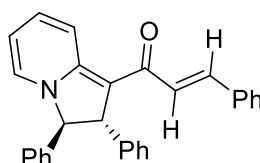
Sodium hydride 60% (0.04 g, 1.00 mmol) was added to a mixture of 1-benzylpyridin-1-ium bromide (0.25 g, 1.00 mmol) and chalcone in CH₃CN (4 mL, 1.00 mmol). The reaction was stirred at room temperature, under argon, for 70 mins. Water (2mL) was added and the resulting orange precipitate isolated by filtration and washed with water to give the desired product as orange solid which was purified *via* recrystallization with hot ethanol to give yellow solid (0.20 g, 53%); m.p.134-138°C, Lit :135-141°C;⁹⁹ IR_{sol} (CDCl₃,cm⁻¹) 3066, 22854, 1730, 1632, 1582, 1097; NMR δ_H (300 MHz, CDCl₃) 7.82-7.52 (5H, m, ArH), 7.31- 7.26 (10H, m, 2 ArH), 5.99 (1H, d, *J*=7.1 Hz, N-CH=CH-CH), 5.94-5.86 (1H, m, N-CH=CH-CH), 5.18 (1H, dt, *J*= 9.3, 2.1 Hz, NCH-CH(COPh)), 5.04 (1H, app. d, *J*=9.3 Hz, N-CH-CH(COPh)), 4.92-4.66 (3H, m, NCH=CH-CH, NCH-CHCH, NCH(Ph)), 3.71 (1H, dd, *J*=10.8, 9 Hz, NCH(Ph)-CH(Ph)); NMR δ_C (100 MHz, CDCl₃) 198.3 (C), 141.4 (C), 139 (CH), 137.8 (C), 134.7 (C), 133.2 (CH),129.4 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 124.5 (CH), 112.9 (CH), 65.1 (CH), 61.5 (CH), 56,6 (CH), 30.9 (CH); *m/z* (HRMS-ESI+) 378.1847 (M+H requires C₂₇H₂₄NO⁺ 378.1852).

1-(2, 3-Diphenyl-2,3-dihydroindolizin-1-yl) ethenone (231)



Potassium tert-butoxide (56.0 mg, 0.50 mmol) was added to 1-benzylpyridin-1-ium bromide (125 mg, 0.50 mmol) in acetonitrile (5ml), under argon and the mixture was stirred at room temperature for 5 minutes, followed by addition of benzylideneacetone (73.0 mg, 0.50 mmol). The mixture of reaction was stirred for 3 hours, water (25 ml) was added, the organic layer extracted with CH₂Cl₂ (3x 25 ml) and the organic layers combined, washed with saturated aq. NH₄Cl and dried over Na₂SO₄, filtered, the solvent was removed in vacuo then purified by column chromatography (9:1; CH₂Cl₂:MeOH /NH₃ as eluent) to give the oxidation product as an orange oil (108 mg, 68%); IR_{sol} (CDCl₃, cm⁻¹) 1710, 1636, 1564, 1488, 1382, 1313; NMR δ_H (400 MHz, CDCl₃) 8.26 (1H, d, J=9.3 Hz, NCH=CHCH), 7.50-7.18 (11H, m, 2 ArH, NCH=CH-CH), 6.92 (1H, dt, J= 6.7, 1.3 Hz, NC-CH=CH), 6.26-6.13 (1H, m, NCH=CHCH), 5.04 (1H, d, J= 4.9 Hz, NCH(Ph)-CH(Ph)), 4.30 (1H, d, J= 4.79 Hz, NCH(Ph)-CH(Ph)), 1.71 (3H, s, CH₃); NMR δ_C (100 MHz, CDCl₃) 198.4 (C), 154.2 (C), 145.1 (C), 143.4 (C), 137.9 (CH), 134.3 (CH), 129.4 (CH), 129.1 (CH), 128.8 (CH), 127.3 (CH), 127.1 (CH), 126.0 (CH), 119.3 (C), 109.8 (CH), 77.6 (CH), 56.6 (CH), 43.2 (CH), 27.8 (CH₃); *m/z* (HRMS-ESI+) 315.1478 (M+H requires C₂₂H₁₉NO⁺ 315.1623).

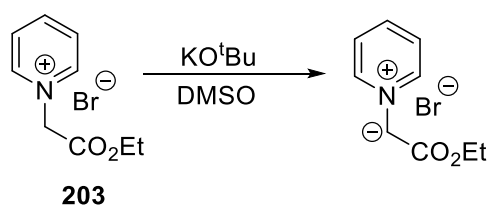
(E)-1-(2,3-Diphenyl-2, 3-dihydroindolizin-1-yl)-3-phenylprop-2-en-1-one (234)



Potassium tert-butoxide (112 mg, 1.00 mmol) was added to 1-benzylpyridin-1-ium bromide (250 mg, 1.00 mmol) in acetonitrile (5 ml), under argon and the mixture was stirred at room temperature for 5 minutes, followed by addition of di-benzalacetone (234 mg, 1.00 mmol). The mixture of reaction was stirred for 4 hours, water (25 ml) was added, the mixture extracted with CH₂Cl₂ (3x25 ml) and the organic layers combined, washed with sat aq NH₄Cl (10 mL) and dried over Na₂SO₄, filtered, and the solvent was removed in vacuo and product purified by column chromatography on silica gel using (9.5:0.5; CH₂Cl₂: MeOH/NH₃) as an eluent to give the oxidation product as an orange oil (200 mg, 50%); IR_{sol}(CDCl₃, cm⁻¹) 3098, 3074, 1682, 1633, 1608, 1589; NMR δ_H (400 MHz, CDCl₃) 8.55 (1H, app t, *J*= 9.2 Hz, NCH=CHCH), 7.50 (1H, dd, *J*= 15.5, 9.3 Hz, COCH=CHPh), 7.46-7.12 (16 H, m, 3 ArH, N-CH=CH-CH), 7.07-6.3 (1H, m, N-C-CH-CH), 6.59 (1H, dd, *J*= 22.5, 15.5 Hz, COCH=CH(Ph)), 6.26 (1H, td, *J*= 6.7, 1.4 Hz, N-C-CH-CH), 5.30 (1H, d, *J*= 5.1 Hz, NCH(Ph)-CH(Ph)), 5.15 (1H, d, *J*= 5.1 Hz, N-CH(Ph)-CH(Ph)); NMR δ_C (100 MHz, CDCl₃) 179.6 (C), 145.4 (C), 140.7 (C), 136.6 (CH), 136.5 (C), 134.7 (CH), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.4 (CH), 127.3 (CH), 127.5 (CH), 127.4 (CH), 126.9 (CH), 126.2 (CH), 120.4 (CH), 120.0 (CH), 110.8 (CH), 102.8 (C), 78.0 (CH), 55.7 (CH), 53.1 (C), 51.7 (CH); *m/z* (HRMS-ESI+) 402.1854 (M+H requires C₂₉H₂₄NO⁺ 402.1857).

Spectroscopic investigation.

As we mentioned before that Mayr *et al.* confirmed the formation of pyridinium ylides by UV-vis spectra ($\lambda_{\text{max}} = 425\text{--}453\text{ nm}$). We also investigated the same method as a reference to monitor the free ylide formation from the deprotonation of pyridinium salt **203** by using KO^tBu as a base in DMSO as a solvent (Scheme 107). We notice that the ylide began to form after the addition a portion of KO^tBu in DMSO (Figure 35).



Scheme 107. Formation of pyridinium ylide using base

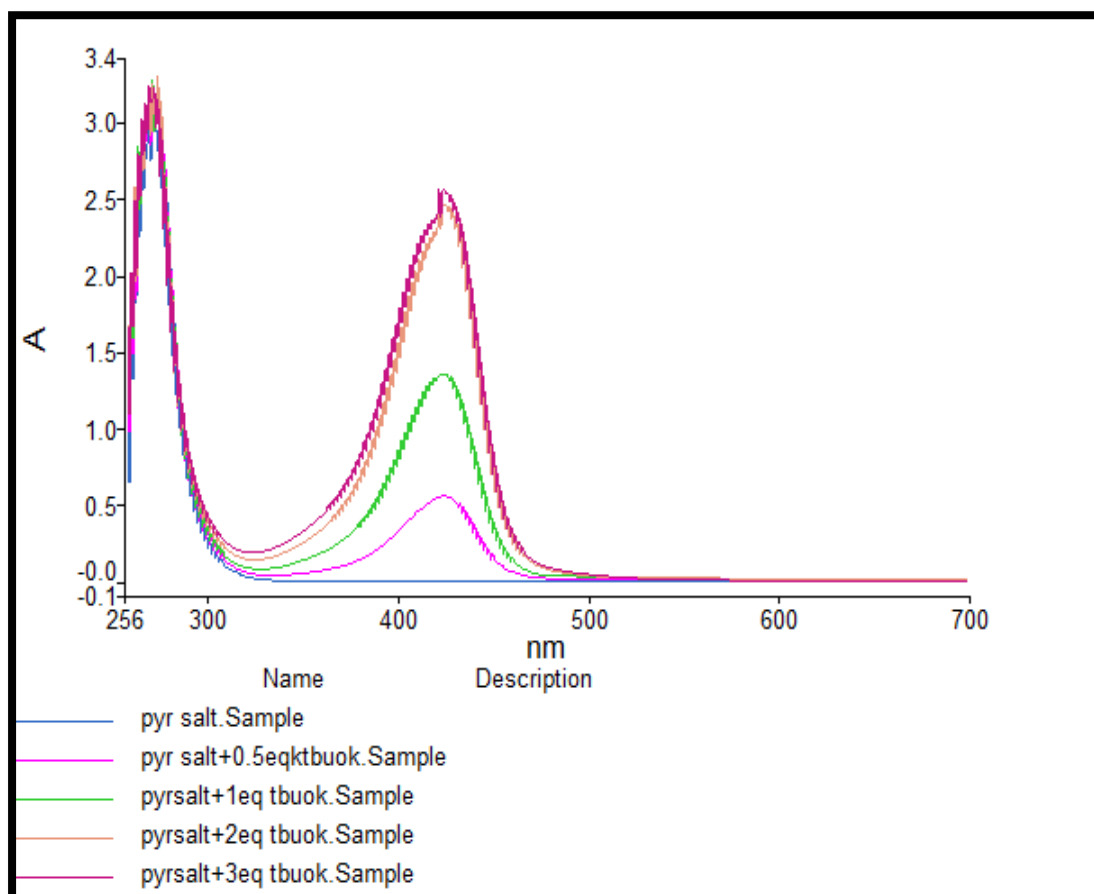
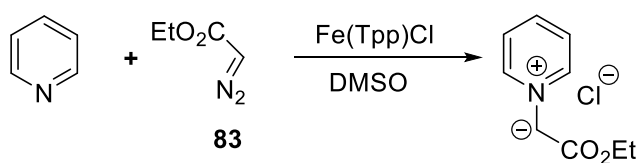


Figure 35

with this result in hand, we also monitored the catalytic reaction by UV-vis after the addition of the diazo compound **83** stepwise to pyridine in DMSO (Scheme 108) at the same concentration of the previous reaction. We also noticed the formation of the ylide during the addition (Figure 36).



Scheme 108. Formation of pyridinium ylide catalytically

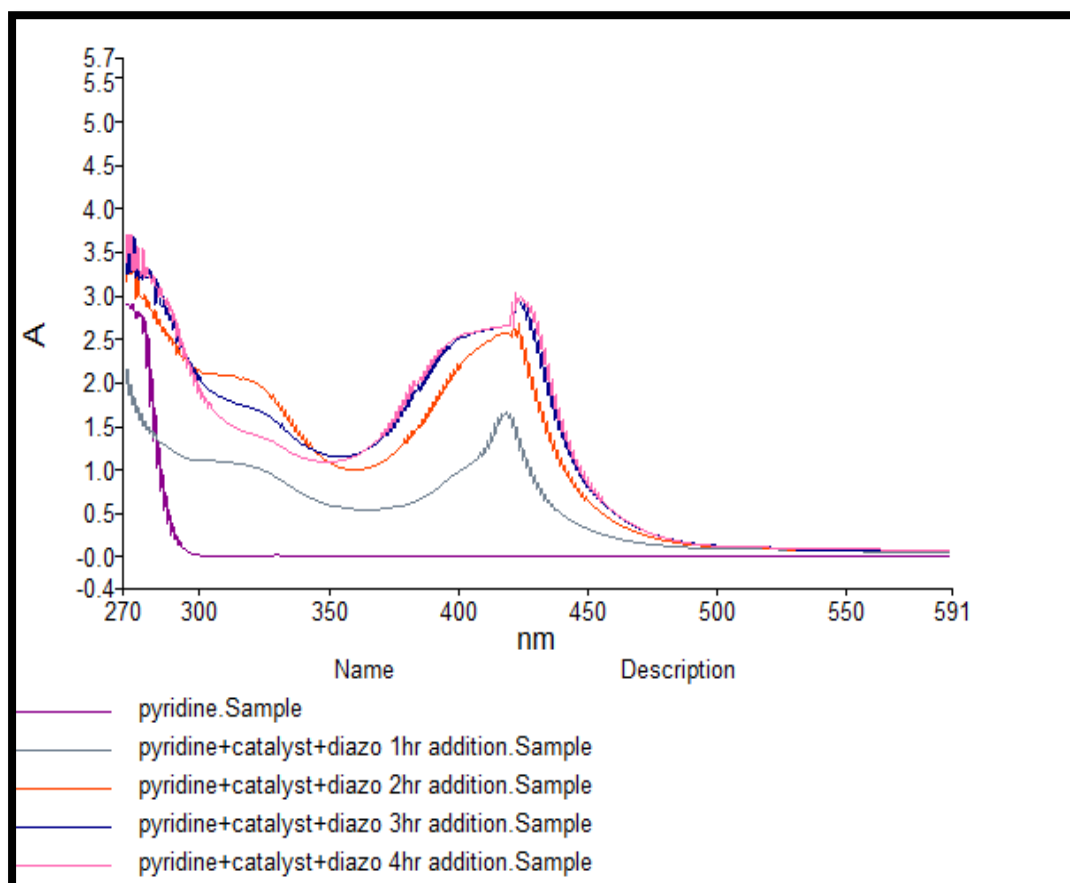


Figure 36

The spectra of the free ylide formation from the metal carbenoids showed that ylide was produced rapidly in the wavelength range 370-470 nm. Hence, the spectra of the formation of the ylide from base shows that the wavelength range 320-480 nm, this may be due to the presence of the catalyst.

RAJDLB (Compound 126)

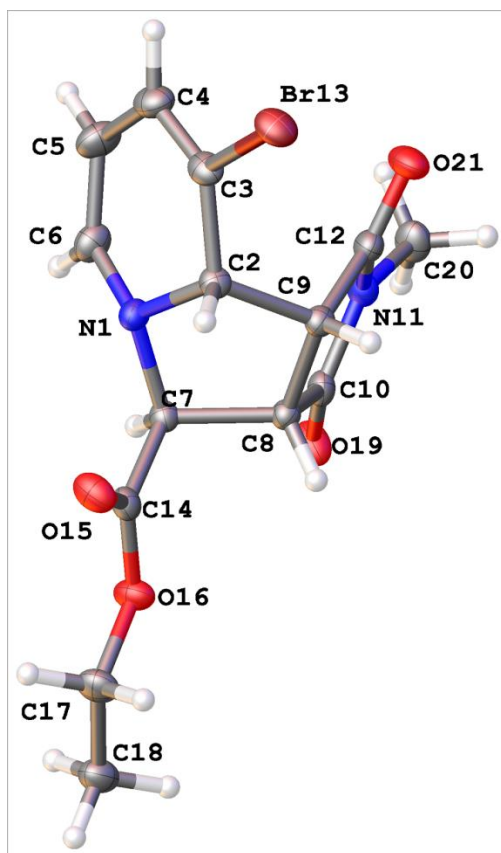


Table 1 Crystal data and structure refinement for RAJDLB.

Identification code	RAJDLB
Empirical formula	C ₁₅ H ₁₆ N ₂ O ₄ Br
Formula weight	368.21
Temperature/K	120.02(12)
Crystal system	Orthorhombic
Space group	Pbca
a/Å	10.84435(16)
b/Å	12.7352(2)
c/Å	20.6328(3)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å ³	2849.50(8)
Z	8
$\rho_{\text{calc}}/\text{cm}^3$	1.717
μ/mm^{-1}	4.133
F(000)	1496.0
Crystal size/mm ³	0.3377 × 0.0906 × 0.0534

Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/ $^{\circ}$	8.572 to 149.464
Index ranges	-13 $\leq$ h $\leq$ 13, -15 $\leq$ k $\leq$ 15, -25 $\leq$ l $\leq$ 25
Reflections collected	282072
Independent reflections	2906 [R_{int} = 0.0533, R_{sigma} = 0.0074]
Data/restraints/parameters	2906/0/192
Goodness-of-fit on F^2	1.077
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0225, wR_2 = 0.0617
Final R indexes [all data]	R_1 = 0.0227, wR_2 = 0.0619
Largest diff. peak/hole / e $\text{\AA}^{-3}$	0.35/-0.53

Experimental

Single crystals of C₁₅H₁₆N₂O₄Br [**RAJDLB**] were [**Diffusion of hexane into a solution of the compound in diethyl ether.**]. A suitable crystal was selected and [**mounted in fomblin film on a micromount**] on a **GV1000, Atlas** diffractometer. The crystal was kept at 120.02(12) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal structure determination of [RAJDLB]

Crystal Data for C₁₅H₁₆N₂O₄Br (M = 368.21 g/mol): orthorhombic, space group Pbca (no. 61), a = 10.84435(16) $\text{\AA}$, b = 12.7352(2) $\text{\AA}$, c = 20.6328(3) $\text{\AA}$, V = 2849.50(8) $\text{\AA}^3$, Z = 8, T = 120.02(12) K, $\mu(\text{CuK}\alpha)$ = 4.133 mm⁻¹, D_{calc} = 1.717 g/cm³, 282072 reflections measured ($8.572^{\circ} \leq 2\Theta \leq 149.464^{\circ}$), 2906 unique (R_{int} = 0.0533, R_{sigma} = 0.0074) which were used in all calculations. The final R_1 was 0.0225 ($I > 2\sigma(I)$) and wR_2 was 0.0619 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso

At 1.2 times of:

All C(H) groups, All C(H,H) groups

At 1.5 times of:

All C(H,H,H) groups

2.a Ternary CH refined with riding coordinates:

C7(H7), C8(H8), C9(H9), C2(H2)

2.b Secondary CH₂ refined with riding coordinates:

C17(H17A,H17B)

2.c Aromatic/amide H refined with riding coordinates:

C4(H4), C6(H6), C5(H5)

2.d Idealised Me refined as rotating group:
C20(H20A,H20B,H20C), C18(H18A,H18B,H18C)

RAJDCC (Compound 131)

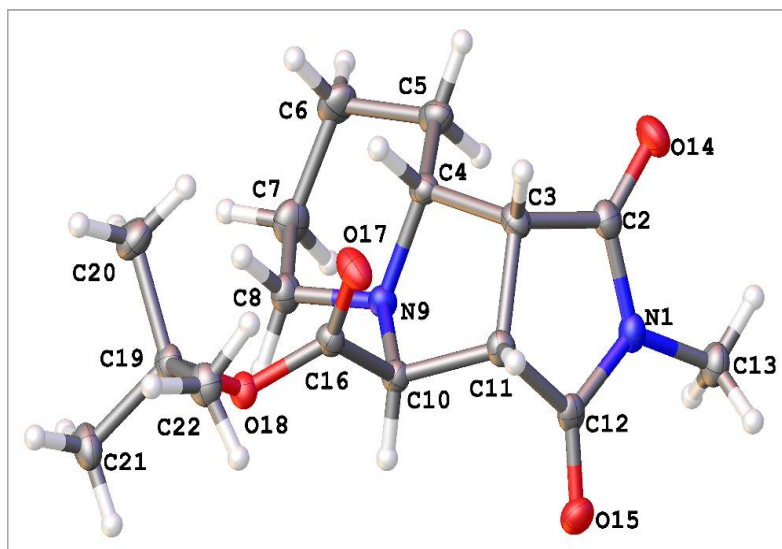


Table 1 Crystal data and structure refinement for RAJDCC.

Identification code	RAJDCC
Empirical formula	C ₁₆ H ₂₄ N ₂ O ₄
Formula weight	308.37
Temperature/K	120(2)
Crystal system	Monoclinic
Space group	P2 ₁ /n
a/Å	5.42707(15)
b/Å	13.7905(4)
c/Å	21.4372(6)
α/°	90
β/°	96.325(3)
γ/°	90
Volume/Å ³	1594.65(8)
Z	4
ρ _{calc} /cm ³	1.284
μ/mm ⁻¹	0.757
F(000)	664.0
Crystal size/mm ³	0.64 × 0.07 × 0.0589

Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/ $^{\circ}$	10.494 to 148.214
Index ranges	$-6 \leq h \leq 6$, $-15 \leq k \leq 17$, $-26 \leq l \leq 20$
Reflections collected	12159
Independent reflections	3208 [R_{int} = 0.0230, R_{sigma} = 0.0166]
Data/restraints/parameters	3208/0/203
Goodness-of-fit on F^2	1.047
Final R indexes [$I \geq 2\sigma(I)$]	R_1 = 0.0363, wR_2 = 0.0938
Final R indexes [all data]	R_1 = 0.0382, wR_2 = 0.0958
Largest diff. peak/hole / e $\text{\AA}^{-3}$	0.28/-0.21

Experimental

Single crystals of $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ [**RAJDCC**] were [**Diffusion of hexane into a solution of the compound in acetone.**]. A suitable crystal was selected and [**in fomblin film on a micromount**] on a **SuperNova, Dual, Cu at zero, Atlas** diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal structure determination of [RAJDCC]

Crystal Data for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_4$ (M = 308.37 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 5.42707(15) $\text{\AA}$, b = 13.7905(4) $\text{\AA}$, c = 21.4372(6) $\text{\AA}$, β = 96.325(3) $^{\circ}$, V = 1594.65(8) $\text{\AA}^3$, Z = 4, T = 120(2) K, $\mu(\text{CuK}\alpha)$ = 0.757 mm^{-1} , D_{calc} = 1.284 g/cm^3 , 12159 reflections measured ($10.494^{\circ} \leq 2\Theta \leq 148.214^{\circ}$), 3208 unique (R_{int} = 0.0230, R_{sigma} = 0.0166) which were used in all calculations. The final R_1 was 0.0363 ($I > 2\sigma(I)$) and wR_2 was 0.0958 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso

At 1.2 times of:

All C(H) groups, All C(H,H) groups

At 1.5 times of:

All C(H,H,H) groups

2.a Ternary CH refined with riding coordinates:

C3(H3), C4(H4), C10(H10), C11(H11)

2.b Secondary CH2 refined with riding coordinates:

C5(H5A,H5B), C6(H6A,H6B), C7(H7A,H7B), C8(H8A,H8B)

2.c Idealised Me refined as rotating group:

C13(H13A,H13B,H13C), C20(H20A,H20B,H20C), C21(H21A,H21B,H21C), C22(H22A,H22B, H22C)

RAJD CD (Compound 144)

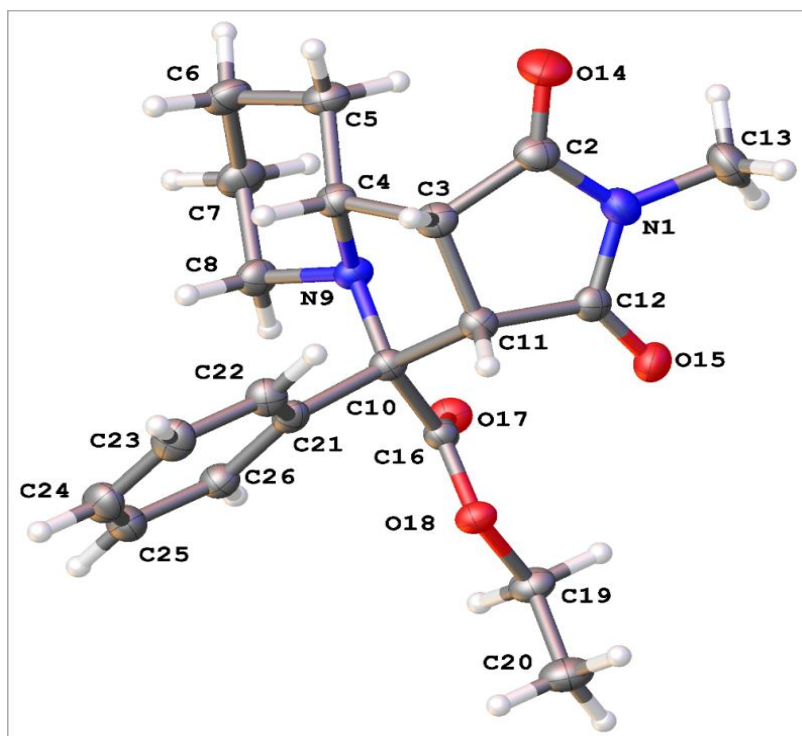


Table 1 Crystal data and structure refinement for RAJD CD.

Identification code	RAJD CD
Empirical formula	C ₂₀ H ₂₄ N ₂ O ₄
Formula weight	356.41
Temperature/K	120(2)
Crystal system	Triclinic
Space group	P-1
a/Å	10.1160(5)
b/Å	13.1850(5)
c/Å	13.9927(6)
α /°	83.580(3)
β /°	76.503(4)
γ /°	88.581(4)
Volume/Å ³	1803.42(14)
Z	4
ρ_{calc} /cm ³	1.313

μ/mm^{-1}	0.749
F(000)	760.0
Crystal size/ mm^3	$0.4742 \times 0.2528 \times 0.0514$
Radiation	$\text{CuK}\alpha$ ($\lambda = 1.54184$)
2θ range for data collection/ $^\circ$	8.87 to 148.338
Index ranges	$-12 \leq h \leq 11, -16 \leq k \leq 15, -17 \leq l \leq 17$
Reflections collected	18029
Independent reflections	7125 [$R_{\text{int}} = 0.0359, R_{\text{sigma}} = 0.0315$]
Data/restraints/parameters	7125/6/484
Goodness-of-fit on F^2	1.064
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0541, wR_2 = 0.1469$
Final R indexes [all data]	$R_1 = 0.0585, wR_2 = 0.1524$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.51/-0.33

Experimental

Single crystals of $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4$ [**RAJDCD**] were [**Diffusion of hexane into a solution of the compound in a mixture of methanol, petroleum ether and diethyl ether.**]. A suitable crystal was selected and [**in fomblin film on a micromount**] on a **SuperNova, Dual, Cu at zero, Atlas** diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.
3. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.

Crystal structure determination of [**RAJDCD**]

Crystal Data for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4$ ($M = 356.41 \text{ g/mol}$): triclinic, space group P-1 (no. 2), $a = 10.1160(5) \text{ \AA}$, $b = 13.1850(5) \text{ \AA}$, $c = 13.9927(6) \text{ \AA}$, $\alpha = 83.580(3)^\circ$, $\beta = 76.503(4)^\circ$, $\gamma = 88.581(4)^\circ$, $V = 1803.42(14) \text{ \AA}^3$, $Z = 4$, $T = 120(2) \text{ K}$, $\mu(\text{CuK}\alpha) = 0.749 \text{ mm}^{-1}$, $D_{\text{calc}} = 1.313 \text{ g/cm}^3$, 18029 reflections measured ($8.87^\circ \leq 2\theta \leq 148.338^\circ$), 7125 unique ($R_{\text{int}} = 0.0359$, $R_{\text{sigma}} = 0.0315$) which were used in all calculations. The final R_1 was 0.0541 ($I > 2\sigma(I)$) and wR_2 was 0.1524 (all data).

Refinement model description

Number of restraints - 6, number of constraints - unknown.
Details:

1. Fixed Uiso

At 1.2 times of:

All C(H) groups, All C(H,H) groups, All C(H,H,H,H) groups

At 1.5 times of:

All C(H,H,H) groups

2. Rigid body (RIGU) restrains

C49, C50, C50A

with sigma for 1-2 distances of 0.004 and sigma for 1-3 distances of 0.004

3. Others

Sof(H49C)=Sof(H49D)=Sof(C50A)=Sof(H50D)=Sof(H50E)=Sof(H50F)=1-FVAR(1)

Sof(H49A)=Sof(H49B)=Sof(C50)=Sof(H50A)=Sof(H50B)=Sof(H50C)=FVAR(1)

4.a Ternary CH refined with riding coordinates:

C3(H3), C4(H4), C11(H11), C33(H33), C34(H34), C41(H41)

4.b Secondary CH2 refined with riding coordinates:

C5(H5A,H5B), C6(H6A,H6B), C7(H7A,H7B), C8(H8A,H8B), C19(H19A,H19B), C35(H35A,H35B), C36(H36A,H36B), C37(H37A,H37B), C38(H38A,H38B), C49(H49A,H49B), C49(H49C,H49D)

4.c Aromatic/amide H refined with riding coordinates:

C22(H22), C23(H23), C24(H24), C25(H25), C26(H26), C52(H52), C53(H53), C54(H54), C55(H55), C56(H56)

4.d Idealised Me refined as rotating group:

C13(H13A,H13B,H13C), C20(H20A,H20B,H20C), C43(H43A,H43B,H43C), C50(H50A,H50B,H50C), C50A(H50D,H50E,H50F)

RAJDCG (Compound 183)

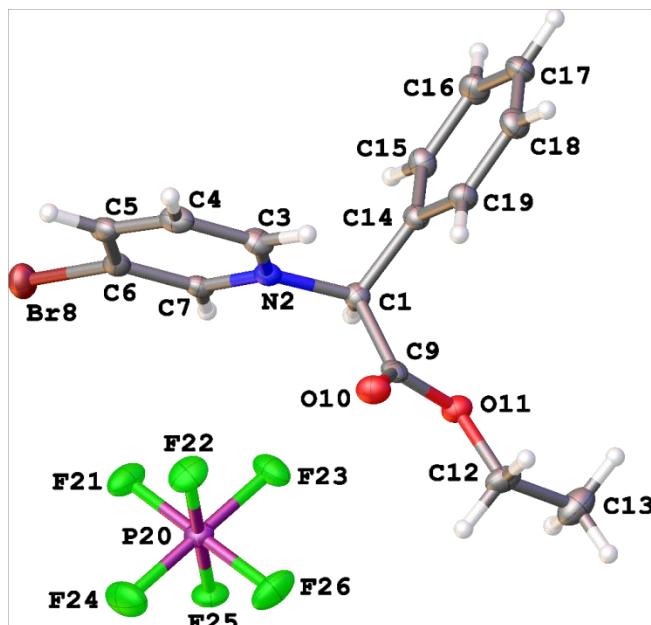


Table 1 Crystal data and structure refinement for RAJDCG.

Identification code	RAJDCG
Empirical formula	C ₁₅ H ₁₅ BrF ₆ NO ₂ P
Formula weight	466.16
Temperature/K	120(2)
Crystal system	Monoclinic
Space group	P2 ₁ /c
a/Å	10.9387(4)
b/Å	15.2336(4)
c/Å	11.4111(4)
α/°	90
β/°	113.670(5)
γ/°	90
Volume/Å ³	1741.55(12)
Z	4
ρ _{calc} /cm ³	1.778
μ/mm ⁻¹	4.779
F(000)	928.0
Crystal size/mm ³	0.478 × 0.036 × 0.016
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	8.826 to 147.51
Index ranges	-13 ≤ h ≤ 12, -17 ≤ k ≤ 18, -14 ≤ l ≤ 14

Reflections collected	13908
Independent reflections	3445 [$R_{\text{int}} = 0.0496$, $R_{\text{sigma}} = 0.0343$]
Data/restraints/parameters	3445/0/236
Goodness-of-fit on F^2	1.023
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0308$, $wR_2 = 0.0780$
Final R indexes [all data]	$R_1 = 0.0370$, $wR_2 = 0.0821$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.58/-0.36

Experimental

Single crystals of $\text{C}_{15}\text{H}_{15}\text{BrF}_6\text{NO}_2\text{P}$ [RAJDCG] were [Diffusion of hexane into a solution of the compound in a mixture of methanol, chloroform, ethanol, acetone and diethyl ether.]. A suitable crystal was selected and [mounted in fomblin film on a micromount] on a **GV1000, AtlasS2** diffractometer. The crystal was kept at 120(2) K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal structure determination of [RAJDCG]

Crystal Data for $\text{C}_{15}\text{H}_{15}\text{BrF}_6\text{NO}_2\text{P}$ ($M = 466.16 \text{ g/mol}$): monoclinic, space group $P2_1/c$ (no. 14), $a = 10.9387(4) \text{ \AA}$, $b = 15.2336(4) \text{ \AA}$, $c = 11.4111(4) \text{ \AA}$, $\beta = 113.670(5)^\circ$, $V = 1741.55(12) \text{ \AA}^3$, $Z = 4$, $T = 120(2) \text{ K}$, $\mu(\text{CuK}\alpha) = 4.779 \text{ mm}^{-1}$, $D_{\text{calc}} = 1.778 \text{ g/cm}^3$, 13908 reflections measured ($8.826^\circ \leq 2\theta \leq 147.51^\circ$), 3445 unique ($R_{\text{int}} = 0.0496$, $R_{\text{sigma}} = 0.0343$) which were used in all calculations. The final R_1 was 0.0308 ($I > 2\sigma(I)$) and wR_2 was 0.0821 (all data).

Refinement model description

Number of restraints - 0, number of constraints - unknown.

Details:

1. Fixed Uiso

At 1.2 times of:

All C(H) groups, All C(H,H) groups

At 1.5 times of:

All C(H,H,H) groups

2.a Ternary CH refined with riding coordinates:

C1(H1)

2.b Secondary CH2 refined with riding coordinates:

C12(H12A,H12B)

2.c Aromatic/amide H refined with riding coordinates:

C3(H3), C4(H4), C5(H5), C7(H7), C15(H15), C16(H16), C17(H17), C18(H18),
C19(H19)

2.d Idealised Me refined as rotating group:

C13(H13A,H13B,H13C)