CARBENOID MEDIATED SYNTHESIS OF *N*-HETEROCYCLES

NANYANG TECHNOLOGICAL UNIVERSITY

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SCHOOL OF PHYSICAL AND MATHMATICAL SCIENCES

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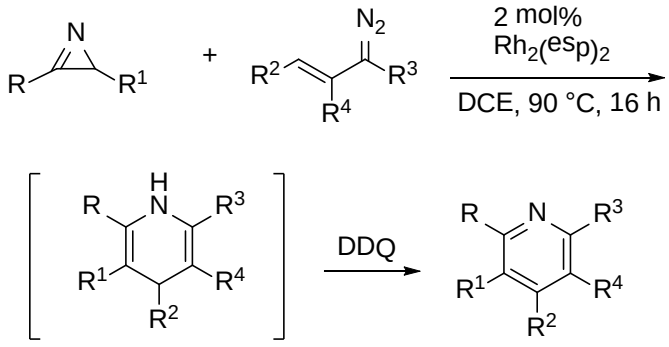
TABLE OF CONTENTS

SUMMARY

The work of this thesis has been directed towards the synthesis of *N*-heterocycles from carbenoids.

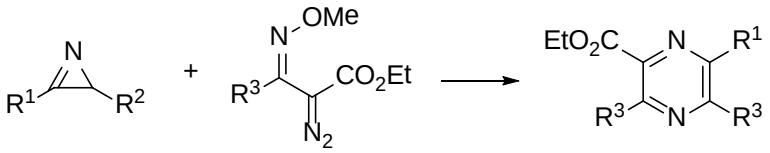
Chapter 1 gives an introduction to α-diazocarbonyl compounds, the methods of diazo synthesis and the chemistry surrounding it. It gives an insight into several transition metals that can form carbenoid from these diazo compounds and the chemistry surrounding carbenoids. A brief introduction of how carbenoids are applied to the synthesis of heterocycles to lead us into Chapter 2.

Chapter 2 aims at the synthesis of pyridines by carbenoid-mediated ring opening of 2*H*-azirines catalysed by rhodium. Firstly, we explore the importance of pyridines and its abundance in natural products and in drugs. Many methods of pyridine synthesis are known, but the application of carbenoids in pyridine synthesis was the main focus of the chapter. We also showed how we derive the idea from several ring expansion strategies to afford the highly substituted pyridines.

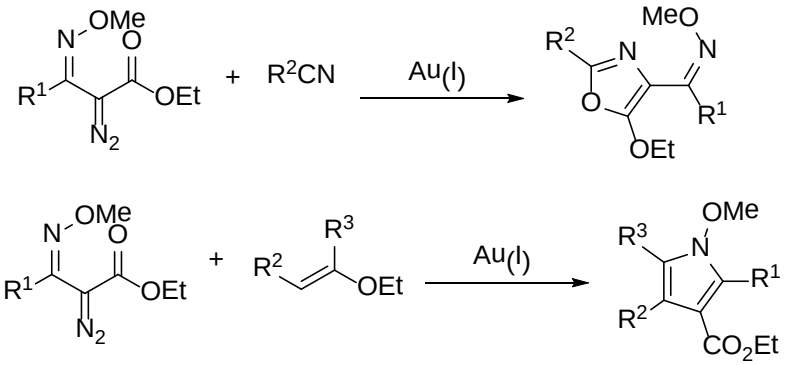


Chapter 3 is directed towards the synthesis of pyrazines from copper carbenoids using the ring expansion strategy. Herein, we did an introduction of the importance of pyrazine and the methods surrounding the synthesis. We also discussed the application of the α-diazo oxime ether chosen for our project and the methods to make it. From the known application and the properties of the α-diazo oxime ether, we

set off to develop a method to synthesize pyrazine utilizing the same ring strain strategy that was used in Chapter 2.



Chapter 4 describes the use of Au(I) catalyst to decompose *α*-diazo oxime ethers to carbenoids. Au(I) is not a common metal to form carbenoids unlike rhodium and copper. Some examples of Au(I) carbenoids were discussed which led us to obtain the idea of using Au(I). In this chapter, we developed a Au(I) mediated reaction of *α*-diazo oxime ethers with different reaction partners such as ethyl vinyl ether and benzonitrile hoping to get pyrrole and imidazole, respectively. To our disappointment, oxazoles were formed instead of imidazole when *α*-diazo oxime ethers were reacted with benzonitriles. But when α-diazo oxime ethers were reacted with ethyl vinyl ether, the pyrrole was formed.



PUBLICATIONS

- "Synthesis of Pyridines by Carbenoid-Mediated Ring Opening of 2*H*-Azirines" Nicole Shen Yen Loy, Alok Singh, Xianxiu Xu, and Cheol-Min Park, *Angew. Chem. Int. Ed.* **2013**, *52*, 1 – 6.
- "Cu(II)-Mediated Synthesis of Pyrazine from α-Diazo Oxime Ethers and 2*H*-Azirines" DOI: 10.1021/ol5034173
- "Au(I)-Mediated Synthesis of Pyrroles from α-Diazo Oxime Ethers and Ethyl Vinyl Ethers" (Manuscript in progress)

LIST OF ABBREVIATIONS

p-ABSA	4-acetamidobenzenesulfonyl azide
Ac	acetate
AIBN	2,2'−azo *bis*isobutyronitrile
Am	amyl (*n*−pentyl)
Boc	*tert*−butyloxycarbonyl
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cacld	calculated
Cat.	catalytic
Cbz	benzyloxycarbonyl
m−CPBA	*meta*−chloroperbenzoic acid
DBU	1,8−diazabicyclo[5.4.0]undec−7−ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3−dichloro−5,6−dicyano−1,4−benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4−dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography

HRMS	high−resolution mass spectrometry
HPLC	high performance liquid chromatography
IBX	*o*−iodoxybenzoic acid
IPA	isopropyl alcohol
^{i}Pr	isopropyl
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	*N*−bromosuccinimide
OAc	acetoxy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
SET	single electron transfer
p−TsOH	*p*−toluenesulfonic acid
TBAB	tetra−*n*−butylammonium bromide
^{t}Bu	tert-butyl
TEA	triethylamine
TLC	thin layer chromatography
THF	tetrahydrofuran
α	alpha
β	beta

γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1 General Introduction

1.1 Overview of diazo compounds in general

Diazo compounds are reactive intermediates and have been investigated extensively for their reactivity as well as their utility in organic synthesis.[1] Diazo compounds generate a short-lived metal carbene in the presence of a metal and can undergo a wide range of chemo-, regio-, and stereoselective reactions. In this sense, diazo compounds are considered as synthetic equivalents to carbocations. Their stability depends on the electronic character of the substituents at the diazo carbon. Some of the unstable ones are diazo alkanes. As seen from the resonance structures, the anion is not stabilised and the N_2 group can be easily eliminated as gas (Figure 1-1).

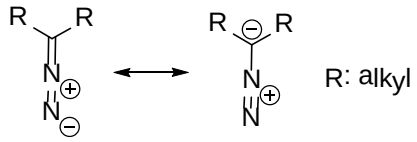


Figure 1-1. Resonance structure of alkyl diazo compound

However, if there are electron-withdrawing groups or carbonyl functionality α to the diazo group, it helps in the stabilisation of the anion by delocalising the negative charge to the carbonyl group (Figure 1-2). Therefore, it makes it stable for use in organic synthesis as a precursor.

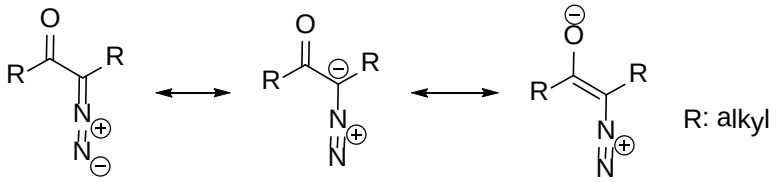


Figure 1-2. Resonance structure of α-keto diazo compound

Diazo compounds are precursors to carbenes as they are readily decomposed photochemically or thermally, or by transition metals to form metal carbenoids with the generation of N_2 gas. Their reactivity and electronic effect differ from diazo compounds and they are largely dependent on the metals that generate the carbenoids. Because of the difference in electronic effect, their reactivity differs and they can undergo a wide variety of reactions which will be discussed later (Figure 1-3).

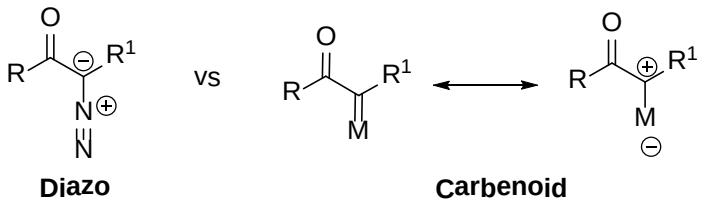
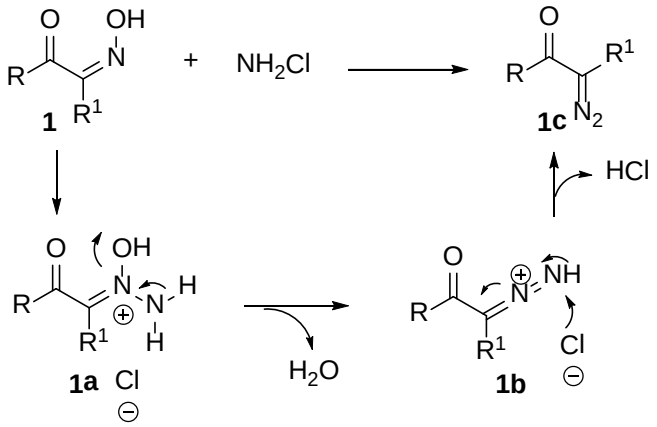


Figure 1-3. Electronic difference between diazo and metal carbenoid compounds

1.1.1 Methods for the synthesis of diazo compounds

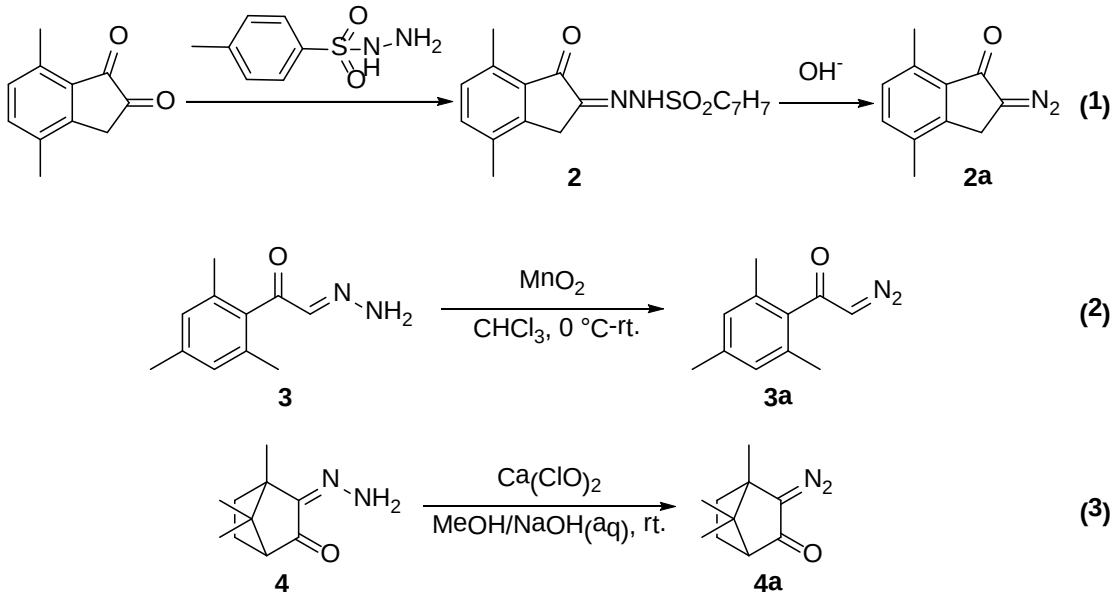
Due to the usefulness of diazo compounds as a precursor for organic synthesis, chemists have long been interested in methods to synthesize them.

The Forster reaction[2] is of the earliest method for the synthesis of alkyl diazoketones. This reaction is the synthesis of alkyl diazoketones from α-oximinoketones and chloramine. There are two plausible mechanisms to explain the reaction. First, nucleophilic attack of the oxime **1** on the chloramine displaces the chloro group to form a hydrazine intermediate **1a** and elimination of water gives the diazo compound **1c**. Another mechanism similar to the Michael addition, is the nucleophilic attack of the chloramine to the oximinoketone **1b**. And with elimination of water and HCl, it gives the desired diazo compound **1c** (Scheme 1-1).



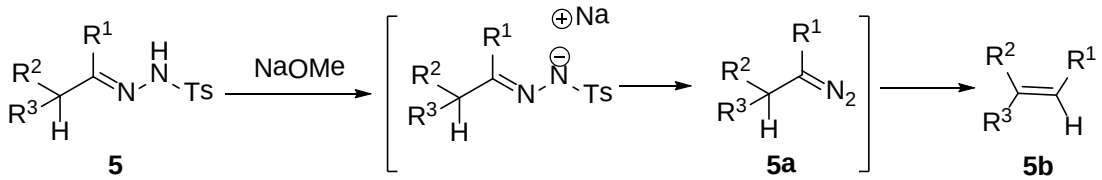
Scheme 1-1. Forster reaction for the synthesis of alkyl diazo compounds

Another method of diazo synthesis involves the oxidation of monohydrazones of α-keto aldehydes or α-diketones, which has long been known. The usual oxidising agent would be mercuric acetamide or mercuric trifluroacetate. However due to the toxicity of the mercuric compounds, three new methods were introduced; α-diazo ketones were prepared (1) by the action of sodium hydroxide on the monotosylhydrazones of α-diketones. The hydrazone **2** undergoes a nucleophilic attack by NaOH to form diazo **2a**. (2) Oxidation of hydrazones by activated manganese dioxide in chloform solution.[3] The hydrazone **3** undergoes oxidation to form diazo **3a** from MnO_2. (3) Oxidation of the corresponding hydrazones **4** in methanolic solution containing sodium hydroxide with calcium hypochlorite provides the diazo **4a** (Scheme 1-2).[3]



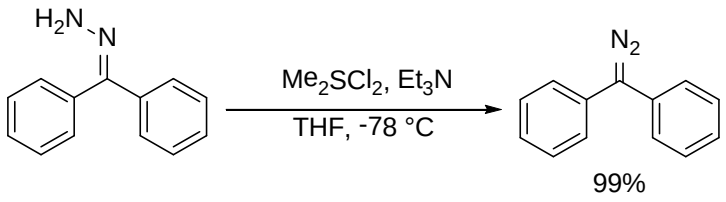
Scheme 1-2. Oxidation of hydrazone

Another classical method is the Bamford-Stevens reaction.[4] In this reaction, the diazo is also derived from hydrazones **5**. The diazo **5a** is formed in situ by nucleophilic attack of the base with H-shift to give the alkene **5b**. However, this reaction is highly dependent on the nature of the solvent after the diazo formation to provide the alkene (Scheme 1-3).



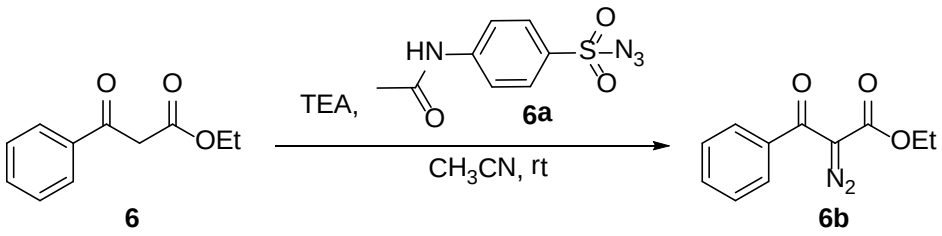
Scheme 1-3. The Bamford-Stevens reaction

More recently, diazoalkanes is synthesized from hydrazone by the Swern oxidation. This is a metal-free alternative from the previous methods using the Swern reagent generated in situ from DMSO and oxalyl chloride in the presence of triethylamine (Scheme 1-4).[5]



Scheme 1-4. Synthesis of diazo compounds by Swern oxidation

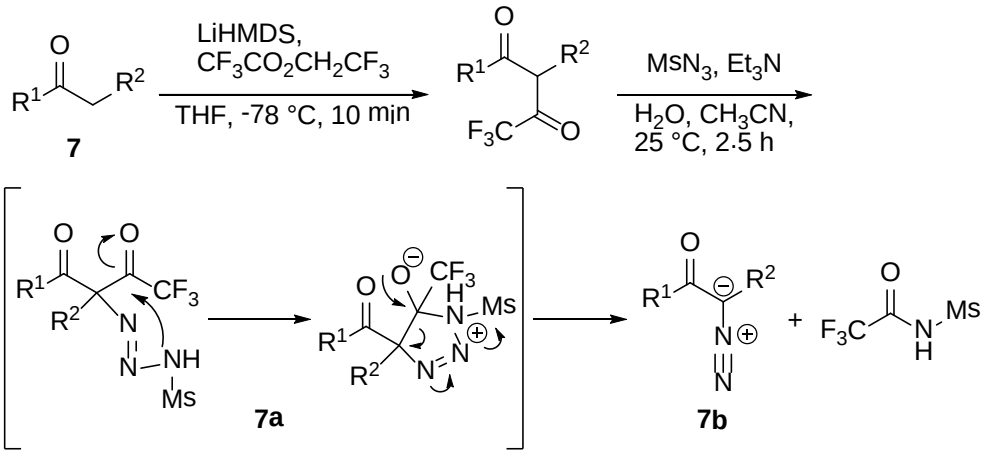
For diazo compounds with electron withdrawing substituents or carbonyl functionality α to the diazo group, the most common method is the use of diazo transfer reagents such as *p*-toluenesulfonylazide.[6] However, the latter is very nonpolar and is often inseparable with the diazo compound which poses as a problem. Thus, other azides such as *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) have emerged as a better diazo transfer reagent as they are more polar and it makes separation easier. This method is only applicable on methylene activated compounds bearing two strong acceptor substituents such as acyl, cyano and nitro.[7] The diazo moiety **6b** can be easily prepared from β-keto ester **6** and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) **6a** with triethylamine (TEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or pyridine as the base (Scheme 1-5).



Scheme 1-5. Example of a diazo compound with an electron-withdrawing group

However, this method does not extend to (diazomethyl)ketone and α-diazocarboxylate deriavatives. These substrates must first be activated by the introduction of a temporary electron-withdrawing group which would be removed during the diazo transfer. This is also known as the "deformylative diazo transfer" strategy in which the ketone **7** is first formylated by the Claisen condensation and then

treated with a sulfonyl azide reagent such as methanesulfonyl azide or *p*-acetamidobenzenesulfonyl azide (*p*-ABSA). The intermediate **7a** which forms under these conditions eliminates the tosylformamide to generate the desired *α*-diazoketone **7b** (Scheme 1-6).[8]

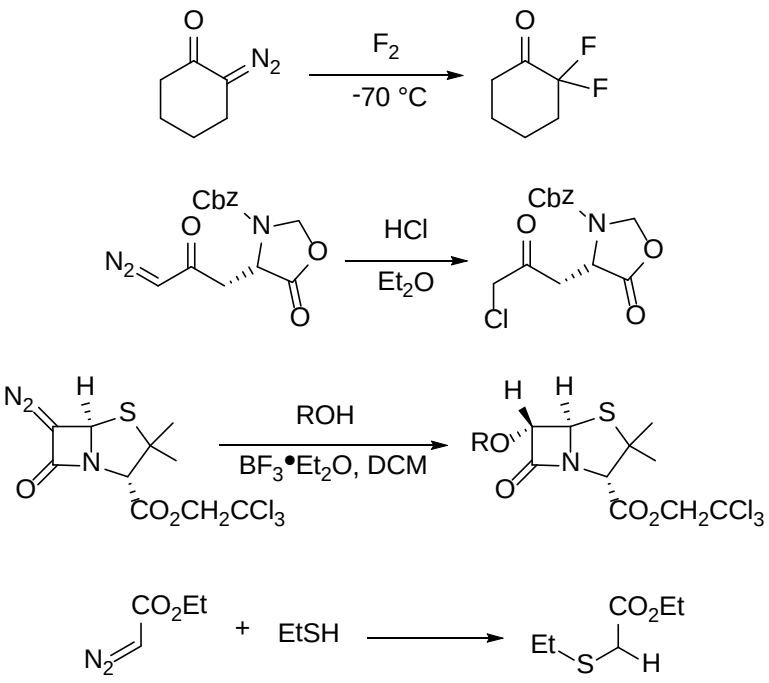


Scheme 1-6. Deformylative diazo transfer strategy.

1.2 Applications of diazo compounds in organic synthesis

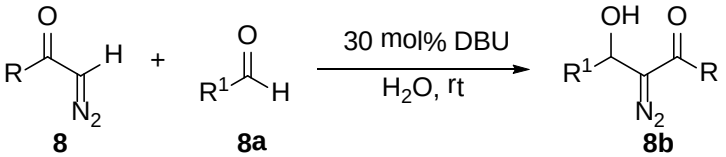
In recent years, much attention has been given to diazo compounds bearing electron-withdrawing substituent such as *α*-diazocarbonyl compounds due to their stability as compared to the alkyl diazo compounds. Their versatility in chemical transformation makes them an important precursor in organic synthesis. Hence, the application of *α*-diazocarbonyl compounds in organic synthesis will be discussed in this chapter.

α-Diazocarbonyl compounds have been long known to undergo *α*, *α*-substituitions where the product is a result of insertion reactions.[1a] The *α*-diazocarbonyl compound undergoes an electrophilic attack on halogens, hydrogen halides and compounds bearing the O-H group, Si-H, S-H, N-H with expulsion of N_2 gas. Some examples of such reactions are shown briefly in Scheme 1-7.



Scheme 1-7. Examples of α,α-substituition insertion reactions on diazo compounds

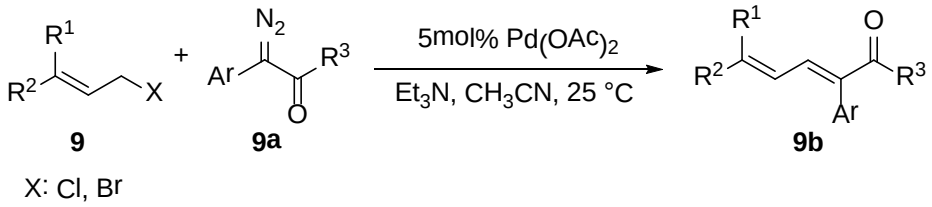
Besides being able to undergo *α,α*-substituitions reactions, more recent examples have shown that α-diazocarbonyl compounds can also undergo nucleophlic addition.[1b] In an example, Jianbo Wang and co-workers have demonstrated the nucleophilic addition of acyl diazomethanes **8** to aldehydes **8a** at room temperature with a catalytic amount of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in water to give the alcohol **8b**. (Scheme 1-8)[9]



Scheme 1-8. Nucleophilic addition of diazo compounds to an aldehyde

Building upon this concept of diazo compounds being a nucleophile, they decided to employ α-diazocarbonyl compounds as nucleophiles in the reaction of π-allylic palladium complexes since these π-allylic palladium complexes are electrophilic in nature. Thus in this example, they developed a palladium-catalyzed

reaction of allylic halide **9** with aryl diazoacetates **9a**. The reaction resulted in the generation of carbon–carbon double bonds yielding 1,3-diene derivatives **9b** as the product (Scheme 1-9).[10]



Scheme 1-9. Nucleophilic addition to Pd complexes

1.3 Metal carbenoids from α-diazocarbonyl compounds

Unlike *α*-diazocarbonyl compounds, metal carbenoids generated from *α*-diazocarbonyl compounds possess a different reactivity. Usually, the metal generates the carbenoid with expulsion of N_2 gas, hence forming an electron deficient carbenoid carbon centre where nucleophilic substitution takes place by electron-rich compounds (Figure 1-4).

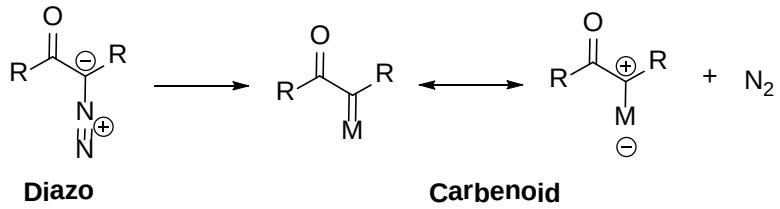


Figure 1-4. Metal generated carbenoids from diazocarbonyl compounds

A metal carbenoid is a carbene stabilised by a metal. It is structurally related to singlet carbenes and possess similar reactivity. The lone pair on the carbon provides a strong σ bond to the metal. The *d* electrons to *p* orbital on carbon provide a weak~moderate π bond, yet maintaining its electrophilicity. The metal binds to the carbene through strong π-acceptor interactions and weak back donation interaction which largely controls the reactivity of the diazo compounds (Figure 1-5).

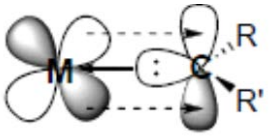


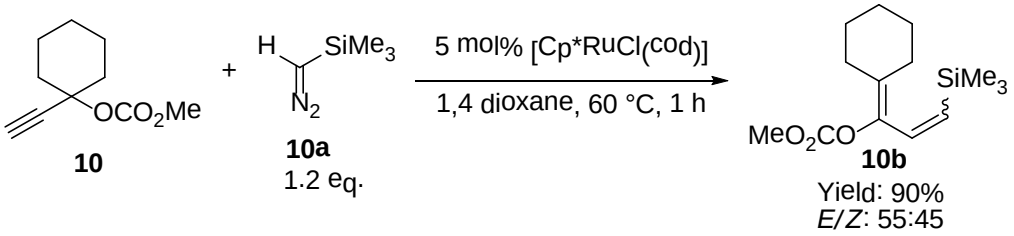
Figure 1-5. Electronic figure of a metal carbenoid

1.3.1 Transition metals that generate metal carbenoids

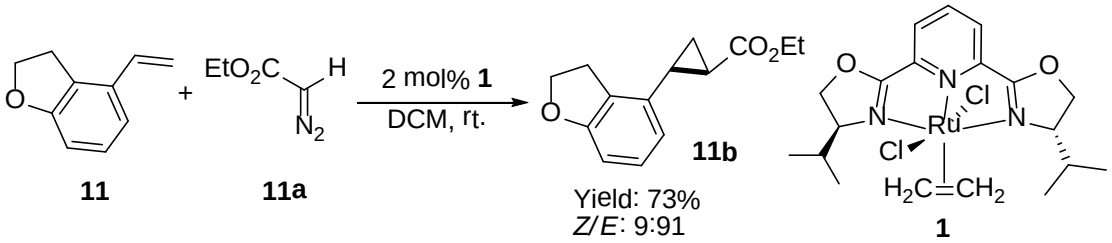
There are several transition metals that could generate metal carbenoids. The most common ones are rhodium and copper which will be discussed throughout the chapter. However there are also examples with gold, palladium, iridium, cobalt and ruthenium which are not widely explored. Each metal has a strong influence on the carbenoid carbon centre, altering the properties to which reactions could take place, thus leading to unique transformations.

Ruthenium is explored in this field because it is cheaper than rhodium and it is a metal that can form a diversity of complexes due to a larger number of oxidation states and posseses rich coordination chemistry. Ruthenium also has the ability to participate in the formation of 1,3-dienes by ene-yne, ring-closing or cross-metathesis reactions.[11] With this knowledge, ruthenium was explored to combine both the ability of cross-metathesis as well as the ability to activate diazo compounds. It was found that indeed, the precatalyst could react with diazo compounds to form ruthenium–carbene species that were capable of activating triple bonds. Herein, Moulin reported the addition of diazo **10** to propargylic carbonates **10a** in the presence of the Ru catalyst to give conjugated dienyl carbonates **10b** (Scheme 1-10).[12] Like rhodium, ruthenium can also undergo enantioselective cyclopropanation with chiral ligands.[13] Ruthenium(II) complexes with multidentate chelating ligands have been prepared for controlling the enantioselectivity of carbenoid cyclopropanation reactions. In Scheme

1-11, the alkene **11** reacts with diazo **11a** in the presence of a chiral Ru catalyst to give the cyclopropane **11b** with good enantioselectivity (Scheme 1-11).

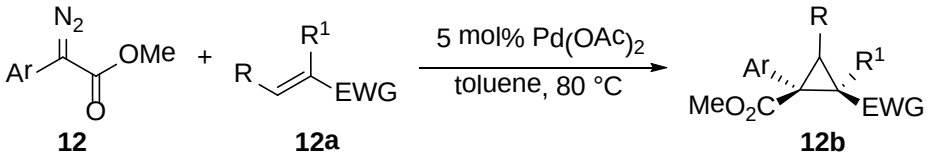


Scheme 1-10. Ruthenium catalysed carbenoid generation and cross metathesis



Scheme 1-11. Enantioselective cyclopropanation by chiral Ru catalyst

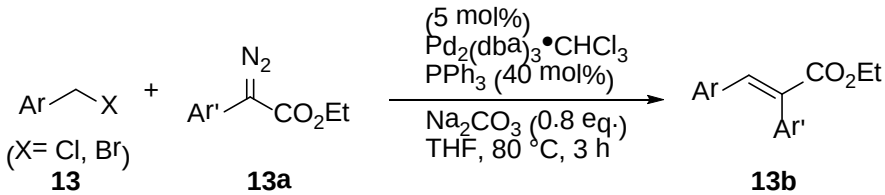
Another example like ruthenium is the palladium metal. It has been known to be the most versatile catalyst in cross-coupling reactions however, it was recently discovered that it can generate Pd-carbene species.[14] Although it is less efficient than rhodium and copper, Pd-carbene can undergo migratory insertion and cyclopropanation. Pd complexes can also catalyse the cross coupling with diazo as part of the synthesis to make a variety of diazo compounds.[15] In Scheme 1-12, $Pd(OAc)_2$ forms the metal carbenoid with the diazo keto ester **12** which reacts with the alkene **12a** to form the cyclopropane **12b** in good yields.[16] In Scheme 1-13, Chan and co-workers describe a stereoselective Pd-catalysed cross coupling of benzyl bromides **13** with α-aryldiazoesters **13a** to form diarylacrylates **13b** through migratory insertion reaction (Scheme 1-13).[17] Besides these reactions, Pd-catalysed cross coupling reaction could also be used in the synthesis of diazo deriavatives (Scheme 1-14).



R, R^1 = H, Me, Ph
EWG= CHO, CO_2R, $C(O)NEt_2$, CN

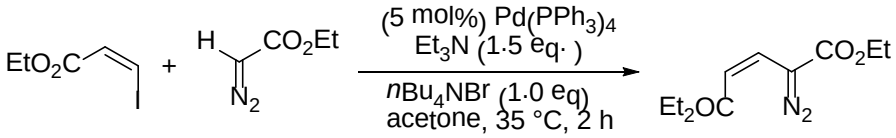
yield up to 86%
cis:trans > 95:5

Scheme 1-12. Pd catalysed cyclopropanation



18 examples
20-92% yield

Scheme 1-13. Pd catalysed benzyl migratory insertion

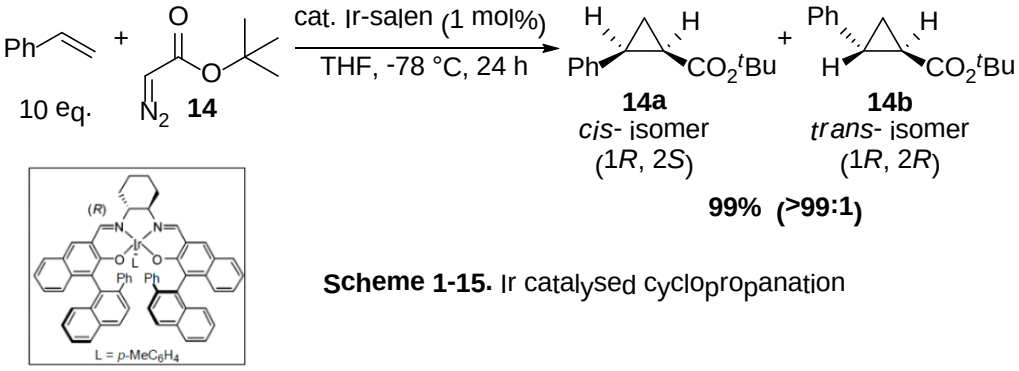


86%

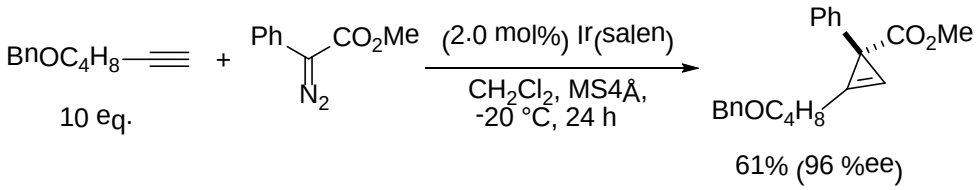
Scheme 1-14. Pd catalysed cross-coupling with diazo compounds

Iridium is another metal that is not widely known in the metal carbenoid formation. However, recently there are a few reports on iridium as a catalyst to generate metal carbenoids. Katsuki and co-workers found that the Ir-salen complex was a good catalyst for *cis*-enantioselective cyclopropanation, cyclopropenation, C-H insertion and Si-H insertion. In an example, an asymmetric cyclopropanation is shown by styrene and *tert*-butyl α-diazoacetate **14** in tetrahydrofuran.[18] It is noteworthy to say that the Ir-salen complex has overcome the challenge of *cis*-selective asymmetric cyclopropanation of conjugated olefins and non-activated olefins that other metals have not achieved so far (Scheme 1-15). Likewise when the olefin is replaced by an alkyne, cyclopropenation would occur and the respective cyclopropene was obtained (Scheme 1-16).[19] In Scheme 1-17, Katsuki found that the Ir-complexes could also take part in carbenoid insertion into the C-H bond at the α-position of tetrahydrofuran

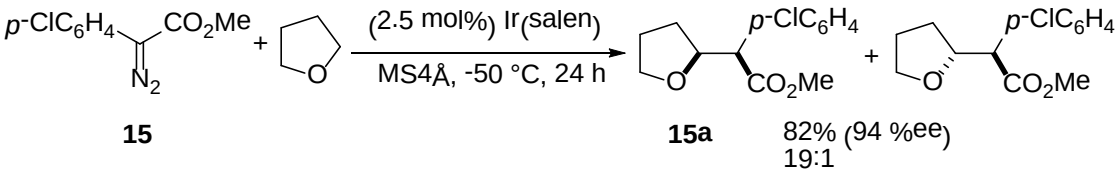
and at the allylic carbon by using various *α*-diazoacetate **15** to give tetrahydrofuran derivatives **15a**.[20] Besides the use of the Ir complex in the reactions mentioned, they also found that Ir complex can assist in Si-H insertion of diazoacetate **16a** to dimethylphenylsilane **16** to give the inserted product **16b** (Scheme 1-18).[21]



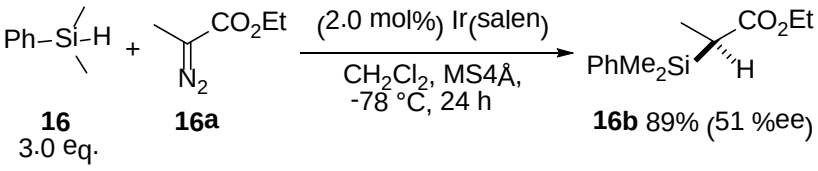
Scheme 1-15. Ir catalysed cyclopropanation



Scheme 1-16. Ir catalysed enantioselective cyclopropenation



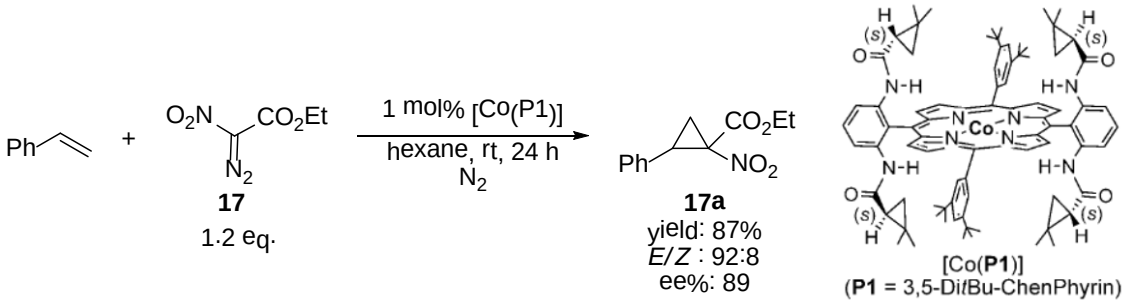
Scheme 1-17. Ir C-H insertion into THF



Scheme 1-18. Si-H insertion with α-alkyl-α-diazoacetate

Another uncommon metal that is used in carbenoid chemistry is cobalt. In this example, cobalt(II) D2-symmetric chiral porphyrins [Co(Por)] with tunable electronic, steric, and chiral environments became a new class of effective catalysts for various asymmetric cyclopropanation reactions with acceptor/acceptor-substituted diazo

reagents. Herein, Zhang reported the [Co(Por)] cyclopropanation of styrene with ethyl α-nitrodiazoacetates **17** to give the cyclopropane **17a** (Scheme 1-18).[22]



Scheme 1-18. Cobalt catalysed enantioselective cyclopropanation

Of all the transition metals discussed, gold has gained the most success even though it is not commonly used in diazo chemistry until recently. Unlike the other metals discussed, gold itself without the diazo precursor can form the metal carbenoid species as an intermediate. The gold catalyst activates the alkyne **18** by coordinating to the π-system, changing the properties of the alkyne to make it more electrophilic for nucleophilic attack. Then an O or N nucleophile does an anti-nucleophilic addition to obtain the gold intermediate **18a** and under acidic conditions, the alkene **18b** is formed (Figure 1-6).

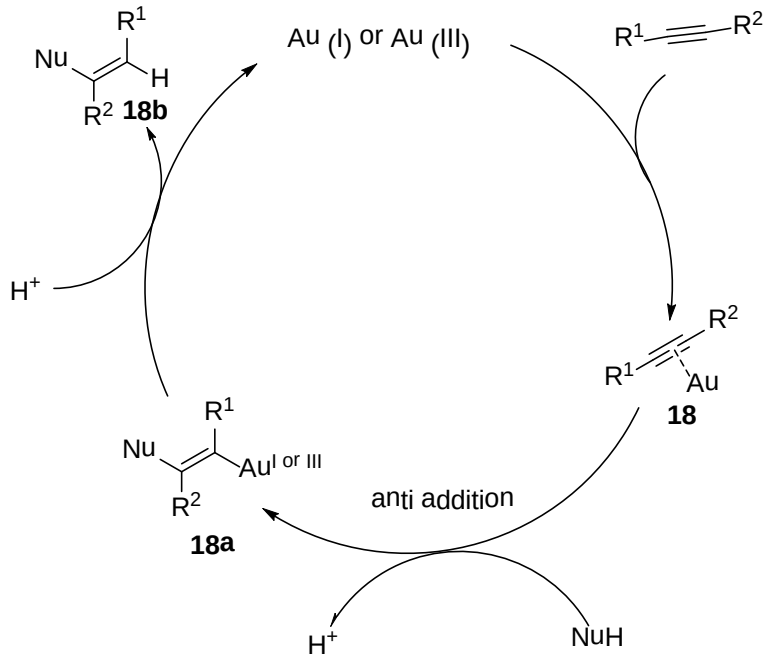
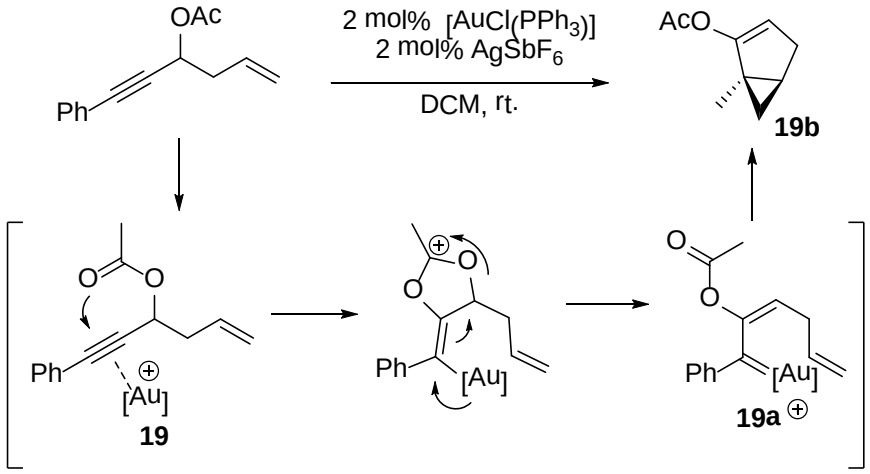


Figure 1-6. General mechanism for internal gold carbenoid

Most examples recently published are like the ones shown in Scheme 1-19,[23] the ester group attacks the gold activated alkyne **19** and undergoes rearrangement to form the metal carbenoid intermediate **19a** which then undergoes ring closing by the cyclopropanation to form the product **19b**.[24]



Scheme 1-19. Intramolecular reaction from Au carbenoid.

1.4 Reactions with metal carbenoids

Transition metal-mediated decomposition of diazo compounds leads to the formation of metal carbenoids, which display various interesting reactivities. The most common catalysts for the decomposition of diazo compounds to metal carbenoids are transition metal complexes, such as Rh, Cu complexes. The activity of transition metal complexes depends on coordinative unsaturation at metal center, which allows them to react as "electrophiles" for diazo compounds (Figure 1-7).[25]

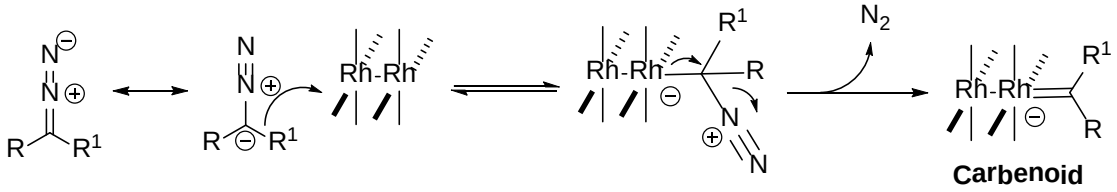


Figure 1-7. Mechanism of Rh-carbenoid formation

Metal carbenoids can take part in various transformations such as cyclopropanation, insertion reactions, cyclopropenation and cycloaddition reactions via ylides.[26] Among transition metals known to generate metal carbenoids, catalysts based on rhodium and copper are the most widely developed (Figure 1-8).

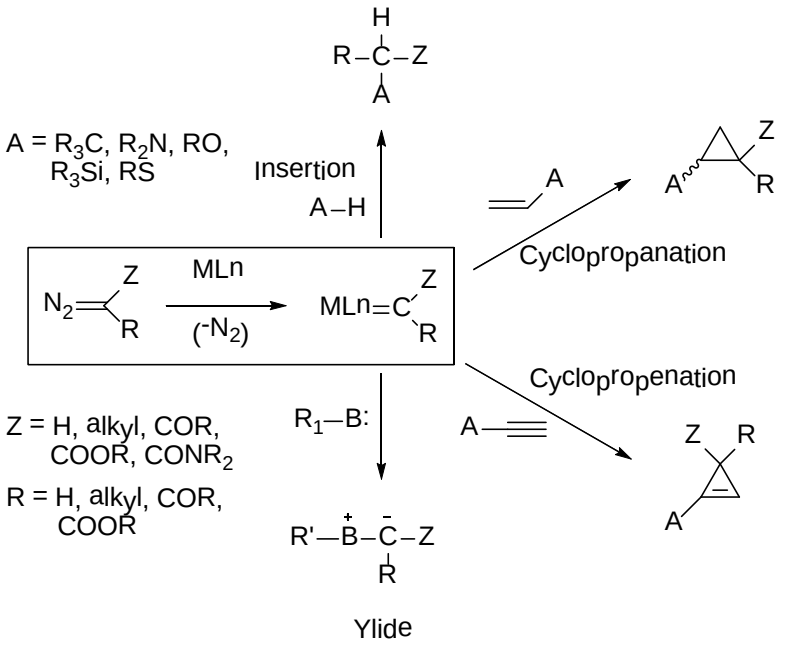
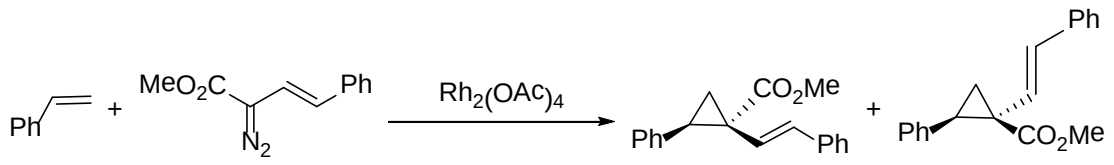


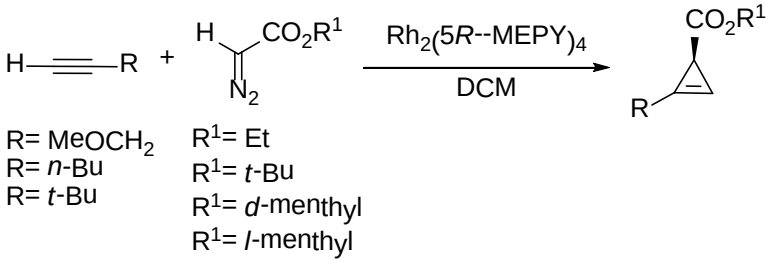
Figure 1-8. Diverse reactivity of metal carbenoids

1.4.1 Cyclopropanation and Cyclopropenation

Due to the frequent occurrence of cyclopropanes in natural products, methods for their preparation have received much attention. Reaction of metal carbenoids with alkenes, provides a powerful means to synthesize cyclopropanes. Among many examples, intermolecular cyclopropanation[27] is described below. Davies and co-workers reported an cyclopropanation of styrene and vinyl diazo compound catalyzed by rhodium acetate (Scheme 1-20). Introduction of chiral ligands on the rhodium enables asymmetric synthesis of cyclopropenes by reacting with alkynes (Scheme 1-21).[28]



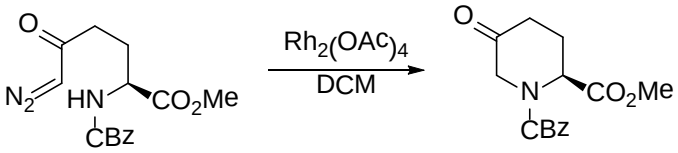
Scheme 1-20. Intermolecular cyclopropanation with Rh catalyst.



Scheme 1-21. Intermolecular cyclopropenation with chiral Rh catalyst

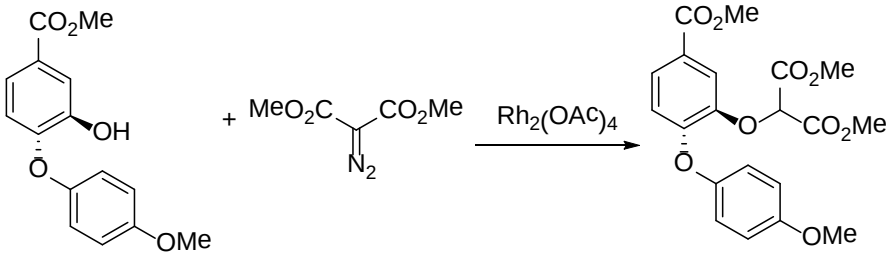
1.4.2 Insertion reactions

Metal carbenoids are known to undergo insertion reactions with Si-H, C-H and heteroatom-H. The mechanism for heteroatom-H insertion, however, is unclear, but a stepwise mechanism involving ylides followed by proton transfer is generally considered. N-H and O-H insertion reactions have been extensively developed. Scheme 1-22 shows an example of N-H insertion in the synthesis of 5-oxo-L-pipecolic acid derivative that are found in plants.[29]



Scheme 1-22. Rh catalysed N-H insertion

Another example for the carbenoid reaction is O-H insertion. In the chorismic acid synthesis, Ganem found the attachment of the enol pyruvate side chain proved to be difficult, which could be overcome by using O-H insertion (Scheme 1-23).[30]



Scheme 1-23. Application of metal carbenoid insertion into O-H bond in natural product synthesis

Besides heteroatom-H insertion, carbenoids can also undergo C-H insertion which is often confused with C-H activation. While C-H activation involves oxidative addition of metals across the C-H bond **20a**, the metals do not directly interact with C-H bonds. (Figure 1-10).[31] The low–polarity of C-H and Si-H bonds makes them undergo insertion reaction via a different mechanism (Figure 1-11). However, an accurate mechanism is still under debate and studied using different computational studies.[32] Scheme 1-24 shows an example of C-H insertion in the natural product synthesis.[32]

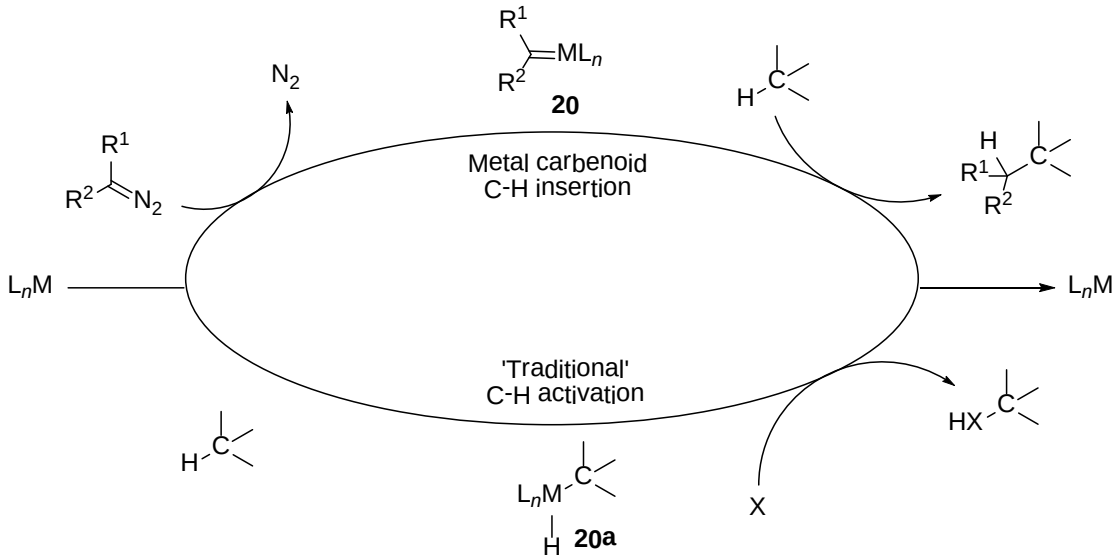


Figure 1-10. Difference between C-H insertion and C-H activation.

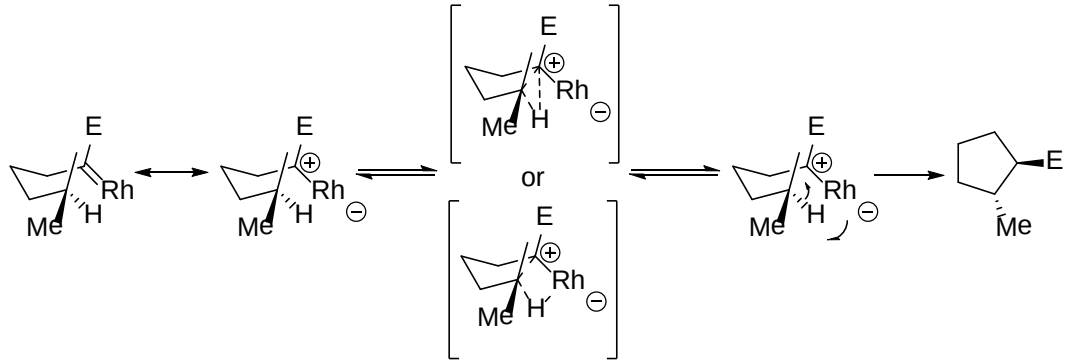
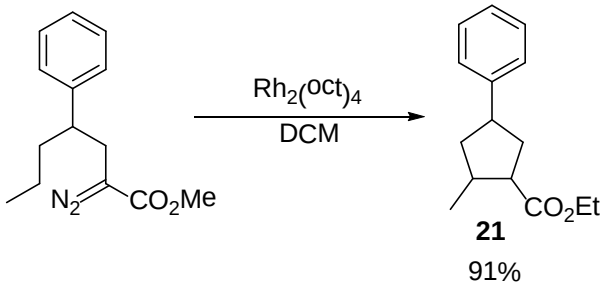


Figure 1-11. Mechanism of C-H insertion



Scheme 1-24. C-H insertion for ring closure

1.4.3 Ylide formation for cycloaddition

Ylides are reactive intermediates that are known to undergo a wide range of useful transformations. Ylides can be viewed as a neutral dipolar molecule containing a negatively charged atom (carbanion) directly attached to a heteroatom with a positive charge.

Metal carbenoid-mediated ylide formation occurs readily when nucleophilic species such as ethers, thiols, amines, nitriles, ketones, aldehydes and halides react with metal carbenoids (Figure 1-12).

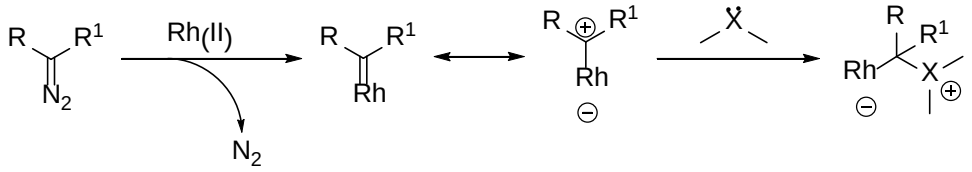
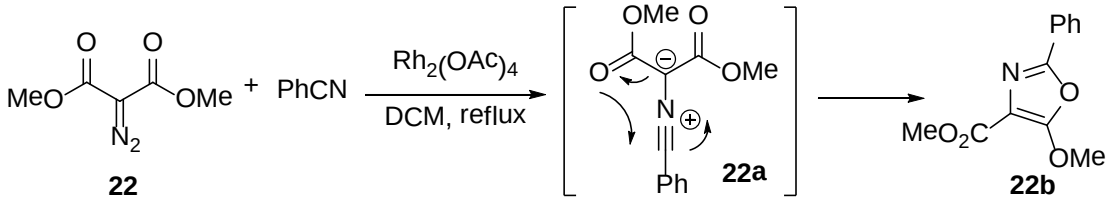
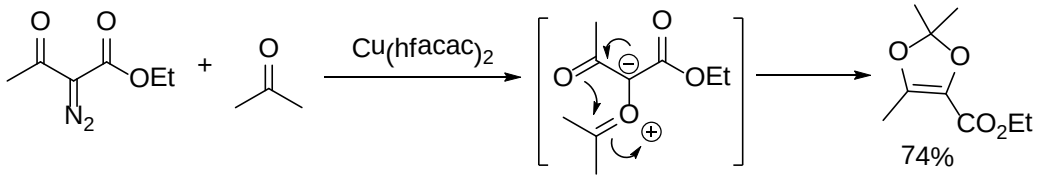


Figure 1-12. Ylide formation

An example is the formation of oxazole **22b** via ylide by the reaction of benzonitrile with diazo ketoester **22** (Scheme 1-25).[33] Likewise, ketones participate in the ylide formation as shown in Scheme 1-26.[34]



Scheme 1-25. Ylide cycloaddition



Scheme 1-26. An oxonium ylide

1.4.4 C-H activation with carbenoid

The use of metal carbenoids has also been investigated in the C-H activation process. Recently, there is a growing interest using diazo compounds as a coupling agent as the metal-carbenoid approach is a fantastic method for the functionalization of unactivated C-H bonds.[35] The reaction is considered to follow a pathway involving C-H metalation to give **23** followed by metal-carbene formation and migratory insertion (Figure 1-13).[36]

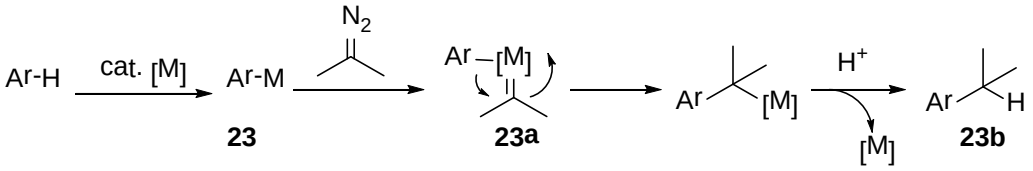
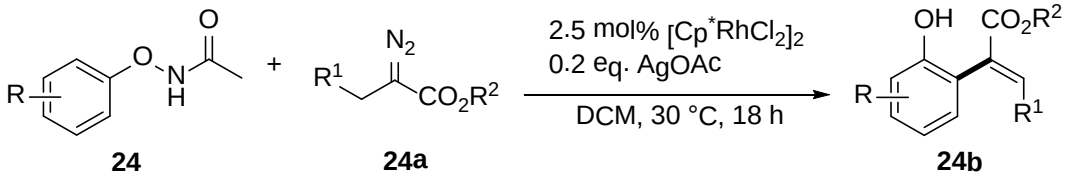


Figure 1-13. C-H bond functionalization with metal carbenoids

In this example, Jianbo Wang and co-workers successfully demonstrated the C-H activation of diazoester **24a** and *N*-phenoxyacetamides **24** to form product **24b** (Scheme 1-27).[37] Coordination of [Cp*Rh(OAc)$_2$] to substrate **24c** followed by electrophilic C-H bond cleavage provides **24e**. Reaction of **24e** with diazo compound generates **24f**, which undergoes migratory insertion to afford rhodacycle **24g**. β-Hydride elimination followed by reductive elimination provides **24i**. Finally, product **24b** is produced along with the regeneration of the Rh(III) catalyst via oxidative addition followed by protonation (Figure 1-14).



Scheme 1-27. C-H activation with diazo compounds

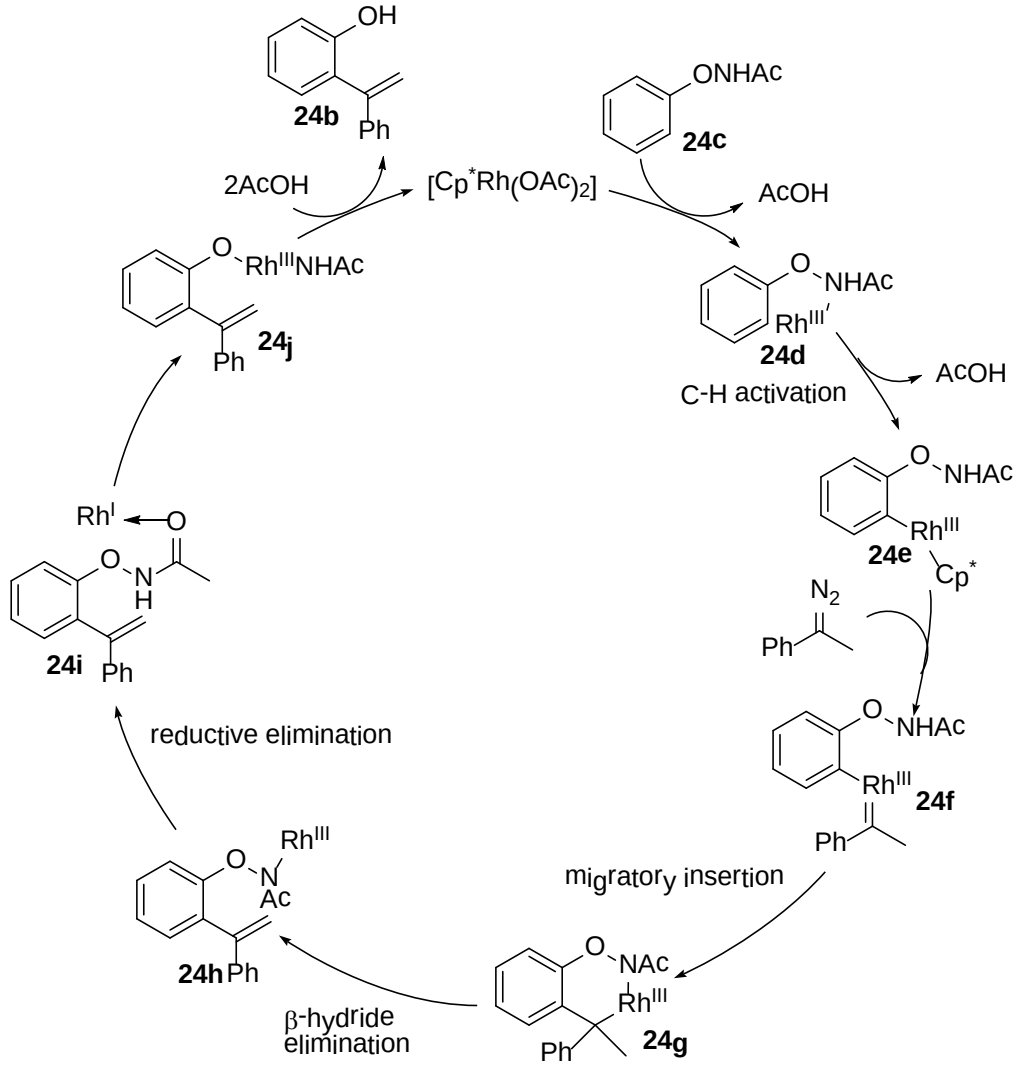


Figure 1-14. Catalytic cycle of the C-H activation

1.5 Application of metal carbenoid in heterocycles

Heterocycles make up the largest family of organic compounds. Amongst these, aromatic heterocycles are found in many biologically active natural products and drugs. As a result, many synthetic methods for these heterocycles have been developed.[38] Metal carbenoids have shown their versatility in the synthesis of various heterocycles based on insertion, cyclopropanation-rearrangement, and cycloaddition reactions. The following chapters describe the development of the synthesis of several heterocycles based on the various reactivities of metal carbenoids.

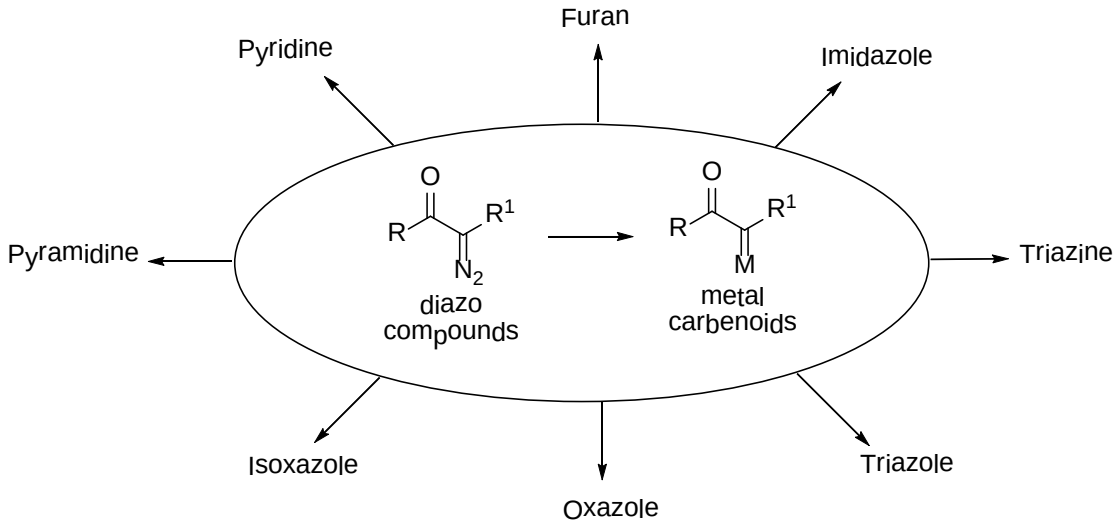


Figure 1-15. Application of metal carbenoids on heterocycles

1.6 References

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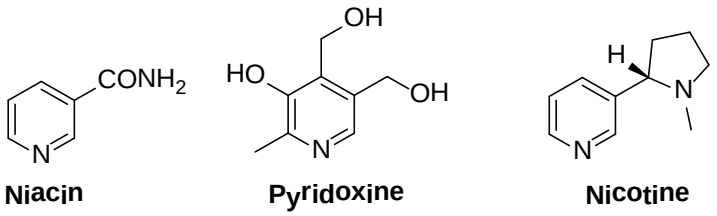
Chapter 2: Synthesis of Pyridines by Carbenoid-Mediated Ring Opening of 2*H*-Azirines

2.1 Introduction

2.1.1 Overview

Pyridines are known for their widespread occurrence in nature and the pyridine moiety forms part of numerous natural and synthetic biologically active compounds.[1]

In living organism, the pyridine moiety forms part of the nucleotide (NADP) which is involved in oxidation and reduction processes. It plays an important role for generating free radicals in immune cells and these radicals in turn, are used to destroy pathogens. Another importance of pyridine moiety is its presence in vitamins such as niacin (vitamin B_3) and pyridoxine (vitamin B_6) which the human body requires. Niacin is involved in both DNA repair and the production of steroid hormones in the adrenal gland while pyridoxine is a cofactor in many reactions of amino acid metabolism. As opposed to these essential vitamins, the pyridine moiety is also present in harmful and highly toxic alkaloids such as nicotine which is an active ingredient in cigarettes (Figure 2-1).

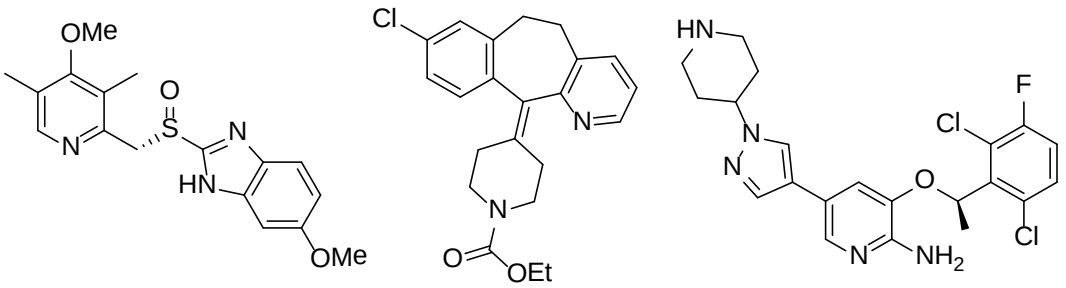


Niacin **Pyridoxine** **Nicotine**

Figure 2-1. Alkaloids containing pyridine moiety

Over the years, it was found that the pyridine ring is an important motif in bioactive pharmaceutical compounds. One example is Nexium which is the treatment of acid reflux. Another example would be Loratadine which is the treatment of

allergies. And the most important marketed drug containing the pyridine motif would be the Xalkori which is the treatment for lung cancer (Figure 2-2.). Hence, there is a continual need to develop methods for pyridine deriavative synthesis to meet the demand in pharmaceutical companies.



Nexium **Loratadine** **Xalkori**

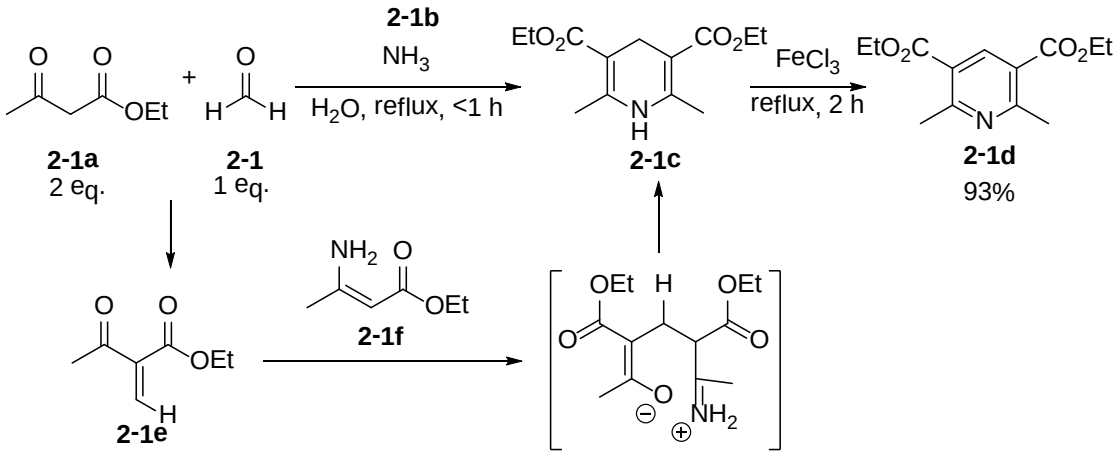
Figure 2-2. Drugs containing the pyridine motif

2.1.2 Classical methods of pyridine synthesis

The importance of the pyridine motifs in drugs highlights the need for the discovery of the synthesis of pyridine derivatives. The following shows the early stages of development of the construction of pyridine.

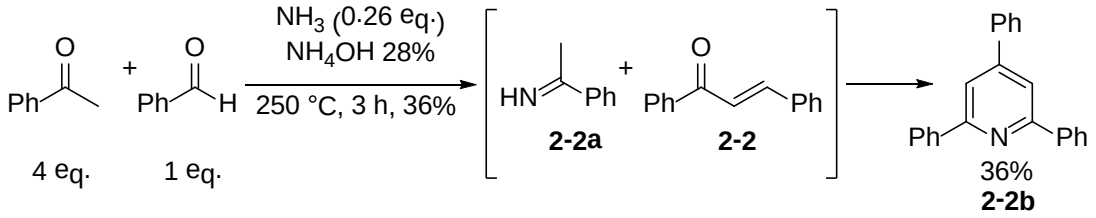
One of the earliest examples is the Hantzsch pyridine synthesis.[2] It is a multi-component reaction between an aldehyde **2-1**, β-keto ester **2-1a** and a nitrogen donor such as ammonium acetate **2-1b**. The initial product is a dihydropyridine **2-1c** which can be easily oxidised to pyridine **2-1d** by aromatisation. The mechanism is the Knoevenagel condensation forming the key intermediate **2-1e** and condensation of the second equivalent of the β-keto ester with ammonia gives the ester enamine **2-1f** and further condensation gives the dihydropyridine **2-1c** which could be oxidise to give pyridine **2-1d** (Scheme 2-1). The advantages of this method are that the reaction could be carried out in water and high yields are observed. A disadvantage however, is that

the pyridine formed are symmetrical which limits the variety of substituents on the ring.



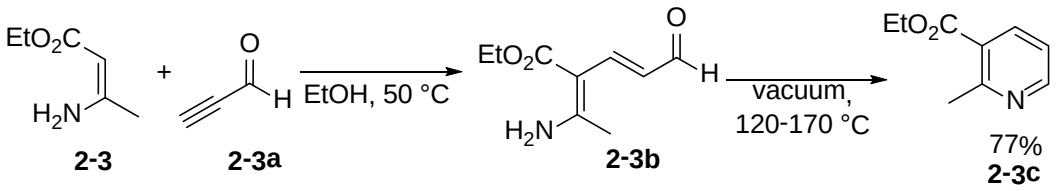
Scheme 2-1. Hantzsch pyridine synthesis

Another method is Chichibabin pyridine synthesis.[3] The reaction can be described as an aldol condensation of aldehydes, ketones or α, β-unsaturated carbonyl compounds to form α,β-unsaturated ketone **2-2** and Michael addition with imine **2-2a** and subsequently ring closure to form pyridine **2-2b** (Scheme 2-2). The drawbacks are that high temperatures are required and furthermore, low yields were observed due to the prevalence of large amounts of byproducts formed which may occur in the aldol step or the imine step or the pyridine synthesis step. Thus, this method is unsuitable for industrial synthesis.



Scheme 2-2. An example of Chichibabin pyridine synthesis

The Bohlmann Rahtz approach[4] is another method for pyridine synthesis. It is the reaction of enamine and ethynyl ketone or aldehyde in a two-step synthesis.[5] The first step is the regioselective Michael addition of enamine **2-3** and ketone **2-3a** or aldehyde to give a dienone **2-3b** intermediate which undergoes condensation to give 2,3-disubstituted pyridine **2-3c** in excellent overall yield (Scheme 2-3). The only drawback of this reaction is the high condensation temperature.

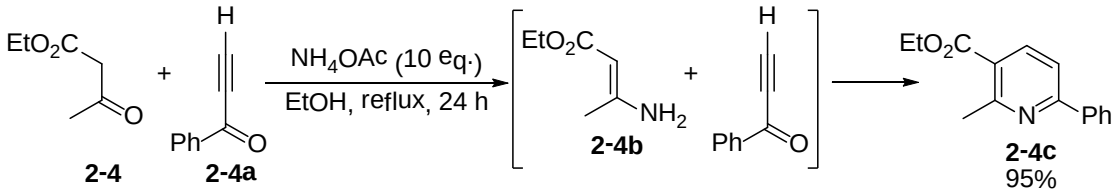


Scheme 2-3. An example of the Bohlmann Rahtz pyridine synthesis

2.1.3 Recent methods of pyridine synthesis

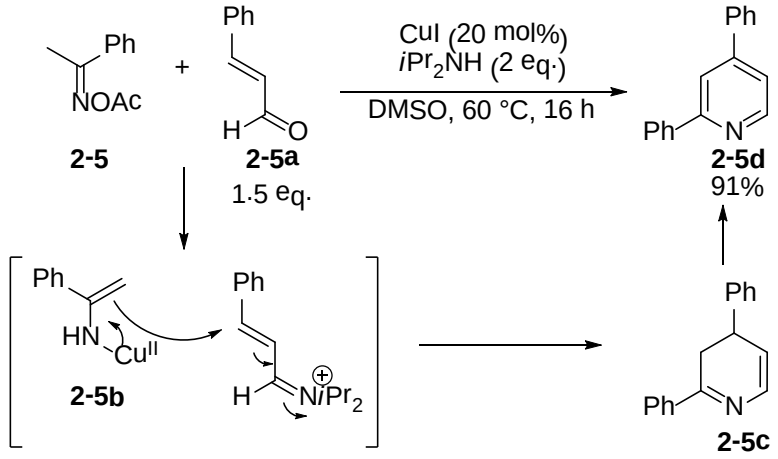
The importance of the pyridine moieties in bioactive pharmaceutical drugs leads to the development of highly efficient and versatile methodologies for pyridine synthesis. Over the past few years, various transition metal catalysed methods for pyridine ring construction have been invented.

Following the Bohlmann Rahtz pyridine synthesis, a new and mild method has been developed using ammonium acetate in a one-pot three-component condensation. Reaction of the β-keto ester **2-4** with alkynone **2-4a** in the presence of a large amount of ammonium acetate at reflux forms the imine **2-4b** *in situ* which condenses with the alkynone **2-4a** to give the pyridine **2-4c** in high yields (Scheme 2-4).[6]



Scheme 2-4. Modification of the Bohlmann Rahtz pyridine synthesis

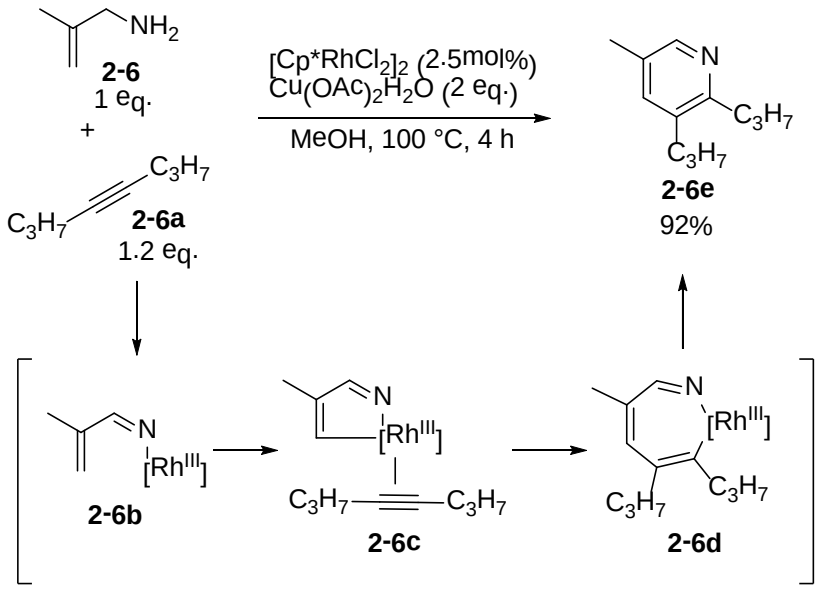
Recently, Yoshikai found a method for the synthesis of a variety of substituted pyridines under mild conditions. The reaction can be described to undergo a [3+3]–type condensation reaction of *O*-acetyl ketoxime **2-5** and *α,β*-unsaturated aldehyde **2-5a** catalysed by copper(I) salt and secondary ammonium salt or amine. The first step is the reduction of oxime N-O bond by copper(I) to generate a nucleophilic copper(II) enamide **2-5b** and subsequent condensation affords the dihydropyridine **2-5c** intermediate which is oxidised by copper(II) to pyridine **2-5d**. This reaction is environmentally benign as the byproducts are water and acetic acid (Scheme 2-5).[7]



Scheme 2-5. Synthesis of pyridine by copper catalysed redox neutral reaction.

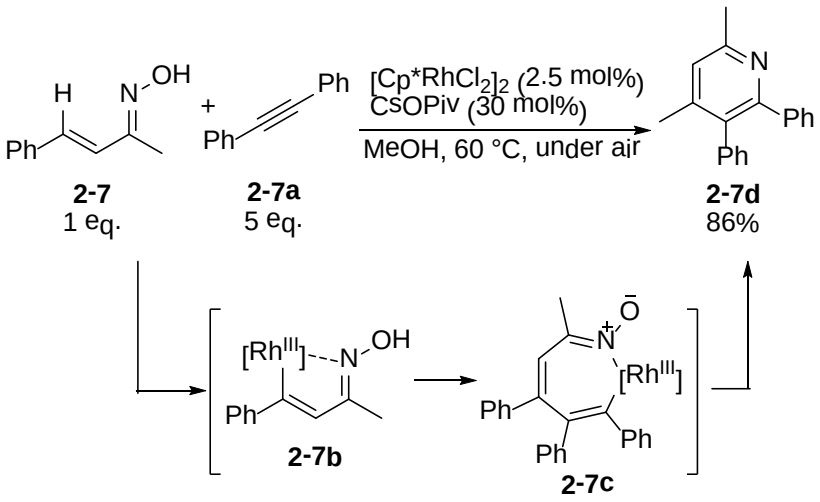
Another method is for the synthesis of pyridine is through $Cu(OAc)_2$ oxidation and Rh(III)-catalysed *N*-annulation sequence. Allylamine **2-6** undergoes $Cu(OAc)_2$ induced oxidation to form imine **2-6b** then Rh(III) catalyst assists in chelation to undergo C-H activation at the γ position to form the rhodacycle complex **2-6c**.

Carbometallation of **2-6c** into the alkyne **2-6a** leads a seven membered rhodacycle complex **2-6d** which undergoes reductive elimination to give the pyridine **2-6e** (Scheme 2-6).[8]



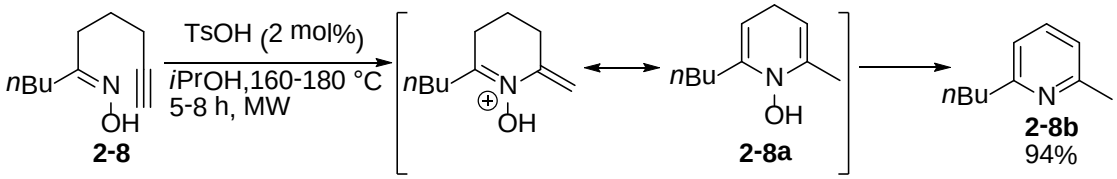
Scheme 2-6. Pyridine synthesis by reaction of allyl amine and alkyne through $Cu(OAc)_2$ oxidation and Rh(III) catalyzed *N*-annulation sequence.

Another method similar to the one discussed above, Chiba and co-workers also utilised Rh(III) as a catalyst for the synthesis of pyridine from *α,β*-unsaturated ketoxime and internal alkyne. It first undergoes a vinylic C-H activation of *α,β*-unsaturated oxime **2-7** with the oxime sp^2-nitrogen to give a vinyl rhodium intermediate **2-7b**, insertion to alkyne **2-7a** affords a seven-membered ring rhodacyclic iminium cation intermediate **2-7c** which undergoes a redox process of C-N reductive elimination to afford the pyridine **2-7d** (Scheme 2-7).[9]



Scheme 2-7. Rhodium(III) catalysed synthesis of pyridine

In this method of pyridine synthesis, the acid catalysed hydroamination from acyclic alkynyl oxime **2-8** to pyridine **2-8b**. This cascade process starts off with the intramolecular hydroamination across the alkyne and then subsequent isomerisation gives the dihydropyridine **2-8a** and then aromatisation to give the pyridine. Even though this method allows the synthesis of pyridine in moderate to high yields, one drawback is that high temperature is required for the reaction to proceed (Scheme 2-8).[10]

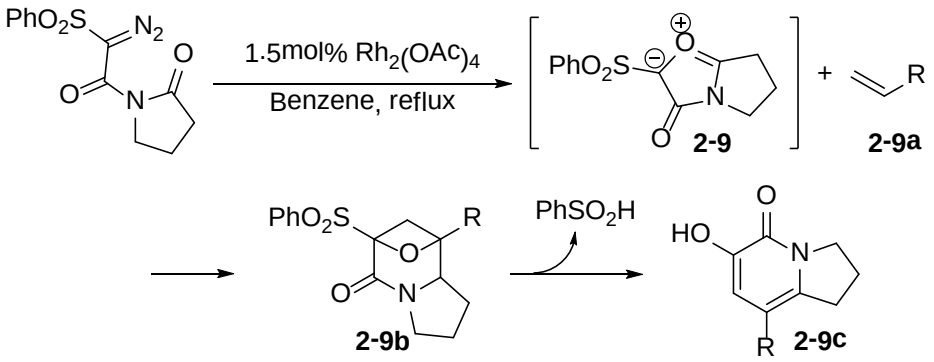


Scheme 2-8. Synthesis of pyridine using intramolecular hydroamination-based reaction

2.1.4 Application of carbenoid on pyridine synthesis

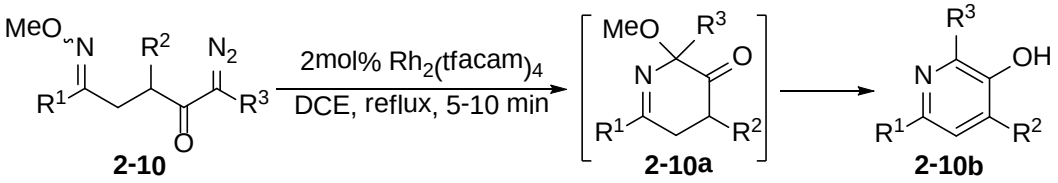
Based on the versatility of the type of reactions carbenoid can undergo, carbenoids have been used for the synthesis of pyridines. Padwa and co-workers utilised the Rh(II) catalysed [4+2] cycloaddition for the synthesis of pyridine. The

reaction forms an oxonium ylide **2-9** which undergoes cycloaddition with the alkene **2-9a** to form **2-9b**. Ring opening and aromatisation by elimination of $PhSO_2H$ provide the pyridone **2-9c** (Scheme 2-9).[11]



Scheme 2-9. Rh-catalysed intramolecular cycloaddition to form pyridine

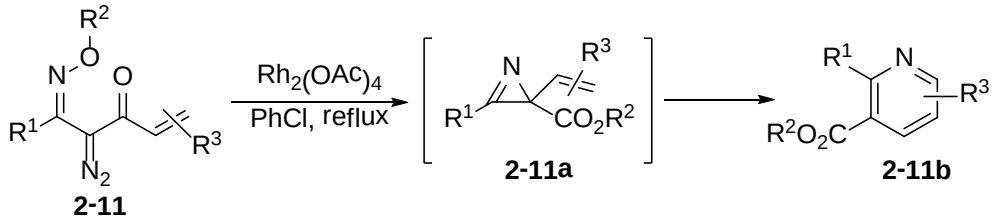
Park developed a simple method for the synthesis of pyridine utilising the N-O insertion property of carbenoid. In this method, the diazo oxime ether could be easily prepared from the Michael addition and then diazo transfer. The carbenoid **2-10** then undergoes an intramolecular N-O insertion to give the intermediate **2-10a** which spontaneously gives the pyridine **2-10b** with elimination of MeOH (Scheme 2-10).[12]



R^1: Aryl, alkyl
R^2: Me
R^3: Ester, ketone, phosphonate

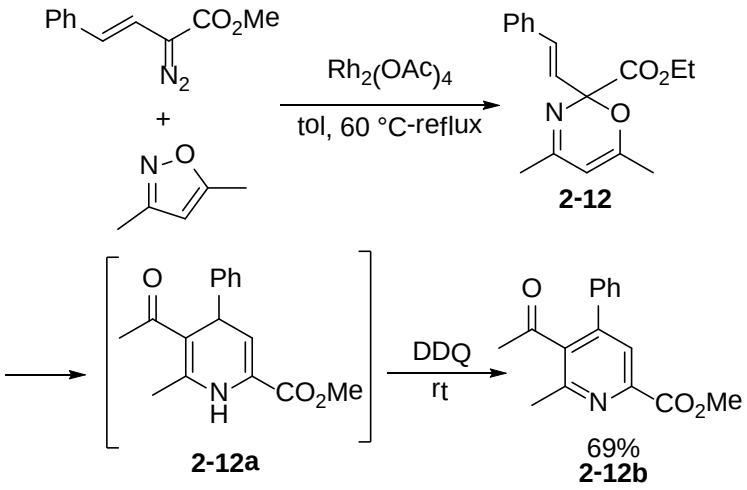
Scheme 2-10. Intramolecular Rh-catalysed N-O insertion to form pyridine

Again in this example, they make use of the intramolecular N-O insertion of the diazo oxime ether **2-11** for the synthesis of pyridine. In this example, the intermediate 2*H*-azirine **2-11a** generates a nitrene which would undergo 6π-electrocyclization to form pyridine **2-11b** (Scheme 2-11).[13]



Scheme 2-11. Rh-catalysed N-O insertion to form pyridine

Another method that is closer to our project is the synthesis of pyridine by rhodium carbenoid induced ring expansion of isoxazoles. The proposed mechanism goes through an N-O insertion product **2-12** which could undergo Claisen rearrangement to directly give 3,4-dihydropyridine **2-12a**. Another mechanism proposed is it could undergo an electrocyclic ring opening to azatriene followed by a 6π electrocyclization and tautomerization leads to dihydropyridine **2-12a**. Oxidation by 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the pyridine **2-12b** (Scheme 2-12).[14]

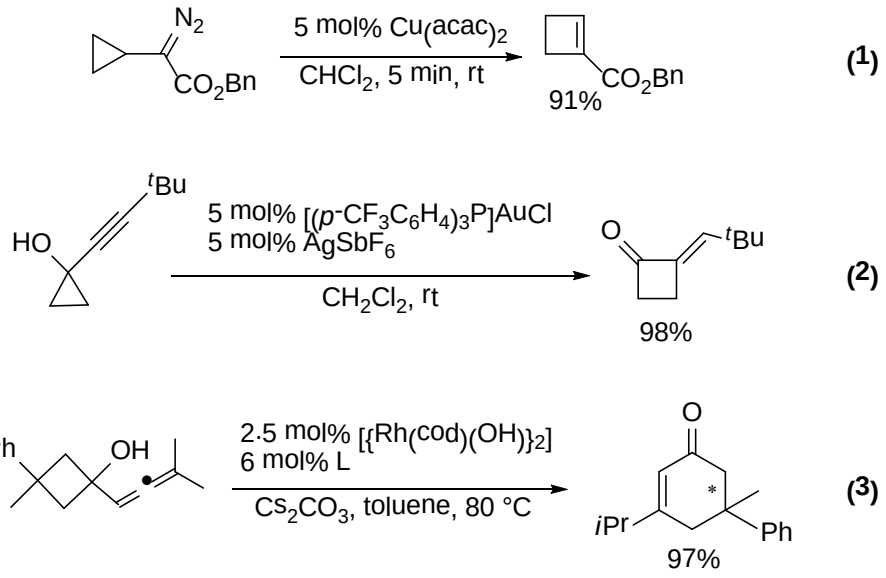


Scheme 2-12. Rhodium carbenoid induced ring expansion of isoxazole to pyridine

2.2 Aims and objectives

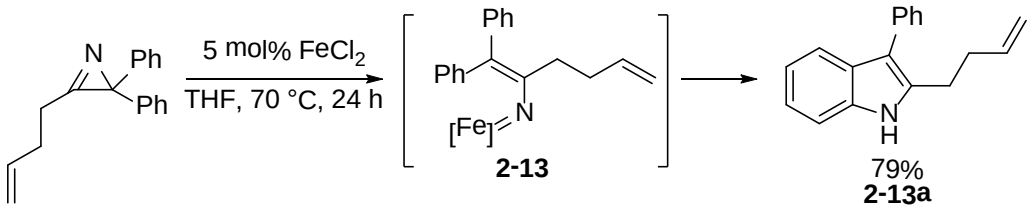
Inspired by the various carbenoid synthesis of pyridine, we explore the strain-driven ring expansion property of azirines as a strategy for the synthesis of pyridines using the vinyl diazo discussed in Scheme 2-12.

Ring strain is a strategy widely used as a tool for ring opening.[15] Some examples are the ring opening of cyclopropanes to form poly-substituted cyclobutenes[16], cyclopropanol to cyclobutanol[17] and cyclobutanes to cyclohexenone[18] (Scheme 2-13).

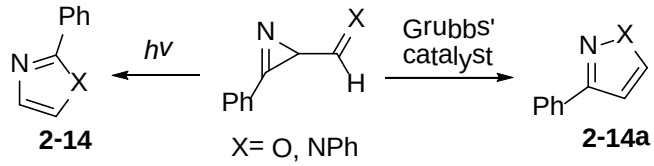


Scheme 2-13. Examples of ring expansion

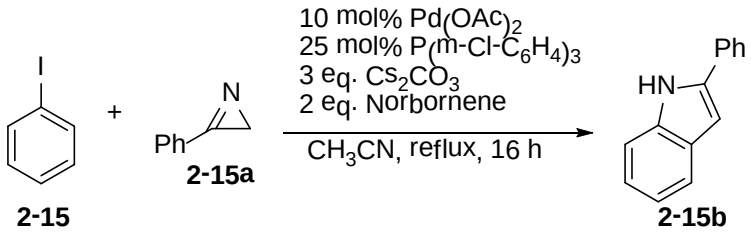
Another class of three-membered heterocycle commonly involved in ring expansion is azirine. An example is the ring opening of azirine catalysed by Fe(II) to synthesize indoles. The azirine is proposed to go through a nitrene intermediate **2-13** which then undergoes a five centered 6-π electrocyclization to form the pyrrole **2-13a** (Scheme 2-14).[19] Besides the ring expansion azirine to form pyrrole, azirines can also form isoxazole **2-14** and pyrazole **2-14a** by using the Grubbs catalyst and by photolysis (Scheme 2-15).[20] Another example shown in Scheme 2-16, the strained alkene (norbornene) aids the reaction of 2*H*-azirine **2-15** with aryl iodide **2-15a** under palladium to form indole **2-15b**.[21] In Scheme 2-17, the indole **2-16b** was formed from azid **2-16** via the azirine intermediate **2-16a** even without a catalyst.[22]



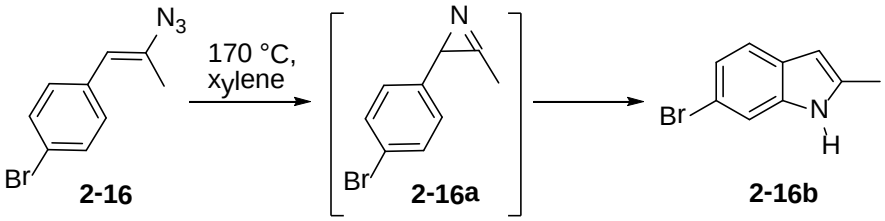
Scheme 2-14. Azirine ring opening to form pyrrole



Scheme 2-15. Azirine to 5-membered heterocycle

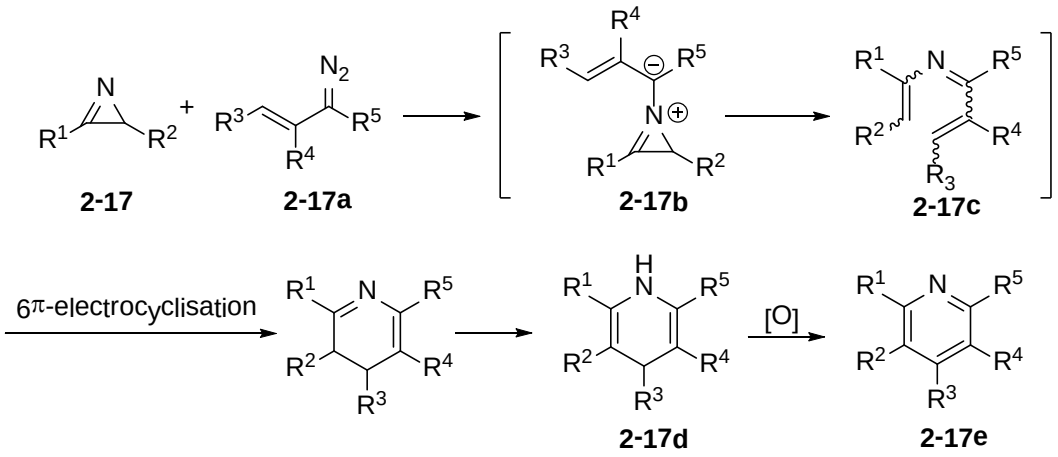


Scheme 2-16. Ring expansion to indole



Scheme 2-17. Thermolysis of azirine to indole

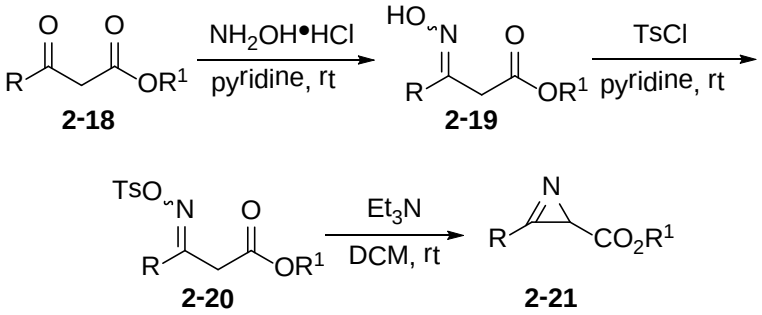
Having seen the examples of ring-strain-driven synthesis of *N*-heterocycles, we envisioned that activation of 2*H*-azirines, which are readily accessible through the Neber reaction[23] in two steps from ketones may lead to the formation of pyridines upon reaction with vinyl carbenoids **2-17a** through a cascade of rearrangements shown in Scheme 2-18. The reaction is first initiated by the formation of the ylide **2-17b** which triggers ring opening of 2*H*-azirine **2-17** to afford the 3-azatriene **2-17c**. Subsequent 6π electrocyclization leads to the formation of the 3,4 dihydropyridine **2-17d**, which could be readily oxidized to pyridine **2-17e** (Scheme 2-18).



Scheme 2-18. Proposed mechansim of carbenoid mediated ring opening of azirine to pyridine

2.3 Results and Discussion

2.3.1. Synthesis of azirines from *β*-keto esters



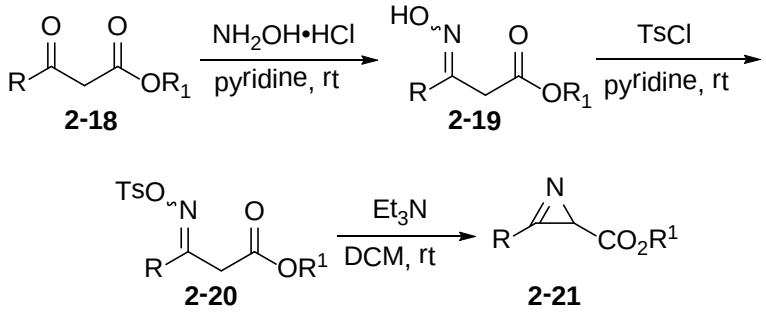
Scheme 2-19. General method for the synthesis of azirine

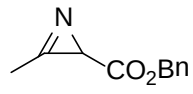
The azirines were prepared by the Neber reaction as shown in Scheme 2-19. The *β*-keto ester **2-18** first undergoes condensation with the hydroxylamine to form the oxime **2-19**. Tosyl group is installed on -OH to make it a good leaving group during the nucleophilic substituition to form the azirine **2-21**. Most of the azirines were prepared by this method (Table 2-1). As seen in Table 2-1, the Neber reaction tolerates oximes with substituents that have no steric hinderance to give azirine **2-21a** and **2-21b** in good yields. The synthesis of aromatic azirine such as **2-21 f**, **g**, **h**, **i**, **j**, **m**, **n** were also well tolerated to give good yields. Azirine **2-21k** with an alkene substituent also gave moderate yields of 53%. For azirine **2-21c** bearing the sterically

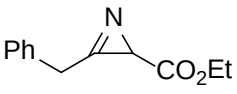
hindered cyclohexyl substituent gave low yield of 18%. This is due to the -OTs geometry of the oxime that is trans to the substituent. It needs to be cis relative to the substituent for nucleophilic attack (Scheme 2-20). The low yield of azirine **2-21d** is due to the first step, the bulky aromatic group pushes the hydroxyl oxime to be trans from it resulting in self-condensation to the five-membered isoxazolone.[24] Therefore to inhibit the self-condensation, we decided to synthesize tert-butyl ester for all other azirine (Table 2-1).

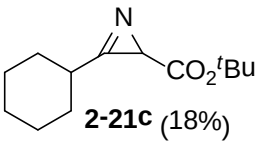
There are also some limitations to the Neber reaction which only works for substituent that possess electron-withdrawing groups to ensure that the methylene proton is sufficiently acidic to undergo deprotonation. Other methods were used to prepare substrates bearing electron-donating groups or when the methylene protons were not acidic. Another method to prepare azirine **2-21l** is as shown in Scheme 2-21. IN_3 was generated *in situ* and added across the alkene double bond. Anti elimination of HI gives the vinyl azide **2-22** which is highly unstable and is used directly in the next step.[25] Thermal rearrangement of azide in dichloromethane (DCM) provides the disubstituted azirine **2-21l** (Scheme 2-21). For substrates that are electron donating, the first step in the preparation of azirine **2-21e** is the condensation of hydroxylamine to form the 5-membered isoxazole ring **2-23a** then subsequent chlorination to form the isoxazole **2-23b** then replacement of the –Cl with the –OMe group and rearrangement gives the electron–donating azirine **2-21e** (Scheme 2-22).[24, 26]

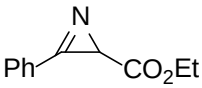
Table 2-1. Synthesis of aziridines[a]

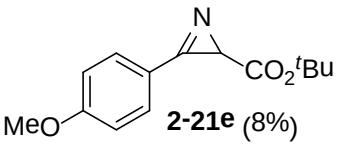


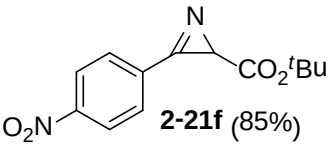

2-21a (70%)

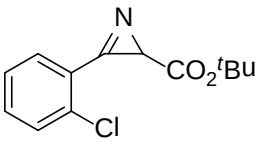

2-21b (80%)

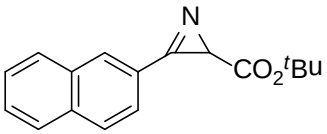

2-21c (18%)

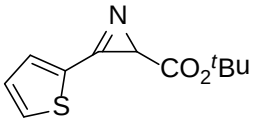

2-21d (20%)

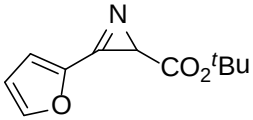

2-21e (8%)

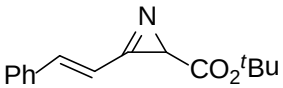

2-21f (85%)

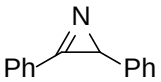

2-21g (65%)

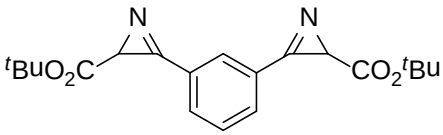

2-21h (70%)

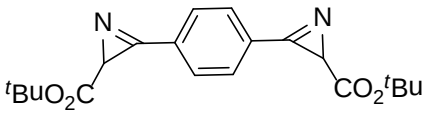

2-21i (66%)


2-21j (62%)

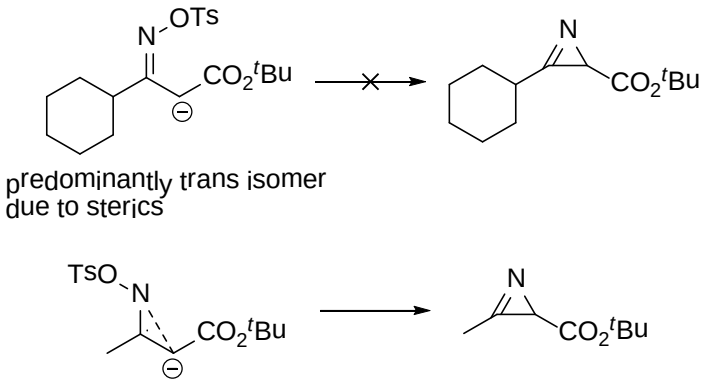

2-21k (52%)


2-21l (85%)[b]

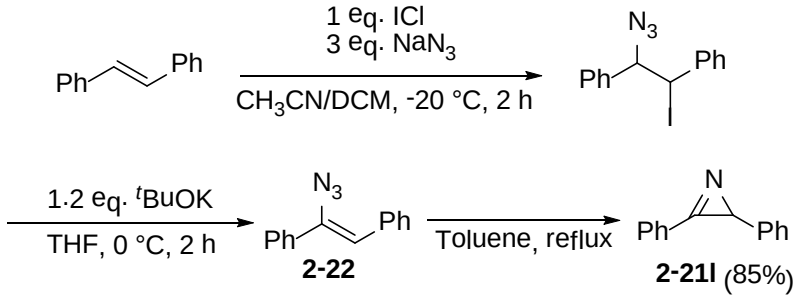

2-21m (70%)


2-21n (56%)

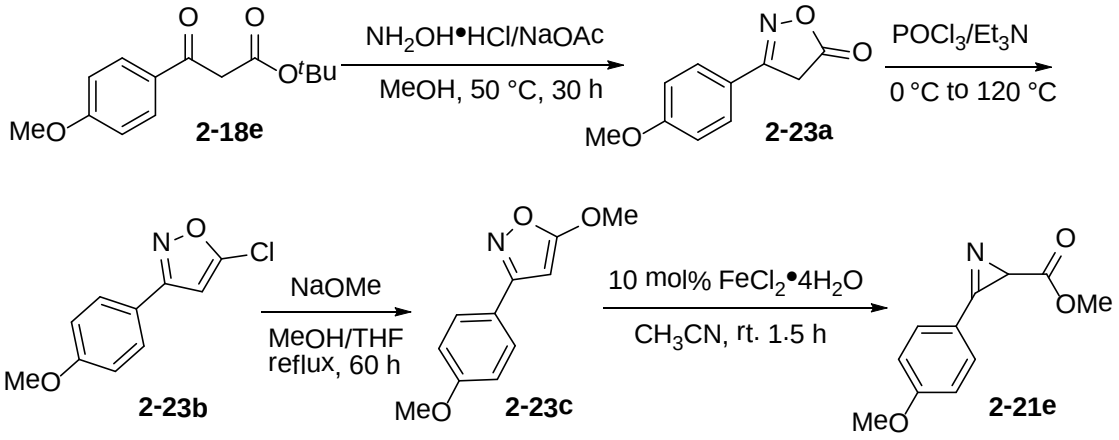
[a] The reported yields in the parentheses are of the isolated products. [b] **2-21l** was synthesized using a different method.



Scheme 2-20. Bürgi-Dunitz Trajectory

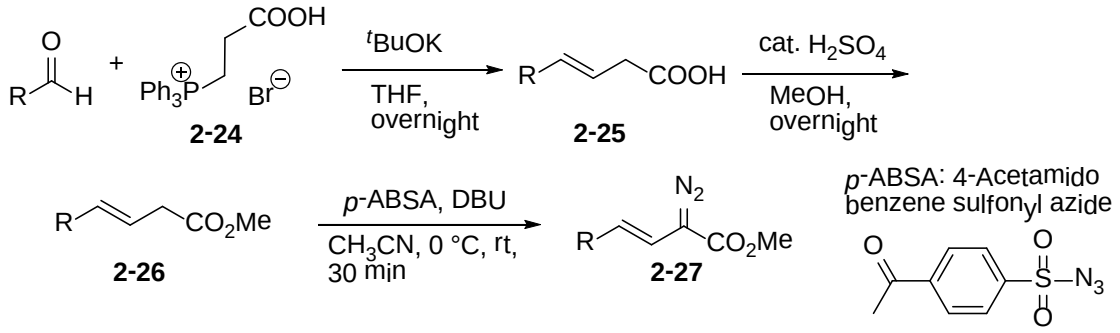


Scheme 2-21. Another method of 2*H*-azirine synthesis



Scheme 2-22. Different route for the synthesis of electron-donating azirine

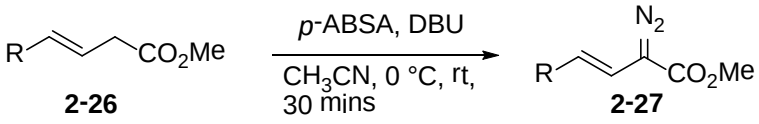
2.3.2 Synthesis of vinyl diazo compound

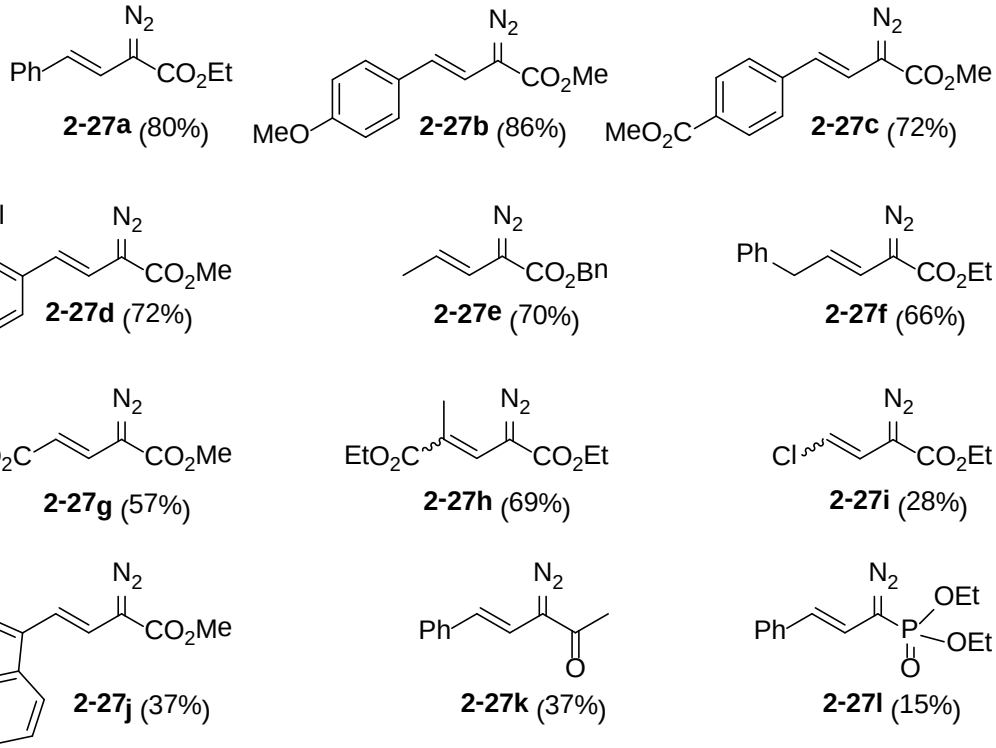


Scheme 2-23. Synthesis of vinyl diazo compound

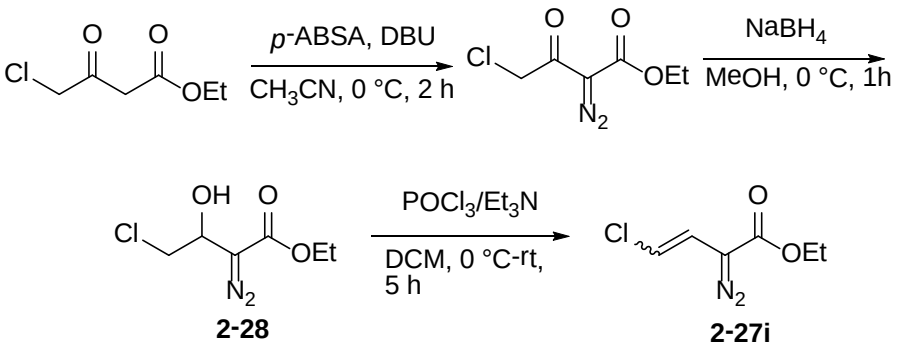
The vinyl diazo compounds were prepared according to Scheme 2-23. The first step of the reaction is the Wittig reaction between the aldehyde and the Wittig salt **2-24** to give allylic acid **2-25**. Further esterification was done to provide the allylic ester **2-26** and subsequent deprotonation and diazo transfer of allylic ester **2-26** gives the desired vinyl diazo **2-27** (Table 2-2).The diazo transfer is well tolerated with varying substituents such as aromatic (**2-27a**, 80%) and electron–donating (**2-27b**, 86%) and electron-withdrawing group (**2-27c**, 72%). Sterically hindered substituents, such as 2-chlorophenyl are also well tolerated which gives a yield of 72%. Alkyl substituents such as **2-27e**, **f** gave 70% and 66% respectively. Ester substituted diazo **2-27g**, **2-27h** gave moderate yields of 57% and 69% respectively. Diazo **2-27j**, **k**, **l** was found to have low yield probably due to the instability of the vinyl diazo formed (Table 2-2). However for vinyl diazo compound **2-27i**, diazo transfer takes place first followed by reduction to alcohol **2-28** then dehydration to give the desired vinyl diazo **2-27i** (Scheme 2-24).

Table 2-2. Synthesis of vinyl diazo compounds





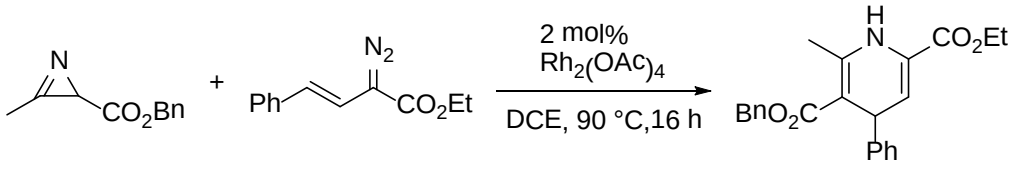
[a] The reported yields in the parentheses of the isolated products.



Scheme 2-24. Synthesis of diazo **2-27i**

2.3.2 Optimisation of reaction conditions

Our initial efforts to realize the transformation commenced with the reaction of azirine **2-21a** with the vinyl diazoacetate **2-27a** in the presence of [$Rh_2(OAc)_4$] in 1,2-dichloroethane (DCE) at 90°C. The reaction proceeded smoothly to give 1,4-dihydropyridine **2-29** in 44% yield (Scheme 2-25).

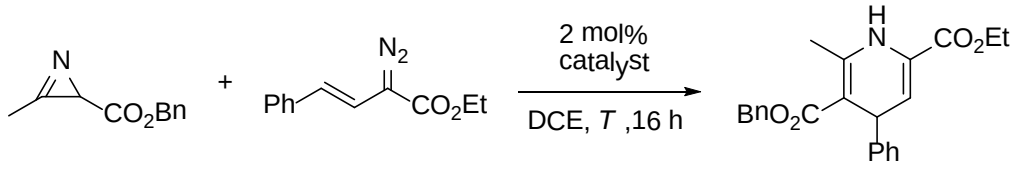


2-21a **2-27a** **2-29** (44%)

Scheme 2-25. Initial studies to synthesize dihydropyridine

A variety of metal complexes were screened to optimise the reaction with fixed temperature at 90°C and fixed solvent as 1,2-dichloroethane (DCE) in Table 2-3. Apart from screening different catalysts, different concentrations and temperatures were also screened with $Rh_2(OAc)_4$.

Table 2-3. Development of 1,4-dihydropyridine synthesis.[a]



2-21a **2-27a** **2-29**

Entry	Catalyst	*T* (°C)	Yield [%][b]
1	$Cu(OTf)_2$	90	0
2	$[Cu(hfacac)_2]$	90	0
3	$[Rh_2(OAc)_4]$	90	44
4[c]	$[Rh_2(OAc)_4]$	90	38
5	$[Rh_2(OAc)_4]$	70	38
6	$[Rh_2(tfa)_4]$	90	28
7	$[Rh_2(tfacam)_4]$	90	34
8	$[Rh_2(pfb)_4]$	90	34
9	$[Rh_2(piv)_4]$	90	71
10	$[Rh_2(esp)_2]$	90	80

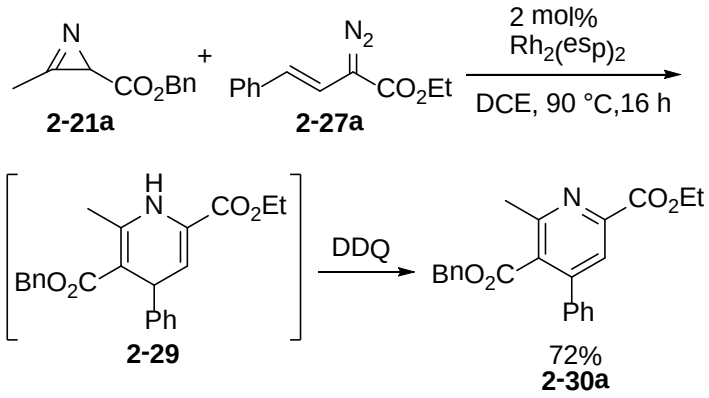
[a] Reaction conditions: **2-21a** (0.3 mmol), **2-27a** (0.48 mmol), 0.15M of azirine in DCE. [b] Yields determined by NMR vs. 1,1,2,2 tetrachloroethane as standard. [c] Reaction performed in 0.05M. esp=a,a,a',a'-tetramethyl- 1, 3-benzenedipropionate, pfb=perfluorobutyrate, piv=pivalate, hfacac=hexafluoroacetylacetonate, tfa= trifluoroacetate, tfacam= trifluoroacetamide.

The copper catalyst that was screened failed to give the dihydropyridine **2-29** (Table 2-3, entries 1 and 2). Changing the temperature to 70°C and changing the concentration to 0.05M all gave poor yields of the dihydropyridine **2-29** (Table 2-3, entries 4 and 5). From the different rhodium catalyst that was screened, electron-deficient dirhodium complexes such as $[Rh_2(tfa)_4]$, $[Rh_2(tfacam)_4]$, and $[Rh_2(pfb)_4]$ gave the desired product but in low yield (Table 2-3, entries 6, 7 and 8). The yields were drastically improved when dirhodium complexes with sterically bulky ligands such as $[Rh_2(piv)_4]$ and $[Rh_2(esp)_2]$ were used (Table 2-3, entries 9 and 10). Thus the best condition obtained is $[Rh_2(esp)_2]$ at 90°C in (0.15M) of 1,2-dichloroethane (DCE) affording 81% of dihydropyridine **2-29**. From the results obtained, it suggests that the steric effect of ligands plays an important role in this reaction. We postulate that the

steric demand of catalysts steers the formation of 3-azatriene with the correct configuration necessary for cyclization among potentially multiple isomers. See structure **2-17c**.

2.3.2 Scope and limitation

We develop a one-pot synthesis of pyridine by direct oxidation of dihydropyridine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 15 minutes after the completion of the reaction with $[Rh_2(esp)_2]$. We were pleased to find that the one-pot reaction provided pyridine **2-30a** in 72% yield (Scheme 2-26). With the conditions fixed, we set out to screen various 2*H*-azirine with vinyl diazoacetate **2-27a**.

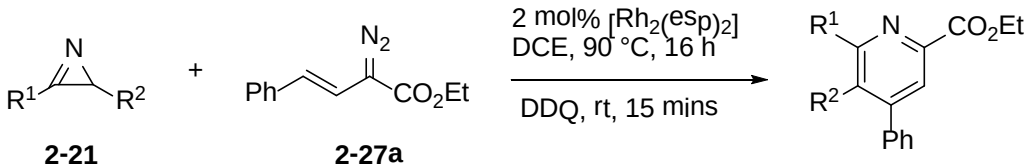


Scheme 2-26. One-pot reaction to pyridine

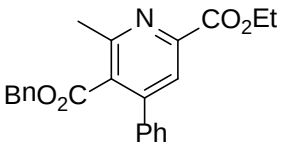
Generally, reactions proceeded smoothly to give pyridines in good to excellent yields (Table 2-4). 3-Alkyl-substituted 2*H*-azirines reacted well, including those with primary and secondary alkyl groups, thus providing pyridines (**2-30a–c**) with yields from 72-86%. Reactions with 3-aryl-substituted 2*H*-azirines also proceeded smoothly to afford 6-arylpyridines and those with both electron-rich and electron-deficient aryl groups gave the corresponding products in good yields from 72% to 93% (**2-30d–f**). The 2*H*-azirine having an ortho-chloro phenyl group reacted smoothly to afford the corresponding pyridine **2-30g** in 94% yield, thus suggesting that steric hinderance is

well tolerated. In addition, the substrate bearing the naphthalyl substituent, also provided **2-30h** in 84%. Extension of the reaction to heteroaryl-substituted 2*H*-azirines proved successful to afford 6-(2-thienyl)pyridine **2-30i** and 6-(2-furanyl)pyridines **2-30j** in 78% and 74%, respectively. Furthermore, 6-vinyl-substituted pyridines such as **2-30k** were readily accessed by using 3-vinyl-2*H*-azirine as the reaction partner. Last but not least, to examine the necessity of an ester group at the 2-position of 2*H*-azirine for successful transformation, 2,3-diphenyl-2*H*-azirine was subjected to the optimized reaction condition. It provides the pyridine **2-30l** in 79% yield. Thus, we show that the ester group is not necessary for the reaction to take place.

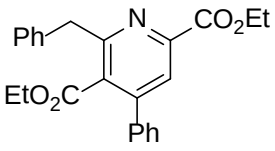
Table 2-4. Scope of 2*H*-azirines in the pyridine synthesis.[a]



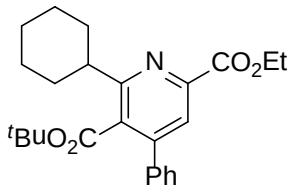
2-21 + **2-27a** → **2-30**



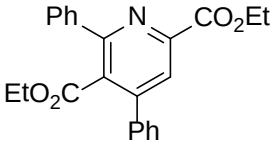
2-30a (72%)



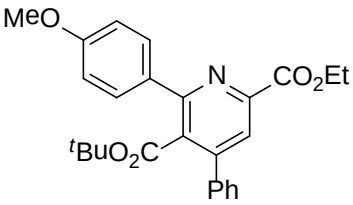
2-30b (82%)



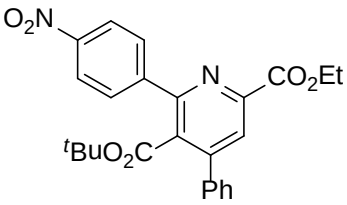
2-30c (86%)



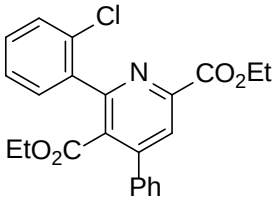
2-30d (72%)



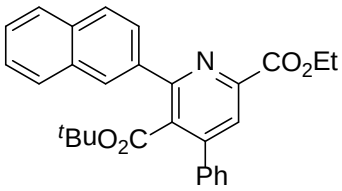
2-30e (95%)



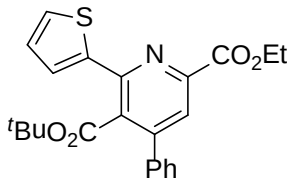
2-30f (93%)



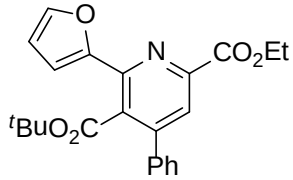
2-30g (94%)



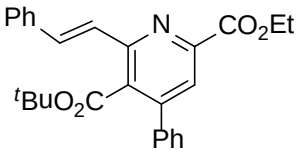
2-30h (84%)



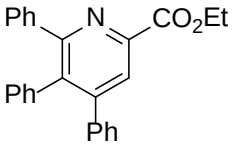
2-30i (78%)



2-30j (74%)



2-30k (84%)

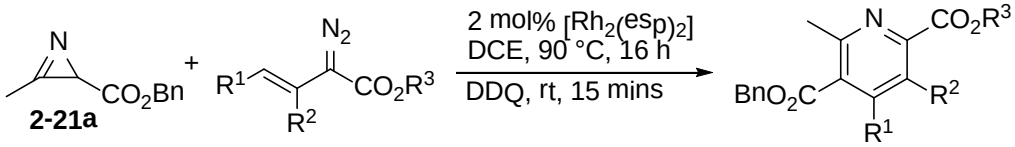


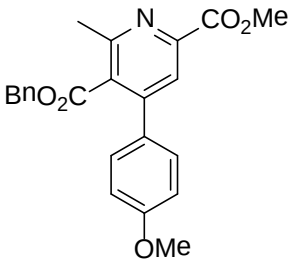
2-30l (79%)

[a] Reaction conditions: azirine (0.3 mmol), **2-27a** (0.48 mmol), DCE (0.15 M). The reported yields in the parentheses are of the isolated products.

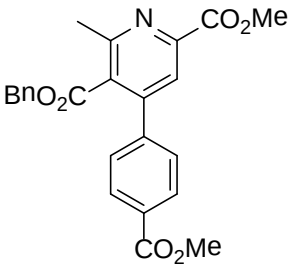
We then move on to screen various vinyl diazoacetate with azirine **2-21a**, keeping the standard conditions fixed.

Table 2-5. Scope in the pyridine synthesis.[a]

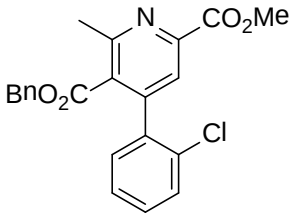




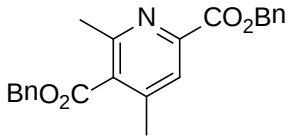
2-30m (76%)



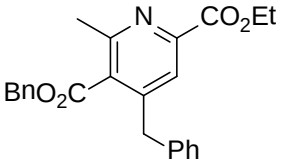
2-30n (67%)



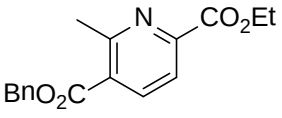
2-30o (55%)



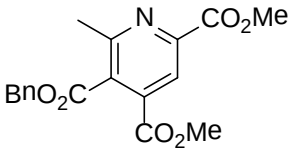
2-30p (80%)



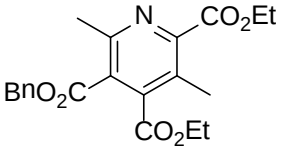
2-30q (44%)



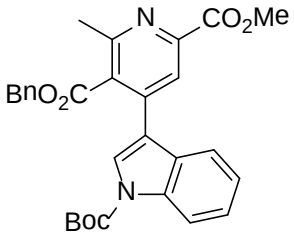
2-30r (61%)



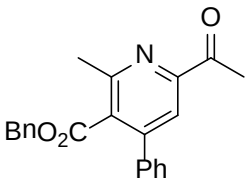
2-30s (77%)[b]



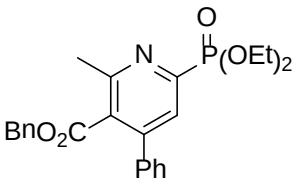
2-30t (65%)



2-30u (81%)



2-30v (72%)



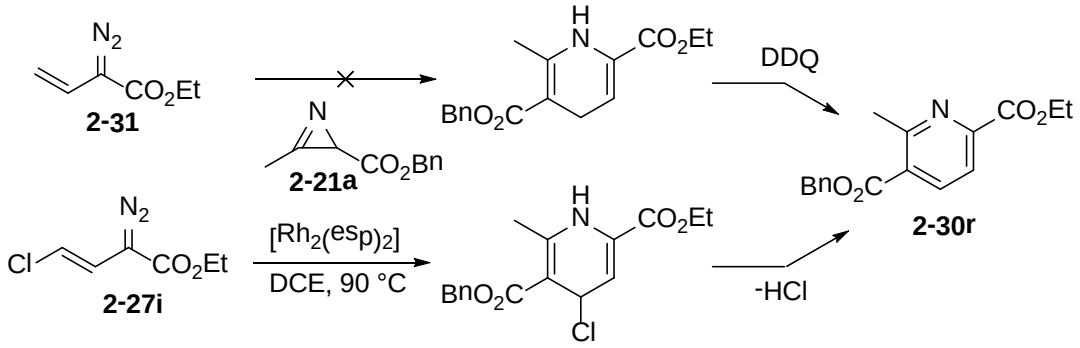
2-30w (71%)

[a] Reaction conditions: **2-21a** (0.3 mmol), diazo (0.48 mmol), DCE (0.15M). The reported yields in the parentheses are of the isolated products. [b] Reaction was done in dichlorobenzene and 90°C first then 170°C without any DDQ.

From the results obtained, vinyl diazoacetate with varying substituents are well tolerated to provide the pyridine in good yield. By varying electron-donating and electron withdrawing groups on the phenyl ring, the reaction yield is marginally

affected such as with 4-$MeOC_6H_4$ (**2-30m,** 76%), Ph (**2-30a**, 72%), and 4-$MeO_2CC_6H_4$ (**2-30n**, 67%). The reaction with a sterically hindered 2-chlorophenyl substituent, led to a moderate decrease in yield (**2-30o**, 55%). The yield of **2-30p** is higher (80%) due to $\mathbf{R^1}$ which is a sterically less bulky methyl group. This shows that the steric effect plays a role in the reaction. In addition, pentasubstituted pyridines could be prepared by employing 3,4-disubstituted vinyl diazoacetates. Thus, the reaction with azirine bearing a 3-methyl substitutent proceeded smoothly to afford **2-30t** in 65% yield. The indole substituted pyridine **2-30u** could be prepared in excellent yield (81%) by using the corresponding diazo compound. To expand the scope of functional groups that could be tolerated on pyridines, we examined the reaction with the diazoketone ((*E*)-3-Diazo-5-phenylpent-4-en-2-one) **2-27k** and diazophosphonate ((*E*)-diethyl 1-diazo-3-phenylallylphosphonate) **2-27l**. Gratifyingly, the reactions provided the pyridines **2-30v** (72%) and **2-30w** (71%) bearing these useful functional groups (Table 2-5).

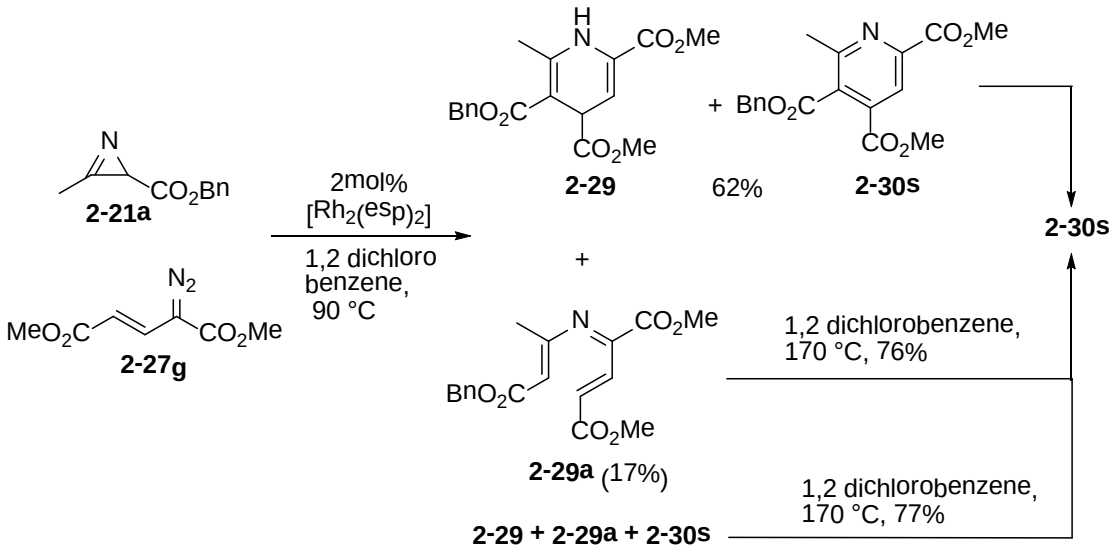
In an attempt to access 4-unsubstituted pyridines such as **2-30r**, we performed the reaction with the unsubstituted vinyl diazoacetate **2-31**, which turned out to be sluggish and provided a complex mixture (Scheme 2-27).



Scheme 2-27. Synthesis of the 4-unsubstituted pyridine by a different route.

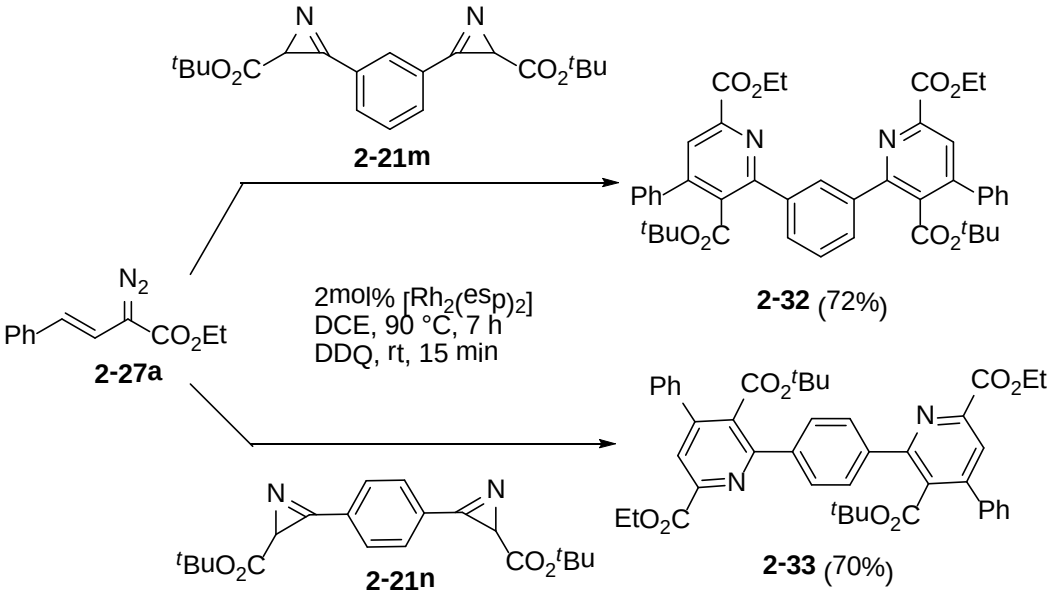
We reasoned that no substitution at C4 of **2-31** might cause complication in the reaction and that introduction of a chloro group as a temporary removable substituent may help overcome the problem by imposing some steric hindrance. In addition, elimination of the chloro group from the corresponding 1,4-dihydropyridine would provide the pyridine **2-30r** in 61% without the need for oxidation.

Also, introduction of an additional ester group on the pyridine ring was made possible by employing the 4-alkoxycarbonyl vinyl diazoacetate **2-27g**, thus resulting in the formation of the highly deactivated trialkoxycarbonyl pyridine **2-30s** in 77% yield (Scheme 2-28). Under the standard reaction conditions, the reaction provided an inseparable mixture of the expected 1,4-dihydropyridine **2-29** and pyridine **2-30s** in 62% along with 3-azatriene **2-29a** in 17%. This 3-azatriene **2-29a** smoothly underwent cyclization when heated at 170°C in 1,2-dichlorobenzene to give the pyridine **2-30s** in 76% after spontaneous oxidation. This observation suggests that the pyridine formation is likely to involve 6π electrocyclization of 3-azatrienes. Alternatively, **2-30s** was obtained in higher yield by directly heating the mixture of **2-30s**, **2-29**, and **2-29a** at170°C when the starting materials were consumed (Scheme 2-28).



Scheme 2-28. Mechanistic evidence of 3-azatriene intermediacy.

For application of the synthesis of pyridine in the area of functional materials[27], we envisioned that double annulation of bis-2*H*-azirines would offer a powerful means for the synthesis of such poly aryl pyridine systems. Indeed, the annulation reaction of **2-21m** and **2-21n** with vinyl diazoacetate **2-27a** proceeded remarkably well, providing extended aryl-heteroaryl systems **2-32** and **2-33** in 72% and 70%, respectively (Scheme 2-29).



Scheme 2-29. Double cyclization for polyarylpyridines.

2.4 Conclusion

In conclusion, we have developed a novel synthesis of pyridines via the activation of 2*H* azirines with carbenoids. This method allows the formation of pyridines bearing a broad range of substitution in good to excellent yields and requires a low catalyst loading. It is noteworthy that pentasubstituted pyridines could be synthesized in good yields. We have also demonstrated the utility of this transformation in the synthesis of highly conjugated poly aryl pyridine systems.

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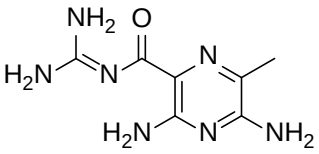
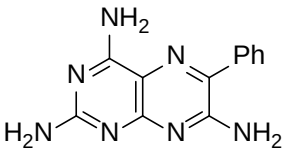
Chapter 3: Cu(II)-Mediated Synthesis of Pyrazine from *α*-Diazo Oxime Ethers and 2*H*-Azirines

3.1 Introduction of pyrazines

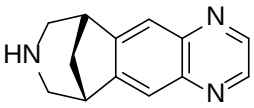
Pyrazine is an important class of azaheterocycle found in many natural products,[1] active pharmaceuticals as well as in our everyday life.[2] An example is the potassium-sparing diuretic, Amiloride and Triamterene which is used in the management of hypertension and congestive heart failure. Also, Pyrazinamide and Morinamide are antibacterial drugs used to treat tuberculosis. The pyrazine moiety is also found in Varenicline which stimulates nicotine receptors weakly than nicotine and it is used to treat people with smoking addiction.[3]



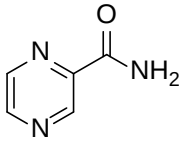
Amiloride



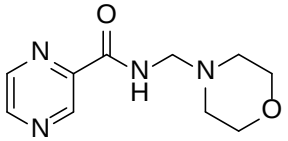
Triamterene



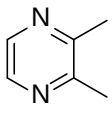
Varenicline



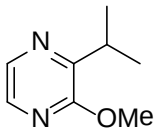
Pyrazinamide



Morinamide



Alkylpyrazine

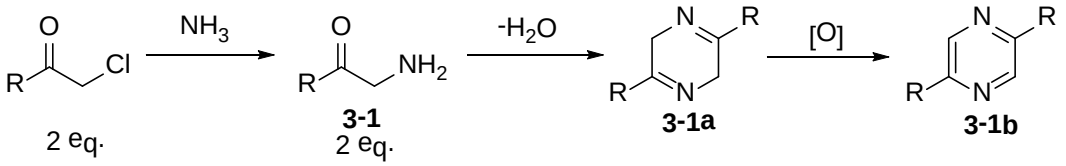


Isopropyl methoxy pyrazine

Besides the relevance of pyrazines in drugs, they also contribute to the flavours found in food,[2d] including alkyl pyrazine[4] in flavours of meat and isopropyl methoxypyrazine in some flavours of coffee and red wine.[5] Due to the prevalence of pyrazine in these compounds, there is a continual need to develop methods in the synthesis of pyrazines.

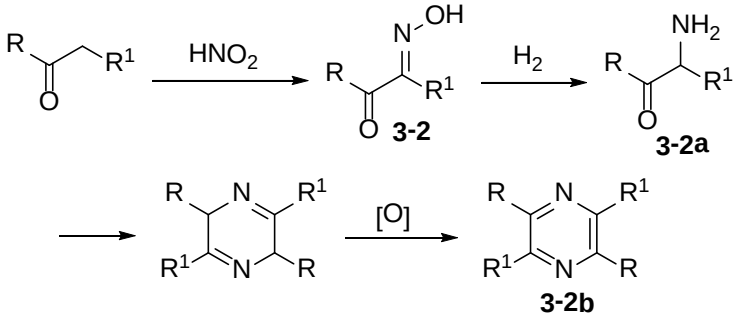
To date, only a few methods have been developed for the synthesis of pyrazines. The earliest example of the synthesis of pyrazine is the Staedel-Rugheimer pyrazine synthesis. The reaction first undergoes nucleophilic substitution with

ammonia to form intermediate **3-1** which self condenses to form intermediate **3-1a**. Further oxidation gives the pyrazine **3-1b**.



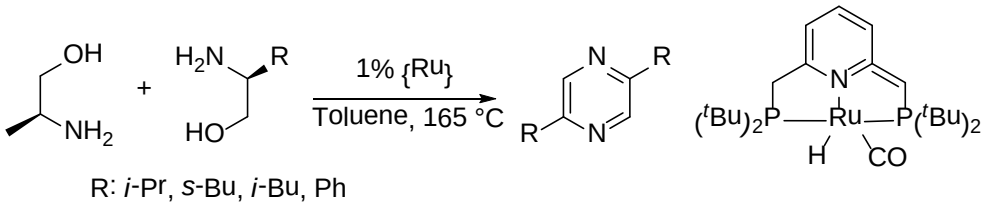
Scheme 3-1. Staedel-Rugheimer pyrazine synthesis

Another example is the Gutknecht pyrazine synthesis, which employs condensation to form the oxime intermediate **3-2**. Reduction of **3-2** provides the secondary amine **3-2a**. Self condensation and oxidation gives pyrazine **3-2b**.



Scheme 3-2. Gutknecht pyrazine synthesis

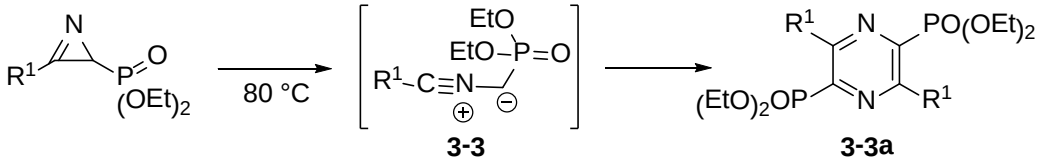
More recently, Milstein reported the Ru catalysed synthesis of symmetrical pyrazine through dehydrogenative dimerization of β-amino alcohol which requires high temperatures (Scheme 3-3).[6]



Scheme 3-3. Dehydrogenative synthesis of pyrazine

Another strategy for the pyrazine synthesis is the ring opening of azirine to form an ylide intermediate **3-3** which undergoes selective dimerisation at 80°C in neat

conditions (Scheme 3-4). This reaction however provides only symmetrical pyrazine such as **3-3a**.[7]



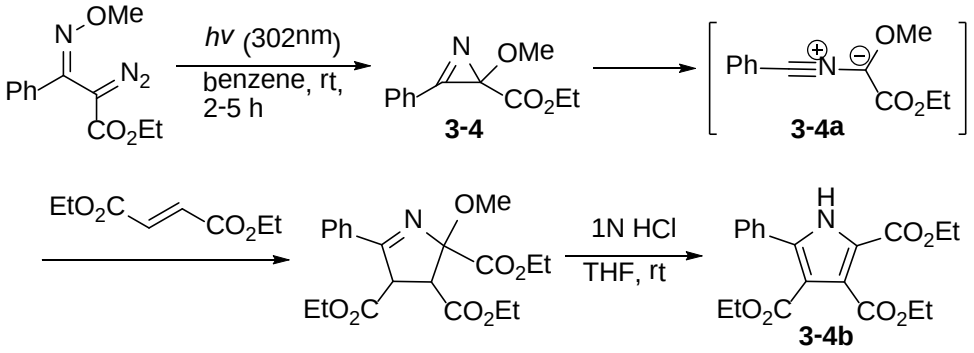
Scheme 3-4. Ring expansion of azirine to form pyrazine

Through the examples we have seen so far, all the existing methods only allow the synthesis of symmetrical pyrazines and it still remains a challenge to develop methods for the synthesis of these *N*-heterocycles.

3.2 Studies on *α*-diazo oxime ethers

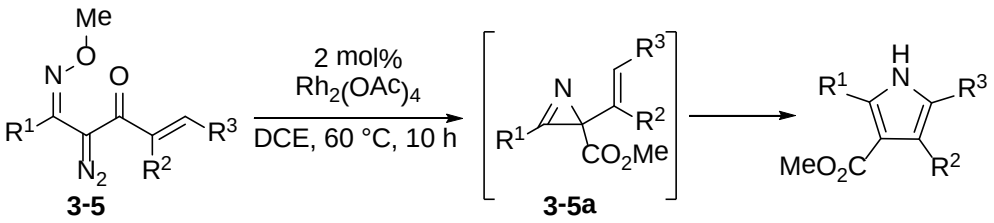
Recently, our group reported a synthetic method for *α*-diazo oxime ethers. In conjunction with studies on their reactivity, we became interested in that of free carbenes generated from *α*-diazo oxime ethers. In this section, we examine the reactivity and some of the reactions that *α*-diazo oxime ethers can undergo.

α-Diazo oxime ethers were found to undergo intramolecular N-O insertion to the carbenoid to form azirine **3-4**.[8] Subsequently, the azirine forms the nitrile ylide **3-4a** which undergoes 1,3-cycloaddition with alkenes to give pyrrole **3-4b** (Scheme 3-5).



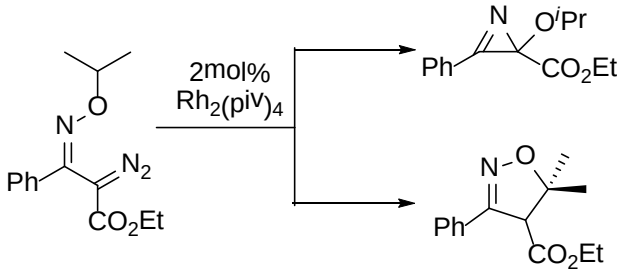
Scheme 3-5. Application of N-O insertion to azirine

Further development on this strategy, our group investigated the feasibility of metal-mediated cascade Wolff rearrangement on *α*-diazo oxime ether **3-5** leading to formation of 2*H*-azirine-2-carboxylic ester **3-5a** and subsequent rearrangement to pyrroles by introduction of vinyl groups on *α*-diazo oxime ethers (Scheme 3-6).[9]



Scheme 3-6. Wolff rearrangement of α-diazo oxime ether

Also, our group found that rhodium carbenoids derived from *α*-diazo oxime ethers provide N-O insertion products as well as 2-isoxazolines via C-H insertion (Scheme 3-7).[10]



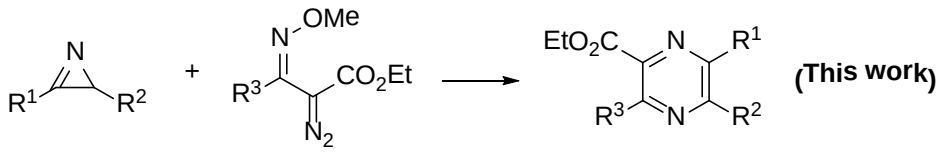
Scheme 3-7. C-H insertion of α-diazo oxime ethers

3.3 Aims and objectives

At the present moment, there are limited methods for the synthesis of symmetrical and unsymmetrical pyrazine, hence, this area of research remains a challenge and has great potential to be explored.

Inspired by the reactivity of *α*-diazo oxime ethers that lead to the formation of various *N*-heterocycles, we exploit the ring strain strategy of azirines we used in

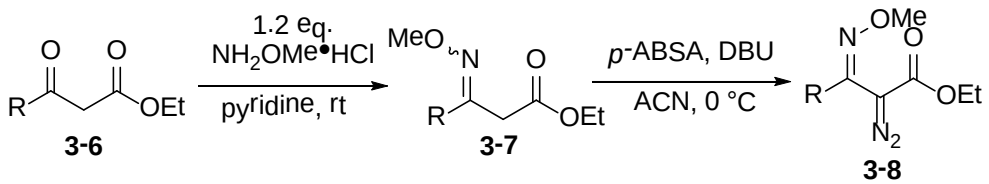
Chapter 2 to synthesis unsymmetrical pyrazines. We envisioned that 2*H*-azirines may lead to the formation of unsymmetrical pyrazines upon reaction with α-oximino carbenoids formed from α-diazo oxime ethers (Scheme 3-8).



Scheme 3-8. Synthesis of unsymmetrical pyrazine

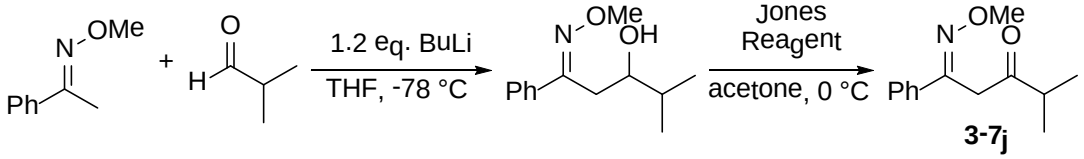
3.4 Results and Discussion

3.4.1 Synthesis of *α*-diazo oxime ethers



Scheme 3-9. Synthesis of α-diazo oxime ether

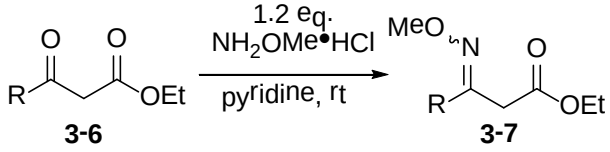
The synthesis of α-diazo oxime ethers **3-8** begins with the synthesis of oximes **3-7** from β-ketoesters **3-6**. At this stage, mixtures of cis and trans isomers of the oxime **3-7** were obtained in excellent yields (75-90%) and is well tolerated with varying substituents on β-ketoester (Table 3-1). However for the synthesis of oximes **3-7j**, it begins with the condensation of $MeONH_2 \bullet HCl$ with the ketone then aldol reaction to form the alcohol and finally oxidation with Jones reagent to give the oxime **3-7j** (Scheme 3-10). It is noteworthy to mention that the ratio of isomers is largely dependent on the bulkiness of the substitutents.

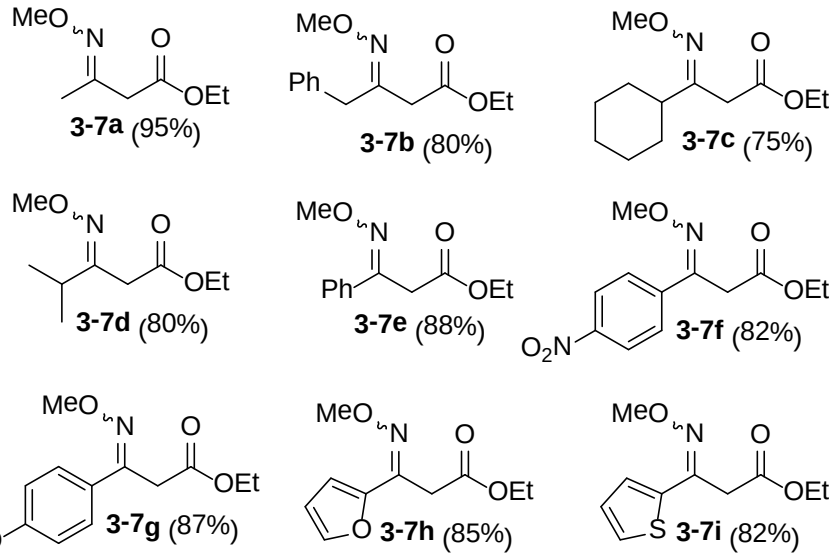


Scheme 3-10. Synthesis of **3-7j**

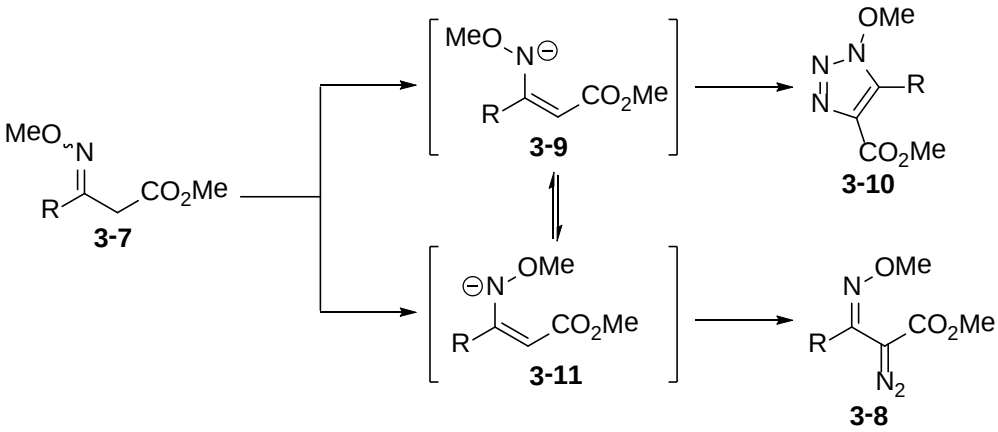
However, after diazo transfer of the azide to form the α-diazo oxime ether, only the cis diazo isomer was obtained.[11] Our group found that triazoles **3-10** also form as byproducts alongside with the cis isomers **3-8**. We reasoned that the triazole formation is due to the lone pair cis to the incoming diazo group **3-9** and it could be avoided if the geometry of an imine is controlled such that the lone pair is disposed trans to the diazo group **3-11** (Scheme 3-11).[11] In Table 3-2, the low yield of α-diazo oxime ethers **3-8a** and **3-8b** is accountable to the formation of cis and trans isomers of the corresponding oximes, providing mixtures of α-diazo oxime ethers and triazoles. For sterically hindered substituents such as **3-8c** and **3-8d**, the methoxy oxime obtained in the first step is predominantly trans to the incoming diazo group, therefore they are all converted to the α-diazo oxime ether. In oxime compounds possessing the aromatic group such as **3-8e**, **f**, **g**, **h**, **i**, **j**, the isomers from the first step are predominantly trans to the incoming diazo group which gets converted to α-diazo oxime ether in good yields (Table 3-2).

Table 3-1. Synthesis of oximes[a]



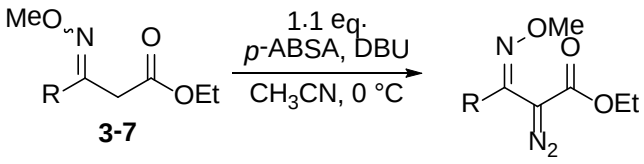


[a] β-keto ester **3-6** (2mmol), $NH_2OMe•HCl$ (2.4mmol), pyridine (1M)
[b]The reported yields in parentheses are of the isolated products.

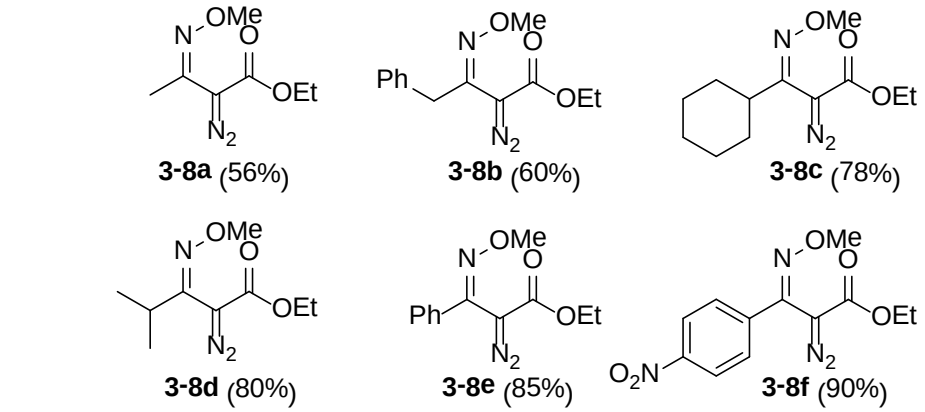


Scheme 3-11. Diazo transfer reaction on the mixture of cis/trans oxime isomers

Table 3-2. Synthesis of α-diazo oxime ether [a]



3-7 **3-8**



3-8a (56%) **3-8b** (60%) **3-8c** (78%)

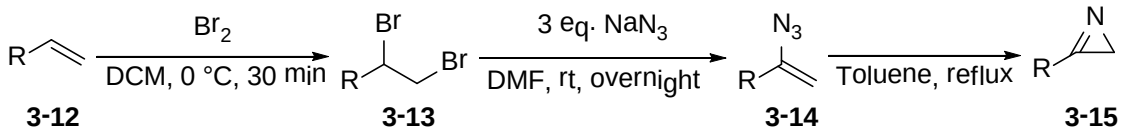
3-8d (80%) **3-8e** (85%) **3-8f** (90%)

3-8g (87%) **3-8h** (77%) **3-8i** (80%)

3-8j (85%)

[a] Oxime **3-7** (2 mmol), *p*-ABSA (2.2 mmol), DBU (2.2 mmol), CH_3CN (0.5M)
[b]The reported yields in parentheses are of the isolated products.

3.4.2 Synthesis of azirines



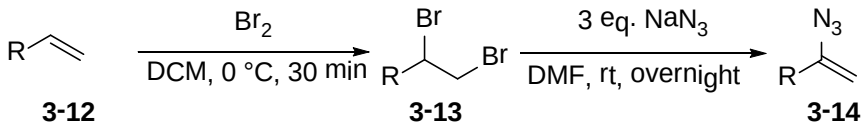
3-12 **3-13** **3-14** **3-15**

Scheme 3-12. Synthesis of mono-substituted azirines

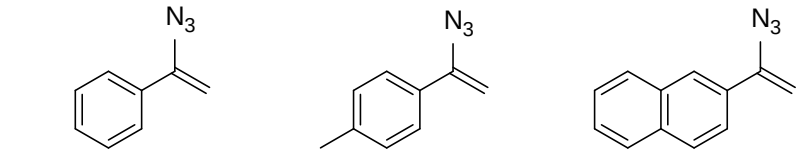
The synthesis of electron-withdrawing monosubstituted azirines began with terminal alkenes. Bromomination of alkenes, nucleophilic substitution with NaN_3,

followed by elimination of HBr give the vinyl azides **3-14**, which were converted to monosubstituted azirines **3-15** under thermal conditions (Scheme 3-12). Several electron withdrawing azides were prepared by bromination. The presence of electron withdrawing groups causes the tertiary carbon centre to be more electrophilic and thus more susceptible to nucleophilic attack of NaN_3. The second equivalent of NaN_3 acts as a base in abstracting the acidic proton at the secondary carbon centre to promote elimination. With this method, several electron-withdrawing vinyl azides **3-14** were prepared in good yields (Table 3-3).

Table 3-3. Synthesis of electron withdrawing vinyl azides [a]



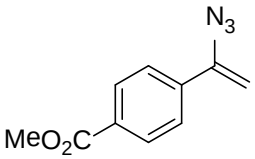
3-12 **3-13** **3-14**



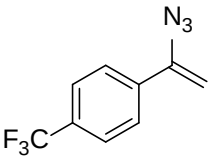
3-14a (80%)

3-14b (85%)

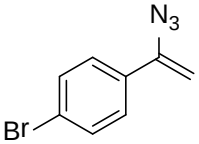
3-14c (72%)



3-14d (85%)



3-14e (89%)



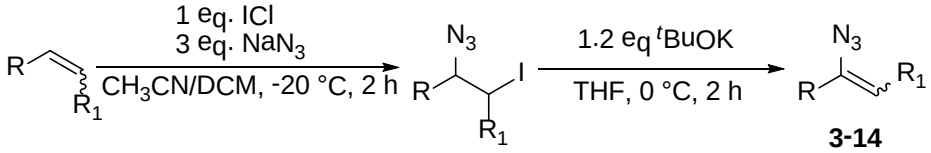
3-14f (77%)

[a] The reported yields in the parentheses are of the isolated yields.

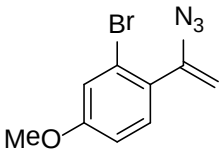
Since mixtures of regioisomers of vinyl azides were formed when the procedure above was employed, a method involving IN_3 were used. Thus by generating IN_3 *in situ*, the reaction becomes highly stereospecific (*anti*) and regiospecific as IN_3 is added across the double bond. Addition of IN_3 proceeds via a three-membered ring iodonium species, resulting in azide undergoing a backside

nucleophilic attack at the more substituted carbon or at the position that can stabilise the positive charge transition state. Anti elimination of HI gives the vinyl azide.[12] As seen from Table 3-4, the electron-donating azides **3-14** were prepared in good yields.

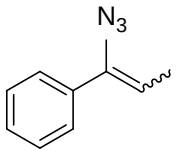
Table 3-4. Synthesis of electron donating vinyl azides [a]



3-14



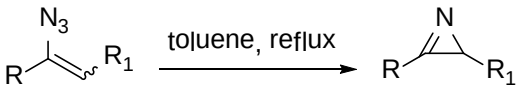
3-14g (87%)



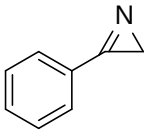
3-14h (70%)

[a] The reported yields in the parentheses are of the isolated yields.

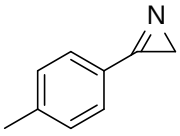
Table 3-5. Synthesis of azirines [a]



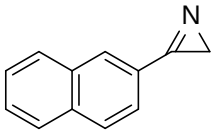
3-14 **3-15**



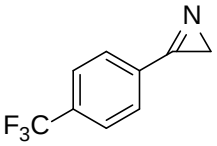
3-15a (65%)[b]



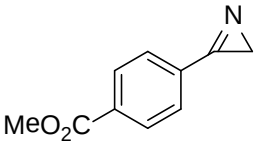
3-15b (80%)



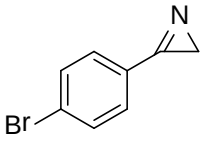
3-15c (75%)



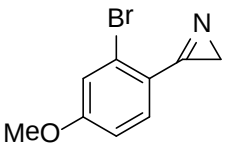
3-15d (78%)



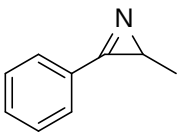
3-15e (85%)



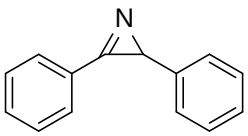
3-15f (80%)



3-15g (70%)



3-15h (75%)



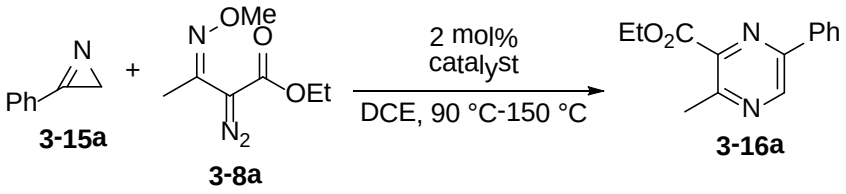
2-21l (85%)

[a] Azide **3-14** (1 mmol), toluene (0.1M) [b]The reported yields in the parentheses are of the isolated yields. [c] Azide **3-14a** (0.3 mmol), DCM (0.1M), 150°C

Besides the preparation of azirines from the Neber reaction as discussed in Chapter 2, azirines can be easily prepared from vinyl azides via the nitrene intermediate with expulsion of nitrogen gas. However, azirines are thermally unstable with slight decomposition even at ambient temperature.[13] The nitrene intermediate are known to cause side reactions such as polymerization and triazole formation.[12, 14] Thus, the reaction should be sufficiently diluted and minimise prolong heating. Therefore, the optimal condition is such that the vinyl azides were dissolved in toluene at 0.1M to ensure sufficient dilution and heated at reflux for a short period of time. As seen in Table 3-5. the azirines were prepared in good yields however, there is a decrease in yield of azirine **3-15a** as it is volatile.[14]

3.4.3 Optimisation of reaction conditions

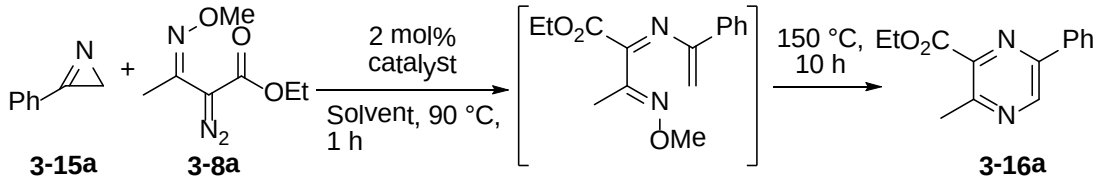
Our initial efforts to realize the transformation commenced by screening different catalyst with azirine **3-15a** and *α*-diazo oxime ether **3-8a** in 1,2-dichloroethane (DCE) at 90 °C and subsequently heating the reaction to 150 °C to ensure complete cyclisation (Scheme 3-13).



Scheme 3-13. Initial studies to synthesize pyrazine

Herein, a variety of metal complexes were screened to optimise the reaction with fixed temperature at 90 °C and then at 150 °C in Table 3-6. Apart from screening different catalysts, different solvents were also screened.

Table 3-6. Optimisation pyrazine synthesis.[a]



3-15a **3-8a** **3-16a**

Entry	Catalyst	Solvent	Yield%[b]
1	$Rh_2(OAc)_4$	DCE	-
2	$Rh_2(esp)_2$	DCE	-
3	$Cu(OAc)_2$	DCE	30
4	$Cu(acac)_2$	DCE	55
5	$Cu(OTf)_2$	DCE	64
6	$(CuOTf)_2 \bullet C_6H_6$	DCE	50
7	$Cu(Tfacac)_2$	DCE	60
8	$Cu(hfacac)_2$	DCE	87
9	$Cu(hfacac)_2$	Toluene	83
10	$Cu(hfacac)_2$	Chlorobenzene	79

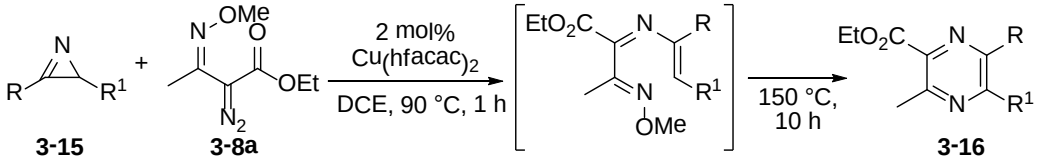
[a] Reaction conditions: **3-15a** (0.3 mmol), **3-8a** (0.36 mmol), solvent (0.15M). [b] Yields are isolated yields.

Reaction with rhodium catalysts failed to give the pyrazine **3-16a** (Table 3-6, entries 1 and 2). From the different copper catalysts that were screened, $Cu(OAc)_2$ and $Cu(acac)_2$ gave the desired product albeit in low yield, 30% and 55% respectively (Table 3-6, entries 3 and 4). In table 3-6, entries 5 and 6, a comparison was made by using Cu(II) and Cu(I) and the reaction seems to work better with Cu(II) yielding 64% and 50% respectively. In contrast, with electron-deficient Cu catalyst such as $Cu(OTf)_2$, $Cu(Tfacac)_2$ and $Cu(hfacac)_2$ (Table 3-6, entries 5, 7 and 8), the yields were drastically improved as $Cu(hfacac)_2$ emerged as the best catalyst for the reaction providing the pyrazine **3-16a** in 87%. Reaction of $Cu(hfacac)_2$ with different solvents such as toluene and chlorobenzene gave similar yields of 83% and 79%, respectively (Table 3-6, entries 9-10). Ultimately, we decided on the optimised condition using

$Cu(hfacac)_2$ as a catalyst and DCE as a solvent. We postulate that the electron deficient Cu catalyst is necessary for the formation of ylide from the Cu carbenoid.

Encouraged by these results, we turned our attention to the substrate scope of the reaction. To develop a synthetic protocol which provides unsymmetrical pyrazines with a wide range of substitution, we first surveyed various 2*H*-azirines by reacting with *α*-diazo oxime ethers **3-8a** (Table 3-7).

Table 3-7. Scope of azirines in unsymmetrical pyrazine synthesis.[a]



3-15 **3-8a** **3-16**

3-16a (87%) **3-16b** (65%) **3-16c** (57%)

3-16d (82%) **3-16e** (76%) **3-16f** (67%)

3-16g (78%) **3-16h** (68%) **3-16i** (63%) **3-16j** (42%)

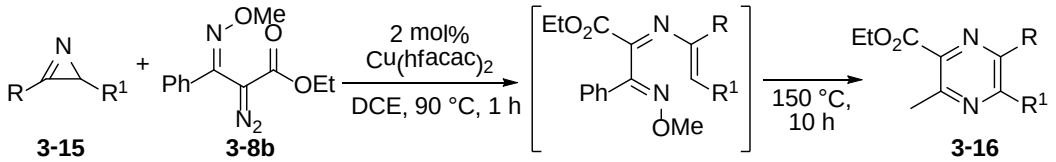
[a] Reaction conditions: azirine **3-15** (0.3 mmol), **3-8a** (0.36 mmol), DCE (0.15 M). The reported yields in the parentheses are of the isolated products.

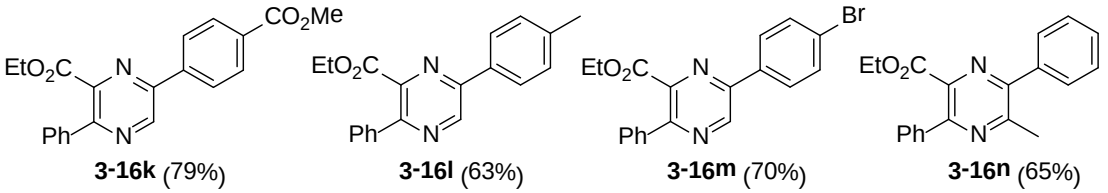
A survey of 2*H*-azirines with various substitutions showed that the transformation is generally well tolerated and provides the pyrazine in good yields (Table 3-7). 3–Phenyl-substituted 2*H*-azirine reacted well including those with tolyl and naphthyl groups (**3-16a-c**) yielding 87%, 65% and 57% respectively. The presence of electron-withdrawing azirines probably makes the terminal alkene on the triene

more susceptible for nucleophlic attack by the oxime thus gave excellent yields of the corresponding pyrazine in 82%, 76% and 78% (**3-16d**, **3-16e**, **3-16g**). Electron donating azirine also gave good yield of the pyrazine in 67% (**3-16f**). Disubstituted azirine **3-16h**, **3-16i**, **3-16j** gave moderate to low yields of the corresponding pyrazine providing 68%, 63% and 42%. The low yield of **3-16j** is probably due to sterics causing the triene to be in a wrong conformation for cyclisation.

With the optimised conditions, we went on to screen various 2*H*-azirines by reacting with *α*-diazo oxime ether **3-8b** (Table 3-8).

Table 3.8 Scope of azirine in pyrazine synthesis.[a]





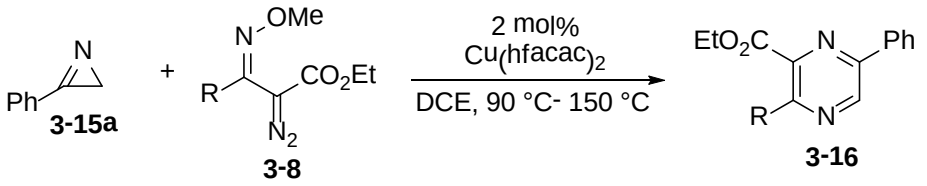
[a] Reaction conditions: azirine **3-15** (0.3 mmol), **3-8b** (0.36 mmol), DCE (0.15M). The reported yields in the parentheses are of the isolated products.

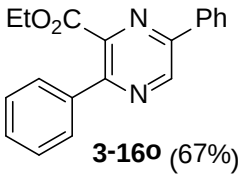
Similarly, tolyl substituted 2*H*-azirine gave the corresponding pyrazine **3-16l** in good yields of 63%. Reactions with electron-withdrawing azirines also gave excellent yields of the corresponding pyrazine in 79% and 70% (**3-16k**, **3-16m**). Disubstituted azirine gave moderate yield of the corresponding pyrazine **3-16n** in 65%.

Next, we turned our attention to examine the scope of the other reaction partner. A survey of α-diazo oxime ether with various substitutions showed that the

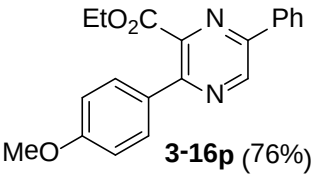
transformation is also generally well tolerated and provides the pyrazines in good yields (Table 3-9).

Table 3-9. Scope of α-diazo oxime ether in unsymmetrical pyrazine synthesis.[a]

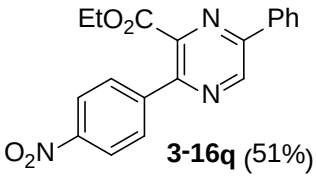




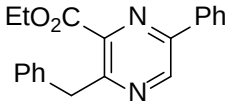
3-16o (67%)



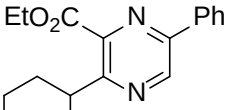
3-16p (76%)



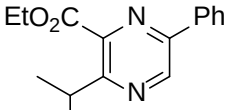
3-16q (51%)



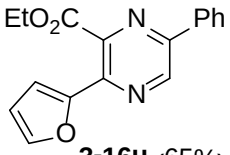
3-16r (77%)



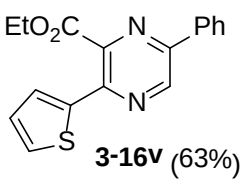
3-16s (76%)



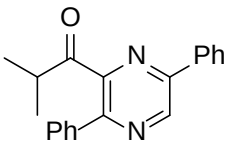
3-16t (80%)



3-16u (65%)



3-16v (63%)



3-16w (60%)

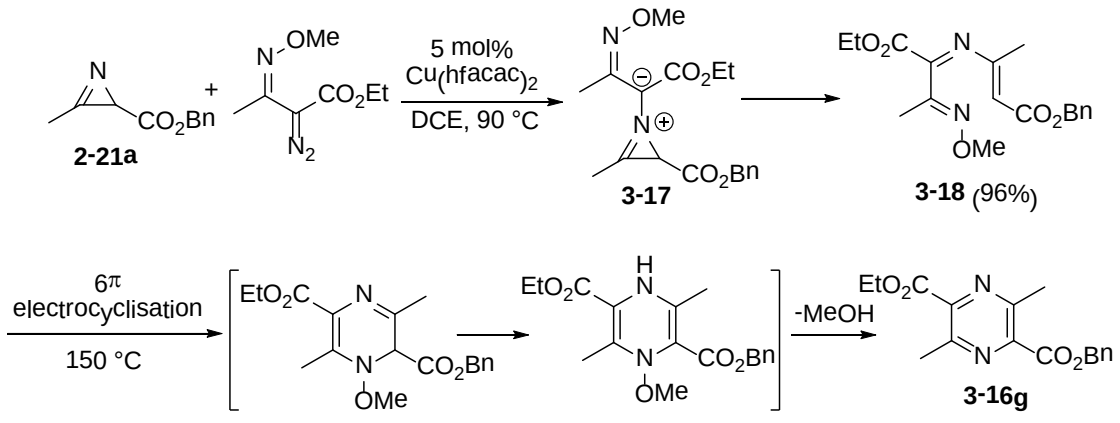
[a] Reaction conditions: azirine **3-15a** (0.3 mmol), α-diazo oxime ether **3-8** (0.36 mmol), DCE (0.15M). The reported yields in the parentheses are of the isolated products.

Examination of the electronic effect by substitution of the phenyl group on the α-diazo oxime ether with electron-donating and electron-withdrawing groups showed a trend in reactivity. The diazo compounds with electron-donating group gave the corresponding pyrazine **3-16p** in good yield of 76%. A non substituted phenyl diazo compound gave the corresponding pyrazine **3-16o** in 67% and diazo compound with electron-withdrawing group gave a slight decrease in yield of **3-16q** in 51%. This trend shows that electron-donating group on the diazo compound aids in the cyclisation perhaps making the nitrogen of the oxime more electron rich for

nucleophilic attack. Screening of the alkyl substituted diazo compounds including those with primary and secondary alkyl groups reacted well providing pyrazine **3-16r**, **s**, **t** in 77%, 76% and 80% yield. Extension of the reaction to heteroaryl-substituted diazo compounds proved successful to afford pyrazine **3-16u** and **3-16v** in 65% and 63% respectively. To examine the necessity of an ester group at the 2-position of the α-diazo oxime ether for successful transformation, the ketone substituted diazo compound was subjected to the optimised reaction conditions. Delightfully, the substrate smoothly reacted to give the pyrazine **3-16w** in 60% yield.

3.4.4 Mechansitic studies

When the reaction was carried out with azirine **2-21a**, the triene **3-18** was isolated in 96% and was further subjected to thermal conditions at 150°C to provide the pyrazine **3-16g** in 70% yield. This indicates that the reaction was proposed to be initiated by the formation of the ylide **3-17** which triggers ring opening of 2*H*-azirine **2-21a** to afford the azatriene **3-18**. Subsequent 6π-electrocyclization and elimination of methoxy group leads to the formation of unsymmetrical pyrazine **3-16g** (Scheme 3-14).



Scheme 3-14. Carbenoid mediated ring opening of azirine to form pyrazine

3.4.5 Conclusion

In conclusion, we have successfully developed a novel synthesis of unsymmetrical pyrazines via the activation of 2*H*-azirines with *α*-oximino carbenoids. This method allows the formation of unsymmetrical pyrazines bearing a broad range of substitution in good yields and requires a low catalyst loading.

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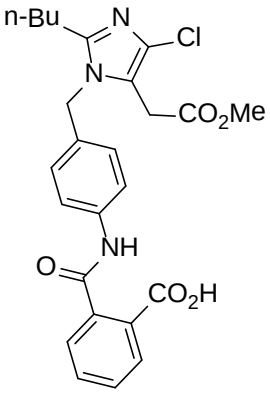
Chapter 4: Au(I)-Mediated Reaction of *α*-Diazo Oxime Ethers with Alkenyl Ethers and Nitriles

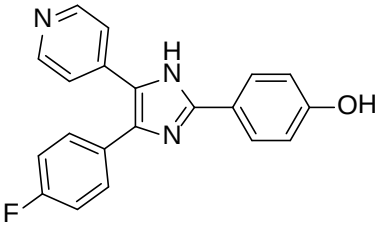
4.1 Introduction

4.1.1 Overview

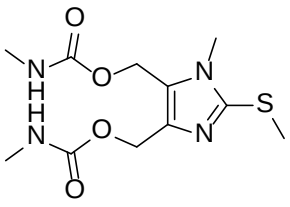
Imidazoles and pyrroles represent important classes of heterocycles that are widely found in drug molecules, natural products. Imidazole moieties are found in many natural product and drug cores, such as angiotensin II inhibitors[1], anti-inflammatory[2] and anti-cancer agents[3], as well as building blocks of naturally occurring products such asin the root extract of *Lepidiummeyenii*[4].



angiotensin II

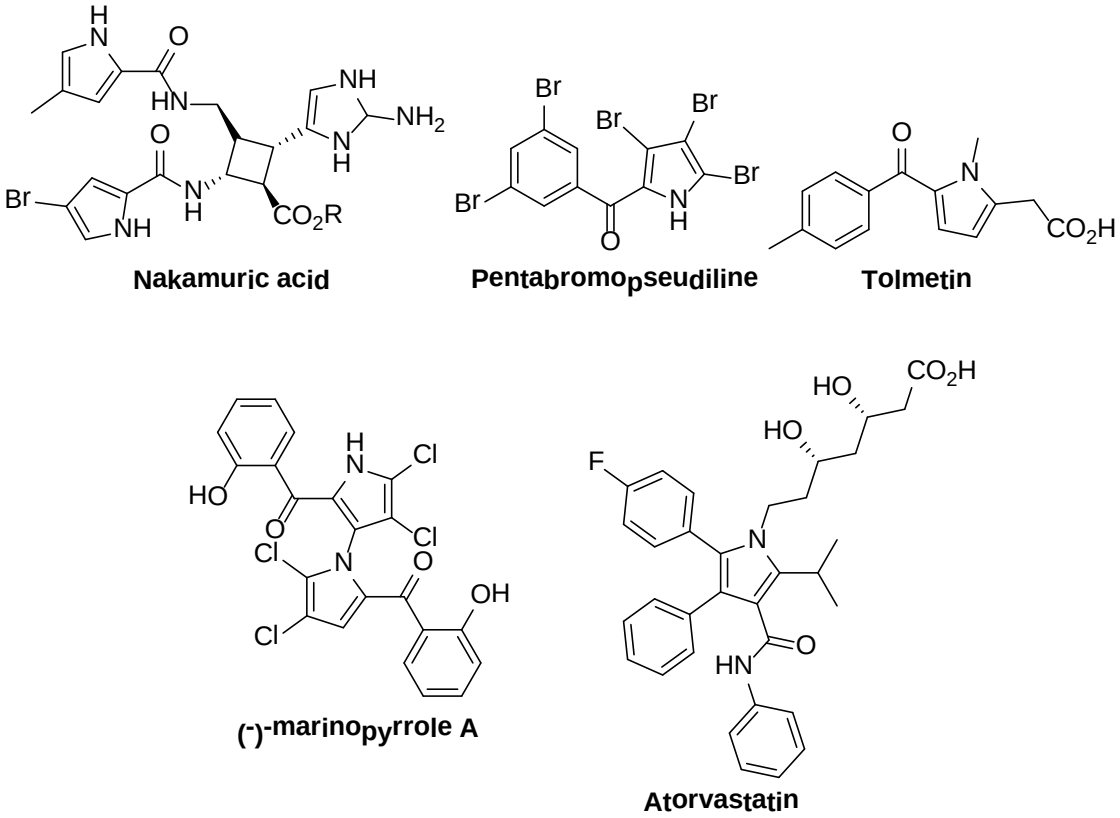


anti-inflammatory agent



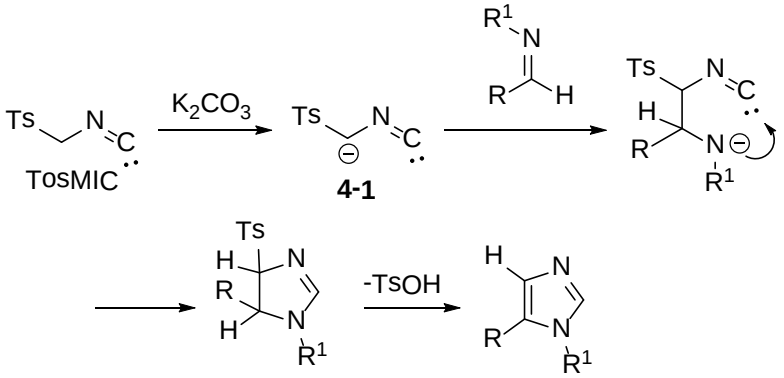
anti-cancer agent

Pyrroles are also found in marine natural products such as nakamuric acid[5] and marinopyrroles[6], which showed good activity against metacillin-resistant Staphylococcusaureus strains.[7] They are also found in top selling drugs such as the anticancer drug tallimustine[8], anti-inflammatory compound tolmetin[9], and the cholesterol-lowering agent atorvastatin[10]. With a huge market for pyrrole deriavatives as a precursor, it further highlights the importance to develop novel and efficient ways to synthesize pyrroles.



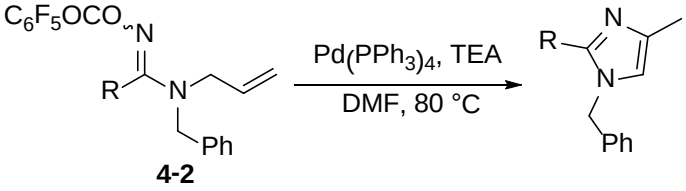
4.1.2 Methods for imidazole synthesis

Owing to the wide applicability of imidazoles, methodologies for this class of compounds have been intensively developed. The classical method is the Van Leusen imidazole synthesis. The reaction is driven by TosMIC which undergoes a deprotonation to form intermediate **4-1**. Subsequently, stepwise cycloaddition to a polarized double bond under basic conditions and elimination of *p*-toluenesulfinic acid (TsOH) from the intermediate 4-tosyl-2-imidazoline provides a 1,5-disubstituted imidazole.[11]



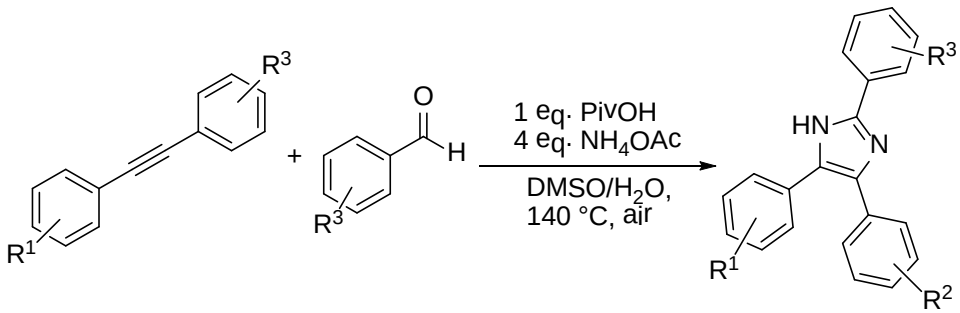
Scheme 4-1. Van Leusen imidazole synthesis

Recently, Abell found that the substrate **4-2** undergoes amino Heck reaction and cycloisomerization to give the imidazole with $Pd(PPh_3)_4$ (Scheme 4-2).[12]



Scheme 4-2. Synthesis of imidazole via cycloisomerization

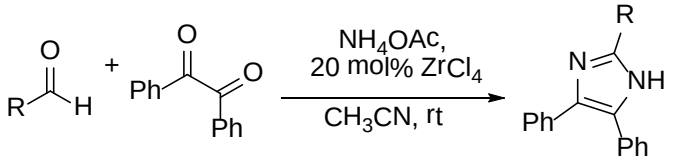
In the example of metal-free synthesis of substituted imidazoles, Wang used an internal alkyne, aldehyde in one-pot via pivalic acid promoted benzil formation followed by cyclocondensation of amidines through a multicomponent strategy. This strategy allows the synthesis of highly substituted imidazoles (Scheme 4-3).[13]



Scheme 4-3. Metal free synthesis of imidazole

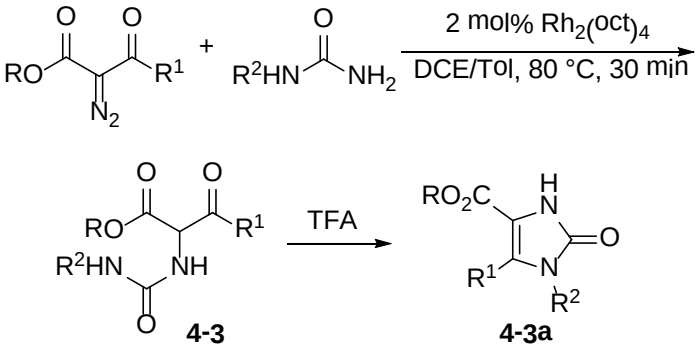
In another example, Sharma developed the three component Zr-catalysed synthesis of imidazole from benzil, aldehyde and NH_4OAc. Although the mechanism was not proposed in the paper, the reaction was believed to undergo Zr-catalysed

condensation with NH_4OAc to form the diamine and further condensation with aldehyde to form the imidazole under mild conditions (Scheme 4-4).[14]



Scheme 4-4. Zr-catalysed synthesis of imidazole

Closer to our work with the use of diazo compounds, Janda used N-H insertion reaction of primary ureas into highly reactive rhodium carbenoid intermediates. Then, acid-catalyzed cyclodehydration of intermediate **4-3** affords the desired imidazolone **4-3a** (Scheme 4-5).[15]

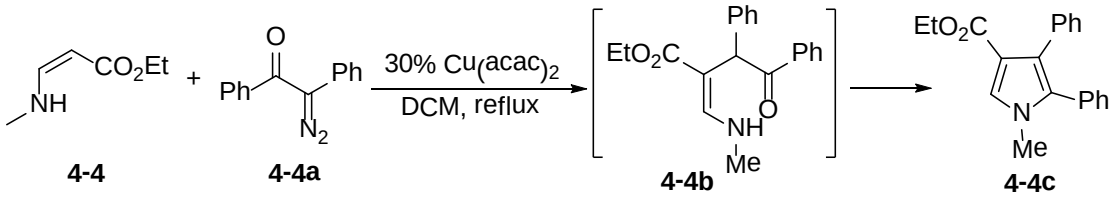


Scheme 4-5. Synthesis of imidazole from diazo

4.1.3 Methods for pyrrole synthesis

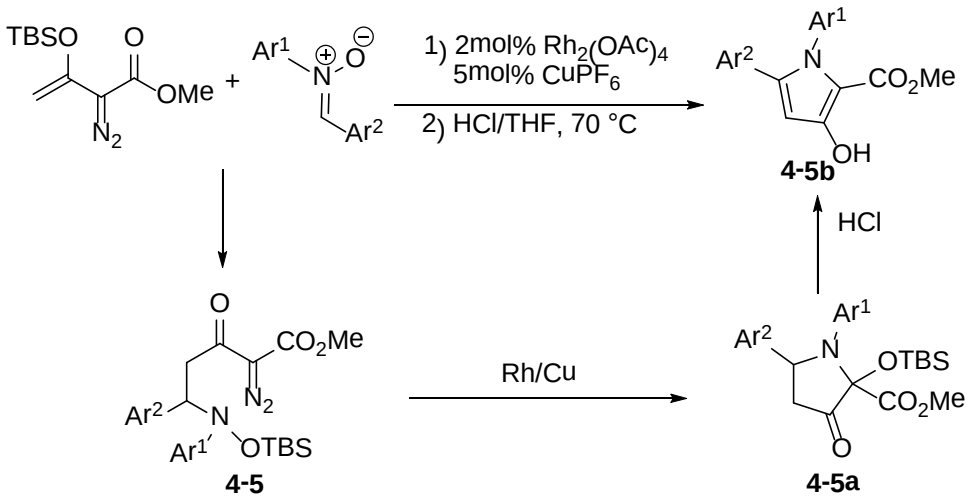
The prevalence of the pyrrole moiety in drugs and natural products has led to continual efforts in discovering new methods for the synthesis of pyrrole. The classical methods are Piloty-Robinson pyrrole synthesis[16], Paal Knorr pyrrole synthesis[17] and Hantzsch pyrrole synthesis[18]. Despite the success of pyrrole synthesis, many methods are constantly being developed. Herein, we decided to focus on the application of carbenoid on the synthesis of pyrroles.

Eberlin and Kascheres developed the synthesis of pyrroles by the Cu(II)-catalysed cycloaddition of enamines **4-4** and diazoketone **4-4a**. The reaction proceeds through nucleophilic attack of enamine **4-4b** to the copper carbene complex followed by a cyclisation to give the pyrrole **4-4c**. However, a mixture of regioisomeric pyrroles was formed due to competing N-H insertion of the enamine (Scheme 4-6).[19]



Scheme 4-6. Cu(II) catalysed cycloaddition of enamine and diazoketone

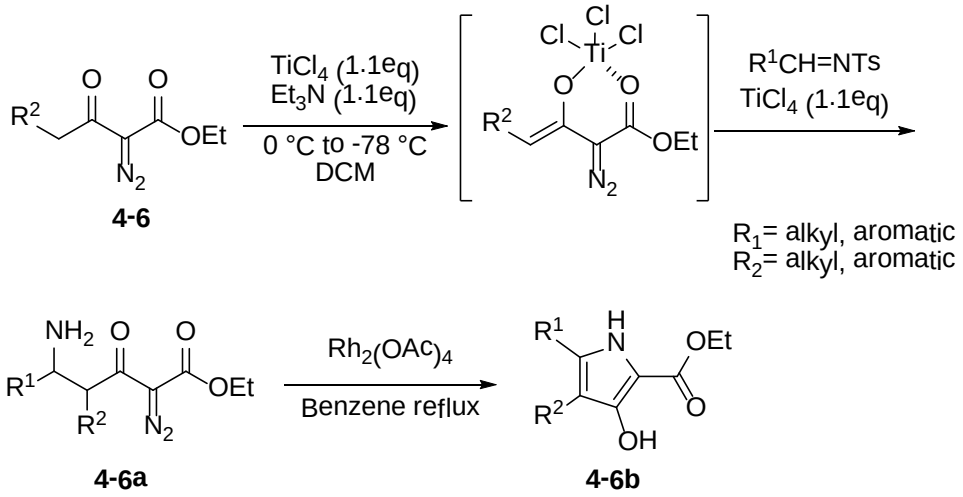
Similarly, Doyle and co-workers reported Cu(II)-catalysed Mannich reaction for the synthesis of the diazo **4-5** which would undergo the Rh/Cu catalysed N-O insertion to give the pyrrolidinone **4-5a**. Under acidic conditions, the pyrrolidinone would provide the pyrrole **4-5b** in one-pot (Scheme 4-7).[20]



Scheme 4-7. Rh catalysed N-O insertion to form pyrrole

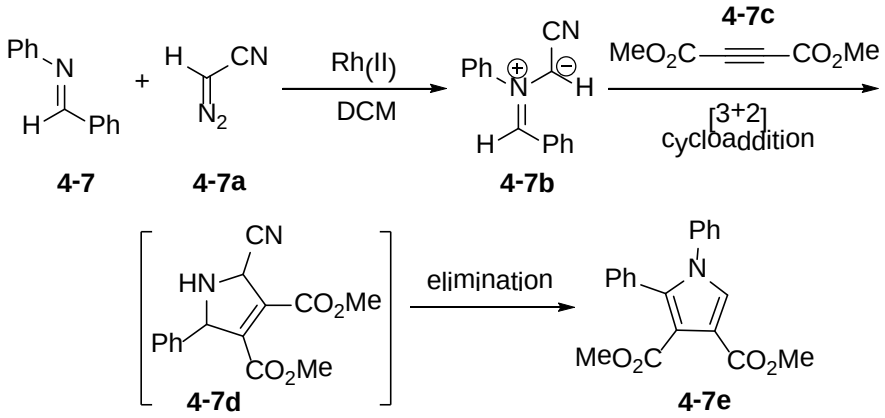
Shown in Scheme 4-8, Wang and co-workers developed pyrrole synthesis based on N-H insertion.Nucleophilic addition of Ti(IV) enolates derived from α-diazo-β-keto carbonyl compounds **4-6** to *N*-tosylimines gives the diazo intermediate **4-6a**,

which would subsequently undergo Rh-catalysed N-H insertion to give tetrasubstituted pyrrole **4-6b** (Scheme 4-8).[21]



Scheme 4-8. Intramolecular N-H insertion to pyrrole

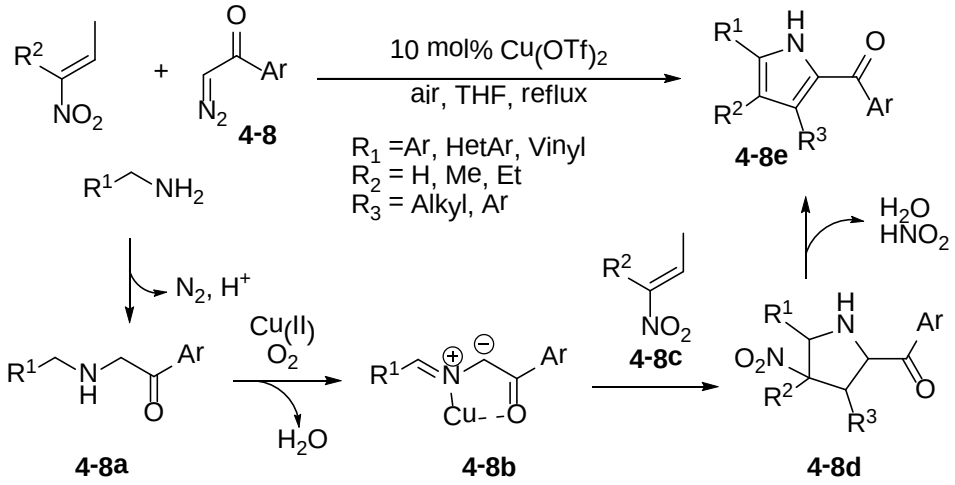
In another example, Scheidt and co-workers developed cycloaddition of ylides for the synthesis of multi component trisubstituted pyrroles from diazo compounds. In this Rh-catalysed reaction, the diazo **4-7a** forms an azomethine ylide **4-7b** with imine **4-7** which then undergoes a [3+2] cycloaddition with the alkynyl dipolarophile **4-7c**. This intermediate **4-7d** then undergoes spontaneous elimination to form the aromatic pyrrole **4-7e** (Scheme 4-9).[22]



Scheme 4-9. Rh catalysed cycloaddition to pyrrole

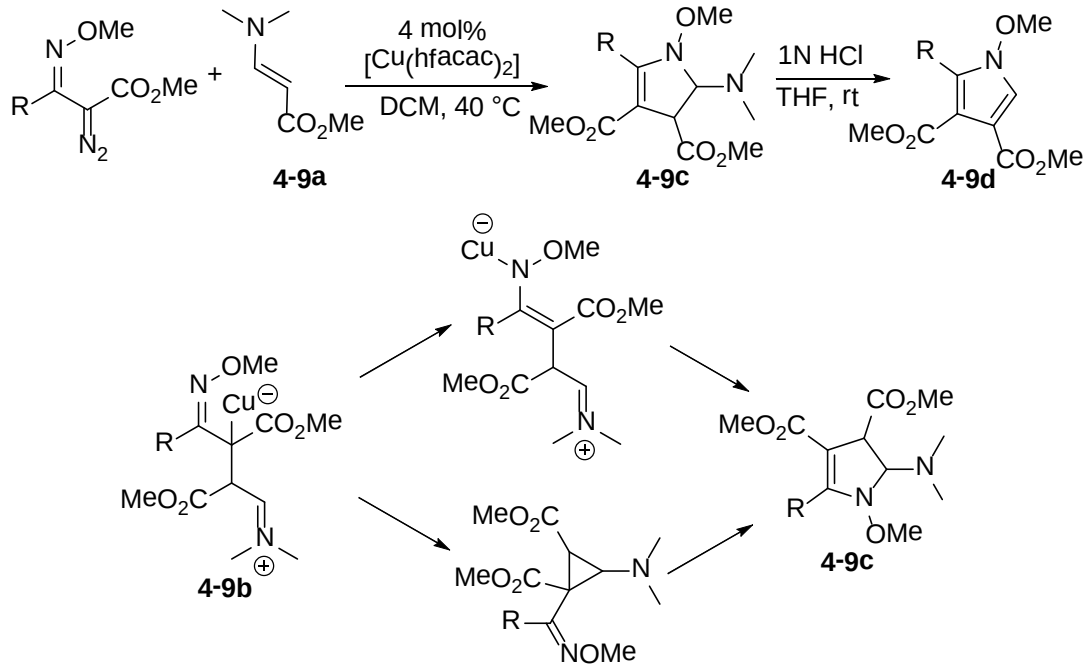
Similarly, Wang and co-workers reported a Cu(I)-catalysed N-H insertion to carbenoid followed by [3+2] cycloaddition. The reaction first undergoes an N-H

insertion reaction to the keto diazo **4-8** to form the secondary amine **4-8a** which then oxidative dehydrogenation and [3+2] cycloaddition to form azomethine ylide **4-8b** with nitroalkene **4-8c** to form the pyrrolidine **4-8d**. The pyrrolidine **4-8d** then undergoes a HNO_2 elimination and dehydrogenative aromatization to form the pyrrole **4-8e** (Scheme 4-10).[23]



Scheme 4-10. $Cu_{(I)}$ catalysed N-H insertion of diazo to form pyrrole

Our group has also showed the synthesis of pyrroles from α-diazo oxime ethers. It was proposed that nucleophilic addition of the enamine **4-9a** to the electrophilic carbenoid **4-9** forms the zwitterionic intermediate **4-9b**. Two possible pathways are shown and one undergoes a metallotropy and nucleophilic addition to give **4-9c**, while the other goes through a cyclopropane intermediate and ring exapansion to give **4-9c**. Treatment with acid gives the pyrrole **4-9d** (Scheme 4-11).[24]

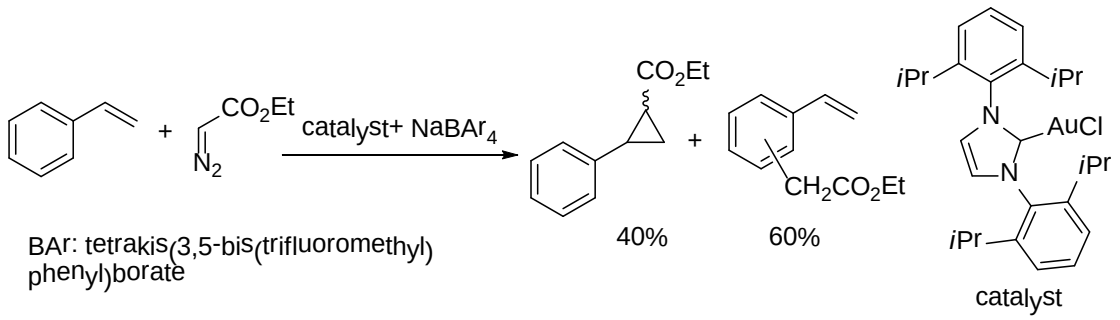


Scheme 4-11. Synthesis of pyrrole from oximino carbenoid

4.1.4 Studies on gold carbenoid reactions

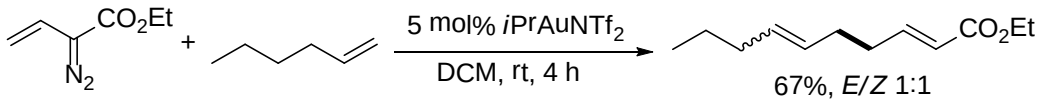
Inspired by the various strategies for the synthesis of imidazoles and pyrroles, we explored gold(I) catalyst in the synthesis of imidazoles and pyrroles via the oximino carbenoid.

Gold has gained popularity in the area of generating carbenoids without the diazo precursor, leading to the synthesis of various heterocycles.[25] Recently, the use of gold catalyst to decompose diazo compounds to form carbenoids has been reported. The first reported example demonstrated the use of Au catalyst transfer of carbene from ethyl diazoacetate to olefins (Scheme 4-12).[26]

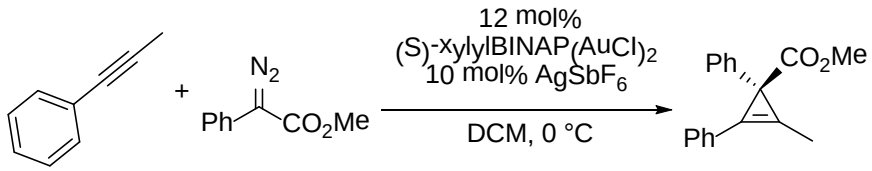


Scheme 4-12. First example of Au carbenoid from diazo compound

Following this seminal contribution, several methods with gold have been developed. One example is the formation of C-C bond via the Au-mediated vinyl carbenoid (Scheme 4-13).[27] Also, Davies demonstrated the Au(I)-catalysed cyclopropenation from an internal alkyne and diazo compound (Scheme 4-14).[28]

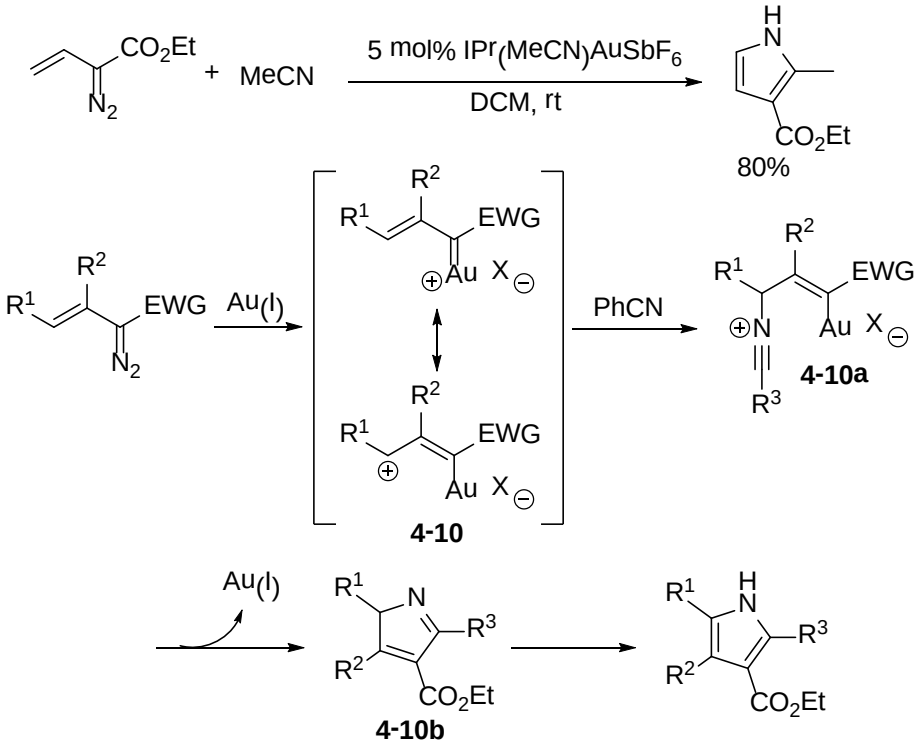


Scheme 4-13. Au(I) catalysed vinyl carbenoid in C-C bond formation



Scheme 4-14. Cyclopropanation from Au(I) carbenoid

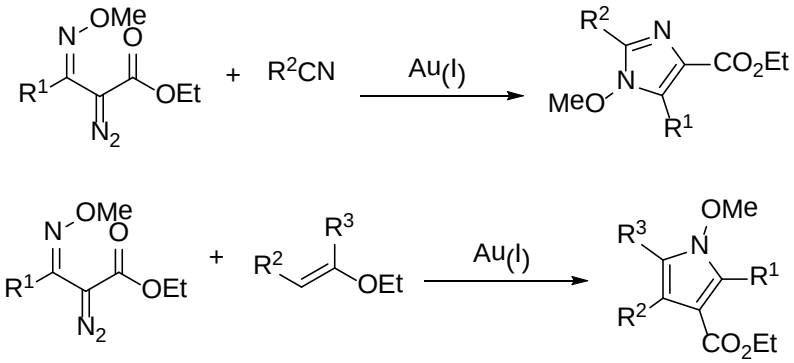
Another example closer to our project is the synthesis of pyrroles via the Au(I) catalysed [3+2] cycloaddition of vinyl diazo compounds and nitriles.[29] The first step of this reaction is the formation of carbenoid **4-10**. Subsequent nucleophilic addition of the nitrile leads to intermediate **4-10a** which cyclises spontaneously to form **4-10b** and it forms the corresponding pyrrole after tautomerisation (Scheme 4-15).



Scheme 4-15. Synthesis of pyrrole from Au carbenoid

4.2 Aims and Objectives

Based on the above example and the findings from our group (Scheme 4-11), we set out to demonstrate the Au(I)-catalysed synthesis of imidazoles and pyrroles from α-diazo oxime ethers used in chapter 3. With the α-diazo oxime ethers fixed, we decided to examine nitriles and vinyl ethers as the reaction partners for the synthesis of imidazoles and pyrroles, respectively (Scheme 4-16). We predict that under Au(I) catalysis, the reaction would proceed via the similar mechanism as that shown in Scheme 4-15.

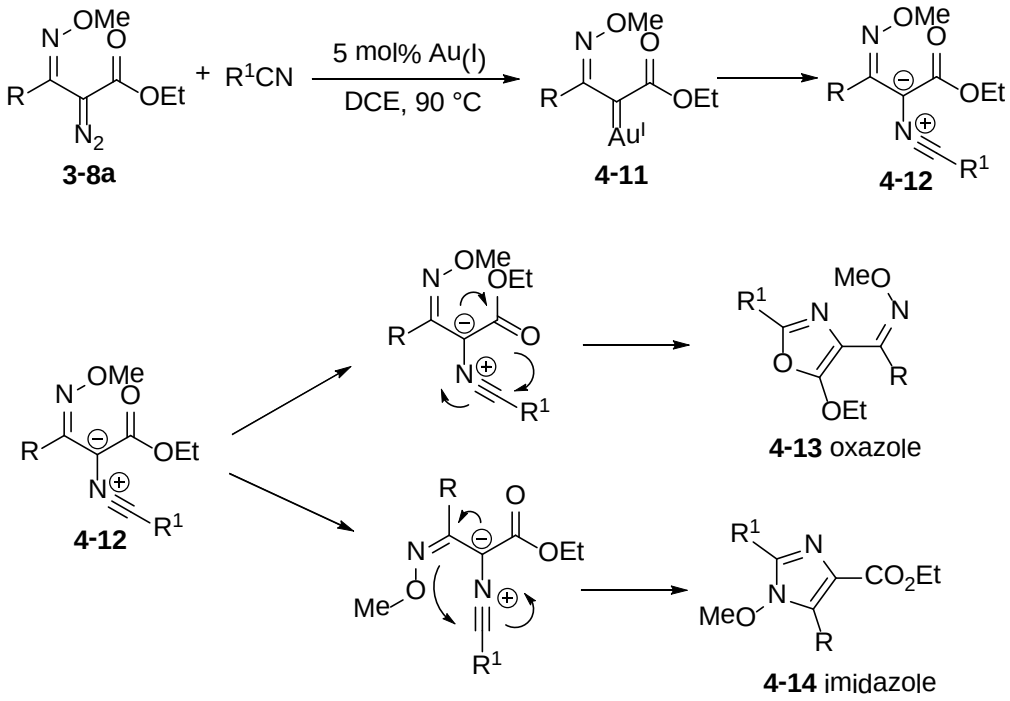


Scheme 4-16. Proposed reaction for the synthesis of imidazole and pyrrole

4.3 Results and discussion

4.3.1 Proposed mechanism of the synthesis of imidazole

Scheme 4-17 shows the mechanistic rationale for imidazole formation. It is noteworthy that two competing pathways seem feasible. In both pathways, the reaction is thought to be initiated by a nucleophilic addition of nitrile to the gold carbenoid **4-11** to form the ylide **4-12**. Subsequently, either the oxime moiety reacts to cyclise to form the imidazole or the carbonyl moiety reacts to give the oxazole (Scheme 4-17).



Scheme 4-17. Two possible reaction pathways

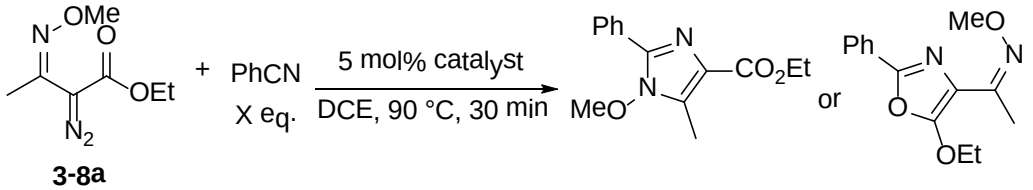
4.3.2 Optimisation of reaction conditions

A variety of metal complexes were screened to optimise the reaction in 1,2-dichloroethane (DCE) at 90°C (Table 4-1). In addition to screening different catalysts, several temperatures were also screened with 5 mol% PPh_3AuCl and AgOTf.

We were delighted to find that among different ligands screened for Au(I) catalyst, *in situ* generated PPh_3AuPF_6, PPh_3AuBF_6, PPh_3AuNTf_2 gave a cyclized

product in 78%, 45%, 79%, respectively with PPh_3AuOTf providing the highest yield (81%) (Table 4-1, entries 3-6). However, based on the ^{1}H and ^{13}C NMR data obtained, we were unable to unequivocally determine the structure. We performed IR analysis on the compound and found a peak at $1701cm^{-1}$ which is still inconclusive if the product contains an ester or an oxime. Also, the product was an oil, which made X-ray crystallographic analysis impossible. We also attempted two dimensional NMR spectroscopy on the product including COSY, NOESY, HMBC and HMQC, but due to the lack of neighbouring protons and distinct correlation, we were unable to conclude on the structure. As we continue to screen various catalysts, reaction with rhodium catalysts gave a complex mixture (Table 4-1, entries 2) whilst $Cu(hfacac)_2$ gives only 16% yield of the product with the corresponding dimer arising from dimerization of the diazo compound in 54% yield. Since the active catalyst was generated *in situ*, control experiments were done with AgOTf to examined for catalytic activity and found to give the product in 26% yield with extensive decomposition probably due to its acidic nature. Another reaction with PPh_3AuCl failed to give the product with the α-diazo oxime ether recovered in 66% yield (Table 4-1, entries 7, 8). This investigation allowed us to conclude that the active catalyst is PPh_3AuOTf and it was successfully generated *in situ*. When several reaction temperatures including room temperature, 50°C, and 70°C were examined using PPh_3AuOTf as a catalyst, the product formed in the yields of 50%, 64%, and 72%, respectively (Table 4-1, entries 9-11). Reaction at 90°C still gives the highest yield of 81%. The use of less amount of benzonitrile resulted in lower yield of the product when compared with reaction using 10 equivalents of benzonitrile. (Table 4-1, entries 12, 13).

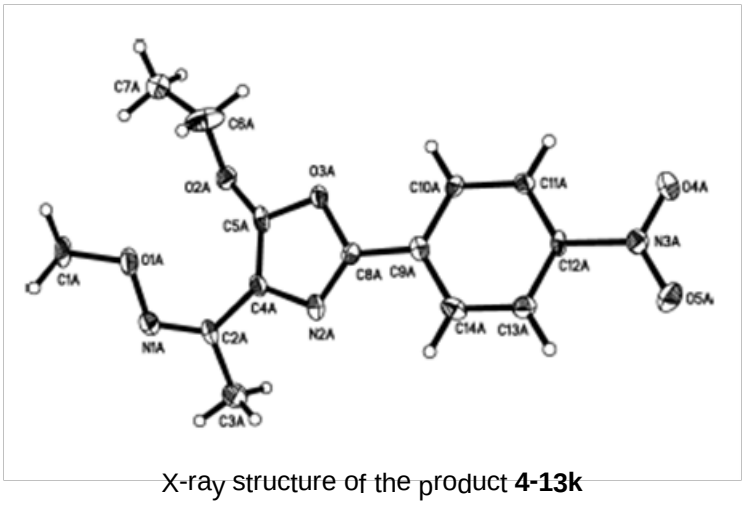
Table 4-1. Optimisation of imidazole synthesis[a]



Entry	Catalyst	*T* (°C)	X eq.	Yield [%][b]
1	$Cu(hfacac)_2$	90	10	16
2	$Rh_2(OAc)_4$	90	10	-
3	$PPh_3AuCl+AgPF_6$	90	10	78
4	$PPh_3AuCl+AgBF_4$	90	10	45
5	$PPh_3AuCl+AgNTf_2$	90	10	79
6	$PPh_3AuCl+AgOTf$	90	10	81
7	AgOTf	90	10	26
8	PPh_3AuCl	90	10	-
9	$PPh_3AuCl+AgOTf$	RT	10	50
10	$PPh_3AuCl+AgOTf$	50	10	64
11	$PPh_3AuCl+AgOTf$	70	10	72
12	$PPh_3AuCl+AgOTf$	90	2	35
13	$PPh_3AuCl+AgOTf$	90	5	64

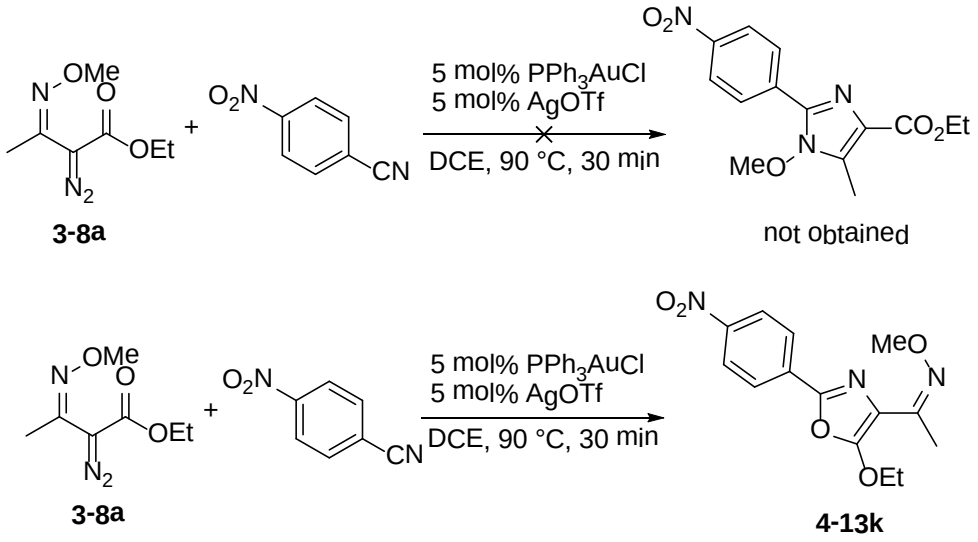
[a] Reaction conditions: **3-8a** (0.3 mmol), PhCN (X mmol), DCE (0.15 M). [b] Yields reported are of the isolated product.

Encouraged by these results, we turned our attention to the substrate scope of the reaction. While preparation of structurally diverse products, we also anticipated to find a product that is suitable for an X-ray analysis to conclude on structures. We surveyed various *α*-diazo oxime ethers **3-8** and nitriles (Table 4-2) and found that the reaction with 4-nitrobenzonitrile gives a product as solid, which allowed us to obtain a crystal structure.



X-ray structure of the product **4-13k**

Unexpectedly, the product was confirmed to be the oxazole **4-13k** instead of the imidazole. Nucleophilic attack of the carbonyl group of the ester in place of the oxime ether group resulted in the formation of the oxazole (Scheme 4-18).

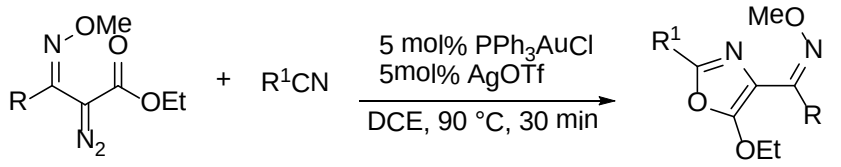


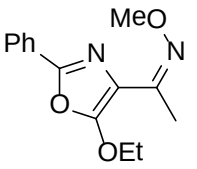
Scheme 4-18. Reaction pathway

Nevertheless, in the process of determining the structure of the product, various *α*-diazo oxime ethers **3-8** and nitriles were screened (Table 4-2). Generally, the reaction tolerates well with various diazo compounds and nitriles. When screening the *α*-diazo oxime ethers, substrates with methyl, phenyl, electron-donating, and furyl groups (**4-13a**, **4-13b**, **4-13c,4-13d**) gave excellent yields (81%, 89%, 87% and 80%, respectively). When nitriles were screened, primary and secondary alkyl groups all

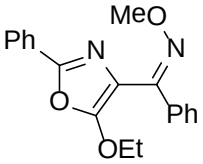
reacted well to give 95% and 86%, **4-13e**, **4-13f**. Vinyl substituted oxazole **4-13g** was also formed in good yields of 75%. Examination of the electronic effect by substitution of the phenyl group on the nitrile with electron-donating and electron-withdrawing groups showed no compromise in yields. Tolyl and bromo substituted oxazole **4-13h**, **4-13i** were formed in 83% and 70% respectively, thienyl substituted oxazole **4-13j** was formed in 80%. Electron donating substituted oxazole **4-13k** was formed in 86% and electron withdrawing substituted oxazole **4-13l** gave 76%.

Table 4-2. Scope of α-diazo oxime ethers and nitriles in oxazole synthesis[a]

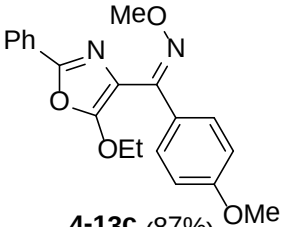




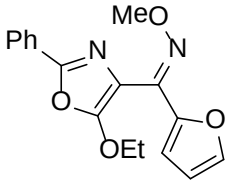
4-13a (81%)



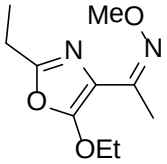
4-13b (89%)



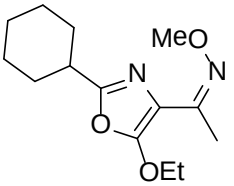
4-13c (87%)



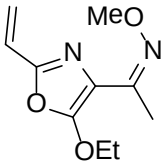
4-13d (80%)



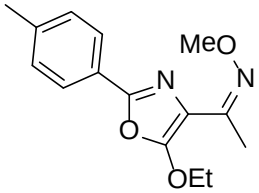
4-13e (95%)



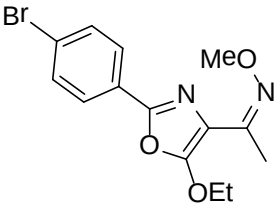
4-13f (86%)



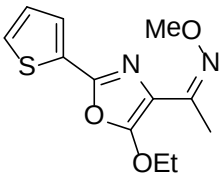
4-13g (75%)



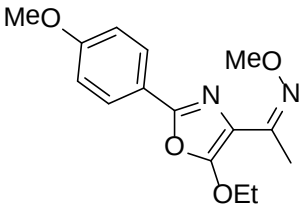
4-13h (83%)



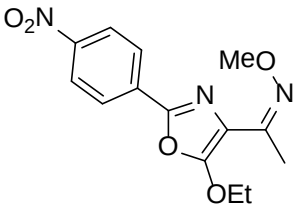
4-13i (70%)



4-13j (80%)



4-13k (86%)

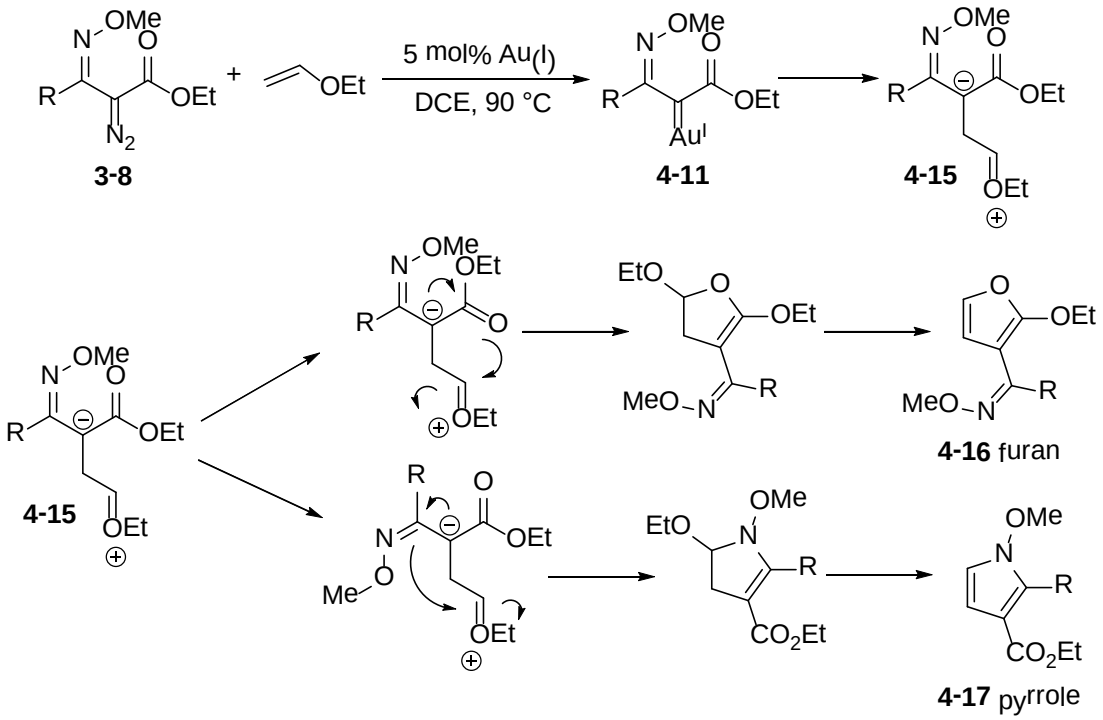


4-13l (76%)

[a] Reaction conditions: **3-8** (0.3 mmol), R^1CN (3 mmol), DCE (0.15M). [b] Reported yields are of the isolated product.

4.4 Results and discussion of the synthesis of pyrroles

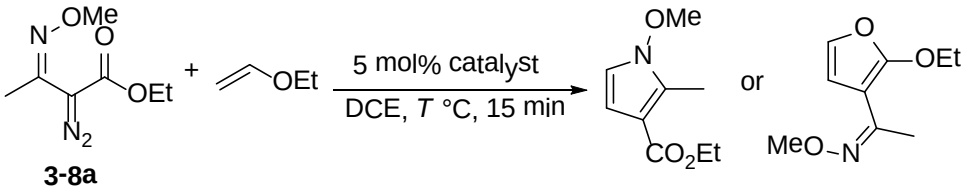
While the reaction of gold carbenoids with nitriles provides oxazoles, we were intrigued by the reactivity of those with vinyl ethers. Similar to Scheme 4-17, two competing pathways are plausible. The reaction is initiated by nucleophilic addition of vinyl ether to the gold carbenoid **4-11** to form the ylide **4-15**. Then two pathways are competing, either the oxime moiety reacts to cyclise to form the pyrrole or the carbonyl moiety reacts to cyclise to give the furan (Scheme 4-19).



Scheme 4-19. Two possible reaction pathways

Our initial efforts to synthesize pyrroles commenced with screening different gold catalyst with α-diazo oxime ether **3-8a** and ethyl vinyl ether in 1,2-dichloroethane (DCE) at 90°C (Table 4-3).

Table 4-3. Optmisation for the synthesis of pyrrole[a]



3-8a

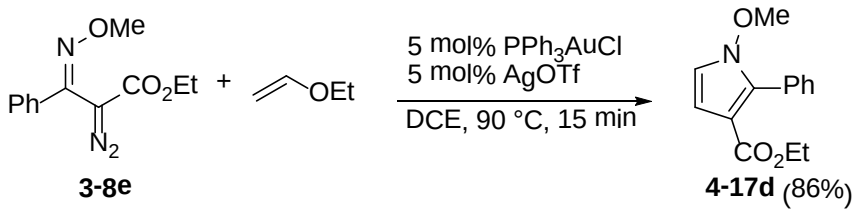
Entry	Catalyst	*T*/°C	Yield[%][b]
1	$PPh_3AuCl+AgPF_6$	90	65
2	$PPh_3AuCl+AgBF_4$	90	73
3	$PPh_3AuCl+AgNTf_2$	90	65
4	$PPh_3AuCl+AgOTf$	90	91
5[c]	$PPh_3AuCl+AgOTf$	90	57
6[d]	$PPh_3AuCl+AgOTf$	90	53
7	$PPh_3AuCl+AgOTf$	rt	50

[a] Reaction conditions: **3-8a** (0.3 mmol), vinyl ethyl ether (10 eq.), DCE (0.15M). [b] Yields reported are of the isolated products. [c] Reaction done with vinyl ethyl ether (2 eq.) with other conditions the same. [d] Reaction done with vinyl ethyl ether (2 eq.) in DCE (0.5M).

From the different ligands that were screened with Au(I) catalyst, *in situ* generated PPh_3AuPF_6, PPh_3AuBF_6, PPh_3AuNTf_2 gave the product in 65%, 73% and 65%, respectively with PPh_3AuOTf providing the best yield of 91% (Table 4-3, entries 1-4). Due to its low boiling point, excess amount of (10 equiv.) ethyl vinyl ether was employed. In an attempt to reduce the amount of ethyl vinyl ether to 2 equiv., the yield decreased to 57% (Table 4-3, entry 5). Higher concentration of ethyl vinyl ether did not improve the reaction yield (53%) (Table 4-3, entry 6). Finally, reaction temperature was screened. At room temperature, the reaction took 16 h providing only 50% yield of the product (Table 4-3, entry 7).

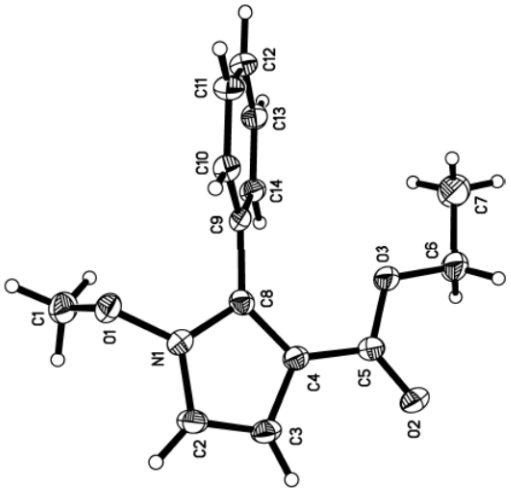
As encountered in the oxazole formation, the reaction with enol ether also raises the question of regioselectivity; pyrrole or furan. Fortunately, when phenyl oxime diazo **3-8e** was reacted with vinyl ethyl ether, the product obtained was a solid

which was recrystallised to determine the structure by X-ray diffraction analysis (Scheme 4-20).



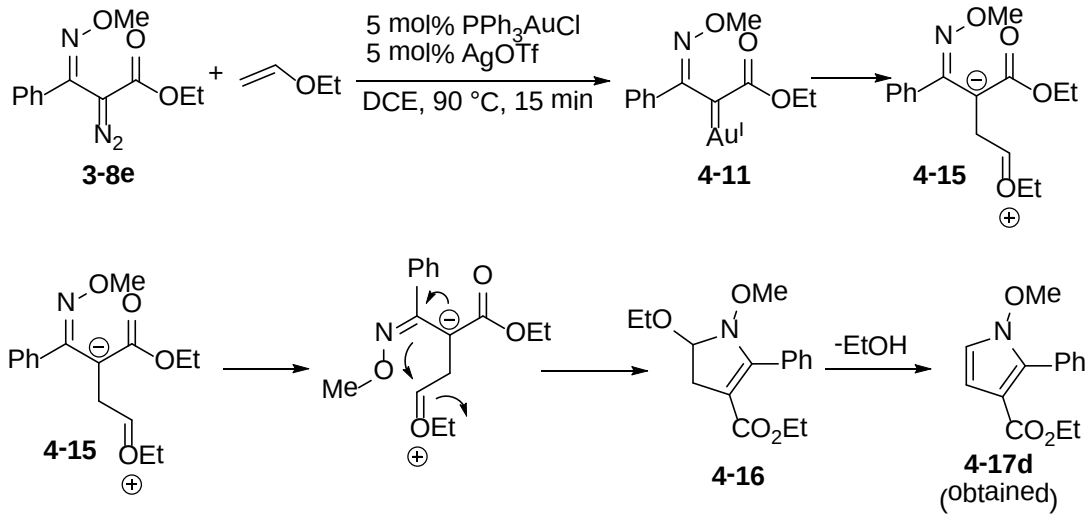
3-8e **4-17d** (86%)

Scheme 4-20. Attempts to get a crystal product



X-ray structure of **4-17d**

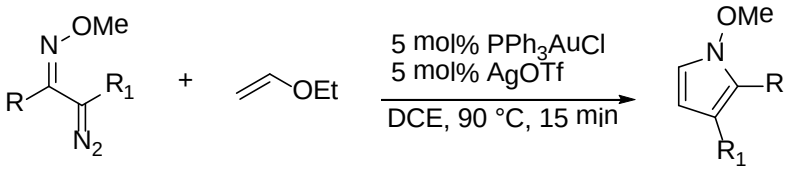
We were delighted to find that the oxime moiety reacted instead of the carbonyl moiety to give the pyrrole in this reaction (Scheme 4-22). We proposed that the reaction proceeds via the gold carbenoid intermediate **4-11** which then undergoes nucleophilic addition to form the intermediate **4-15**. Intramolecular cyclisation of the oxonium ion gave **4-16**, followed by an elimination of EtOH to provide the pyrrole **4-17d** (Scheme 4-21).



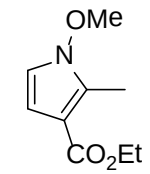
Scheme 4-21. Proposed reaction mechanism

We turned our attention to the substrate scope of the reaction. To develop a methodology which provides highly substituted pyrroles with a wide range of substitution, we first surveyed various *α*-diazo oxime ether **3-8** with ethyl vinyl ether (Table 4-4). Generally, the method works well to give pyrroles in good yields. Primary and secondary alkyl substituted *α*-diazo oxime ether worked well to give **4-17a** to **4-17c** in 91%, 81% and 88%, respectively. Aromatic substitutents with electron-donating and electron withdrawing groups showed no compromise in yields, providing **4-17d**, **4-17e** and **4-17f** in excellent yields of 86%, 80% and 90%. Heteroaryl-substituted *α*-diazo oxime ethers were also well tolerated to give pyrrole **4-17g** and **4-17h** in 79% and 88%. To determine the reactivity of oxime diazo substrates, an oxime substrate bearing a ketone group **3-8j** was synthesized to afford the pyrrole **4-17i** in moderate yield of 66% (Table 4-4).

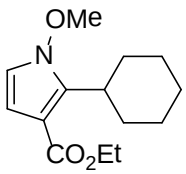
Table 4-4. Scope of α-diazo oxime ether in pyrrole synthesis [a]



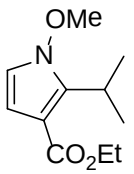
3-8 **4-17**



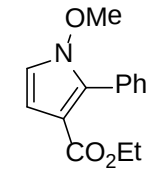
4-17a (91%)



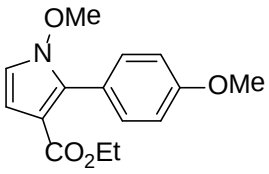
4-17b (81%)



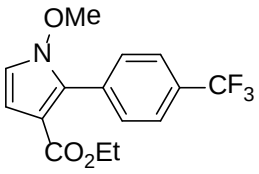
4-17c (88%)



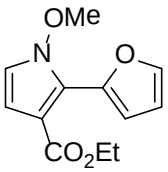
4-17d (86%)



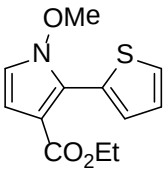
4-17e (80%)



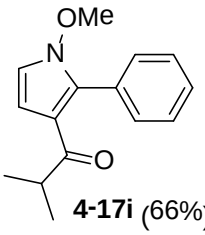
4-17f (90%)



4-17g (79%)



4-17h (88%)

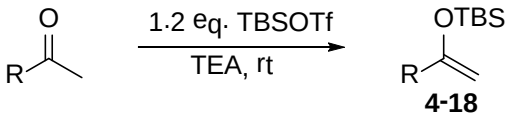


4-17i (66%)

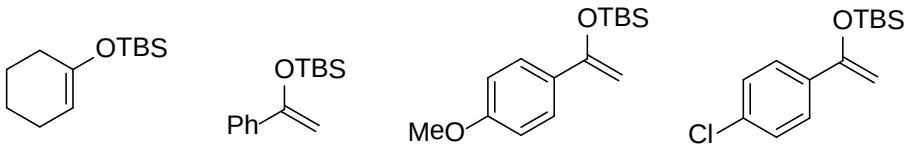
[a] Reaction conditions: **3-8a** (0.3 mmol), vinyl ethyl ether (10 eq.), DCE (0.15M).
[b] The reported yields in the parentheses are of the isolated products.

Next, we went on to synthesize various vinyl ether to expand the scope with several *α*-diazo oxime ethers (Table 4-6). It is noteworthy that in the screening of vinyl ethers, 3 equivalents of vinyl ethers were sufficient for efficient formation of pyrroles compared to the large excess amount of ethyl vinyl ether due to its low boiling point (Table 4-4). All the vinyl ethers synthesized from TBSOTf and ketone affording excellent yields (Table 4-5).

Table 4-5. Synthesis of vinyl ethers



4-18

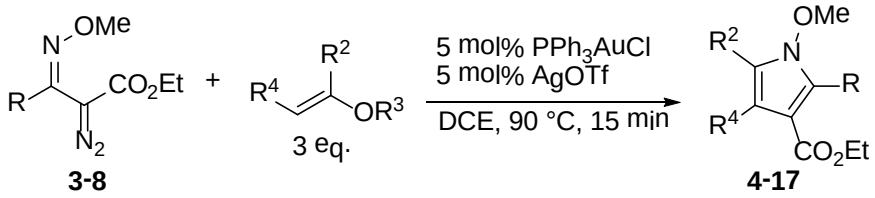


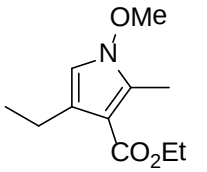
4-18a (95%) **4-18b** (100%) **4-18c** (96%) **4-18d** (95%)

[a] Reported yields in the parentheses are all isolated yields.

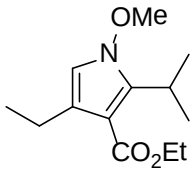
The reaction generally tolerates a wide range of substituents. When the primary and secondary diazo compounds were screened with methyl substituted vinyl ether, the reaction proceeded smoothly to give **4-17j** and **4-17k** in 76% and 77% yield. Reaction of primary and secondary diazo compounds **3-8l** (R= CH_3) and **3-8m** (R= ^{i}Pr) with cyclohexyl ennol ether affords tetrasubstituted pyrroles in 75% and 56% yields, respectively. Also, the reaction of phenyl substituted diazo gives **4-17n** in 76%. The reaction also works well with phenyl vinyl ether **4-18b** and several α-diazo oxime ethers bearing primary and secondary alkyl substituted diazo compounds to give **4-17o** and **4-17p** in 82% and 76%. Reaction of phenyl vinyl ether **4-18b** with electron-donating and electron-withdrawing aromatic diazo compounds showed a trend that the diazo compound with an electron withdrawing group works better to give **4-17s** (92%) compared to **4-17q** and **4-17r** (70% and 66%, respectively). This trend may indicate that electron-withdrawing substituents stabilises the transition state necessary for cyclisation. When vinyl ethers bearing electron-rich aryl groups were reacted with methyl and phenyl diazo compounds, pyrroles **4-17t** and **4-17u** were formed in 60% and 70%, respectively. Likewise, the reaction with 4-chlorophenyl-substituted vinyl ether **4-18d** proceeds smoothly to give **4-17v** (74%) and **4-17w** (70%).

Table 4-6. Scope of vinyl ether in pyrrole synthesis [a]

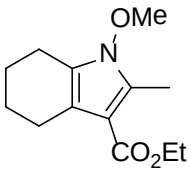




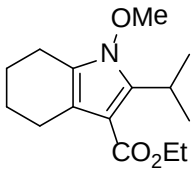
4-17j (76%)



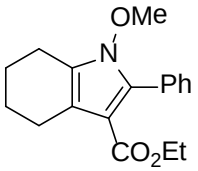
4-17k (77%)



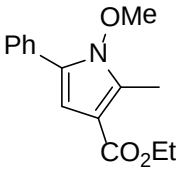
4-17l (75%)



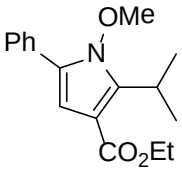
4-17m (56%)



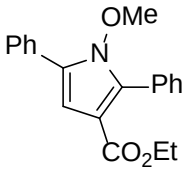
4-17n (76%)



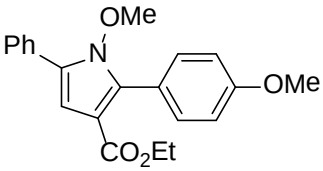
4-17o (82%)



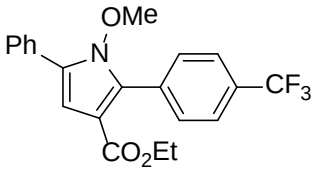
4-17p (76%)



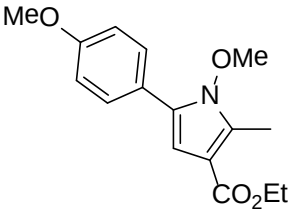
4-17q (70%)



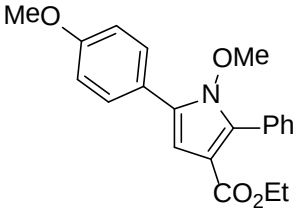
4-17r (66%)



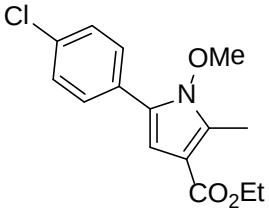
4-17s (92%)



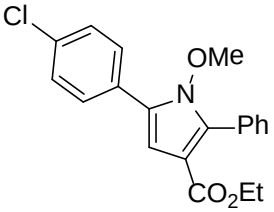
4-17t (60%)



4-17u (70%)



4-17v (74%)

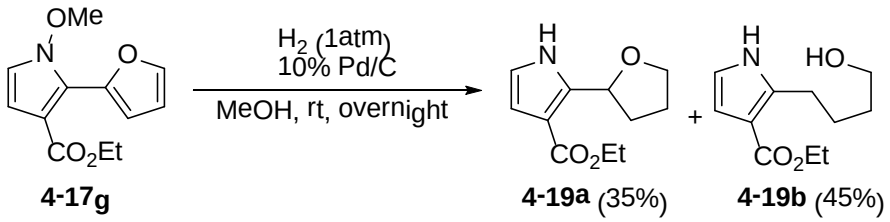


4-17w (70%)

[a] Reaction conditions: **3-8a** (0.3 mmol), vinyl ethyl ether (3 eq.), DCE (0.15M). [b] The reported yields in the parentheses are of the isolated products.

To provide more synthetic application to our methodology, the product **4-17** obtained was reduced to pyrrole. Thus, when we ran the reaction in H_2 (1 atm), Pd/C in MeOH at room temperature, we were delighted to find that the pyrroles **4-20** were obtained in good yields (Table 4-7). When **4-17g** was reduced, overreduction occurred

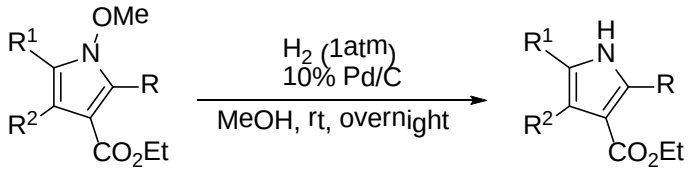
to give **4-19a** and **4-19b** in 35% and 45% yield instead of the desired pyrrole (Scheme 4-22).



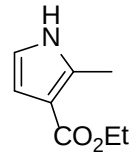
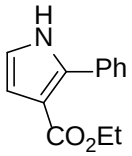
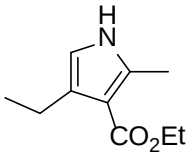
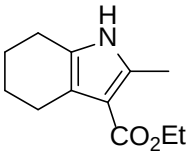
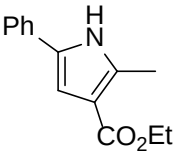
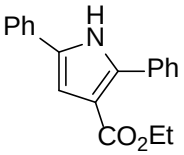
4-17g **4-19a** (35%) **4-19b** (45%)

Scheme 4-22. Reduction of **4-17g**

Table 4-7. Reduction of **4-17** to pyrrole[a]



4-17 **4-20**

 **4-20a** (86%)	 **4-20b** (91%)	 **4-20c** (93%)
 **4-20d** (87%)	 **4-20e** (79%)	 **4-20f** (90%)

[a] Reported yields in the parentheses are all isolated yields

4.5 Conclusion

Despite our initial failure at synthesizing imidazoles with *in situ* generated PPh_3AuOTf, we have successfully developed a method for the synthesis of pyrroles with gold carbenoid from easily prepared starting materials. The reaction proceeds smoothly with a wide variety of substituents to give the pyrroles in good to excellent yields.

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[1] a) D. J. Carini, J. V. Duncia, A. L. Johnson, A. T. Chiu, W. A. Price, P. C. Wong, P. B. M. W. Timmermans, *J. Med. Chem.* **1990**, *33*, 1330-1336; b) A. D. Palkowitz, M. I. Steinberg, K. J. Thrasher, J. K. Reel, K. L. Hauser, K. M. Zimmerman, S. A. Wiest, C. A. Whitesitt, R. L. Simon, *J. Med. Chem.* **1994**, *37*, 4508-4521; c) F. Messina, M. Botta, F. Corelli, M. P. Schneider, F. Fazio, *J. Org. Chem.* **1999**, *64*, 3767-3769.

[2] J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green, D. McNulty, M. J. Blumenthal, J. R. Keys, S. W. Land vatter, J. E. Strickler, M. M. McLaughlin, I. R. Siemens, S. M. Fisher, G. P. Livi, J. R. White, J. L. Adams, P. R. Young, *Nature* **1994**, *372*, 739-746.

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Chapter 5: Experimental Section

5.1 General information

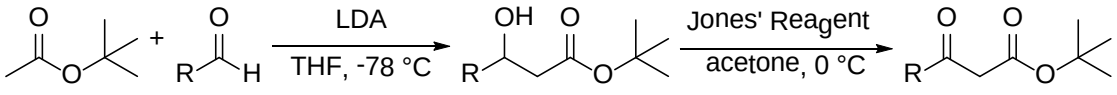
All chemical reagents were purchased and used without further purification. All solvents were distilled under nitrogen from the following drying agents immediately before use: acetonitrile and dichloroethane were distilled from P_2O_5. Anhydrous pyridine and DBU were purchased from commercial suppliers and used without further purification. Systematic nomenclature for the compounds follows the numbering system as defined by IUPAC with assistance from CS Chemdraw software. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). After elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.

^{1}H and ^{13}C NMR spectra were measured at 298 K on a Bruker Avance III 400 Fourier Transform NMR spectrometer. Chemical shifts were reported in δ (ppm), relative to the internal standard of TMS. The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets). Coupling constants are reported as *J* value in Hz, 13C NMR are reported as δ (ppm) in downfield from TMS and relative to the signal of chloroform-*d* (δ 77.00, triplet).

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. High Resolution Mass (HRMS) pectra were obtained using Q-Tof Premier LC HR mass spectrometer. Melting points are uncorrected and were recorded on a Buchi B-54 melting point apparatus.

5.2 Synthesis of Pyridine by Carbenoid-Mediated Ring opening of 2*H*-Azirines

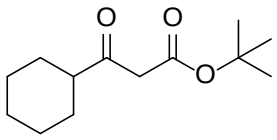
General procedure for *β*-keto esters (A):



To a solution of LDA prepared from *n*-BuLi (1.2 mL, 2.4 mmol, 2 M hexane solution) and diisopropylamine (373.7 µL, 2.8 mmol) in dry THF (5 mL) at -78 °C was added *t*-butyl acetate (322.0 µL, 2.4 mmol) dropwise under a nitrogen atmosphere. The solution was stirred for 30 min, and a solution of aldehyde (1 eq.) in THF was added. After stirring at -78 °C for another 3h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After concentration, the crude material was purified by column chromatography to afford the corresponding alcohol.

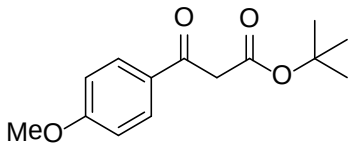
To a solution of alcohol in acetone in ice bath was added Jones Reagent (2 eq.) dropwise. The reaction mixture was stirred for 30 min until all the alcohol are reacted. The excess Jones Reagent was quenched with isopropyl alcohol in ice bath until the mixture turned green. The mixture was evaporated to dryness and the organic compound was diluted with diethyl ether and washed with water, brine and dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography to give the corresponding *β*-keto ester.

Butyl 3-cyclohexyl-3-oxopropanoate (2-18c):[1]



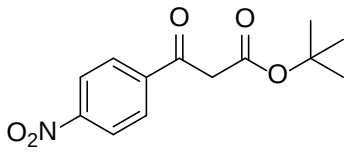
The title compound was prepared according to the general procedure (A). The product was obtained as a colorless oil in 1:1 mixture of keto and enol forms. Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.3 (s, 1H, enol OH), 4.86 (s, 1H from enol), 3.38 (s, 2H), 2.45 (m, 1H), 2.05 (m, 1H), 1.83 (m, 9H), 1.48 (s, 18H); ^{13}C NMR of both isomer (100 MHz, $CDCl_3$) δ 206.4, 182.1, 173.0, 166.7, 88.2, 81.7, 80.5, 50.7, 48.7, 43.4, 29.9, 28.3, 28.1, 27.9, 25.9, 25.7, 25.4.

***tert*-Butyl 3-(4-methoxyphenyl)-3-oxopropanoate (2-18e):[2]**



The title compound was prepared according to the general procedure (A). The product was obtained as a colorless oil. Yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, J = 2.8, 9.2Hz, 2H), 6.94 (dd, J = 2.8, 9.2 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 167.0, 163.8, 130.8, 129.4, 113.8, 81.9, 55.5, 47.2, 27.9.

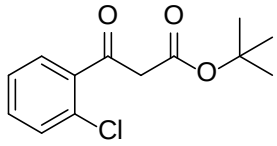
***tert*-Butyl 3-(4-nitrophenyl)-3-oxopropanoate (2-18f):**



The title compound was prepared according to the general procedure (A). The product was obtained as a yellow oil in 1:4 mixture of keto and enol forms. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1H, enol OH), 8.34 (d, J = 9.0 Hz, 2H from keto), 8.25 (dd, J = 1.8, 9.0 Hz, 2H from enol), 8.11 (d, J = 9.0 Hz, 2H from keto),

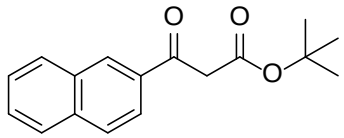
7.92 (dd, *J* = 1.8, 9.0 Hz, 2H from enol), 5.69 (s, 1H, enol =CH), 3.96 (s, 2H keto= CH2), 1.55 (s, 9H, enol ^{t}Bu), 1.44 (s, 9H, keto ^{t}Bu); ^{13}C NMR of major isomer (100 MHz, $CDCl_3$) δ 172.4, 165.8, 150.0, 140.5, 129.4, 126.7, 91.7, 82.0, 27.7; HRMS(ESI) m/z [M+H]+: Calcd for $C_{13}H_{16}NO_5$: 266.1028. Found: 266.1025.

***tert*-Butyl 3-(2-chlorophenyl)-3-oxopropanoate (2-18g):**



The title compound was prepared according to the general procedure (A). The product was obtained as a viscous yellow oil in 2:1 mixture of keto and enol forms. Yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.62 (s, 1H, enol OH), 7.46 (m, 4H), 5.44 (s, 1H, enol =CH), 3.94 (s, 2H keto CH_2), 1.54 (s, 9H, enol ^{t}Bu), 1.39 (s, 9H, keto ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 166.0, 137.9, 132.4, 131.5, 130.8, 130.7, 130.5, 130.1, 130.0, 126.9, 126.7, 94.7, 82.1, 81.5, 50.5, 28.3, 27.8; HRMS(ESI) m/z [M+H]+: Calcd for $C_{13}H_{16}ClO_3$: 255.0788. Found: 255.0789.

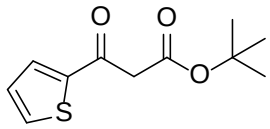
***tert*-Butyl 3-(naphthalen-2-yl)-3-oxopropanoate (2-18h):**



The title compound was prepared according to the general procedure (A). The product was obtained as a yellow oil in 3:1 mixture of keto and enol forms. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.82 (s, 1H, enol OH), 8.45 (s, 1H from keto), 8.34 (s, 1H from enol), 8.01 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.87 (m, 10H), 7.80 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.63 (m, 8H), 5.73 (s, 1H from enol), 4.03 (s, 2H from keto), 1.56 (s, 9H enol ^{t}Bu), 1.44 (s, 9H keto ^{t}Bu); ^{13}C NMR for keto (100 MHz, $CDCl_3$) δ 192.7, 166.7, 135.6, 133.4, 132.2, 130.3, 129.5, 128.6, 127.6, 126.8, 123.7,

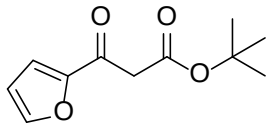
81.8, 47.3, 27.8; HRMS(ESI) m/z [M+H]+: Calcd for $C_{17}H_{19}O_3$: 271.1334. Found: 271.1323.

***tert*-Butyl 3-oxo-3-(thiophen-2-yl)propanoate (2-18i):**



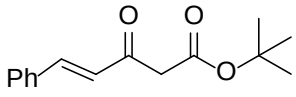
The title compound was prepared according to the general procedure (A). The product was obtained as a colorless oil. Yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (dd, J = 0.8, 2.7 Hz, 1H), 7.67 (dd, J = 0.6, 3.6 Hz, 1H), 7.13 (dd, J = 3.0, 3.9 Hz, 1H), 3.83 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3, 166.0, 143.2, 134.4, 132.9, 128.1, 81.9, 47.6, 27.7; HRMS(ESI) m/z [M+H]+: Calcd for $C_{11}H_{15}SO_3$: 227.0742. Found: 227.0743.

***tert*-Butyl 3-(furan-2-yl)-3-oxopropanoate (2-18j):**



The title compound was prepared according to the general procedure (A). The product was obtained as a white solid. Yield 86%; mp = 74-75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 1.2 Hz, 1H), 7.25 (dd, J = 0.3, 3.6 Hz, 1H), 6.57 (dd, J = 1.5, 3.3 Hz, 1H), 3.76 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 166.0, 152.0, 146.7, 117.9, 112.5, 81.9, 46.7, 27.7; HRMS(ESI) m/z [M+H]+: Calcd for $C_{11}H_{15}O_4$: 211.0970. Found: 211.0971.

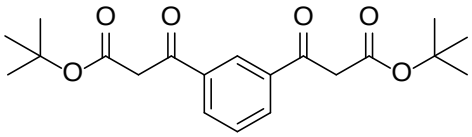
(*E*)-*tert*-Butyl 3-oxo-5-phenylpent-4-enoate (2-18k):



The title compound was prepared according to the general procedure (A). The product was obtained as a yellow solid in 3:2 mixture of keto and enol forms. Yield 72%; mp =

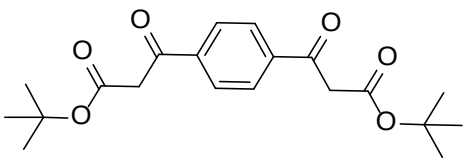
78-79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.14 (s, 1H, enol OH), 7.58 (d, J = 16.1 Hz, 1H keto=CHPh), 7.43 (m, 5H keto Ph, 5H enol Ph), 6.80 (d, J = 16.2 Hz, 1H keto =CH), 6.39 (dd, 1H,enol =CH, J = 1.2, 15.9 Hz), 5.08 (s, 1H, enol =CH), 3.60 (s, 2H keto CH_2), 1.51 (s, 9H,enol ^{t}Bu), 1.47 (s, 9H, keto ^{t}Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 172.8, 168.7, 166.6, 144.3, 136.1, 135.5, 134.2, 130.8, 129.2, 129.0, 128.8, 128.4, 127.5, 125.4, 122.2, 93.6, 82.0, 81.1, 49.1, 28.3, 28.0; HRMS(ESI) m/z [M+H]+: Calcd for $C_{15}H_{19}O_3$: 247.1334. Found: 247.1337.

Di-*tert*-butyl 3,3'-(1,3-phenylene)bis(3-oxopropanoate) (2-18m):



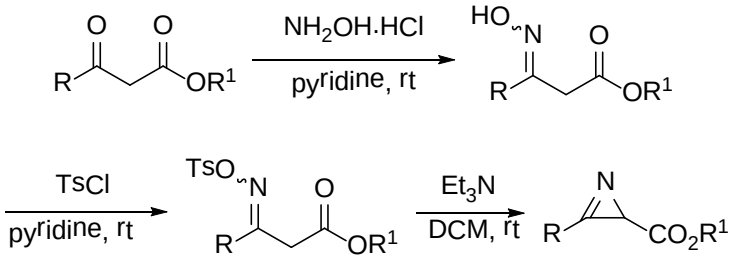
The title compound was prepared according to the general procedure (A). The product was obtained as a yellow oil in a mixture of keto and enol forms. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.74 (s, 1H from enol OH), 12.72 (s, 1H from enol OH), 8.50 (t, J = 1.5 Hz, 1H), 8.32 (t, J = 1.5 Hz, 1H), 8.14 (m, 3H), 8.00 (m, 2H), 7.96 (m, 2H), 7.83 (dd, J = 3.8, 7.8 Hz, 3H), 7.62 (t, J = 7.8 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 5.66 (s, 1H from enol =CH), 5.63 (s, 1H from enol =CH), 3.94 (s, 2H from keto), 3.92 (s, 2H from keto), 1.54 (s, 18H), 1.43 (s, 18H); ^{13}C NMR for both isomer (100 MHz, $CDCl_3$) δ 192.4, 192.1, 172.9, 172.8, 169.9, 169.2, 166.4, 166.3, 136.6, 136.5, 134.4, 134.1, 133.0, 130.6, 129.3, 129.0, 128.7, 128.4, 128.2, 125.9, 123.4, 89.8, 89.5, 82.4, 82.2, 81.6, 81.4, 47.4, 47.3, 28.3, 28.3, 27.9; HRMS(ESI) m/z [M+H]+: Calcd for $C_{20}H_{27}O_6$: 363.1808. Found: 363.1828.

Di-*tert*-butyl 3,3'-(1,4-phenylene)bis(3-oxopropanoate) (2-18n):



The title compound was prepared according to the general procedure (A). The product was obtained as a yellow soild in 1:1 mixture of keto and enol forms. Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.62 (s, 1H, enol OH), 12.61 (s, 1H, enol OH), 7.94 (s, 1H from keto), 7.87 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 7.8 Hz, 2H), 7.69 (s, 2H), 5.58 (s, 1H from enol), 5.54 (s, 1H from enol), 3.84 (s, 2H from keto), 3.82 (s, 2H from keto), 1.45 (s, 9H enol ^{t}Bu), 1.34 (s, 9H keto ^{t}Bu); ^{13}C NMR for keto (100 MHz, $CDCl_3$) δ 192.2, 172.8, 172.6, 169.5, 168.8, 166.4, 166.1, 139.5, 138.2, 137.6, 135.8, 128.6, 128.5, 126.0, 125.9, 90.7, 89.7, 82.2, 82.0, 81.6, 81.3, 47.4, 47.3, 28.2, 28.2, 27.8; HRMS(ESI) m/z [M+H]+: Calcd for $C_{20}H_{27}O_6$: 363.1808. Found: 363.1810.

General procedure for azirine esters (B):

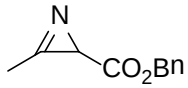


To a solution of $NH_2OH{\bullet}HCl$ (2eq.) in pyridine (12eq.) was added β-ketoester (1.0 eq.) dropwise. The solution was stirred for 1-20h and the solvent was removed under reduced pressure. The residue was extracted twice with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo* to give ketoxime, which was used for the next step without purification.

To the ketoxime was added TsCl (1.2 eq) and pyridine (12eq.). The solution was stirred for 20 h and quenched with saturated aqueous NH_4Cl. The mixture was extracted three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated in *vacuo*. The crude material was purified by column chromatography using hexane: ethyl acetate (4:1). To a solution of ketoxime tosylate in DCM was added Et_3N dropwise, and the mixture was stirred at rt for 3h. Upon

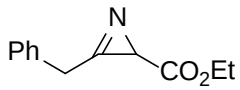
completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O, and the layers were separated. The aqueous layer was extracted with DCM, and the combined layers were washed with water, brine and dried over anhydrous Na_2SO_4. The crude material was purified by column chromatography using hexane:ethyl acetate (6:1).

Benzyl 3-methyl-2*H*-azirine-2-carboxylate (2-21a):



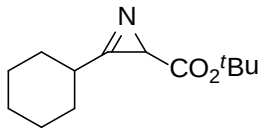
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 70% (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.16 (m, 2H), 2.53 (s, 3H), 2.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 158.7, 135.4, 128.3, 128.0, 127.9, 66.5, 28.5, 12.2; HRMS(ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{12}NO_2$: 190.0868. Found: 190.0862.

Ethyl 3-benzyl-2*H*-azirine-2-carboxylate (2-21b):



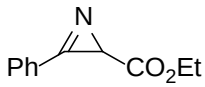
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 80% (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.13 (m, 4H), 2.50 (s, 1H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 171.1, 160.9, 131.4, 128.5, 128.4, 127.1, 60.5, 32.4, 28.7, 13.6; HRMS(ESI) m/z [M+H]+: Calcd for $C_{12}H_{14}NO_2$: 204.1025. Found: 204.1023.

***tert*-Butyl 3-cyclohexyl-2*H*-azirine-2-carboxylate (2-21c):**



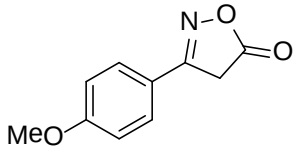
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 18% (from the corresponding keto ester).1H NMR (400 MHz, CDCl3) δ 2.89 (m, 1H), 2.34 (s, 1H), 1.97 (m, 2H), 1.75 (m, 2H), 1.58 (m, 3H), 1.41 (m, 12H); 13C NMR (100 MHz, CDCl3) δ 171.6, 164.6, 81.2, 35.8, 29.5, 28.1, 28.0, 27.9, 27.9, 25.6, 24.8; HRMS (ESI) m/z [M+H]+: Calcd for C13H22NO2: 224.1651. Found: 224.1649.

Ethyl 3-phenyl-2*H*-azirine-2-carboxylate (2-21d):



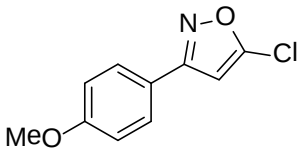
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 20% (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.62 (m, 3H), 4.22 (q, J = 7.2 Hz, 2H), 2.85 (s, 1H), 1.28 (t, J= 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.1, 133.5, 129.9, 128.9, 121.9, 60.8, 29.2, 13.8; HRMS(ESI) m/z [M+H]+: Calcd for $C_{11}H_{12}NO_2$: 190.0868. Found: 190.0872.

3-(4-Methoxyphenyl)isoxazol-5(4H)-one (2-23a):[3]



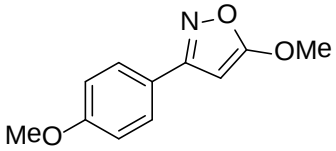
The title compound was prepared according to the literature.[4] The product was obtained as a colorless oil. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, J = 2.0, 6.8 Hz, 2H), 7.96 (dd, J = 2.0, 6.8 Hz, 2H), 3.87 (s, 3H), 3.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 162.6, 162.6, 128.3, 120.0, 114.6, 55.5, 34.2.

5-Chloro-3-(4-methoxyphenyl)isoxazole (2-23b):[5]



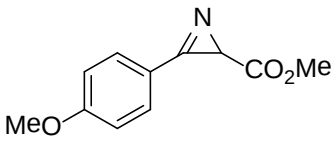
The title compound was prepared according to the literature.[5] The product was obtained as a colorless oil. Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.43 (s, 1H), 3.86 (s, 3H).

5-Methoxy-3-(4-methoxyphenyl)isoxazole (2-23c):[5]



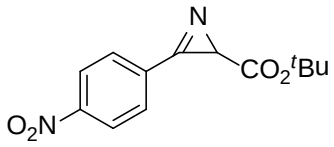
The title compound was prepared according to the literature.[5] The product was obtained as a colorless oil. Yield 12%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 1.6, 6.8 Hz, 2H), 6.95 (dd, J = 1.6, 6.8 Hz, 2H), 5.47 (s, 1H), 4.04 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 163.9, 161.1, 127.9, 122.1, 114.2, 75.2, 58.8, 55.4.

Methyl 3-(4-methoxyphenyl)-2*H*-azirine-2-carboxylate (2-21e):



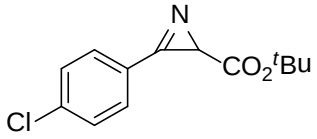
The title compound was prepared according to the literature. The product was obtained as a colorless oil. Yield 8% (from the corresponding keto ester). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dt, J = 2.8, 8.8 Hz, 2H), 7.06 (dt, J = 2.8, 8.8 Hz, 2H), 3.90 (s, 3H), 3.73 (s, 3H), 2.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 164.1, 157.1, 132.6, 114.9, 114.4, 55.6, 52.2, 29.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{12}NO_3$: 206.0817. Found: 206.0822.

***tert*-Butyl 3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate (2-21f):**



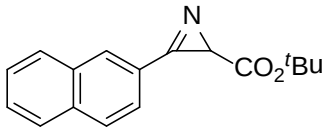
The title compound was prepared according to the general procedure (B). The product was obtained as a yellow solid. Yield 85% (from the corresponding keto ester).[1]H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 2.0, 6.8 Hz, 2H), 8.09 (dd, *J* = 2.0, 6.8 Hz, 2H), 2.89 (s, 1H), 1.48 (s, 9H); [13]C NMR (100 MHz, $CDCl_3$) δ 169.8, 158.7, 150.4, 130.9, 128.0, 124.3, 82.0, 31.2, 27.8; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{15}N_2O_4$: 263.1032. Found: 263.1032.

***tert*-Butyl 3-(2-chlorophenyl)-2*H*-azirine-2-carboxylate (2-21g):**



The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 65% (from the corresponding keto ester); [1]H NMR (300 MHz, $CDCl_3$) *δ* 7.89 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 3.9 Hz, 2H), 7.47 (m, 1H), 2.83 (s, 1H), 1.49 (s, 9H); [13]C NMR (75 MHz, $CDCl_3$) *δ* 170.7, 158.0, 136.7, 134.4, 132.4, 130.8, 127.4, 121.4, 81.7, 31.3, 28.1; HRMS(ESI) m/z [M+H]+: Calcd for $C_{13}H_{15}NClO_2$: 252.0791. Found: 252.0794.

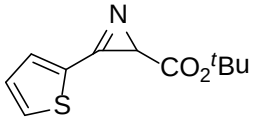
***tert*-Butyl 3-(naphthalen-2-yl)-2*H*-azirine-2-carboxylate (2-21h):**



The title compound was prepared according to the general procedure (B). The product was obtained as a yellow oil. Yield 70% (from the corresponding keto ester); [1]H NMR (400 MHz, $CDCl_3$) *δ* 8.27 (s, 1H), 7.95 (s, 2H), 7.90 (d overlap with s, *J* = 8.0 Hz,

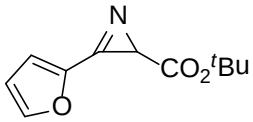
1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.58 (m, 2H), 2.85 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 158.8, 135.5, 132.5, 132.4, 129.2, 129.0, 128.8, 128.0, 127.1, 124.6, 119.7, 81.5, 30.2, 27.9; HRMS(ESI) m/z [M+H]+: Calcd for $C_{17}H_{18}NO_2$: 268.1338. Found: 268.1338.

***tert*-Butyl 3-(thiophen-2-yl)-2*H*-azirine-2-carboxylate (2-21i):**



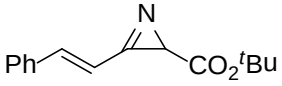
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 66% (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.70 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.27 (t, *J* = 4.5 Hz, 1H), 2.78 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 151.6, 134.9, 134.6, 128.1, 124.2, 81.1, 30.7, 27.5; HRMS(ESI) m/z [M+H]+: Calcd for $C_{11}H_{14}NSO_2$: 224.0745. Found: 224.0750.

***tert*-Butyl 3-(furan-2-yl)-2*H*-azirine-2-carboxylate (2-21j):**



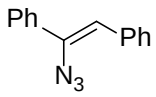
The title compound was prepared according to the general procedure (B). The product was obtained as a colorless oil. Yield 62% (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (t, *J* = 0.6 Hz, 1H), 7.25 (t, *J* = 1.5 Hz, 1H), 6.67 (dd, *J* = 1.5, 3.3 Hz, 1H), 2.75 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 148.9, 148.7, 139.5, 121.1, 112.8, 81.7, 30.1, 27.9; HRMS(ESI) m/z [M+H]+: Calcd for $C_{11}H_{14}NO_3$: 208.0974. Found: 208.0977.

***tert*-Butyl 3-styryl-2*H*-azirine-2-carboxylate (2-21k):**



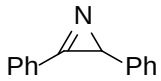
The title compound was prepared according to the general procedure (B**)**. The product was obtained as a white solid. Yield 52%; (from the corresponding keto ester); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.44 (m, 3H), 7.33 (d, J = 15.8 Hz, 1H), 7.15 (d, J = 15.8 Hz, 1H), 2.61 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 156.8, 148.4, 133.7, 130.6, 128.7, 128.0, 109.3, 80.9, 29.2, 27.6; HRMS(ESI) m/z [M+H]+: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1333.

(Z)-(1-Azidoethene-1,2-diyl)dibenzene (2-22):[6]



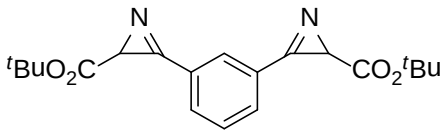
The titled compound was prepared according to the literature.[7] However, the compound was highly unstable and used directly for the next step.

2,3-Diphenyl-2*H*-azirine (2-21l):[8]



The titled compound was prepared according to the literature.[9] The product was obtained as a white solid. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.56 (m, 3H), 7.25 (m, 3H), 7.15 (m, 2H), 3.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 140.8, 133.2, 129.9, 129.2, 128.3, 127.1, 126.1, 124.1, 34.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{12}N$: 194.0970. Found: 194.0973.

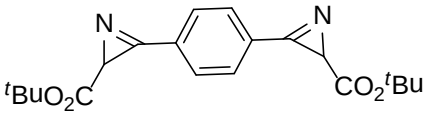
Di-*tert*-butyl 3,3'-(1,3-phenylene)bis(2*H*-azirine-2-carboxylate) (2-21m):



The title compound was prepared according to the general procedure (B). The product was obtained as a yellow oil. Yield 70% (from the corresponding keto ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.2 Hz, 1H), 8.17 (m, 2H), 7.83 (t, J = 7.6 Hz, 2H), 2.86 (s, 2H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 158.7,

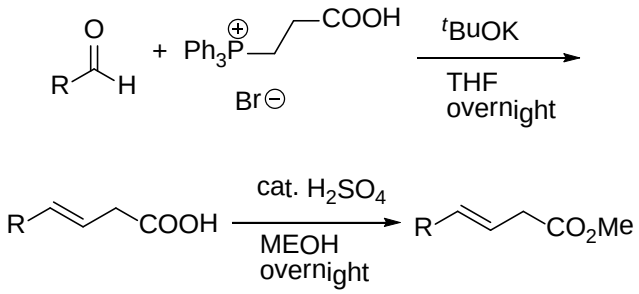
134.5, 134.5, 131.6, 131.4, 130.4, 124.2, 82.1, 82.1, 31.1, 31.0, 28.0, 28.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{25}N_2O_4$: 357.1814. Found: 357.1805.

Di-*tert*-butyl 3,3'-(1,4-phenylene)bis(2*H*-azirine-2-carboxylate) (2-21n):



The title compound was prepared according to the general procedure (B). The product was obtained as a yellow solid. Yield 56% (from the corresponding keto ester). mp = 147.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 4H), 2.87 (s, 1H), 2.86 (s, 1H), 1.48 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.1, 130.8, 127.1, 82.1, 31.2, 28.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{25}N_2O_4$: 357.1814. Found: 357.1804.

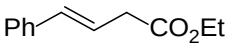
General procedure for *β, γ*-unsaturated esters (C):



The title compound was prepared according to the literature.[10] To a stirred solution benzaldehyde (1 eq.) and (2-carboxyethyl)-triphenylphosphonium chloride (1.1 eq.) in THF (60 mL) at 0 °C was added dropwise a solution of potassium *tert*-butoxide (2.2 eq.) in THF (50 mL) over 1 h. After 0.5 h, the reaction was allowed to warm to rt and stirred at rt for 12 h. The reaction mixture was added to 1L of ice water/saturated sodium bicarbonate (1:1), and the layers were separated. The aqueous layer was extracted with ether (3 x 150 mL), acidified with HCl (6 M) to ~ pH 1, and extracted with EtOAc (3 x 150 mL). The combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The crude product was used directly for the next step. The residue was dissolved in MeOH (150 mL) and treated with concentrated

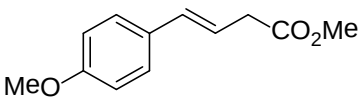
sulfuric acid (0.5 mL). After stirred at rt for 15 h, the reaction mixture was added to saturated aqueous sodium bicarbonate (400 mL) and extracted with ether (3 x 75 mL). The combined organic layers were washed with brine, dried over MgSO4 and concentrated under reduced pressure. The crude material was purified by column chromatography to afford the desired ester.

(*E*)-Ethyl 4-phenylbut-3-enoate (2-26a):



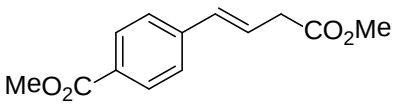
The title compound was prepared according to the literature.[11] The product was obtained as a colorless oil. Yield: 55 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.30 (m, 2H), 7.22 (m, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 7.2, 16.0 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.23 (dd, *J* = 1.2, 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 136.9, 133.3, 128.5, 127.5, 126.3, 121.8, 60.8, 38.5, 14.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{12}H_{15}O_2$: 191.1072. Found: 191.1071.

(*E*)-Methyl 4-(4-methoxyphenyl)but-3-enoate (2-26b):



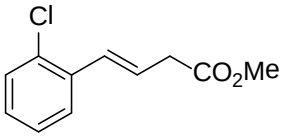
The title compound was prepared according to the general procedure (C). The product was obtained as a white solid. Yield: 86%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 1.8, 8.7 Hz, 2H), 6.84 (dd, *J* = 1.8, 8.7 Hz, 2H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.15 (dt, *J* = 7.2, 15.6 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.22 (dd, *J* = 1.2, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 159.1, 132.8, 129.6, 127.4, 119.3, 113.9, 55.2, 51.9, 38.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{12}H_{15}O_3$: 207.1021. Found: 207.1025.

(*E*)-Methyl 4-(4-methoxy-4-oxobut-1-enyl)benzoate (2-26c):



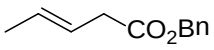
The title compound was prepared according to the general procedure (C). The product was obtained as a white solid. Yield: 43%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.41 (m, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.26 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 166.7, 141.1, 132.4, 129.8, 128.8, 126.0, 124.4, 51.9, 51.9, 38.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{15}O_4$: 235.0970. Found: 235.0970.

(*E*)-Methyl 4-(2-chlorophenyl)but-3-enoate (2-26d):



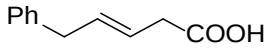
The title compound was prepared according to the general procedure (C). The product was obtained as a colorless oil as 1:4 mixture of cis and trans isomers. Yield: 59%; ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.35 (m, 1H), 7.17 (m, 2H), 6.87 (d, *J* = 15.8 Hz, 1H), 6.29 (dt, *J* = 7.2, 15.8 Hz, 1H), 3.72 (s, 3H), 3.30 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ171.7, 134.8, 134.0, 129.6, 128.5, 128.2, 126.7, 124.5, 122.3, 51.9, 36.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{12}O_2Cl$: 211.0526. Found: 211.0527.

(*E*)-Benzyl pent-3-enoate (2-26e):



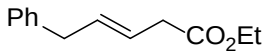
The title compound was prepared according to the literature.[12] The product was obtained as a colorless liquid. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.56 (m, 2H), 5.12 (s, 2H), 3.06 (d, *J* = 4.4 Hz, 2H), 1.69 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 135.9, 129.6, 128.5, 128.2, 122.5, 66.3, 38.0, 17.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{15}O_2$: 191.1072. Found: 191.1068.

(*E*)-5-Phenylpent-3-enoic acid:



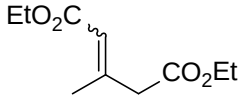
The title compound was prepared according to the literature.[11] The product was obtained as a colorless liquid. Yield: 75%; ^{1}H NMR (400 MHz, CDCl3) δ 7.29 (m, 2H), 7.19 (m, 3H), 5.75 (m, 1H), 5.61 (m, 1H), 3.38 (d, *J* = 6.8 Hz, 2H), 3.10 (dd, *J* = 0.8, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 178.6, 139.9, 133.8, 128.5, 128.4, 126.1, 122.3, 38.8, 37.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{13}O_2$: 177.0916. Found: 177.0915.

(*E*)-Ethyl 5-phenylpent-3-enoate (2-26f):



The title compound was prepared according to the literature.[11] The product was obtained as a colorless liquid. Yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.20 (m, 3H), 5.68 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.38 (d, *J* = 6.4 Hz, 2H), 3.06 (d, *J* = 6.4 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.0, 132.9, 128.4, 128.3, 125.9, 123.2, 60.4, 38.8, 37.8, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{17}O_2$: 205.1229. Found: 205.1227.

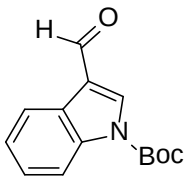
Diethyl 3-methylpent-2-enedioate (2-26h):[13]



The title compound was prepared according to the literature.[13] The product was obtained as a colorless oil as 1:1 mixture of cis and trans isomers. Yield: 55%; ^{1}H NMR of both isomers (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.77 (s, 1H), 4.15 (m, 8H), 3.73 (s, 2H), 3.13 (s, 2H), 2.23 (s, 3H), 1.97 (s, 3H), 1.27 (m, 12H); ^{13}C NMR of both isomers (100 MHz, $CDCl_3$) δ 170.2, 169.9, 166.1, 166.0, 150.9, 150.7, 119.5, 119.1,

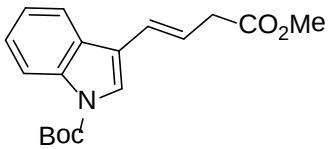
61.0, 60.7, 59.7, 59.7, 45.9, 38.4, 25.6, 18.8, 14.2, 14.1, 14.1, 14.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{17}O_4$: 201.1127. Found: 201.1123.

***tert*-Butyl 3-formyl-1*H*-indole-1-carboxylate:[14]**



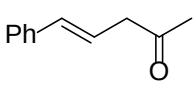
The title compound was prepared according to the literature.[14] The product was obtained as a white solid. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.28 (d, *J* = 7.2 Hz, 1H), 8.22 (s, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 7.38 (m, 2H), 1.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 148.8, 136.5, 136.0, 126.1, 126.1, 124.6, 122.1, 121.6, 115.2, 85.7, 28.1.

(*E*)-*tert*-Butyl 3-(4-methoxy-4-oxobut-1-enyl)-1*H*-indole-1-carboxylate (2-26j):



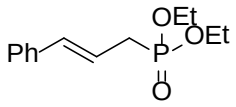
The title compound was prepared according to the general procedure (C). The product was obtained as a yellow oil. Yield: 18%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.60 (s, 1H), 7.33 (td, *J* = 1.2, 7.4 Hz, 1H), 7.26 (dt, *J* = 1.2, 7.4 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.36 (dt, *J* = 9.0, 16.0 Hz, 1H), 3.73 (s, 3H), 3.29 (dd, *J* = 1.2, 7.4 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 149.5, 135.8, 128.6, 124.6, 123.6, 122.8, 122.0, 119.8, 118.2, 115.3, 83.8, 51.9, 38.7, 28.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{22}NO_4$: 316.1549. Found: 316.1546.

(*E*)-5-Phenylpent-4-en-2-one (2-26k):



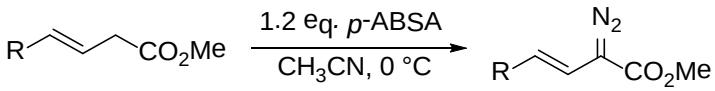
The title compound was prepared according to the literature.[15] The product was obtained as a colorless oil. Yield: 20%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (m, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.30 (dt, *J* = 7.2, 15.6 Hz,1H), 3.31 (d, *J* = 7.2 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 136.9, 133.8, 128.6, 127.6, 126.3, 121.9, 47.8, 29.7; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{13}O$: 161.0966. Found: 161.0966.

Diethyl cinnamylphosphonate (2-26l):



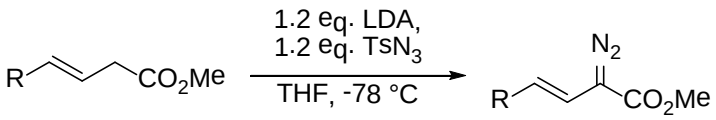
The title compound was prepared according to the literature.[16] The product was obtained as a white solid. Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 6.52 (dd, *J* = 5.2, 16.0 Hz, 1H), 6.17 (m, 1H), 4.13 (m, 4H), 2.77 (ddd, *J* = 1.2, 7.6, 22.4 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (d, *J* = 3.4 Hz), 134.1 (d, *J* = 15.0 Hz), 128.0, 127.0, 125.6 (d, *J* = 1.9 Hz), 118.2 (d, *J* = 12.0 Hz), 61.4 (d, *J* = 6.8 Hz), 30.5 (d, *J* = 139.6 Hz), 15.9 (d, *J* = 5.9 Hz); HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{20}O_3P$: 255.1150. Found: 255.1148.

General procedure for diazo compounds (D):



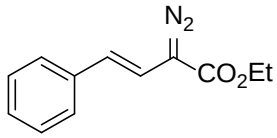
To a solution of β,γ-unsaturated ester (1 eq.) and 4-acetylbenzenesulfonyl azide, *p*-ABSA (1.2 eq.) in CH_3CN at 0°C was added dropwise DBU (1.2 eq.). The resulting orange solution was stirred for 30 min at 0°C and allowed to warm to rt. The reaction mixture was extracted with diethyl ether and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuo. The crude material was purified by column chromatography to afford the desired diazo compound.

General procedure for diazo compounds (E):



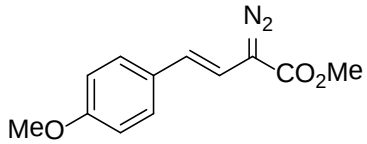
To a solution of LDA prepared from *n*-BuLi (2 M hexane solution, 1.2 eq.) and diisopropylamine (1.4 eq.) in dry THF at -78 °C was added dropwise HMPA (2.0 eq.) and ester (1.0 eq.). After stirred for 30 min, TsN_3 (1.2 eq.) was added, and the reaction mixture was allowed to warm to rt. Upon completion as indicated by TLC, the reaction mixture was quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography to afford the desired diazo compound.

(*E*)-Ethyl 2-diazo-4-phenylbut-3-enoate (2-27a):



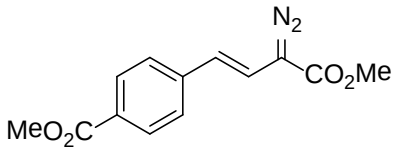
The title compound was prepared according to the general procedure (D). The product was obtained as a red oil. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 4H), 7.19 (m, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 136.8, 128.7, 127.0, 125.8, 122.9, 111.4, 61.3, 14.5. HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{13}N_2O_2$: 217.0977. Found: 217.0974.

(*E*)-Methyl 2-diazo-4-(4-methoxyphenyl)but-3-enoate (2-27b):



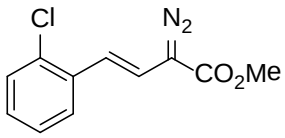
The title compound was prepared according to the general procedure (D). The product was obtained as a red liquid. Yield: 86% ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.28 (d, J = 16.4 Hz, 1H), 6.13 (d, J = 16.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 158.8, 129.6, 126.9, 122.7, 114.0, 108.5, 55.2, 52.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{12}H_{13}N_2O_3$: 233.0926. Found: 233.0929.

(*E*)-Methyl 4-(3-diazo-4-methoxy-4-oxobut-1-enyl)benzoate (2-27c):



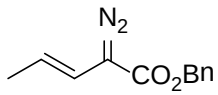
The title compound was prepared according to the general procedure (D). The product was obtained as a red solid. Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 6.62 (d, J =21.6 Hz, 1H), 6.22 (d, J =21.6 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.1, 141.2, 130.1, 128.3, 125.5, 121.7, 114.4, 52.4, 52.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{13}N_2O_4$: 261. 0875. Found: 261.0874.

(*E*)-Methyl 4-(2-chlorophenyl)-2-diazobut-3-enoate (2-27d):



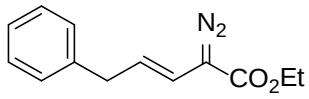
The title compound was prepared according to the general procedure (D). The product was obtained as a orange liquid. Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 1.2 Hz, 1H), 7.42 (m, 1H), 7.23 (m, 1H), 7.12 (m, 1H), 6.57 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 16.4 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 134.7, 132.3, 129.7, 128.0, 126.9, 126.2, 118.6, 114.3, 52.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{10}ClN_2O_2$: 237.0431. Found: 237.0429.

(*E*)-Benzyl 2-diazopent-3-enoate (2-27e):



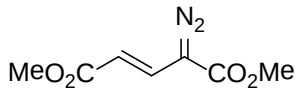
The title compound was prepared according to the general procedure (E). The product was obtained as a red oil. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.74 (dd, *J* = 1.6, 16.0 Hz, 1H), 5.32 (m, 1H), 5.23 (s, 2H), 1.81 (dd, *J* = 1.6, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 135.8, 128.5, 128.2, 128.1, 120.4, 112.5, 66.5, 18.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{13}N_2O_2$: 217.0977. Found: 217.0979.

(*E*)-Ethyl 2-diazo-5-phenylpent-3-enoate (2-27f):



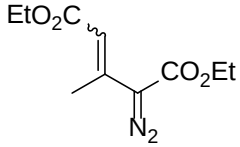
The title compound was prepared according to the general procedure (E). The product was obtained as a red oil.Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.19 (m, 3H), 5.85 (dt, *J* = 1.6, 15.6 Hz, 1H), 5.45 (dt, *J* = 1.6, 15.6 Hz, 1H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.50 (d, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 139.9, 128.5, 126.2, 123.7, 116.0, 113.4, 61.1, 39.1, 14.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{15}N_2O_2$: 231.1134. Found: 231.1131.

(*E*)-Dimethyl 4-diazopent-2-enedioate (2-27g):



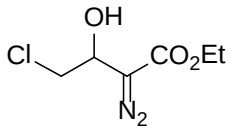
The title compound was prepared according to the general procedure (D). The product was obtained as a red solid. Yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* =15.6 Hz, 1H), 5.73 (dd, *J* =15.6 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 163.5, 131.0, 111.2, 52.6, 51.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_7H_9N_2O_4$: 185.0562. Found: 185.0562.

Diethyl 4-diazo-3-methylpent-2-enedioate (2-27h):



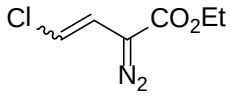
The title compound was prepared according to the general procedure (D). The product was obtained as an orange liquid as 1:3 mixture of cis and trans isomers. Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 5.74 (s, 1H), 4.27 (m, 4H), 4.15 (m, 4H), 2.36 (s, 3H), 2.25 (s, 3H), 1.29 (m, 12H); ^{13}C NMR of major isomer (100 MHz, $CDCl_3$) δ 166.6, 163.4 140.2, 111.7, 61.2, 59.6, 15.5, 14.3, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{15}N_2O_4$: 227.1032. Found: 227.1025.

Ethyl 4-chloro-2-diazo-3-hydroxybutanoate (2-28):[17]



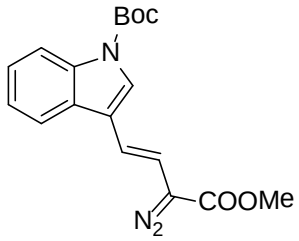
The title compound was prepared according to the literature.[17] The product was obtained as a yellow oil. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (q, *J* = 6.0 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.75 (dd, *J* = 1.6, 5.6 Hz, 2H), 3.50 (bs, 1H), 1.30 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.0, 66.7, 61.3, 46.8, 14.4.

(*E*)-Ethyl 4-chloro-2-diazobut-3-enoate (2-27i):[17]



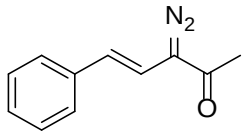
The title compound was prepared according to the literature.[17] The product was obtained as a yellow oil. Yield: 28%; ^{1}H NMR (400 MHz, $CDCl_3$) for major isomer: δ 6.20 (d, *J* = 13.6 Hz, 1 H), 6.07 (d, *J* =13.6 Hz, 1 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 164.4, 116.3, 112.5, 61.6, 61.5, 14.4; HRMS calcd for $C_6H_8ClN_2O_2$: 175.0274; found: 175.0269.

(*E*)-*tert*-Butyl 3-(3-diazo-4-methoxy-4-oxobut-1-enyl)-1*H*-indole-1-carboxylate (2-27j):



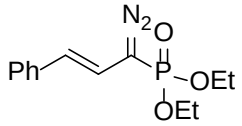
The title compound was prepared according to the general procedure (D). The product was obtained as an orange solid. Yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 10.6 Hz, 1H), 6.49 (d, *J* = 16.4 Hz, 1H), 6.30 (d, *J* = 16.4 Hz, 1H), 3.85 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 149.4, 135.8, 128.2, 124.7, 122.9, 122.7, 119.5, 118.4, 115.3, 114.5, 110.7, 83.8, 52.2, 28.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{20}N_3O_4$: 342.1454. Found: 342.1456.

(*E*)-3-Diazo-5-phenylpent-4-en-2-one (2-27k):



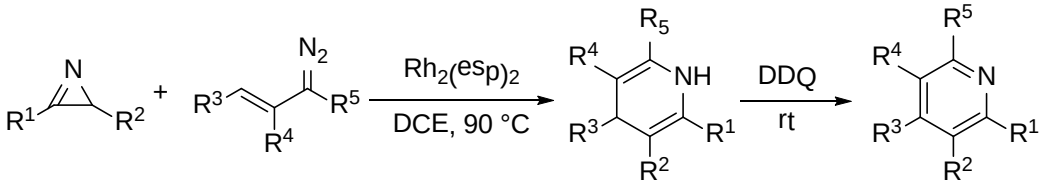
The title compound was prepared according to the general procedure (D). The product was obtained as a red solid. Yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.19 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.16 (d, *J* = 16.0 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 136.4, 128.5, 127.2, 125.8, 123.8, 110.4, 25.9; Calcd for $C_{11}H_{11}N_2O$: 187.0871. Found: 187.0872.

(*E*)-Diethyl 1-diazo-3-phenylallylphosphonate (2-27l):



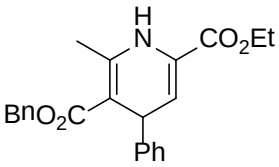
The title compound was prepared according to the general procedure (E). The product was obtained as an orange liquid. Yield: 15%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.19 (m, 1H), 6.27 (d, *J* = 16.1 Hz, 1H), 6.17 (dd, *J* = 10.8, 16.1 Hz, 1H), 4.19 (m, 4H), 1.38 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 128.6, 127.0, 125.5, 123.9, 112.6 (d, *J* = 10.0 Hz), 62.9 (d, *J* = 5.1 Hz), 16.1 (d, *J* = 6.9 Hz); HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{18}N_2O_3P$: 281.1055. Found: 281.1043.

General procedure for pyridines (F):



An oven dried Schlenk tube charged with $Rh_2(esp)_2$ (2 mol%) was purged with nitrogen, and a solution of azirine (0.3 mmol, 1 eq.) in DCE (1 mL) was added. To the suspension was added dropwise a solution of freshly prepared diazo compound (1.6 eq.) in DCE (1 mL) under nitrogen. The reaction mixture was then heated to 90 °C for 3-20 h. The solution was cooled to rt and treated with DDQ (1 eq.). The suspension was stirred at rt for 15 min and filtered through a plug of silica gel. The filtrate was concentrated in *vacuo*, and the crude material was purified by flash chromatography using hexanes: ethyl acetate (4:1) as eluent to give the desired product.

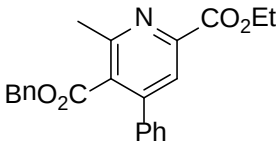
5-Benzyl 2-ethyl 1,4-dihydro-6-methyl-4-phenylpyridine-2,5-dicarboxylate (2-29):



The title compound was prepared according to the general procedure (F), except for isolation without oxidation. The product was obtained as a yellow oil. Yield:62%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.15 (m, 8H), 7.05 (m, 2H), 6.28 (bs, 1H), 6.00 (dd, *J* =

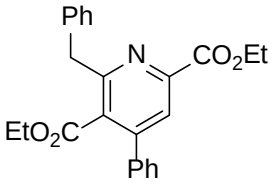
1.8, 5.9 Hz, 1H), 5.00 (q, *J* = 12.6 Hz, 2H), 4.71 (d, *J* = 5.9 Hz, 1H), 4.23 (t, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 167.6, 162.8, 147.6, 147.1, 136.7, 128.5, 128.3, 127.7, 127.6, 126.5, 126.0, 115.3, 97.1, 65.2, 61.6, 40.9, 20.3, 14.0; HRMS(ESI) m/z [M+H]+: Calcd for $C_{23}H_{24}NO_4$: 378.1705. Found: 378.1705.

5-Benzyl 2-ethyl 6-methyl-4-phenylpyridine-2,5-dicarboxylate (2-30a):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.40 (m, 5H), 7.27 (m, 3H), 7.01 (dd, *J* = 1.2 Hz, 2H), 5.11 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 2.69 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 164.7, 156.3, 149.0, 148.0, 137.4, 134.4, 130.8, 129.0, 128.8, 128.6, 128.5, 128.5, 127.9, 123.2, 67.7, 62.2, 23.0, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{23}H_{22}NO_4$: 376.1549. Found: 376.1552.

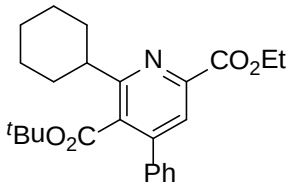
Diethyl 6-benzyl-4-phenylpyridine-2,5-dicarboxylate (2-30b):



The title compound was prepared according to the general procedure (F). The product was obtained as a white gum. Yield 82%; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.02 (s, 1H), 7.39 (m, 5H), 7.21 (m, 5H), 4.49 (q, *J* = 7.1 Hz, 2H), 4.44 (s, 2H), 3.85 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 167.9, 164.7, 158.5, 149.5, 148.0, 138.3, 137.6, 131.4, 129.2, 128.9, 128.6, 128.2,

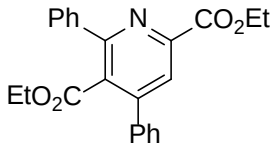
127.9, 126.3, 123.7, 62.1, 61.5, 42.3, 14.3, 13.3; HRMS(ESI) m/z [M+H]+: Calcd for $C_{24}H_{24}NO_4$: 390.1705. Found: 390.1712.

5-*tert*-Butyl 2-ethyl 6-cyclohexyl-4-phenylpyridine-2,5-dicarboxylate (2-30c):



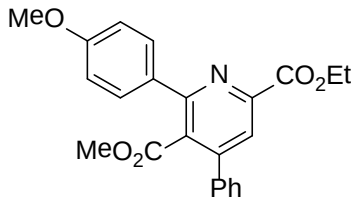
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.43 (s, 5H), 4.44 (q, J = 7.2 Hz, 2H), 2.90 (m, 1H), 1.87 (m, 6H), 1.39 (t, J = 7.2 Hz, 3H), 1.34 (s, 9H), 1.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 165.0, 162.7, 148.0, 147.7, 137.8, 131.7, 128.6, 128.4, 128.3, 122.9, 82.9, 61.6, 43.8, 32.0, 27.6, 26.5, 25.7, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{25}H_{32}NO_4$: 410.2331. Found: 410.2321.

Diethyl 4,6-diphenylpyridine-2,5-dicarboxylate (2-30d):



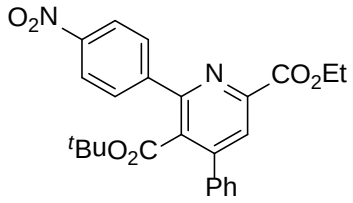
The title compound was prepared according to the general procedure (F). The product was obtained as a white solid. Yield 72%; mp = 111-112°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.66 (m, 2H), 7.43 (m, 8H), 4.50 (q, J = 7.2 Hz, 2H), 3.97 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 164.7, 157.2, 149.7, 148.1, 138.8, 137.3, 131.1, 129.0, 129.0, 128.6, 128.6, 128.3, 128.0, 124.0, 62.1, 61.6, 14.2, 13.3; HRMS(ESI) m/z [M+H]+: Calcd for $C_{23}H_{22}NO_4$: 376.1549. Found: 376.1548.

2-Ethyl 5-methyl 6-(4-methoxyphenyl)-4-phenylpyridine-2,5-dicarboxylate (2-30e):



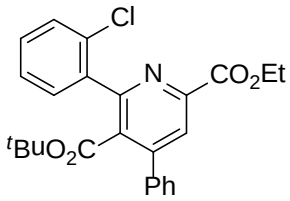
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.66 (dt, *J* = 2.8, 8.8 Hz, 2H), 7.46 (m, 5H), 6.98 (dd, *J* = 2.0, 6.8 Hz, 2H), 4.50 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 3.55 (s, 3H), 1.46 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 164.8, 160.4, 156.6, 149.7, 148.2, 137.4, 131.4, 130.3, 130.0, 129.0, 128.7, 127.9, 123.5, 113.9, 62.1, 55.3, 52.4, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{23}H_{22}NO_5$: 392.1498. Found: 392.1501.

5-*tert*-Butyl 2-ethyl 6-(4-nitrophenyl)-4-phenylpyridine-2,5-dicarboxylate (2-30f):



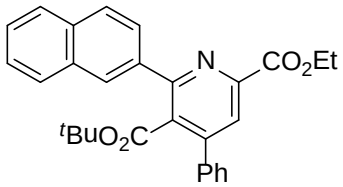
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow solid. Yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dt, *J* = 2.4, 8.8 Hz, 1H), 8.15 (s, 1H), 7.88 (dt, *J* = 2.8, 8.8 Hz, 2H), 7.46 (m, 5H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 164.3, 154.5, 149.9, 148.1, 148.0, 145.1, 137.0, 132.4, 130.1, 129.1, 128.6, 128.2, 125.1, 123.4, 84.0, 62.3, 27.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{25}H_{25}N_2O_6$: 449.1713. Found: 449.1707.

5-*tert*-Butyl 2-ethyl 6-(2-chlorophenyl)-4-phenylpyridine-2,5-dicarboxylate (2-30g):



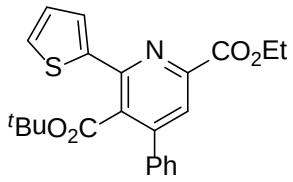
The title compound was prepared according to the general procedure (F). The product was obtained as a white solid. Yield 94%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.40 (m, 9H), 4.50 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 164.4, 155.4, 148.9, 147.6, 137.8, 137.1, 133.3, 132.8, 130.8, 129.8, 129.2, 128.8, 128.4, 128.1, 126.1, 124.7, 82.8, 61.9, 27.0, 14.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{25}H_{25}NClO_4$: 438.1472. Found: 438.1472.

5-*tert*-Butyl 2-ethyl 6-(naphthalen-2-yl)-4-phenylpyridine-2,5-dicarboxylate (2-30h):



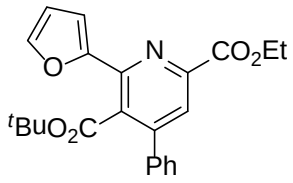
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow gum. Yield 84%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.86 (m, 3H), 7.48 (m, 7H), 4.49 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.9, 156.9, 149.6, 147.8, 137.6, 136.6, 133.5, 132.9, 132.6, 128.9, 128.5, 128.5, 128.4, 128.2, 127.8, 126.6, 126.4, 124.2, 83.3, 62.1, 27.5, 14.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_{29}H_{28}NO_4$: 454.2018. Found: 454.2019.

5-*tert*-Butyl 2-ethyl 4-phenyl-6-(thiophen-2-yl)pyridine-2,5-dicarboxylate (2-30i):



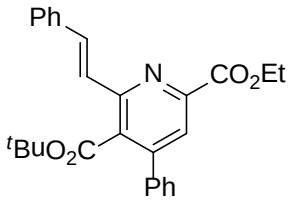
The title compound was prepared according to the general procedure (F). The product was obtained as a white solid. Yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.51 (m, 6H), 7.42 (s, 1H), 7.06 (dd, J = 3.9, 5.1 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 164.5, 149.7, 149.2, 147.5, 141.9, 137.2, 130.5, 129.2, 128.8, 128.5, 128.4, 127.8, 127.5, 123.7, 83.5, 62.0, 27.4, 14.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{23}H_{24}NSO_4$: 410.1426. Found: 410.1421.

5-*tert*-Butyl 2-ethyl 6-(furan-2-yl)-4-phenylpyridine-2,5-dicarboxylate (2-30j):



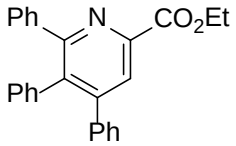
The title compound was prepared according to the general procedure (F). The product was obtained as a white solid. Yield 74%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.50 (s, 1H), 7.44 (s, 5H), 7.27 (s, 1H), 6.55 (dd, J = 1.8, 3.6 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 164.3, 151.7, 149.4, 147.4, 145.2, 143.5, 137.0, 128.9, 128.5, 128.3, 128.1, 123.5, 112.2, 111.9, 82.9, 61.8, 27.3, 14.0; HRMS(ESI) m/z [M+H]+: Calcd for $C_{23}H_{24}NO_5$: 394.1654. Found: 394.1650.

5-*tert*-Butyl 2-ethyl 4-phenyl-6-styrylpyridine-2,5-dicarboxylate (2-30k):



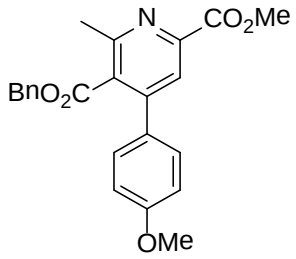
The title compound was prepared according to the general procedure (F). The product was obtained as a white solid. Yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 15.6 Hz, 1H), 7.95 (s, 1H), 7.60 (m, 2H), 7.37 (m, 9H), 4.50 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 164.9, 152.3, 149.1, 148.9, 137.7, 136.8, 136.5, 131.3, 128.8, 128.8, 128.7, 128.5, 128.3, 127.5, 123.6, 123.1, 83.4, 62.1, 27.8, 14.3; HRMS(ESI) m/z [M+H]+: Calcd for $C_{27}H_{28}NO_4$: 430.2018. Found: 430.2018.

Ethyl 4,5,6-triphenylpicolinate (2-30l):



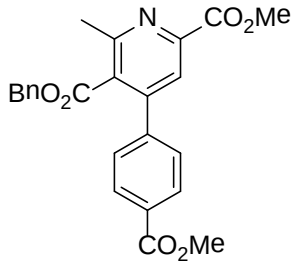
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow solid. Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.30 (m, 2H), 7.17 (m, 6H), 7.07 (m, 5H), 6.87 (dd, J = 1.2, 7.8 Hz, 2H), 4.50 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 158.8, 150.7, 146.8, 139.9, 138.6, 137.4, 137.0, 131.0, 130.1, 129.2, 127.9, 127.7, 127.6, 127.5, 127.0, 124.9, 61.8, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{26}H_{22}NO_2$: 380.1651. Found: 380.1652.

5-Benzyl 2-methyl 4-(4-methoxyphenyl)-6-methylpyridine-2,5-dicarboxylate (2-30m):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.29 (m, 5H), 7.09 (d, *J* = 6.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.16 (s, 2H), 4.00 (s, 3H), 3.82 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 165.3, 160.3, 156.1, 148.6, 147.4, 134.4, 130.8, 129.4, 129.2, 128.6, 128.4, 128.4, 123.2, 114.2, 67.5, 55.2, 53.0, 22.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{23}H_{22}NO_5$: 392.1498. Found: 392.1495.

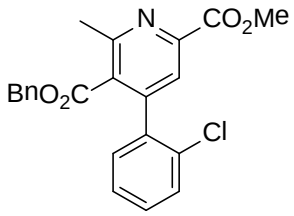
5-Benzyl 2-methyl 4-(4-(methoxycarbonyl)phenyl)-6-methylpyridine-2,5-dicarboxylate (2-30n):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.97 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.39 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.26 (m, 3H), 7.05 (dd, *J* = 1.2, 7.6 Hz, 2H), 5.12 (s, 2H), 4.02 (s, 3H), 3.97 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 166.3, 165.0, 156.6, 148.1, 147.8, 141.6, 134.1, 130.8,

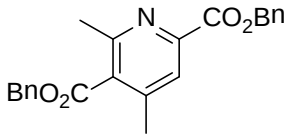
130.6, 129.9, 128.8, 128.6, 128.5, 127.9, 123.0, 67.8, 53.2, 52.3, 23.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{24}H_{22}NO_6$: 420.1447. Found: 420.1453.

5-Benzyl 2-methyl 4-(2-chlorophenyl)-6-methylpyridine-2,5-dicarboxylate (2-30o):



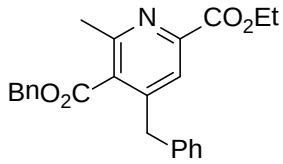
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.38 (d, *J* = 0.8 Hz, 1H), 7.31 (m, 4H), 7.18 (m, 2H), 7.07 (dd, *J* = 1.6, 7.2 Hz, 2H), 5.08 (br, 2H), 4.01 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.0, 156.9, 147.4, 147.1, 136.0, 134.4, 132.1, 131.2, 130.0, 129.9, 129.7, 128.6, 128.4, 128.4, 126.6, 124.2, 67.5, 53.1, 23.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_{22}H_{19}ClNO_4$: 396.1003. Found: 396.0998.

Dibenzyl 4,6-dimethylpyridine-2,5-dicarboxylate (2-30p):



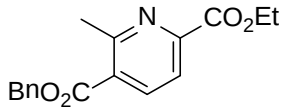
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.42 (m, 4H), 7.31 (m, 6H), 5.43 (s, 2H), 5.39 (s, 2H), 2.57 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.5, 162.2, 155.7, 147.3, 145.9, 135.5, 134.8, 132.1, 128.7, 128.6, 128.5, 128.4, 128.3, 124.2, 67.5, 67.4, 22.9, 19.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{23}H_{22}NO_4$: 376.1549. Found: 376.1543.

5-Benzyl 2-ethyl 4-benzyl-6-methylpyridine-2,5-dicarboxylate (2-30q):



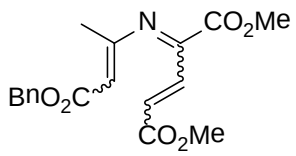
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.25 (s, 5H), 7.16 (m, 3H), 6.99 (d, *J* = 6.8 Hz, 2H), 5.17 (d, *J* = 5.2 Hz, 2H), 4.34 (d, *J* = 7.2 Hz, 2H), 3.91 (s, 2H), 2.49 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 164.7, 155.9, 148.6, 148.0, 137.6, 134.5, 131.9, 129.0, 128.7, 128.7, 128.6, 128.6, 126.8, 123.7, 67.6, 62.0, 38.7, 23.0, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{24}H_{24}NO_4$: 390.1705. Found: 390.1714.

5-Benzyl 2-ethyl 6-methylpyridine-2,5-dicarboxylate (2-30r):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.40 (m, 5H), 5.38 (s, 2H), 4.48 (q, *J* = 6.8 Hz, 2H), 2.92 (s, 3H), 1.44 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 164.5, 160.1, 149.6, 139.4, 135.2, 128.6, 128.5, 128.4, 128.0, 122.1, 67.4, 62.2, 24.9, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{18}NO_4$: 300.1236. Found: 300.1225.

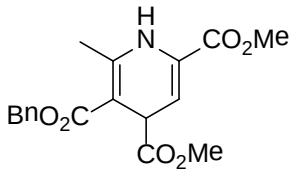
Dimethyl 4-(4-(benzyloxy)-4-oxobut-2-en-2-ylimino)pent-2-enedioate (2-29a):



The title compound was prepared according to the general procedure (F), except for isolation without oxidation. The product was obtained as a yellow oil. Yield: 17%; ^{1}H

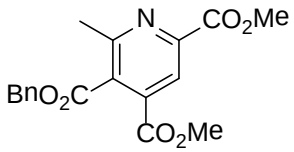
NMR (400 MHz, CDCl3) δ 7.30 (m, 5H, another 1H of the alkene buried inside), 6.72 (d, J = 16.4 Hz, 1H), 5.15 (bs, 1H), 5.06 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.0, 161.4, 160.2, 152.2, 136.0, 130.3, 128.4, 128.3, 128.0, 97.7, 65.8, 52.9, 52.2, 22.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{20}NO_6$: 346.1291. Found: 346.1289.

5-Benzyl 2,4-dimethyl 6-methyl-1,4-dihydropyridine-2,4,5-tricarboxylate (2-29):



The title compound was prepared according to the general procedure (F), except for isolation without oxidation. The product was obtained as a mixture containing **2-26s** as a minor component. Yield: 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.29 (bs, 1H), 5.92 (dd, J = 1.6, 5.6 Hz, 1H), 5.19 (d, J = 12.4 Hz, 1H), 5.06 (d, J = 12.4 Hz, 1H), 4.50 (d, J = 5.6 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 167.1, 162.6, 148.3, 136.6, 128.4, 128.2, 127.9, 127.9, 109.0, 93.3, 65.6, 52.7, 52.2, 42.3, 20.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{18}H_{20}NO_6$: 346.1291. Found: 346.1293.

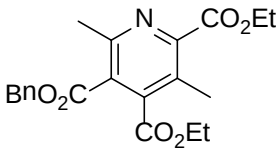
5-Benzyl 2,4-dimethyl 6-methylpyridine-2,4,5-tricarboxylate (2-30s):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.45 (m, 2H), 7.39 (m, 3H), 5.43 (s, 2H), 4.03 (s, 3H), 3.84 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 164.5, 164.1, 157.1, 148.4, 136.6, 134.7, 131.4,

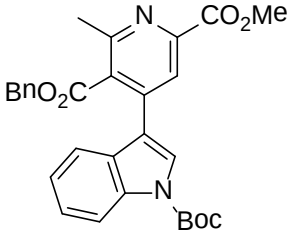
128.9, 128.7, 128.6, 121.9, 68.2, 53.2, 53.1, 22.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{18}NO_6$: 344.1134. Found: 344.1128.

5-Benzyl 2,4-diethyl 3,6-dimethylpyridine-2,4,5-tricarboxylate (2-30t):



The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 5H), 5.33 (s, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.66 (s, 3H), 2.41 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 166.0, 165.9, 154.9, 151.2, 142.8, 134.6, 128.6, 128.6, 126.8, 126.1, 67.9, 62.1, 62.0, 23.4, 15.3, 14.1, 13.8; HRMS (ESI) m/z [M+H]+: Calcd for $C_{21}H_{24}NO_6$: 386.1604. Found: 386.1598.

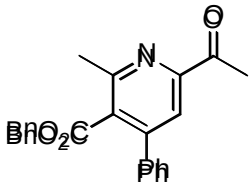
5-Benzyl 2-methyl 4-(1-(*tert*-butoxycarbonyl)-1H-indol-3-yl)-6-methylpyridine-2,5-dicarboxylate (2-30u):



The title compound was prepared according to the general procedure (F). The product was obtained as a orange oil. Yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 7.65 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.26 (m, 2H), 7.17 (t, *J* = 7.0 Hz, 2H), 6.97 (d, *J* =7.2 Hz, 2H), 5.09 (s, 2H), 4.02 (s, 3H), 2.70 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 165.2, 156.6, 149.0, 147.7, 141.3, 135.3, 134.3, 131.3, 128.4, 128.3, 128.3, 128.2, 125.2, 124.9,

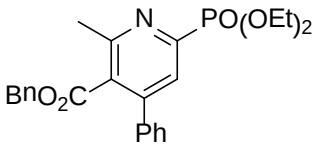
123.7, 123.3, 119.3, 117.3, 115.5, 84.3, 67.6, 53.1, 28.1, 23.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{29}H_{29}N_2O_6$: 501.2026. Found: 501.2025.

Benzyl 6-acetyl-2-methyl-4-phenylnicotinate (2-30v):



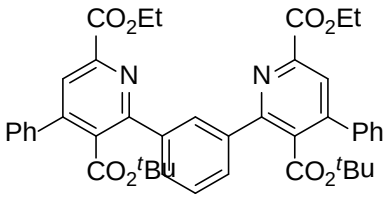
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.37 (m, 5H), 7.26 (m, 3H), 7.00 (dd, *J* = 2.0, 7.2 Hz, 2H), 5.10 (s, 2H), 2.74 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 168.2, 155.4, 152.9, 148.8, 137.7, 134.4, 130.7, 128.8, 128.7, 128.5, 128.4, 128.4, 127.8, 119.5, 67.6, 25.8, 22.8; HRMS (ESI) m/z [M+H]+: Calcd for $C_{22}H_{20}NO_3$: 346.1443. Found: 346.1430.

Benzyl 6-(diethoxyphosphoryl)-2-methyl-4-phenylnicotinate (2-30w):



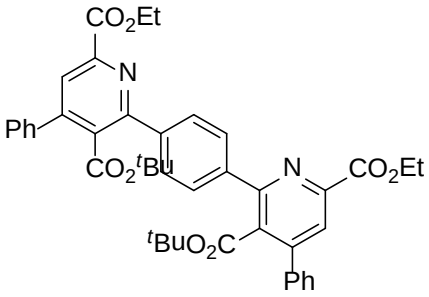
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 1H), 7.38 (m, 5H), 7.28 (m, 3H), 7.01 (d, 6.4 Hz, 2H), 5.10 (s, 2H), 4.25 (m, 4H), 2.66 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 156.7 (d, *J* = 23.8 Hz), 151.9 (d, *J* = 225.6 Hz), 147.8 (d, *J* = 12.8 Hz), 137.3 (d, *J* = 1.9 Hz), 134.4, 130.0 (d, *J* = 4.2 Hz), 129.0, 128.7, 128.5, 128.5, 128.4, 127.9, 126.1 (d, *J* = 25.3 Hz), 67.6, 63.1 (d, *J* = 5.9 Hz), 22.9, 16.3 (d, *J* = 6.2 Hz); HRMS (ESI) m/z [M+H]+: Calcd for $C_{24}H_{27}NO_5P$: 440.1627. Found: 440.1627.

5-Di-tert-butyl 2-diethyl 6,6'-(1,3-phenylene)bis(4-phenylpyridine-2,5 dicarboxylate) (2-31):



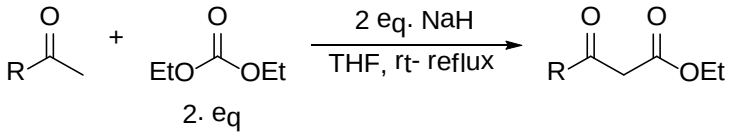
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.05 (d, *J* = 1.6 Hz, 2H), 7.82 (dd, *J* = 1.6, 7.6 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.45 (m, 10H), 4.49 (q, *J* = 6.8 Hz, 4H), 1.44 (t, *J* = 6.8 Hz, 6H), 1.09 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 164.9, 156.1, 149.4, 147.6, 138.8, 137.5, 132.5, 129.6, 129.5, 128.7, 128.4, 128.3, 128.1, 124.2, 83.4, 62.1, 27.3, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{44}H_{45}N_2O_8$: 729.3176. Found: 729.3177.

5-Di-tert-butyl 2-diethyl 6,6'-(1,4-phenylene)bis(4-phenylpyridine-2,5-dicarboxylate) (2-32):



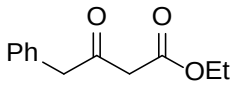
The title compound was prepared according to the general procedure (F). The product was obtained as a yellow oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 2H), 7.85 (s, 4H), 7.45 (s, 10H), 4.49 (q, *J* = 7.2 Hz, 4H), 1.44 (t, *J* = 7.2 Hz, 6H), 1.16 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.8, 156.0, 149.5, 147.8, 139.7, 137.5, 132.3, 129.0, 128.8, 128.4, 128.4, 124.2, 92.9, 83.5, 62.1, 27.5, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{44}H_{45}N_2O_8$: 729.3176. Found: 729.3173.

General procedure for synthesis of *β*-keto esters (G):



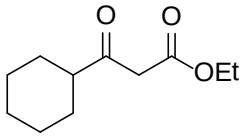
To an oven-dried 2 neck round bottomed flask under nitrogen, 2 eq. of NaH was added and stirred in THF 20 mL. Diethyl carbonate (2.eq) was added to the mixture at rt, and subsequently the ketone (5 mmol) was added dropwise. The mixture was allowed to stir at rt until hydrogen gas evolution has ceased, the mixture was then heated to reflux. Upon completion as indicated by TLC, the reaction mixture was cooled to 0°C and quenched with aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography to afford the desired *β*-keto esters.

Ethyl 3-oxo-4-phenylbutanoate (3-6b):[18]



The title compound was prepared according to the literature.[18] The product was obtained as a colourless oil in 1:10 mixture of enol and keto form. Yield 60%; ^{1}H NMR of keto form (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.20 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 2H), 3.84 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR of keto form (100 MHz, $CDCl_3$) δ 200.3, 167.0, 133.1, 129.4, 128.7, 127.2, 61.3, 49.9, 48.2, 13.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{15}O_3$: 207.1021. Found: 207.1028.

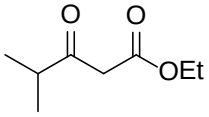
Ethyl 3-cyclohexyl-3-oxopropanoate (3-6c):[19]



The title compound was prepared according to the general procedure (G). The product was obtained as a colourless oil in 1:10 mixture of enol and keto form. Yield 70%; ^{1}H

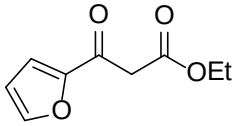
NMR of both enol and keto (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 5.00 (s, 1H), 4.18 (m, 2H), 3.47 (s, 2H), 2.45 (m, 1H), 1.88 (m, 2H), 1.78 (m, 2H), 1.67 (m, 2H), 1.27 (m, 10H); ^{13}C NMR of both isomers (100 MHz, $CDCl_3$) δ 205.8, 182.7, 173.0, 167.4, 86.9, 61.2, 59.8, 50.8, 47.3, 43.4, 29.9, 28.1, 25.8, 25.6, 25.4, 14.2, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{19}O_3$: 199.1334. Found: 199.1334.

Ethyl 4-methyl-3-oxopentanoate (3-6d):



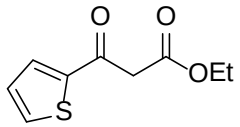
The title compound was prepared according to the general procedure (G). The product was obtained as a colourless oil in 1:1 mixture of enol and keto form. Yield 84%; ^1H NMR of both enol and keto (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 4.94 (m, 1H), 4.15 (m, 2H), 3.45 (s, 2H), 2.69 (m, 1H), 2.38 (m, 1H), 1.26 (m, 6H), 1.10 (m, 6H); ^{13}C NMR of both isomers (100 MHz, $CDCl_3$) δ 206.4, 183.5, 173.0, 167.3, 86.6, 63.6, 61.2, 59.8, 47.0, 41.1, 33.7, 29.6, 19.6, 17.8, 14.2, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_{15}O_3$: 159.1021. Found: 159.1031.

Ethyl 3-(furan-2-yl)-3-oxopropanoate (3-6h):[20]



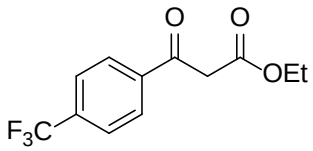
The title compound was prepared according to the general procedure (G). The product was obtained as a colourless oil in keto form. Yield 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 1H), 7.27 (d, *J* = 4.0 Hz, 1H), 6.57 (dd, *J* = 1.6, 3.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.0, 166.9, 151.9, 146.9, 118.2, 112.6, 61.4, 45.4, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{11}O_4$: 183.0657. Found: 183.0643.

Ethyl 3-oxo-3-(thiophen-2-yl)propanoate (3-6i):[21]



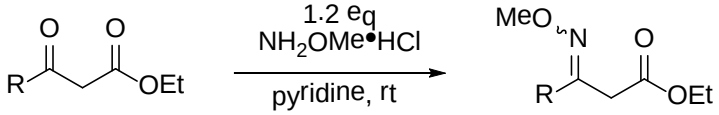
The title compound was prepared according to the general procedure (G). The product was obtained as a colourless oil in keto form. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 0.8, 3.6 Hz, 1H), 7.70 (dd, *J* = 0.8, 4.8 Hz, 1H), 7.15 (dd, *J* = 4.0, 5.2 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.9, 166.8, 143.1, 134.8, 133.2, 128.2, 61.4, 46.3, 13.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{11}O_3S$: 199.0429. Found: 199.0431.

Ethyl 3-oxo-3-(4-(trifluoromethyl)phenyl)propanoate:[22]



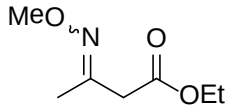
The title compound was prepared according to the general procedure (G). The product was obtained as a colourless oil in 1:2 mixture of enol and keto form. Yield 75%; ^{1}H NMR of both isomers (400 MHz, $CDCl_3$) *δ* 12.6 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 5.72 (s, 1H), 4.23 (m, 2H), 4.01 (s, 2H), 1.30 (m, 3H); HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{12}O_3F_3$: 261.0739. Found: 261.0738.

General procedure for synthesis of oxime esters (H):



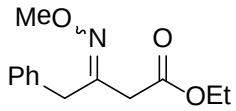
To a solution of β-keto ester (5 mmol, 1 eq.) in pyridine (10 mL) was added $NH_2OMe{\bullet}HCl$ (1.2 eq.) and stirred at room temperature. Upon completion, the reaction was diluted with water and extracted with diethyl ether. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by column chromatography to afford the desired oxime ester.

Ethyl 3-(methoxyimino)butanoate (3-7a):[23]



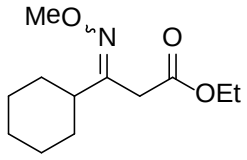
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:1 mixture of cis and trans. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (m, 4H), 3.86 (d, *J* = 1.2 Hz, 3H), 3.82 (d, *J* = 1.2 Hz, 3H), 3.32 (d, *J* = 0.8 Hz, 2H), 3.20 (d, *J* = 0.8 Hz, 2H), 1.96 (d, *J* = 0.8 Hz, 3H), 1.91 (d, *J* = 0.8 Hz, 3H), 1.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.8, 151.3, 150.3, 61.4, 61.3, 61.0, 60.9, 41.3, 35.2, 20.4, 14.3, 14.1, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_7H_{14}NO_3$: 160.0974. Found: 160.0980.

Ethyl 3-(methoxyimino)-4-phenylbutanoate (3-7b):[23]



The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:2 mixture of cis and trans. Yield: 93%; ^{1}H NMR of trans form (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.24 (m, 3H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.62 (s, 2H), 3.18 (s, 2H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.6, 152.5, 136.0, 129.2, 128.6, 126.9, 61.5, 60.8, 40.6, 33.1, 14.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{18}NO_3$: 236.1287. Found: 236.1290.

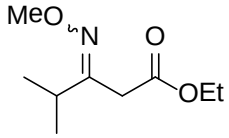
Ethyl 3-cyclohexyl-3-(methoxyimino)propanoate (3-7c):[23]



The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:6 mixture of cis and trans. ^{1}H NMR of both isomers (400 MHz, $CDCl_3$) *δ* 4.15 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.22 (s, 2H),

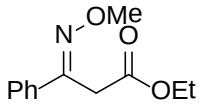
3.15 (s, 2H), 2.23 (m, 1H), 1.76 (m, 7H), 1.31 (m, 10H); ^{13}C NMR of trans isomer (100 MHz, $CDCl_3$) δ 169.1, 157.3, 151.3, 61.2, 60.7, 43.7, 32.9, 29.9, 26.0, 14.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{22}NO_3$: 228.1600. Found: 228.1597.

Ethyl 3-(methoxyimino)-4-methylpentanoate (3-7d):



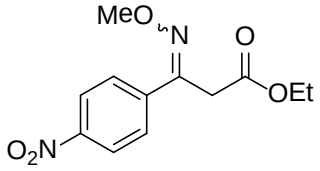
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:4 mixture of cis and trans. ^{1}H NMR of trans isomers (400 MHz, $CDCl_3$) δ 4.14 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.21 (s, 2H), 2.58 (quint, J = 6.8 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.8 Hz, 6H); ^{13}C NMR of trans isomer (100 MHz, $CDCl_3$) δ 169.0, 157.6, 61.1, 60.6, 33.6, 32.3, 19.5, 14.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{18}NO_3$: 188.1287. Found: 188.1291.

(*E*)-Ethyl 3-(methoxyimino)-3-phenylpropanoate (3-7e):[23]



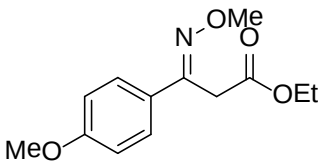
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil. Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.37 (m, 3H), 4.14 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 3.75 (s, 2H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 151.3, 135.3, 129.2, 128.4, 126.1, 62.1, 61.0, 33.2, 14.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{16}NO_3$: 222.1130. Found: 222.1128.

Ethyl 3-(methoxyimino)-3-(4-nitrophenyl)propanoate (3-7f):[23]



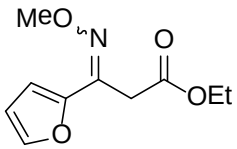
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil. Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 1.6, 6.8 Hz, 2H), 7.82 (d, J = 2.0, 6.8 Hz, 2H), 4.16 (d, J = 7.2 Hz, 2H), 4.07 (s, 3H), 3.79 (s, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 149.4, 148.0, 141.2, 129.2, 126.9, 126.8, 123.6, 123.3, 62.8, 61.3, 32.6, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{15}N_2O_5$: 267.0981. Found: 267.0979.

(*E*)-Ethyl 3-(methoxyimino)-3-(4-methoxyphenyl)propanoate (3-7g):[23]



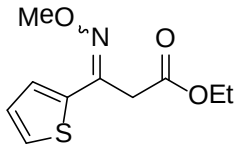
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil. Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 2.0, 6.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 3.80 (s, 2H), 3.72 (s, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.5, 150.8, 127.8, 127.5, 113.9, 62.0, 61.0, 55.2, 33.1, 14.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{18}NO_4$: 252.1236. Found: 252.1224.

Ethyl 3-(furan-2-yl)-3-(methoxyimino)propanoate (3-7h):[23]



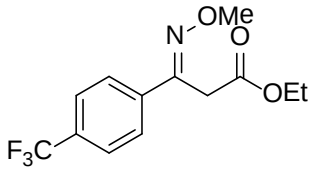
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:10 mixture of cis and trans. Yield: 85%; ^{1}H NMR of trans isomer (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.66 (d, J = 3.2 Hz, 1H), 6.44 (m, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.65 (s, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 149.0, 143.7, 143.6, 111.4, 110.2, 62.4, 61.0, 32.2, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{14}NO_4$: 212.0932. Found: 212.0932.

Ethyl 3-(methoxyimino)-3-(thiophen-2-yl)propanoate (3-7i):



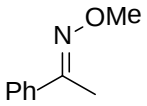
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil in 1:2 mixture of cis and trans. Yield: 82%; ^{1}H NMR of cis and trans isomers (400 MHz, $CDCl_3$) δ 7.50 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 4.0 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.05 (m, 1H), 6.99 (m, 1H), 4.14 (m, 2H), 4.07 (s, 3H), 3.96 (s, 3H), 3.73 (s, 2H), 3.67 (s, 2H), 1.21 (m, 3H); ^{13}C NMR of both isomers (100 MHz, $CDCl_3$) δ 169.6, 168.2, 147.0, 143.8, 138.9, 131.5, 130.7, 129.1, 127.1, 127.0, 126.4, 125.5, 62.2, 62.1, 61.1, 61.1, 39.8, 33.2, 14.0; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{14}NO_3S$: 228.0694. Found: 228.0694.

(*E*)-Ethyl 3-(methoxyimino)-3-(4-(trifluoromethyl)phenyl)propanoate:



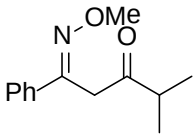
The title compound was prepared according to the general procedure (H). The product was obtained as a colourless oil. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 4.15 (q, J = 7.2 Hz, 2H), 4.10 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 150.0, 138.7, 131.0 (q, J = 33.3 Hz, C-CF_3), 128.5, 126.4, 125.4 (q, J = 3.0 Hz, CH), 123.8 (q, J = 253.5 Hz, CF_3), 62.5, 61.2, 32.8, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –-62.8 ppm. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{15}NO_3F_3$: 290.1004. Found: 290.1004.

(*E*)-Acetophenone O-methyl oxime:[24]



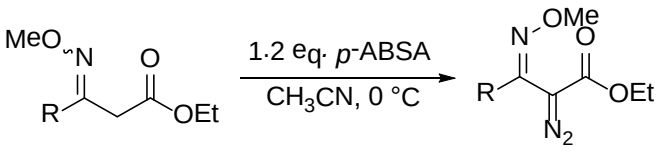
The title compound was prepared according to the literature.[25] The product was obtained as a colorless oil in 1:5 mixture of cis and trans. Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.35 (m, 3H), 4.00 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 136.6, 129.0, 128.4, 126.0, 61.9, 12.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{12}NO$: 150.0919. Found: 150.0923.

(*E*)-1-(Methoxyimino)-4-methyl-1-phenylpentan-3-one (3-7j):[25]



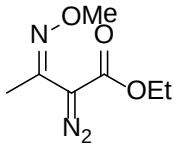
The title compound was prepared according to the literature.[25] The product was obtained as a colourless oil. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 2H), 7.35 (m, 3H), 4.00 (s, 3H), 3.86 (s, 2H), 2.76 (quint, *J* = 6.8 Hz, 1H), 1.12 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 152.5, 135.6, 129.2, 128.4, 126.1, 62.0, 40.6, 39.6, 18.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{18}NO_2$: 220.1338. Found: 220.1340.

General procedure for diazo compounds (I):



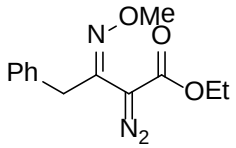
To a solution of α-diazo oxime ether (1 eq.) and 4-acetylbenzenesulfonyl azide, *p*-ABSA (1.2 eq.) in CH_3CN at 0°C was added dropwise DBU (1.2 eq.). The resulting orange solution was stirred for 30 min at 0°C and allowed to warm to room temperature. The reaction mixture was concentrated and the crude material was purified by column chromatography to afford the desired diazo compound.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)butanoate (3-8a):[23]



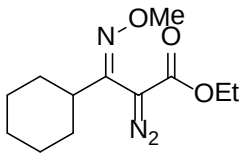
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow oil. Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (d, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 2.20 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 141.5, 61.6, 61.1, 19.1, 14.3. HRMS (ESI) m/z [M+H]+: Calcd for $C_7H_{12}N_3O_3$: 186.0879. Found: 186.0874.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-4-phenylbutanoate (3-8b):[23]



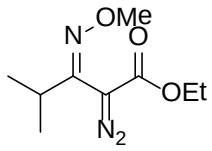
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow oil. Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 5H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 144.2, 137.4, 128.9, 128.4, 126.7, 62.0, 61.1, 37.6, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{16}N_3O_3$: 262.1192. Found: 262.1199.

(*Z*)-Ethyl 3-cyclohexyl-2-diazo-3-(methoxyimino)propanoate (3-8c):[23]



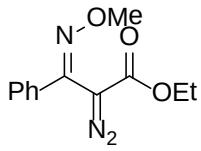
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow oil. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 2.80 (m, 1H), 1.90 (d, *J* = 11.2 Hz, 2H), 1.77 (m, 2H), 1.67 (d, *J* = 11.6 Hz, 1H), 1.29 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 148.1, 61.7, 60.9, 40.2, 31.4, 26.4, 26.1, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{20}N_3O_3$: 254.1505. Found: 254.1502.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-4-methylpentanoate (3-8d):



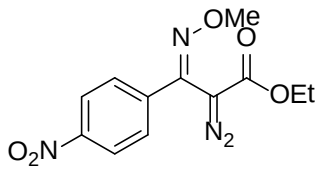
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.16 (quint, J = 7.2 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.16 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 148.7, 61.8, 61.0, 30.6, 20.7, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{16}N_3O_3$: 214.1192. Found: 214.1197.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-3-phenylpropanoate (3-8e):[23]



The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.37 (m, 3H), 4.10 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 144.2, 133.7, 129.5, 128.2, 127.6, 62.6, 61.2, 14.0. HRMS(ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{14}N_3O_3$: 248.1035. Found: 248.1044.

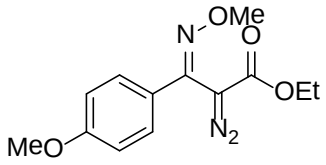
(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-3-(4-nitrophenyl)propanoate (3-8f):[23]



The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 4.10 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 148.2, 142.5, 140.0, 128.5,

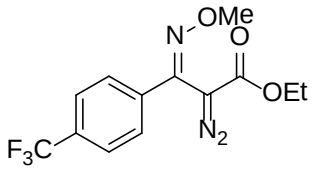
128.5, 123.4, 123.3, 63.1, 61.5, 14.1; HRMS(ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{13}N_4O_5$: 293.0886. Found: 293.0904.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-3-(4-methoxyphenyl)propanoate (3-8g):[23]



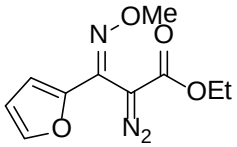
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.02 (s, 3H), 3.81 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.8, 143.7, 129.0, 126.0, 113.7, 62.4, 61.1, 55.2, 31.5, 22.6, 14.1, 14.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}N_3O_4$: 278.1141. Found: 278.1150.

(*Z*)-Ethyl 2-diazo-3-(methoxyimino)-3-(4-(trifluoromethyl)phenyl)propanoate:



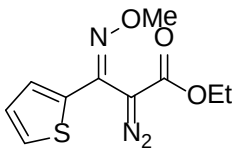
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (q, J = 8.4 Hz, 4H), 4.15 (q, J = 7.2 Hz, 2H), 4.10 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 143.1, 137.3, 131.3 (q, J = 32.2 Hz, C-CF_3), 128.0, 125.1 (q, J = 3.7 Hz, CH), 123.9 (q, J = 270.5 Hz, CF_3), 62.9, 61.3, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.8 ppm. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{13}N_3O_3F_3$: 316.0909. Found: 316.0912.

(*E*)-Ethyl 2-diazo-3-(furan-2-yl)-3-(methoxyimino)propanoate (3-8h):[23]



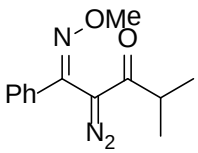
The title compound was prepared according to the general procedure (I). The product was obtained as a yellow solid. Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, J = 0.8 Hz, 1H), 6.66 (d, J = 3.6 Hz, 1H), 6.45 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 146.9, 143.7, 135.6, 111.5, 111.4, 62.8, 61.3, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{12}N_3O_4$: 238.0828. Found: 238.0823.

(*E*)-Ethyl 2-diazo-3-(methoxyimino)-3-(thiophen-2-yl)propanoate (3-8i):



The title compound was prepared according to the general procedure (I). The product was obtained as a yellow oil. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 0.8, 4.8 Hz, 1H), 7.19 (dd, J = 1.2, 3.6 Hz, 1H), 7.00 (dd, J = 4.0, 5.2 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.03 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 138.6, 136.2, 128.3, 127.3, 127.0, 62.7, 61.2, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{12}N_3O_3S$: 254.0599. Found: 254.0592.

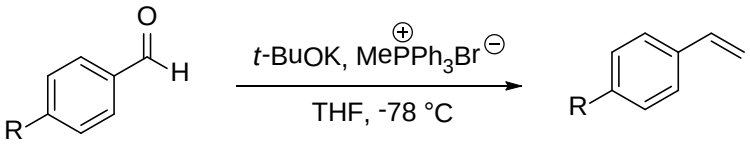
(*Z*)-2-Diazo-1-(methoxyimino)-4-methyl-1-phenylpentan-3-one (3-8j):[25]



The title compound was prepared according to the general procedure (I). The product was obtained as a yellow oil. Yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.40 (m, 3H), 4.07 (s, 3H), 2.44 (quint, J = 6.8 Hz, 1H), 0.99 (d, J = 6.8 Hz, 6H); ^{13}C

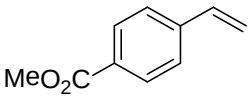
NMR (100 MHz, $CDCl_3$) δ 197.3, 144.0, 133.8, 130.1, 128.8, 127.3, 62.7, 36.7, 18.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{16}N_3O_2$: 246.1243. Found: 246.1244.

General procedure for alkenes (J):



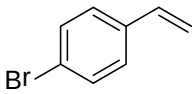
To a suspension of methyltriphenylphosphonium bromide (12 mmol, 1.2 equiv) in THF (30 mL) was added *t*-BuOK (12 mmol, 1.2 equiv) at 0 °C under nitrogen. After stirring for 30 min, the reaction mixture was cooled to –78 °C and a solution of aldehyde (10 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The reaction mixture was stirred at the same teperature for 2 h and then warmed to room temperature for additional 1 h. The reaction was quenched with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over MgSO4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane : ethyl acetate = 95 : 5) to give the alkene.

Methyl 4-vinylbenzoate (3-12d):[26]



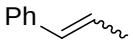
The title compound was prepared according to the general procedure (J). The product was obtained as a white solid. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.32 (s, 2H), 6.73 (m, 1H), 5.84 (d, J = 17.2 Hz, 1H), 5.35 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 141.8, 135.9, 129.8, 129.2, 126.0, 116.3, 51.9; HRMS(ESI) m/z [M+H]+: Calcd for $C_{10}H_{11}O_2$: 163.0759. Found: 163.0761.

1-Bromo-4-vinylbenzene (3-12f):[27]



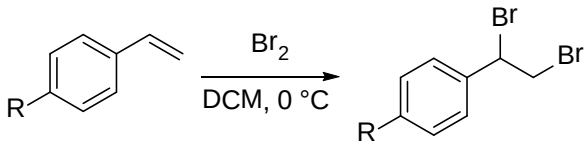
The title compound was prepared according to the general procedure (J). The product was obtained as a white solid. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.2 Hz, 2H), 7.30 (d, J = 7.2 Hz, 2H), 6.68 (dd, J = 10.8, 17.6 Hz, 1H), 5.78 (d, J = 17.6 Hz, 1H), 5.31 (d, J = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.8, 131.7, 127.8, 121.6, 114.6.

Prop-1-enylbenzene (3-12h):[28]



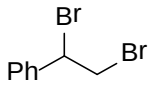
The title compound was prepared according to the literature.[29] The product was obtained as a pale yellow oil. Yield 55%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 4H), 7.20 (m, 1H), 6.43 (dd, J = 2.0, 12.0 Hz, 1H), 5.78 (m, 1H), 1.89 (dd, J = 2.0, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 129.8, 128.8, 128.1, 126.7, 126.4, 14.6; HRMS(ESI) m/z [M+H]+: Calcd for C_9H_{11}: 119.0861. Found: 119.0860.

General procedure for bromination of alkenes (K):



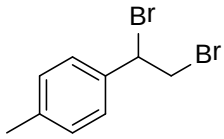
To a solution of alkene (5 mmol) in DCM (10 ml) cooled to 0°C was added bromine (1.2 eq) dropwise. The resulting solution was stirred in ice bath for 1 h. Upon completion as indicated by TLC, the reaction was quenched with saturated $Na_2S_2O_3$ and stirred vigorously until the orange colour disappeared. The reaction was then filtered through a pad of celite and washed with DCM. The filtrate was evaporated and purified by column chromatography using hexane:ether (99:1).

(1,2-Dibromoethyl)benzene (3-13a):[30]



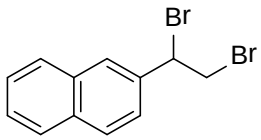
The title compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.12 (m, 1H), 4.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 129.2, 128.8, 127.6, 50.9, 35.0; HRMS(ESI) m/z [M+H]+: Calcd for $C_8H_9{}^{79}Br_2$: 262.9071. Found: 262.9029.

1-(1,2-Dibromoethyl)-4-methylbenzene (3-13b):[31]



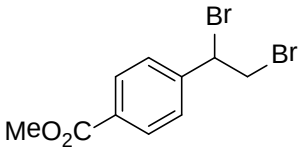
The title compound was prepared according to the procedure (K). The product was obtained as a white solid. Yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.13 (dd, J = 5.2, 10.4 Hz, 1H), 4.05 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.6, 129.6, 127.5, 51.0, 35.0, 21.3; HRMS(ESI) m/z [M+H]+: Calcd for $C_9H_{11}{}^{79}Br^{81}Br$: 278.9207. Found: 278.9202.

2-(1,2-Dibromoethyl)naphthalene (3-13c):[32]



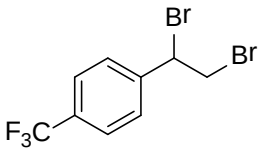
The titled compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 4H), 7.50 (m, 3H), 5.31 (m, 1H), 4.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.4, 132.8, 129.0, 128.1, 127.7, 127.4, 126.8, 126.6, 124.3, 51.3, 34.7; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{11}{}^{79}Br_2$: 312.9227. Found: 312.9214.

Methyl 4-(1,2-dibromoethyl)benzoate (3-13d):



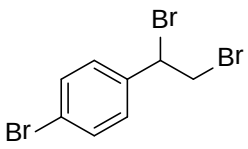
The titled compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 97%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 5.14 (m, 1H), 4.04 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.1, 143.2, 130.6, 130.0, 127.7, 52.1, 49.2, 34.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{11}O_2{}^{79}Br^{81}Br$: 322.9105. Found: 322.9124.

1-(1,2-Dibromoethyl)-4-(trifluoromethyl)benzene (3-13e):



The titled compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 5.14 (m, 1H), 4.06 (m, 1H), 3.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 142.4, 131.1 (q, *J* = 32.4 Hz, C-CF_3), 128.1, 125.8 (q, *J* = 3.7 Hz, CH), 123.7 (q, *J* = 270.7 Hz, CF_3), 48.9, 34.3; ^{19}F NMR (376 MHz, CDCl3): *δ* –62.7 ppm. HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_8{}^{79}Br_2F_3$: 330.8945. Found: 330.8957.

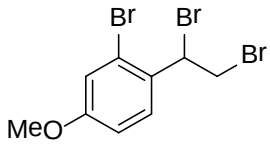
1-Bromo-4-(1,2-dibromoethyl)benzene (3-13f):



The titled compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 2.0, 8.8 Hz, 2H), 5.08 (dd, *J* = 5.2, 11.2 Hz, 1H),

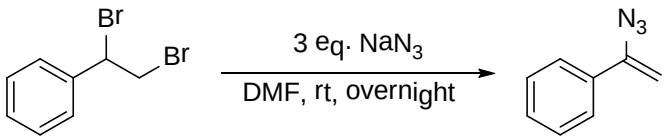
4.05 (dd, *J* = 5.2, 10.4 Hz, 1H), 3.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 132.1, 129.3, 123.2, 49.6, 34.6; HRMS(ESI) m/z [M+H]+: Calcd for $C_8H_8{}^{79}Br_2{}^{81}Br$: 342.8156. Found: 342.8144.

2-Bromo-1-(1,2-dibromoethyl)-4-methoxybenzene (3-13g)



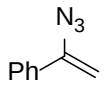
The titled compound was prepared according to the general procedure (K). The product was obtained as a white solid. Yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.0 Hz, 1H), 7.30 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 5.08 (m, 1H), 4.04 (m, 1H), 3.95 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 132.5, 132.0, 127.9, 111.8, 111.7, 56.2, 49.6, 34.8; HRMS(ESI) m/z [M+H]+: Calcd for $C_9H_{10}{}^{79}Br_3$: 370.8282. Found: 370.8279.

General procedure for synthesis of vinyl azide (L):



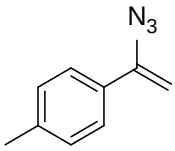
To a solution of dibromide (5 mmol, 1 eq.) in DMF (20 mL) was added NaN_3 (3 eq.). The mixture was stirred overnight at room temperature, then diluted with water and extracted with diethyl ether. The combined organic layers were washed three times with water, dried with $MgSO_4$. After evaporation of solvents, the crude residue was purified by flash column chromatography (hexane : ethyl acetate = 99 : 1) to give vinyl azide.[7]

(1-Azidovinyl)benzene (3-14a):[33]



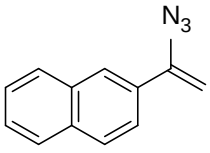
The titled compound was prepared according to the general procedure (L). The product was obtained as a colourless oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.35 (m, 3H), 5.42 (d, *J* = 2.0 Hz, 1H), 4.95 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 145.0, 134.3, 129.1, 128.4, 125.5, 97.9; HRMS(ESI) m/z [M+H]+: Calcd for $C_8H_8N_3$: 146.0718. Found: 146.0715.

1-(1-Azidovinyl)-4-methylbenzene (3-14b):



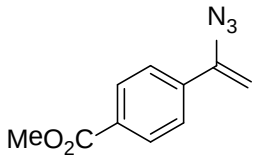
The titled compound was prepared according to the general procedure (L). The product was obtained as a colourless oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.8 Hz, 2H), 7.15 (d, *J* = 6.8 Hz, 2H), 5.37 (s, 1H), 4.90 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 145.0, 139.1, 131.5, 129.1, 125.4, 97.1, 21.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_9H_{10}N_3$: 160.0875. Found: 160.0871.

2-(1-Azidovinyl)naphthalene (3-14c):



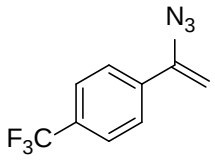
The titled compound was prepared according to the general procedure (L). The product was obtained as a yellow solid. Yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.81 (m, 3H), 7.63 (m, 1H), 7.47 (m, 2H), 5.56 (d, *J* = 2.4 Hz, 1H), 5.03 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 144.9, 133.5, 133.0, 131.4, 128.5, 128.1, 127.6, 126.6, 126.5, 124.9, 123.0, 98.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{12}H_{10}N_3$: 196.0875. Found: 196.0889.

Methyl 4-(1-azidovinyl)benzoate (3-14d):[7]



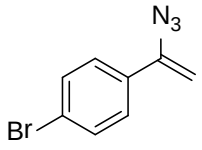
The titled compound was prepared according to the general procedure (L). The product was obtained as a colourless oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.4 Hz, 2H), 7.64 (d, *J* = 6.4 Hz, 2H), 5.57 (d, *J* = 2.8 Hz, 1H), 5.07 (d, *J* = 2.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.5, 144.2, 138.3, 130.5, 129.7, 129.5, 127.2, 125.4, 99.6, 52.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{10}N_3O_2$: 204.0773. Found: 204.0771.

1-(1-Azidovinyl)-4-(trifluoromethyl)benzene (3-14e):



The titled compound was prepared according to the general procedure (L). The product was obtained as a white solid. Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 4H), 5.50 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 143.9, 137.6, 130.9 (q, *J* = 32.6 Hz, C-CF_3), 127.6, 125.8, 125.3 (q, *J* = 3.7 Hz, CH), 99.4; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* = –62.8 ppm. HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_7N_3F_3$: 214.0592. Found: 214.0602.

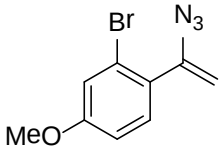
1-(1-Azidovinyl)-4-bromobenzene (3-14f):[7]



The titled compound was prepared according to the general procedure (L). The product was obtained as light yellow oil. Yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 4H), 5.41 (d, *J* = 2.4 Hz, 1H), 4.95 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz,

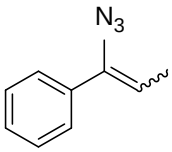
$CDCl_3$) δ 144.2, 133.2, 131.6, 127.1, 123.3, 98.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_7N_3{}^{81}Br$: 225.9803. Found: 225.9797.

1-(1-Azidovinyl)-2-bromo-4-methoxybenzene (3-14g):



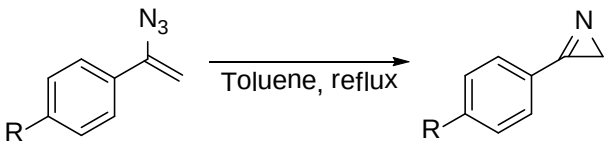
The titled compound was prepared according to the literature.[7] The product was obtained as a white solid. Yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 0.8 Hz, 1H), 7.46 (m, 1H), 6.84 (dd, *J* = 1.6, 6.8, Hz, 1H), 5.33 (d, *J* = 2.4 Hz, 1H), 4.88 (d, *J* = 2.4 Hz, 1H), 3.89 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 143.4, 130.5, 125.7, 111.6, 111.3, 96.9, 56.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_9N_3O^{79}Br$: 253.9929. Found: 253.9939.

(1-Azidoprop-1-enyl)benzene (3-14h):[34]



The titled compound was prepared according to the literature.[7] The product was obtained as a colourless oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.27 (q, *J* = 6.8 Hz, 1H), 1.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 135.3, 128.6, 128.4, 126.8, 115.1, 12.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{10}N_3$: 160.0875. Found: 160.0880.

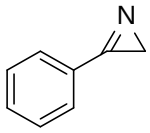
General procedure for synthesis of unsubstituted 2*H*-azirine (M):



To a solution of vinyl azide in toluene was heated in reflux and until completion was showed by TLC. The reaction was allowed to cool to room temperature and toluene

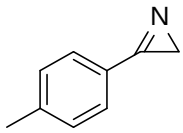
was evaporated. The crude residue was purified by flash column chromatography (in pentane) to give 2*H*-azirine.

3-Phenyl-2*H*-azirine (3-15a):[35]



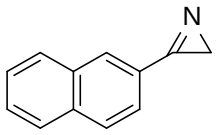
The titled compound was prepared according to the literature.[35] The product was obtained as a colourless oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.56 (m, 3H), 1.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 132.8, 129.5, 129.0, 125.4, 19.6; HRMS (ESI) m/z [M+H]+: Calcd for C_8H_8N: 118.0657. Found: 118.0646.

3-*p*-Tolyl-2*H*-azirine (3-15b):



The titled compound was prepared according to the general procedure (M). The product was obtained as a colourless oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 143.6, 129.7, 129.5, 122.7, 21.8, 19.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{10}N$: 132.0813. Found: 132.0817.

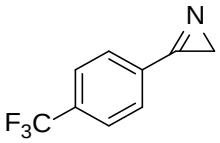
3-(Naphthalen-2-yl)-2*H*-azirine (3-15c):[35]



The titled compound was prepared according to the general procedure (M). The product was obtained as a colourless oil. Yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.98 (m, 3H), 7.89 (m, 1H), 7.59 (m, 2H), 1.87 (s, 2H); ^{13}C NMR (100

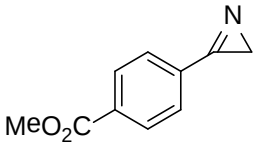
MHz, $CDCl_3$) δ 165.8, 135.4, 132.8, 131.8, 129.0, 128.4, 128.0, 127.0, 124.3, 122.8, 19.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{10}N$: 168.0813. Found: 168.0802.

3-(4-(Trifluoromethyl)phenyl)-2*H*-azirine (3-15d):



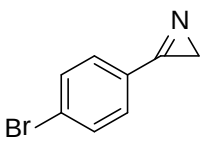
The titled compound was prepared according to the general procedure (M). The product was obtained as a white solid. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 2H), 1.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 134.4 (q, *J* = 32.5 Hz, C-CF_3), 129.8, 128.7, 126.1 (q, *J* = 3.7 Hz, CH), 123.5 (q, *J* = 270.8 Hz, CF_3), 20.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ –63.2 (d, *J* = 3.2 Hz, 1F). HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_7NF_3$: 186.0531. Found: 186.0530.

Methyl 4-(2*H*-azirin-3-yl)benzoate (3-15e):



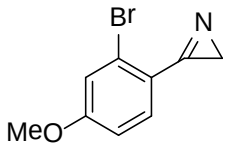
The titled compound was prepared according to the general procedure (M). The product was obtained as a colourless oil. Yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.8 Hz, 2H), 7.98 (dd, *J* = 1.6, 8.4 Hz, 2H), 3.97 (s, 3H), 1.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 165.7, 133.8, 130.1, 129.3, 129.2, 52.5, 20.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{10}NO_2$: 176.0712. Found: 176.0712.

3-(4-Bromophenyl)-2*H*-azirine (3-15f):



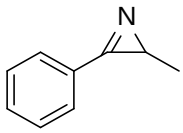
The titled compound was prepared according to the general procedure (M). The product was obtained as a colourless oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 4H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.0, 132.3, 130.7, 127.6, 124.3, 19.8; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_9N^{79}Br$: 209.9918. Found: 209.9924.

3-(2-Bromo-4-methoxyphenyl)-2*H*-azirine (3-15g)



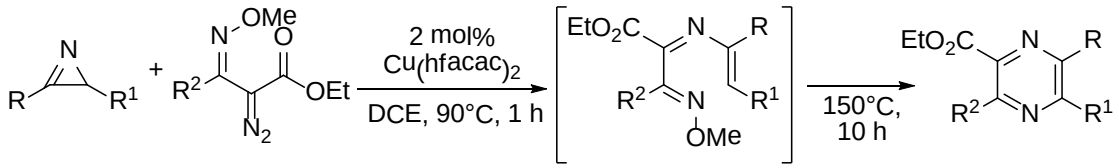
The titled compound was prepared according to the general procedure (M). The product was obtained as a white solid. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.0 Hz, 1H), 7.84 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 4.00 (s, 3H), 1.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.0, 159.3, 134.5, 130.3, 119.3, 112.4, 111.9, 56.5, 19.7; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_9NO^{79}Br$: 225.9868. Found: 225.9876.

2-Methyl-3-phenyl-2*H*-azirine (3-15h):[9]



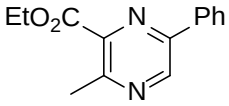
The titled compound was prepared according to the general procedure (M). The product was obtained as a colourless oil. Yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 3.2, 5.6 Hz, 2H), 7.54 (m, 3H), 2.31 (m, 1H), 1.35 (d, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.3, 132.6, 129.1, 129.0, 125.6, 27.3, 18.8; HRMS (ESI) m/z [M+H]+: Calcd for $C_9H_{10}N$: 132.0813. Found: 132.0819.

General procedure for synthesis of unsymmetrical pyrazine (N):



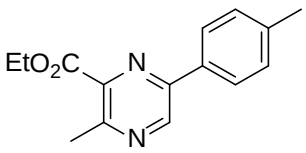
In an oven dried sealed tube was added 2 mol% of $Cu(hfacac)_2$ in DCE (0.5 mL), followed by the addition of azirine (0.3 mmol, 1 eq.) in DCE (0.5 mL), the reaction was allowed to stir at room temperature with the dropwise addition of *α*-diazo oxime ether (1.2 eq.) in DCE (1 mL). The reaction was heated at 90°C until the consumption of the azirine as observed by TLC. The reaction then was further heated at 150°C approximately 10 h. Upon completion of the reaction, the crude was concentrated and purified by flash column chromatography (2:1 Hexane: Ethyl acetate) to give pyrazine.

Ethyl 3-methyl-6-phenylpyrazine-2-carboxylate (3-16a):



The titled compound was prepared according to the general procedure (N). The product was obtained as a brown oil. Yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.69 (s, 1H), 7.51 (m, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.7, 164.7, 164.1, 157.0, 135.9, 131.2, 128.9, 127.4, 117.8, 62.5, 24.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{15}N_2O_2$: 243.1134. Found: 243.1133.

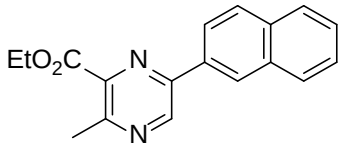
Ethyl 3-methyl-6-p-tolylpyrazine-2-carboxylate (3-16b):



The titled compound was prepared according to the general procedure (N). The product was obtained as a brown oil. Yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04

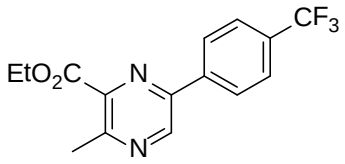
(d, *J* = 6.8 Hz, 2H), 7.66 (s, 1H), 7.30 (d, *J* = 6.8 Hz, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.68 (s, 3H), 2.42 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.4, 164.5, 164.2, 157.0, 141.7, 133.0, 129.6, 127.2, 117.3, 62.4, 24.4, 21.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{17}N_2O_2$: 257.1290. Found: 257.1289.

Ethyl 3-methyl-6-(naphthalen-2-yl)pyrazine-2-carboxylate (3-16c):



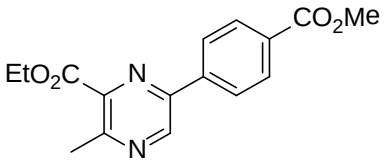
The titled compound was prepared according to the general procedure (N). The product was obtained as a off white solid. Yield 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2H), 8.23 (dd, *J* = 1.6, 8.8 Hz, 1H), 8.00 (m, 2H), 7.90 (m, 2H), 7.57 (m, 2H), 4.59 (q, *J* = 7.2 Hz, 2H), 2.75 (s, 3H), 1.52 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.6, 164.5, 164.2, 157.1, 134.7, 133.1, 129.0, 128.7, 127.9, 127.7, 127.6, 126.6, 123.8, 118.0, 62.6, 24.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{17}N_2O_2$: 293.1290. Found: 293.1292.

Ethyl 3-methyl-6-(4-(trifluoromethyl)phenyl)pyrazine-2-carboxylate (3-16d):



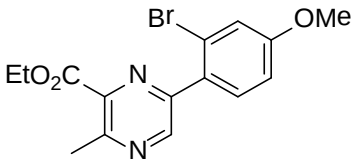
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow sticky gel. Yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.6 Hz, 2H), 7.76 (m, 3H), 4.56 (m, 2H), 2.73 (d, *J* = 3.6 Hz, 3H), 1.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.4, 163.9, 163.2, 157.2, 139.2, 132.8 (q, *J* = 34.3 Hz, C-CF_3), 127.8, 125.9, 123.7 (q, *J* = 270.8 Hz, CF_3), 118.2, 62.7, 24.5, 14.2; 19F NMR (376 MHz, CDCl3): *δ* = –62.9 ppm. HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{14}N_2O_2F_3$: 311.1007. Found: 311.1008.

Ethyl 6-(4-(methoxycarbonyl)phenyl)-3-methylpyrazine-2-carboxylate (3-16e):



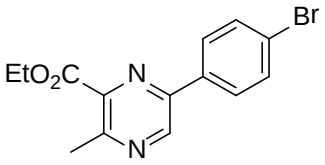
The titled compound was prepared according to the general procedure (N). The product was obtained as a white solid. Yield 82%; mp: 114.5-115.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 4H), 7.75 (s, 1H), 4.56 (q, *J* = 7.2 Hz, 2H), 3.96 (s, 3H), 2.73 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.1, 166.3, 163.9, 163.4, 157.1, 139.8, 132.3, 130.0, 127.3, 118.3, 62.6, 52.2, 24.4, 14.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{16}H_{17}N_2O_4$: 301.1188. Found: 301.1191.

Ethyl 6-(2-bromo-4-methoxyphenyl)-3-methylpyrazine-2-carboxylate (3-16f):



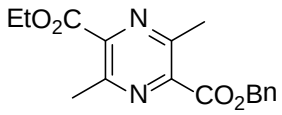
The titled compound was prepared according to the general procedure (N). The product was obtained as a off white solid. mp: 164.9-165.6°C; Yield 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.0 Hz, 1H), 8.11 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.60 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.54 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 2.67 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.6, 164.1, 162.9, 158.3, 157.0, 132.3, 129.5, 128.0, 116.9, 112.4, 111.7, 62.6, 56.4, 24.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{16}N_2O_3{}^{79}$Br: 351.0344. Found: 351.0391.

Ethyl 6-(4-bromophenyl)-3-methylpyrazine-2-carboxylate (3-16g):



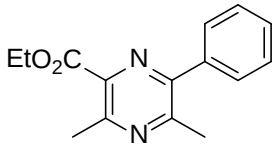
The titled compound was prepared according to the general procedure (N). The product was obtained as a brown oil. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.9, 163.9, 163.4, 157.0, 134.7, 132.1, 128.8, 126.0, 117.5, 62.5, 24.4, 14.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{14}N_2O_4{}^{79}Br$: 321.0239. Found: 321.0232.

2-Benzyl 5-ethyl 3,6-dimethylpyrazine-2,5-dicarboxylate (3-16h):



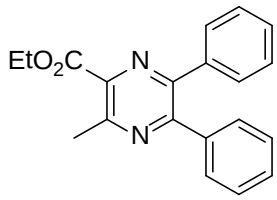
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow solid. Yield 68%; mp: 61.5-62.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.35 (m, 3H), 5.45 (s, 2H), 4.48 (m, 2H), 2.79 (s, 3H), 2.76 (s, 3H), 1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.8, 164.6, 150.6, 150.6, 143.9, 143.6, 134.9, 128.4, 128.3, 128.3, 67.6, 62.1, 22.0, 14.0; HRMS(ESI) m/z [M+H]+: Calcd for $C_{17}H_{19}N_2O_4$: 315.1345. Found: 315.1342.

Ethyl 3,5-dimethyl-6-phenylpyrazine-2-carboxylate (3-16i):



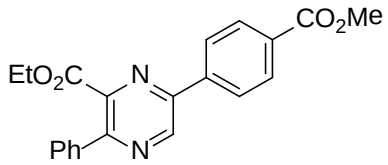
The titled compound was prepared according to the general procedure (N). The product was obtained as a white solid. mp: 117.6-118.6°C; Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.46 (m, 3H), 4.52 (m, 2H), 2.67 (s, 3H), 2.36 (s, 3H), 1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.8, 165.6, 164.1, 153.7, 137.6, 129.2, 129.1, 128.9, 128.3, 62.4, 23.0, 15.8, 14.2; HRMS(ESI) m/z [M+H]+: Calcd for $C_{15}H_{17}N_2O_2$: 257.1290. Found: 257.1286.

Ethyl 3-methyl-5,6-diphenylpyrazine-2-carboxylate (3-16j):



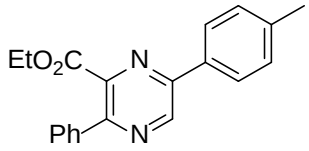
The titled compound was prepared according to the general procedure (N). The product was obtained as a brown sticky gel. Yield 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.22 (m, 3H), 7.11 (m, 2H), 4.55 (q, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 1.47 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.4, 164.4, 164.2, 155.3, 127.3, 135.9, 134.2, 130.0, 129.6, 129.2, 128.8, 128.1, 127.9, 62.6, 23.7, 14.3; HRMS(ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O_2$: 319.1447. Found: 319.1446.

Ethyl 6-(4-(methoxycarbonyl)phenyl)-3-phenylpyrazine-2-carboxylate (3-16k):



The titled compound was prepared according to the general procedure (N). The product was obtained as a off white solid. mp: 171.3-171.8°C; Yield 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (m, 7H), 7.56 (s, 3H), 4.57 (q, *J* = 6.8 Hz, 2H), 3.97 (s, 3H), 1.51 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 166.4, 166.1, 164.5, 164.2, 157.8, 140.3, 136.0, 132.4, 131.5, 130.2, 129.1, 127.5, 127.5, 114.4, 62.6, 52.3, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{21}H_{19}N_2O_4$: 363.1345. Found: 363.1341.

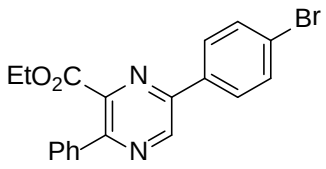
Ethyl 3-phenyl-6-p-tolylpyrazine-2-carboxylate (3-16l):



The titled compound was prepared according to the general procedure (N). The product was obtained as a off white solid. mp: 117.6-118.6°C; Yield 79%; ^{1}H NMR

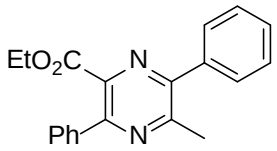
(400 MHz, $CDCl_3$) δ 8.19 (m, 2H), 8.12 (m, 3H), 7.52 (s, 3H), 7.32 (d, *J* = 7.6 Hz, 2H), 4.56 (q, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.50 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.5, 165.4, 164.4, 157.6, 141.8, 136.3, 133.4, 131.2, 129.7, 128.9, 127.4, 127.3, 113.5, 62.4, 21.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O_2$: 319.1447. Found: 319.1449.

Ethyl 6-(4-bromophenyl)-3-phenylpyrazine-2-carboxylate (3-16m):



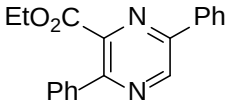
The titled compound was prepared according to the general procedure (N). The product was obtained as a brown oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 2H), 8.14 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.52 (m, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.9, 164.5, 164.3, 157.8, 136.1, 135.1, 132.3, 131.5, 129.1, 129.0, 127.5, 126.2, 113.6, 62.6, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{16}N_2O_2{}^{79}$Br: 383.0395. Found: 383.0403.

Ethyl 5-methyl-3,6-diphenylpyrazine-2-carboxylate (3-16n):



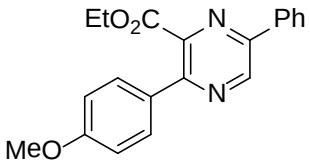
The titled compound was prepared according to the general procedure (N). The product was obtained as a off white solid. mp: 114.4-114.5°C; Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.49 (m, 6H), 4.51 (q, *J* = 6.8 Hz, 2H), 2.40 (s, 3H), 1.44 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.7, 164.2, 154.3, 137.8, 129.5, 129.2, 128.4, 128.0, 62.4, 18.0, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O_2$: 319.1447. Found: 319.1440.

Ethyl 3,6-diphenylpyrazine-2-carboxylate (3-16o):



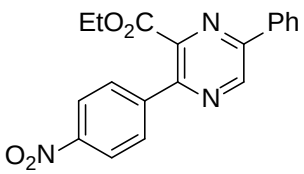
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow solid. Yield 67%; mp: 119.6-120.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 5H), 7.53 (m, 6H), 4.56 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.6, 164.3, 157.7, 136.2, 131.3, 129.0, 127.5, 113.9, 62.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{17}N_2O_2$: 305.1290. Found: 305.1286.

Ethyl 3-(4-methoxyphenyl)-6-phenylpyrazine-2-carboxylate (3-16p):



The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 4H), 8.10 (s, 1H), 7.52 (m, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.55 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.3, 165.0, 164.4, 162.3, 157.6, 136.4, 131.1, 129.0, 128.9, 128.5, 127.4, 114.3, 112.9, 62.4, 55.4, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O_3$: 335.1396. Found: 335.1399.

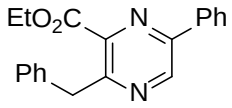
Ethyl 3-(4-nitrophenyl)-6-phenylpyrazine-2-carboxylate (3-16q):



The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow sticky gel. Yield 51%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 4H), 8.24 (m, 3H), 7.57 (m, 3H), 4.58 (q, *J* = 6.8 Hz, 2H), 1.52 (t, *J* = 6.8

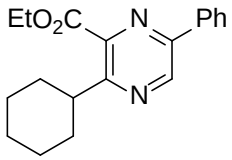
Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 164.0, 163.2, 158.0, 149.5, 142.1, 135.7, 131.8, 129.2, 128.5, 127.6, 124.2, 114.7, 114.5, 62.7, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{16}N_3O_4$: 350.1141. Found: 350.1146.

Ethyl 3-benzyl-6-phenylpyrazine-2-carboxylate (3-16r):



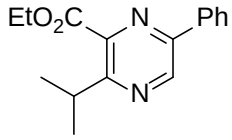
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 1.2, 6.8 Hz, 2H), 7.52 (s, 1H), 7.45 (m, 3H), 7.32 (m, 5H), 4.55 (q, *J* = 7.2 Hz, 2H), 4.30 (s, 2H), 1.48 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 165.2, 164.3, 157.2, 137.1, 136.0, 131.3, 129.4, 129.0, 129.0, 127.5, 127.2, 117.4, 62.6, 44.3, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O_2$: 319.1447. Found: 319.1438.

Ethyl 3-cyclohexyl-6-phenylpyrazine-2-carboxylate (3-16s):



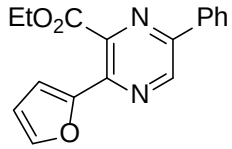
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.67 (s, 1H), 7.51 (m, 3H), 4.54 (q, *J* = 7.2 Hz, 2H), 2.88 (m, 1H), 2.06 (d, *J* = 11.6 Hz, 2H), 1.89 (d, *J* = 12.8 Hz, 2H), 1.77 (m, 2H), 1.60 (m, 2H), 1.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 164.8, 164.4, 157.1, 136.3, 131.0, 128.9, 127.3, 115.2, 62.3, 46.1, 32.1, 26.0, 25.7, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{23}N_2O_2$: 311.1760. Found: 311.1767.

Ethyl 3-isopropyl-6-phenylpyrazine-2-carboxylate (3-16t):



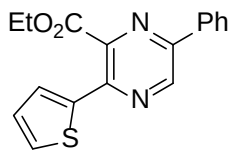
The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (m, 2H), 7.69 (s, 1H), 7.52 (m, 3H), 4.54 (q, *J* = 7.2 Hz, 2H), 3.22 (quint, *J* = 6.8 Hz, 1H), 1.48 (q, *J* = 7.2 Hz, 3H), 1.39 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 177.5, 165.1, 164.5, 157.2, 136.4, 131.2, 129.0, 127.5, 114.9, 62.4, 36.3, 21.9, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{16}H_{19}N_2O_2$: 271.1447. Found: 271.1447.

Ethyl 3-(furan-2-yl)-6-phenylpyrazine-2-carboxylate (3-16u):



The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 65%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 3.6 Hz, 2H), 8.10 (s, 1H), 7.65 (s, 1H), 7.53 (s, 3H), 7.47 (d, *J* = 3.2 Hz, 1H), 6.61 (d, *J* = 0.8 Hz, 1H), 4.55 (q, *J* = 6.8 Hz, 2H), 1.50 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.4, 164.1, 157.6, 156.7, 151.2, 145.4, 136.0, 131.3, 128.9, 127.4, 113.7, 112.7, 111.4, 62.5, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{15}N_2O_3$: 295.1083. Found: 295.1079.

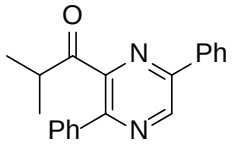
Ethyl 6-phenyl-3-(thiophen-2-yl)pyrazine-2-carboxylate (3-16v):



The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18

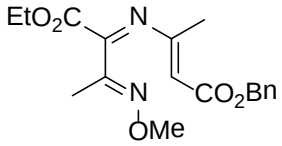
(m, 2H), 8.01 (s, 1H), 7.95 (d, *J* = 3.2 Hz, 1H), 7.58 (d, *J* = 4.8 Hz, 1H), 7.54 (m, 3H), 7.19 (m, 1H), 4.55 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.1, 160.4, 157.7, 141.5, 136.0, 131.3, 130.7, 129.0, 128.5, 128.3, 127.4, 112.1, 62.5, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{15}N_2O_2S$: 311.0854. Found: 311.0850.

1-(3,6-Diphenylpyrazin-2-yl)-2-methylpropan-1-one (3-16w):



The titled compound was prepared according to the general procedure (N). The product was obtained as a yellow oil. Yield 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (m, 4H), 8.21 (s, 1H), 7.56 (m, 6H), 4.16 (quint, *J* = 7.2 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.1, 165.5, 160.8, 136.5, 131.3, 129.1, 127.4, 113.6, 36.3, 18.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}N_2O$: 303.1497. Found: 303.1504.

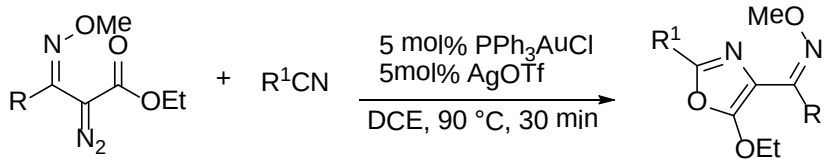
(*E*)-Benzyl 3-((*E*) -((*E*)-1-ethoxy-3-(methoxyimino)-1-oxobutan-2-ylidene)amino) but-2-enoate (3-18):



The titled compound was prepared according to the general procedure (N) but stopping the reaction after 90°C. The product was obtained as a yellow oil. Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.17 (d, *J* = 0.8 Hz, 1H), 5.14 (s, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.00 (s, 3H), 2.33 (d, *J* = 0.4 Hz, 3H), 2.01 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.6, 162.7, 155.8, 153.8,

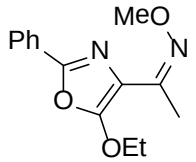
136.5, 128.5, 128.0, 101.0, 65.5, 63.3, 61.6, 18.0, 14.1, 9.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{22}N_2O_5$: 347.1589. Found: 347.1591.

General procedure for synthesis of oxazoles (O):



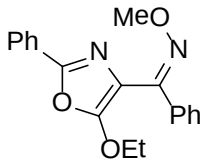
To a oven dried reaction tube was added 5 mol% of PPh_3AuCl and 5 mol% of AgOTf in DCE (1 mL) and the mixture was allowed to stir for 5 mins at room temperature until a white precipitate forms. Benzonitrile (10 eq.), followed by dropwise addition of α-diazo oxime ether (0.3 mmol, 1 eq.) was added to the mixture whilst stirring at room temperature. After the addition of the substrates, the reaction was heated at 90°C for approximately 30 mins. The crude was concentrated and purified by flash column chromatography to give the oxazole.

(*Z*)-1-(5-Ethoxy-2-phenyloxazol-4-yl)ethanone *O*-methyl oxime (4-13a):



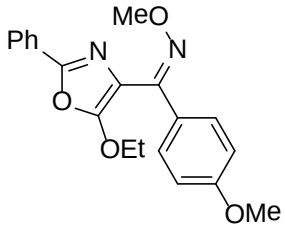
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.41 (m, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.93 (s, 3H), 2.25 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.1, 151.9, 146.4, 129.8, 128.6, 127.2, 125.6, 110.6, 69.7, 61.6, 19.3, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{17}N_2O_3$: 261.1239. Found: 261.1237.

(*Z*)-(5-Ethoxy-2-phenyloxazol-4-yl)(phenyl)methanone *O*-methyl oxime (4-13b):



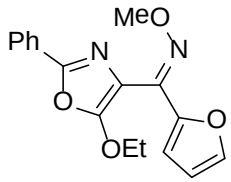
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.67 (m, 2H), 7.37 (m, 6H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.1, 152.3, 148.7, 134.7, 129.8, 129.3, 128.6, 128.2, 127.7, 127.2, 125.6, 108.1, 69.2, 62.4, 14.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{19}N_2O_3$: 323.1396. Found: 323.1394.

(*Z*)-(5-Ethoxy-2-phenyloxazol-4-yl)(4-methoxyphenyl)methanone *O*-methyl oxime (4-13c):



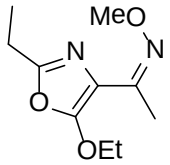
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.40 (m, 3H), 6.89 (dd, *J* = 2.0, 7.2 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.04 (s, 3H), 3.82 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.7, 157.0, 152.2, 148.3, 129.7, 129.1, 128.6, 127.3, 127.3, 125.6, 113.7, 108.2, 69.1, 62.2, 55.2, 14.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{21}N_2O_4$: 353.1501. Found: 353.1508.

(*E*)-(5-Ethoxy-2-phenyloxazol-4-yl)(furan-2-yl)methanone *O*-methyl oxime (4-13d):



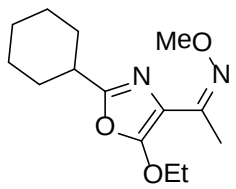
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2H), 7.50 (d, *J* = 1.2 Hz, 1H), 7.41 (m, 3H), 6.72 (d, *J* = 3.2 Hz, 1H), 6.45 (dd, *J* = 1.6, 3.2 Hz, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.07 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 157.0, 152.1, 148.4, 143.7, 140.5, 129.8, 128.6, 128.5, 127.1, 125.5, 113.6, 111.4, 69.3, 62.6, 14.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{17}N_2O_4$: 313.1188. Found: 313.1191.

(*Z*)-1-(5-Ethoxy-2-ethyloxazol-4-yl)ethanone *O*-methyl oxime (4-13e):



The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 2.65 (q, *J* = 7.6 Hz, 2H), 2.14 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.1, 155.9, 146.1, 108.9, 69.5, 61.6, 21.8, 19.2, 14.9, 11.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{17}N_2O_3$: 213.1239. Found: 213.1237.

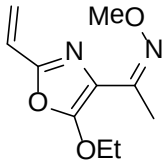
(*Z*)-1-(2-Cyclohexyl-5-ethoxyoxazol-4-yl)ethanone O-methyl oxime (4-13f):



The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ

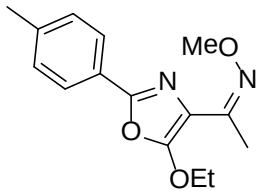
4.21 (m, 2H), 3.89 (s, 3H), 2.66 (dt, *J* = 2.8, 10.8 Hz, 1H), 2.16 (s, 3H), 1.99 (d, *J* = 12.8 Hz, 2H), 1.80 (d, *J* = 12.8 Hz, 2H), 1.69 (d, *J* = 11.2 Hz, 1H), 1.51 (q, *J* = 12.0 Hz, 2H), 1.30 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 158.4, 155.6, 146.5, 108.6, 69.3, 61.5, 37.7, 30.3, 25.7, 25.5, 19.2, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{23}N_2O_3$: 267.1709. Found: 267.1698.

(*Z*)-1-(5-Ethoxy-2-vinyloxazol-4-yl)ethanone O-methyl oxime (4-13g):



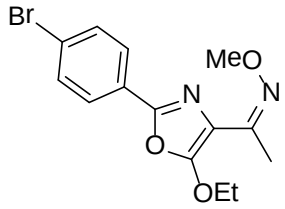
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (dd, *J* = 11.2 Hz, 1H), 5.96 (d, *J* = 17.6 Hz, 1H), 5.52 (d, *J* = 11.6 Hz, 1H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.90 (s, 3H), 2.18 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.8, 151.4, 145.8, 123.2, 120.0, 110.2, 69.5, 61.6, 19.1, 14.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{15}N_2O_3$: 211.1083. Found: 211.1085.

(*Z*)-1-(5-Ethoxy-2-p-tolyloxazol-4-yl)ethanone *O*-methyl oxime (4-13h):



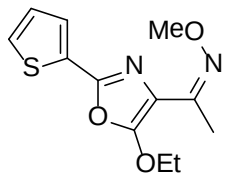
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.38 (s, 3H), 2.24 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.9, 152.2, 146.4, 140.0, 129.3, 125.5, 124.5, 110.5, 69.7, 61.6, 21.4, 19.2, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{19}N_2O_3$: 275.1396. Found: 275.1396.

(Z)-1-(2-(4-Bromophenyl)-5-ethoxyoxazol-4-yl)ethanone *O*-methyl oxime (4-13i):



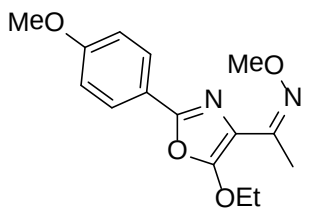
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 1.6, 6.4 Hz, 2H), 7.55 (dd, *J* = 1.6, 6.4 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.24 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.2, 151.0, 146.2, 131.9, 127.0, 126.1, 124.2, 110.8, 69.8, 61.6, 19.2, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{16}N_2O_3Br$: 339.0344. Found: 339.0348.

(*Z*)-1-(5-Ethoxy-2-(thiophen-2-yl)oxazol-4-yl)ethanone *O*-methyl oxime (4-13j):



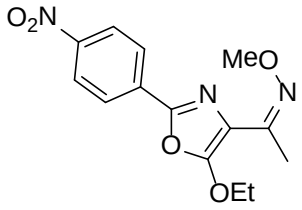
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 1H), 7.53 (d, *J* = 4.8 Hz, 1H), 7.34 (m, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.23 (s, 3H), 1.44 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 155.5, 149.3, 146.2, 129.2, 126.5, 125.5, 124.3, 110.2, 69.8, 61.6, 19.2, 14.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{15}N_2O_3S$: 267.0803. Found: 267.0800.

(*Z*)-1-(5-Ethoxy-2-(4-methoxyphenyl)oxazol-4-yl)ethanone *O*-methyl oxime (4-13k):



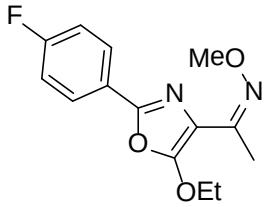
The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 2.24 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.0, 155.8, 152.1, 146.5, 127.2, 120.0, 114.0, 110.4, 69.7, 61.6, 55.3, 19.3, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{19}N_2O_4$: 291.1345. Found: 291.1353.

(*E*)-1-(5-Ethoxy-2-(4-nitrophenyl)oxazol-4-yl)ethanone *O*-methyl oxime (4-13l):



The titled compound was prepared according to the general procedure (O). The product was obtained as a yellow solid. Yield 76%; mp: 65.5-66.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 3.84 (s, 3H), 2.24 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.9, 149.5, 148.1, 145.9, 132.6, 126.0, 124.1, 111.6, 69.9, 61.7, 19.2, 15.0; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{16}N_3O_5$: 306.1090. Found: 306.1088.

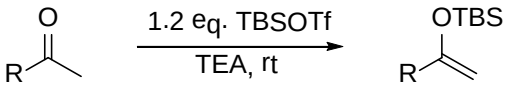
(*Z*)-1-(5-Ethoxy-2-(4-fluorophenyl)oxazol-4-yl)ethanone *O*-methyl oxime (4-13m):



The titled compound was prepared according to the general procedure (O). The product was obtained as a colourless oil. Yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 3H), 2.24 (s, 3H), 1.46 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.0, 162.5, 156.1,

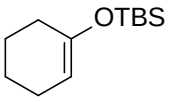
151.2, 146.3, 127.6 (d, J = 8.5 Hz, CH), 123.6 (d, J = 3.1 Hz, CH), 115.8 (d, J = 22.1 Hz, CH), 110.7, 69.8, 61.6, 19.2, 15.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –110.1 (m,1F); HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{16}N_2O_3F$: 279.1145. Found: 279.1140.

General procedure for synthesis of tert-Butyldimethylsilyl ether substrates (P):



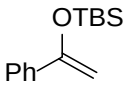
To a oven dried 2 neck round bottom flask under nitrogen was added the corresponding ketone (5 mmol, 1 eq.) in dry DCM (10 mL) and triethylamine (1.2 eq.). The reaction was stirred for 1h at room temperature and TBSOTf (1.1 eq.) was added dropwise. The reaction was allowed to stir for 2-3 h and quenched with cold aqueous NH_4Cl. The mixture was extracted with diethyl ether and dried with $MgSO_4$. After evaporation of solvents, the crude residue was purified by flash column chromatography on triethylamine deactivated silica (100% hexane).

***tert*-Butyl(cyclohexenyloxy)dimethylsilane (4-18a):[36]**



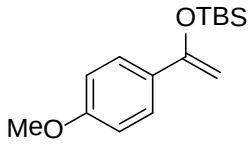
The title compound was prepared according to the general procedure (P). The product was obtained as a colourless oil. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (m, 1H), 1.99 (m, 4H), 1.65 (m, 2H), 1.50 (m, 2H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 104.3, 29.9, 25.7, 23.8, 23.2, 22.4, 18.0, -4.4. HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{25}OSi$: 213.1675. Found: 213.1672.

***tert*-Butyldimethyl(1-phenylvinyloxy)silane (4-18b):[37]**



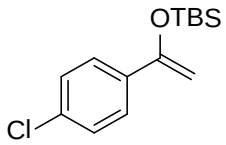
The title compound was prepared according to the general procedure (P). The product was obtained as a colourless oil. Yield: 100%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.27 (m, 3H), 4.86 (d, *J* = 1.6 Hz, 1H), 4.39 (d, *J* = 1.6 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 137.8, 128.2, 128.1, 125.3, 90.9, 25.9, 18.4, -4.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{23}OSi$: 235.1518. Found: 235.1524.

***tert*-Butyl(1-(4-methoxyphenyl)vinyloxy)dimethylsilane (4-18c):[36]**



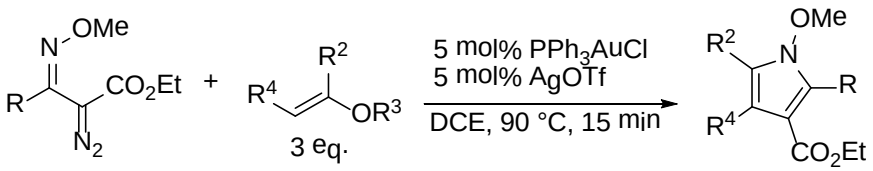
The title compound was prepared according to the general procedure (P). The product was obtained as a colourless oil. Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 9.2 Hz, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 4.67 (d, *J* = 1.6 Hz, 1H), 4.23 (d, *J* = 1.6 Hz, 1H), 3.70 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 155.8, 130.5, 126.6, 113.4, 89.3, 55.2, 25.9, 18.4, -4.6. HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{25}O_2Si$: 265.1624. Found: 265.1624.

***tert*-Butyl(1-(4-chlorophenyl)vinyloxy)dimethylsilane (4-18d):[36]**



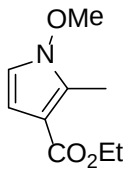
The title compound was prepared according to the general procedure (P). The product was obtained as a colourless oil. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 2.0, 6.8 Hz, 2H), 7.26 (dd, *J* = 2.0, 6.8 Hz, 2H), 4.84 (d, *J* = 1.6 Hz, 1H), 4.41 (d, *J* = 1.6 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 136.3,133.9, 128.2, 126.6, 91.3, 25.8, 18.3, -4.7; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{22}OClSi$: 269.1128. Found: 269.1122.

General procedure for synthesis of pyrrole (Q):



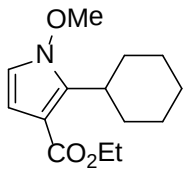
To a oven dried reaction tube was added 5 mol% of PPh_3AuCl and 5 mol% of AgOTf in DCE (1 mL) and the mixture was allowed to stir for 5 mins at room temperature until a white precipitate forms. Vinyl ether (3eq.) or ethyl vinyl ether (10 eq.), followed by dropwise addition of α-diazo oxime ether (0.3 mmol, 1 eq.) in DCE (1.5 mL) was added to the mixture whilst stirring at room temperature. After the addition of the substrates, the reaction was heated at 90°C for approximately 5- 15 mins and stopped upon seeing the mixture turn colourless with black precipitate forming. The crude was concentrated and purified by flash column chromatography to give pyrrole.

Ethyl 1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (4-17a):



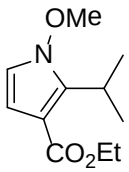
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 3.2 Hz, 1H), 6.44 (d, J = 3.2 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.00 (s, 3H), 2.50 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 130.9, 113.6, 107.9, 106.1, 66.6, 59.3, 14.4, 9.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_{14}NO_3$: 184.0974. Found: 184.0977.

Ethyl 2-cyclohexyl-1-methoxy-1*H*-pyrrole-3-carboxylate (4-17b):



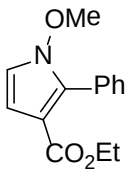
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 3.6 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.98 (s, 3H), 3.44 (m, 1H), 2.00 (m, 2H), 1.83 (m, 2H), 1.71 (m, 3H), 1.35 (m, 7H, triplet from –Et within the muliplet); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 139.2, 113.4, 107.0, 106.8, 67.0, 59.4, 35.2, 30.2, 27.0, 25.8, 14.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{22}NO_3$: 252.1600. Found: 252.1602.

Ethyl 2-isopropyl-1-methoxy-1*H*-pyrrole-3-carboxylate (4-17c):



The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, J = 3.2 Hz, 1H), 6.46 (d, J = 3.2 Hz, 1H), 4.24 (q, J = 6.8 Hz, 2H), 4.00 (s, 3H), 3.82 (quint, J = 7.2 Hz, 1H), 1.37 (d, J = 7.2 Hz, 6H), 1.33 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 139.9, 113.4, 106.9, 106.5, 66.8, 59.4, 24.6, 20.4, 14.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{18}NO_3$: 212.1287. Found: 212.1291.

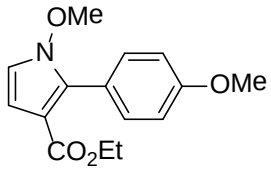
Ethyl 1-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (4-17d):



The title compound was prepared according to the general procedure (Q). The product was obtained as a white solid. Yield: 91%; mp = 75.8-76.6°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.42 (m, 3H), 6.82 (d, J = 3.6 Hz, 1H), 6.61 (d, J = 3.2 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 132.8, 130.6, 128.8, 128.4, 127.7, 115.2, 109.4, 107.0, 66.7,

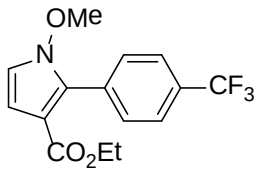
59.6, 14.2. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{16}NO_3$: 246.1130. Found: 246.1133.

Ethyl 1-methoxy-2-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (4-17e):



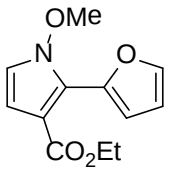
The title compound was prepared according to the general procedure (Q). The product was obtained as a white solid. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 2.0, 6.8 Hz, 2H), 6.95 (dd, J = 2.0, 6.8 Hz, 2H), 6.79 (d, J = 3.2 Hz, 1H), 6.58 (d, J = 3.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 159.7, 132.8, 131.9, 121.0, 115.0, 113.2, 109.0, 106.9, 66.5, 59.5, 55.2, 14.3. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_4$: 276.1236. Found: 276.1240.

Ethyl 1-methoxy-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carboxylate (4-17f):



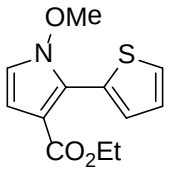
The title compound was prepared according to the general procedure (Q). The product was obtained as a white solid. Yield: 90%; mp = 85.2-85.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 6.87 (d, J = 3.2 Hz, 1H), 6.63 (d, J = 3.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.68 (s, 3H), 3.66 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 132.4, 131.0, 130.2 (q, J = 32.0 Hz, C-CF_3), 127.0, 124.6 (q, J = 3.8 Hz, CH), 124.1 (q, J = 270.5 Hz, CF_3), 116.0, 110.1, 107.5, 66.9, 59.8, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7 ppm. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{15}NO_3F_3$: 314.1004. Found: 314.0994.

Ethyl 2-(furan-2-yl)-1-methoxy-1H-pyrrole-3-carboxylate (4-17g):



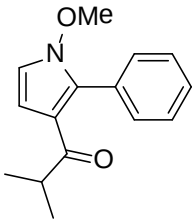
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 0.8, 1.6 Hz, 1H), 6.91 (dd, J = 0.4, 3.2 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.53 (dd, J = 1.6, 3.2 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 142.7, 142.4, 122.6, 116.4, 112.7, 111.0, 110.6, 107.5, 67.3, 59.8, 14.3. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{14}NO_4$: 236.0923. Found: 236.0929.

Ethyl 1-methoxy-2-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (4-17h):



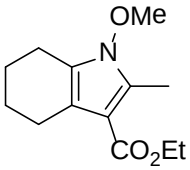
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.2, 3.6 Hz, 1H), 7.44 (dd, J = 1.2, 5.2 Hz, 1H), 7.11 (dd, J = 3.6, 4.8 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H), 6.60 (d, J = 3.2 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 130.1, 128.2, 127.2, 126.5, 125.8, 115.8, 110.2, 107.6, 66.8, 59.8, 14.2. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{14}NO_3S$: 252.0694. Found: 252.0702.

1-(1-Methoxy-2-phenyl-1*H*-pyrrol-3-yl)-2-methylpropan-1-one (4-17i):



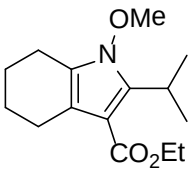
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.43 (m, 3H), 6.84 (d, J = 3.2 Hz, 1H), 6.56 (d, J = 3.2 Hz, 1H), 3.66 (s, 3H), 3.05 (quint, J = 6.8 Hz, 1H), 1.07 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 132.1, 130.5, 129.2, 128.6, 127.9, 117.4, 115.2, 106.5, 66.6, 36.8, 19.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_2$: 244.1338. Found: 244.1346.

Ethyl 1-methoxy-2-methyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (4-17j):



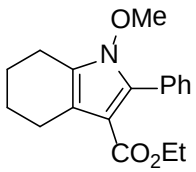
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 2.68 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 2.49 (s, 3H), 1.75 (m, 4H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 129.9, 123.1, 115.0, 105.0, 65.7, 58.9, 23.5, 23.0, 22.5, 20.4, 14.5, 9.7; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{20}NO_3$: 238.1443. Found: 238.1444.

Ethyl 2-isopropyl-1-methoxy-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (4-17k):



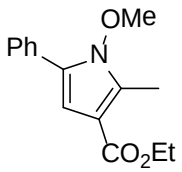
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 3.77 (quint, J = 6.8 Hz, 1H), 2.67 (t, J = 6.0 Hz, 2H), 2.56 (t, J = 6.0 Hz, 2H), 1.37 (d, J = 6.8 Hz, 6H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 138.9, 123.3, 115.4, 104.1, 66.2, 59.1, 24.7, 23.5, 23.4, 22.5, 20.9, 20.6, 14.5; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{24}NO_3$: 266.1756. Found: 266.1753.

Ethyl 1-methoxy-2-phenyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (4-17l):



The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.38 (m, 3H), 4.11 (q, J = 7.2 Hz, 2H), 3.56 (s, 3H), 2.77 (t, J = 6.4 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 1.83 (m, 4H), 1.13 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 131.6, 130.6, 129.8, 127.9, 127.5, 124.7, 116.0, 106.6, 65.6, 59.1, 23.5, 23.1, 22.4, 20.6, 14.1; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{18}H_{22}NO_3$: 300.1600. Found: 300.1596.

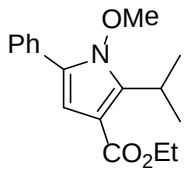
Ethyl 1-methoxy-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (4-17m):



The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.39 (m, 2H), 7.28 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.71 (s, 3H), 2.60 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 132.4, 130.4, 128.6,

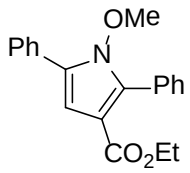
127.1, 127.0, 126.5, 108.0, 105.3, 65.6, 59.5, 14.5, 9.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{18}NO_3$: 260.1287. Found: 260.1290.

Ethyl 2-isopropyl-1-methoxy-5-phenyl-1*H*-pyrrole-3-carboxylate (4-17n):



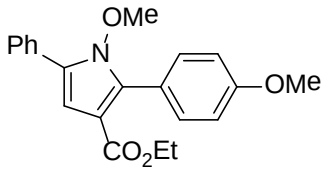
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.53 (m, 2H), 7.41 (m, 1H), 4.32 (q, J = 7.2 Hz, 2H), 4.00 (m, 1H), 3.82 (s, 3H), 1.59 (d, J = 8.0 Hz, 6H), 1.50 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 141.4, 130.4, 128.6, 127.1, 126.8, 126.7, 106.9, 106.5, 66.2, 59.5, 24.8, 20.7, 14.4; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{17}H_{22}NO_3$: 288.1600. Found: 288.1595.

Ethyl 1-methoxy-2,5-diphenyl-1*H*-pyrrole-3-carboxylate (4-17o)



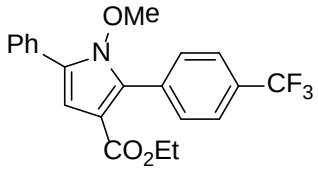
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 2H), 7.63 (m, 2H), 7.44 (m, 5H), 7.32 (m, 1H), 6.82 (s, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.40 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 134.3, 130.7, 130.2, 128.9, 128.7, 128.6, 128.4, 127.7, 127.4, 126.8, 109.5, 106.6, 65.5, 59.7, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{20}H_{20}NO_3$: 322.1443. Found: 322.1439.

Ethyl 1-methoxy-2-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (4-17p):



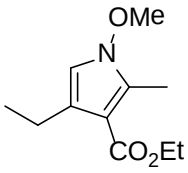
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 2H), 7.59 (m, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 6.98 (dd, J = 1.6, 6.8 Hz, 2H), 6.80 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.39 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 159.7, 134.4, 132.0, 130.3, 128.6, 128.4, 127.3, 126.8, 121.1, 113.2, 109.0, 106.5, 65.3, 59.7, 55.2, 14.3; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{22}NO_4$: 352.1549. Found: 352.1545.

Ethyl 1-methoxy-5-phenyl-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carboxylate (4-17q):



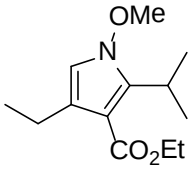
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 92%; mp = 114.1-115.1°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (m, 6H), 7.44 (m, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.83 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.39 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 132.4, 131.1, 130.2 (q, J = 32.3 Hz, C-CF_3), 129.8, 129.4, 128.8, 127.7, 127.0, 124.6 (q, J = 3.8 Hz, CH), 124.1 (q, J = 270.5 Hz, CF_3), 110.3, 106.9, 65.8, 60.0, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –-62.6 ppm. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{19}NO_3F_3$: 390.1317. Found: 390.1320.

Ethyl 4-ethyl-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (4-17r):



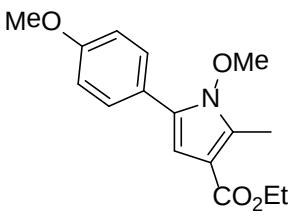
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 2.69 (q, J = 7.6 Hz, 2H), 2.47 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 131.5, 124.6, 111.2, 105.9, 66.3, 59.1, 20.0, 14.4, 14.4, 9.9; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{18}NO_3$: 212.1287. Found: 212.1283.

Ethyl 4-ethyl-2-isopropyl-1-methoxy-1*H*-pyrrole-3-carboxylate (4-17s):



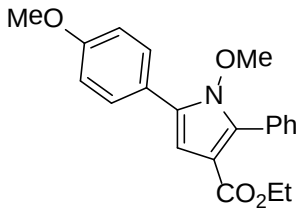
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 3.83 (m, 1H), 2.67 (q, J = 10.8 Hz, 2H), 1.35 (d, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 140.1, 124.6, 111.3, 104.8, 66.4, 59.2, 24.9, 20.6, 20.4, 14.4, 14.2; HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{22}NO_3$: 240.1600. Found: 240.1599.

Ethyl 1-methoxy-5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (4-17t):



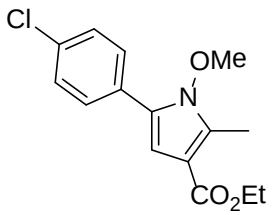
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 2.0, 6.8 Hz, 2H), 6.93 (dd, *J* = 2.0, 6.8 Hz, 2H), 6.55 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 2.58 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 158.8, 131.8, 128.0, 127.1, 123.1, 114.0, 107.7, 104.2, 65.4, 59.5, 55.2, 14.5, 9.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{16}H_{20}NO_4$: 290.1392. Found: 290.1389.

Ethyl 1-methoxy-5-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrole-3-carboxylate (4-17u):



The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 6.96 (dd, *J* = 2.0, 8.8 Hz, 2H), 6.72 (d, *J* = 0.4 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.85 (s, 3H), 3.38 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 159.0, 133.7, 130.7, 129.0, 128.6, 128.3, 127.6, 122.8, 114.1, 109.3, 105.5, 65.3, 59.7, 55.3, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{21}H_{22}NO_4$: 352.1549. Found: 352.1551.

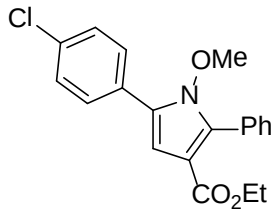
Ethyl 5-(4-chlorophenyl)-1-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate (4-17v):



The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd,

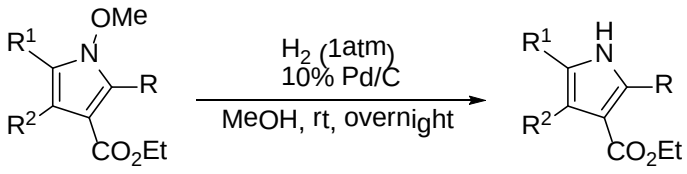
J = 2.0, 6.8 Hz, 2H), 7.35 (dd, *J* = 2.0, 6.8 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 2.59 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 132.8, 132.7, 128.8, 127.6, 125.9, 108.2, 105.6, 65.7, 59.6, 14.5, 9.9; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{17}NO_3Cl$: 294.0897. Found: 294.0905.

Ethyl 5-(4-chlorophenyl)-1-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate (4-17w):



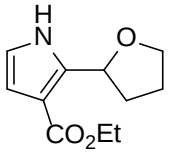
The title compound was prepared according to the general procedure (Q). The product was obtained as a colourless oil. Yield: 70%; mp = 96.8-97.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 1.6, 6.4 Hz, 2H), 7.62 (dd, *J* = 1.6, 6.4 Hz, 2H), 7.42 (m, 5H), 6.81 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 134.6, 133.2, 130.6, 128.9, 128.7, 128.6, 128.5, 127.9, 127.7, 127.4, 109.7, 106.8, 65.5, 59.8, 14.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{19}NO_3Cl$: 356.1053. Found: 356.1049.

General procedure for reduction of pyrrole (R):



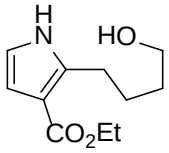
To a solution of the pyrrole (0.3 mmol) in MeOH (2 mL) was added 10% Pd/C under hydrogen gas (1 atm). The reaction mixture was stirred overnight at room temperature and filtered through a pad of celite and wash with 1:1 Hexane: Ethyl acetate. The crude was concentrated and purified by column chromatography to afford the pyrrole.

Ethyl 2-(tetrahydrofuran-2-yl)-1*H*-pyrrole-3-carboxylate (4-19a):



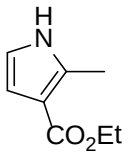
The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 35%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br, 1H), 6.60 (m, 2H), 5.41 (t, *J* = 7.0 Hz, 1H), 4.25 (m, 2H), 4.08 (m, 1H), 3.90 (m, 1H), 2.55 (m, 1H), 1.89 (m, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 140.6, 115.5, 111.0, 110.0, 75.4, 68.9, 59.4, 33.4, 25.9, 14.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{17}NO_3$: 210.1130. Found: 210.1131.

Ethyl 2-(4-hydroxybutyl)-1*H*-pyrrole-3-carboxylate (4-19b):



The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (br, 1H), 6.57 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 3.72 (t, *J* = 2.4 Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 1.76 (m, 2H), 1.62 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 139.6, 115.7, 111.4, 110.6, 62.5, 59.4, 31.5, 26.5, 25.8, 14.5; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{19}NO_3$: 212.1287. Found: 212.1291.

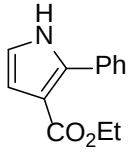
Ethyl 2-methyl-1*H*-pyrrole-3-carboxylate (4-20a):



The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br, 1H), 6.57 (m, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.53 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C

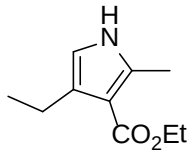
NMR (100 MHz, $CDCl_3$) δ 165.7, 135.1, 115.7, 111.8, 110.5, 59.3, 14.5, 13.2; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_{13}NO_2$: 154.0868. Found: 154.0858.

Ethyl 2-phenyl-1*H*-pyrrole-3-carboxylate (4-20b):



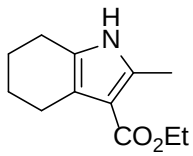
The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br, 1H), 7.57 (m, 2H), 7.37 (m, 3H), 6.74 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 137.0, 132.1, 129.0, 128.2, 128.1, 117.6, 112.3, 112.2, 59.6, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{15}NO_2$: 216.1025. Found: 216.1025.

Ethyl 4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylate (4-20c):



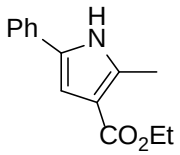
The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br, 1H), 6.36 (m, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 2.71 (m, 2H), 2.49 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 136.0, 128.7, 112.9, 110.2, 59.0, 20.2, 14.6, 14.5, 14.1; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{17}NO_2$: 182.1181. Found: 182.1178.

Ethyl 2-methyl-4,5,6,7-tetrahydro-1*H*-indole-3-carboxylate (4-20d):



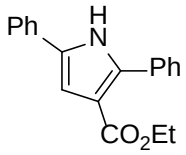
The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.69 (m, 2H), 2.48 (m, 5H), 1.75 (m, 4H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 134.0, 125.3, 118.6, 109.6, 58.9, 23.5, 23.3, 22.9, 22.4, 14.5, 13.6; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{19}NO_2$: 208.1338. Found: 208.1336.

Ethyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (4-20e):



The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.45 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.37 (m, 2H), 7.24 (m, 1H), 6.83 (d, *J* = 3.2 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.1, 131.8, 129.9, 129.0, 126.6, 123.7, 113.5, 107.4, 59.5, 14.6, 13.4; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{17}NO_2$: 230.1181. Found: 230.1176.

Ethyl 2,5-diphenyl-1*H*-pyrrole-3-carboxylate (4-20f):



The title compound was prepared according to the general procedure (R). The product was obtained as a colourless oil. Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.40 (m, 5H), 7.27 (m, 1H), 7.01 (d, *J* = 3.2 Hz, 1H), 4.24 (q, *J* = 3.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 137.7, 132.0, 131.7, 131.5, 129.1, 129.0, 128.4, 128.2,

127.1, 124.0, 113.9, 109.2, 59.8, 14.3; HRMS (ESI) m/z [M+H]+: Calcd for $C_{19}H_{19}NO_2$: 292.1338. Found: 292.1341.

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