ISOTHIOUREAS IN ORGANOCATALYSIS: SYNTHESIS OF HETEROCYCLES AND THEIR *N*- TO *C*-SULFONYL PHOTISOMERISATION

Pei-Pei Yeh

A Thesis Submitted for the Degree of PhD
at the
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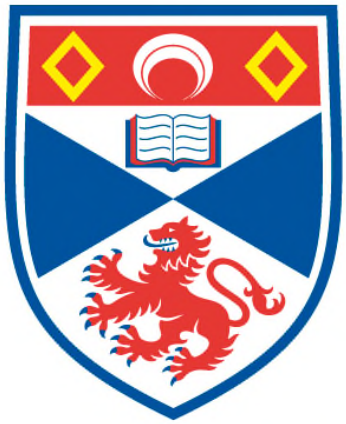

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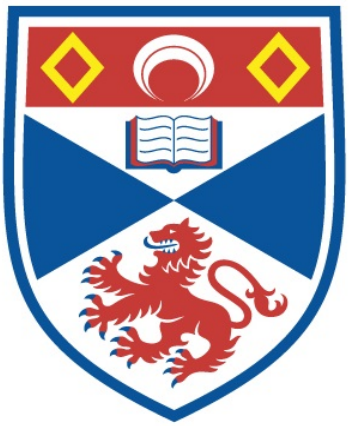
Isothioureas in Organocatalysis;

Synthesis of Heterocycles

and

Their *N*- to *C*-Sulfonyl Photoisomerisation



University of
St Andrews

Pei-Pei Yeh

This thesis is submitted in partial fulfilment for the degree of
Doctor of Philosophy

6th July 2015

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For me, a PhD is not only a training programme or a higher degree; it is also a journey making me becoming who I want to be. The person, who guided me all the way through acts like a lighthouse, who taught me to be independent and not being afraid to question, who told me to be myself and do not worry what other people say, is my supervisor Professor Andrew D. Smith. Thank you for always backing me up and encouraging me to challenge myself.

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Abstract

Chapter 1 describes an introduction to the area of organocatalysis and delineates previous work within the Smith group on the use of isothioureas in asymmetric catalysis.

Chapter 2 showcases a one-pot isothiourea-catalysed Michael addition-lactamisation using cheap and readily available starting materials (carboxylic acids) and easily prepared α,β-unsaturated ketimines *via* an ammonium enolate intermediate to give dihydropyridinones with high diastereo- and enantioselectivity (typically >90:10 dr, up to 99% ee). The resultant dihydropyridinones can be successfully derivatised into multiple products without erosion of stereointegrity.

In chapter 3 the same concept has also been applied to the synthesis of planar molecules by using (phenylthio)acetic acid as a suiTable ammonium enolate precursor. Generation of an ammonium enolate using an achiral isothiourea (DHPB) and reaction with α,β-unsaturated trifluoromethyl ketones allows an isothiourea-mediated Michael addition / lactonisation / thiophenol elimination cascade reaction for the formation of 4,6-disubstituted and 3,4,6-trisubstituted 2-pyrones in good to excellent yields (61-99%). Notably this method allows low catalyst loadings of 1% to be used. The methodology has successfully been applied to the synthesis of a COX-2 inhibitor and a wide range of derivatisations has been performed, giving valuable aromatic and heteroaromatic products containing the trifluoromethyl motif.

In chapter 4 a novel *N*- to *C*-sulfonyl migration of dihydropyridinones *via* photoisomerisation is investigated. The scope and limitations of this process is investigated and the process is shown to proceed without compromising the diastereo- or enantiomeric purity of the starting material, giving 5-sulfonyl products in good to excellent yields (67-95%). Mechanistic crossover has indicated that this migration includes an intermolecular step, while EPR studies provided evidence of its radical nature.

Abbreviation

Aza-DA	Aza-Diels-Alder
aq	aqueous
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Br	broad
^{n}Bu	*n*-butyl
^{t}Bu	*tert* -butyl
BTM	Benzotetramisole
$CDCl_3$	Deuturated chloroform
cm^{-1}	wavenumbers
d	Doublet
dr	Diastereomeric ratio
DMF	*N*,*N*,-dimethylformamide
DA	Diels-Alder
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane
DHPB	3,4-dihydro-2*H*-pyimido [2,1-*b*] benzothiazole
DMAP	4-Dimethylaminopyridine
ee	enantiomeric excess
eq.	equivalent (stoichiometric)
ESI	electrospray ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Gram (s)
h	Hour (s)
HBTM 2.1	Hyperbenzotetramisole
HRMS	High resolution mass spectrometry
IR	Infrared
THF	tetrahydrofuran
TLC	Thin-layer chromatography
KHMDS	Potassium Bis(trimethysilyl)amide
LDA	Lithium di-*iso*-propylamide
м	Molar
m	mutiplet
min	Minute(s)
mL	Millilitre(s)
Me	methyl
mp	Melting point
MS	Mass spectrometry
NEt_3	Triethyl amine
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
PCC	Pyridinium chlorochromate
Ph	phenyl
PhSH	Thiophenol
PMB	*p*-Methoxylbenzyl
Pro	Product
^{i}Pr	*Iso*-propyl
q	Quartet
s	Singlet
set	septet
SM	Starting material
t	Triplet
t	Time
T	Temperature
Ts	tosyl
TFA	Trifluoroacetic acid
$TiCl_4$	Titanium tetrachloride
V	Volume

Contents

Chapter 3. Isothiourea-Mediated Synthesis of Heterocycles

Chapter 4. N- to C-Sulfonyl Migration *via* Photoisomerisation

Chapter 1. Organocatalysis

1.1. Introduction

Asymmetric catalysis has received ever increasing attention in the last few decades. One of the important reasons for this interest is the necessity to prepare enantiomerically pure chiral compounds which are a huge area of study in the pharmaceutical industry.[1] Chiral compounds exist in biological systems; common examples such as enzymes, DNA and amino acids are familiar to all.[2] Natural amino acids exist as single enantiomers, and enzymes in biological systems have chiral binding sites which are activated by specific chiral species. Enantiomers, as two structures which have the same at connectivity but are non-superimposable mirror images of each other, are often recognized as two different compounds in biological systems.[1] Due to this fact, chiral drugs play in a crucial role in medicine, with a selection of chiral, single enantiomer drugs currently in use shown in Figure 1.1.[3,4,5–9]

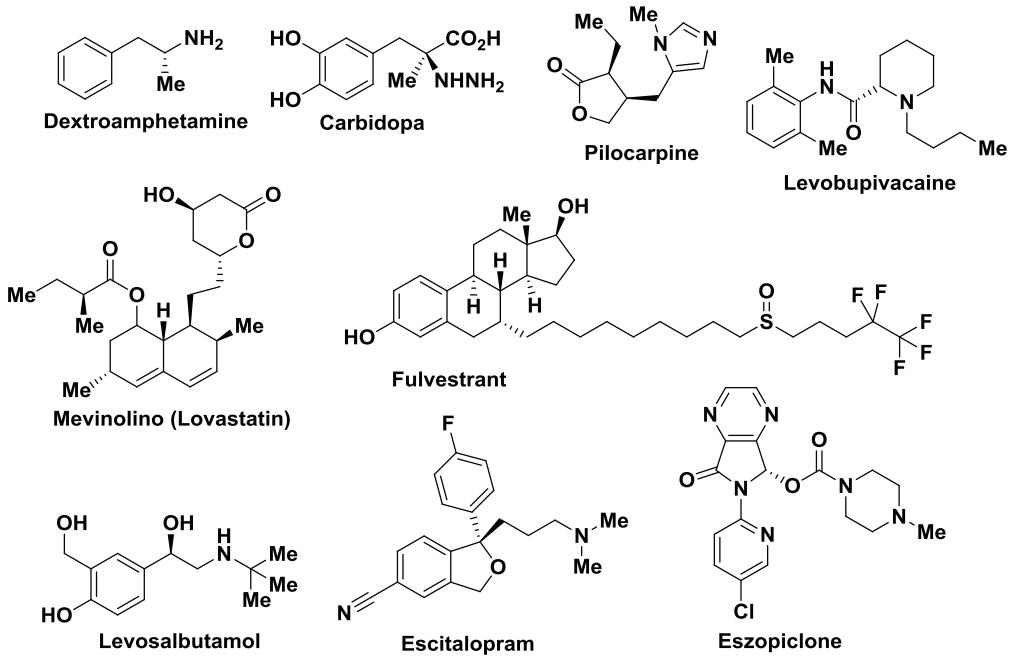


Figure 1.1 A selection of enantiomerically pure drugs.

In many pharmaceutical cases, only one enantiomer of a drug produces the desired physiological effect in the body of a living being. The other enantiomer may not produce any effect, be less active or in some cases, it may even have undesired side effects to live beings such as toxicity.[10,11] A racemic compound that contains two enantiomers (ratio 50:50) therefore could result in 50% efficiency with respect to the biological target system.[1] From the view of economic benefits, it is wasteful of both time and resource to test and produce drugs that only offer 50% effectiveness. To achieve the goal for providing enantiomerically pure compounds, asymmetric organocatalysis, which uses small chiral organic catalysts to promote asymmetric reactions, is potentially one of the solutions. The major target for asymmetric organocatalysis is to develop new reactions which can selectively produce compounds in high enantiomeric excess from cheap, readily available or easily prepared starting materials with chiral catalysts.

1.2. Organocatalysis

Organocatalysis can be defined the uses of an organic molecule as a catalyst to enhance the rate of a reaction.[12] Compared with organometallic catalysts and enzyme macromolecular catalysts which have traditionally dominated asymmetric catalysis, small molecular organocatalysts offer a wide range of practical advantages as detsailed in Table 1.1.

	Advantages	Disadvantages
Enzyme catalysis	-quick and specific reaction -providing pure enantiomer	-limited substrate scope
Organometallic catalysis	-benefit from low catalyst loading	-water and air sensitive -can be difficult to remove trace heavy metals
Organocatalysis	-sTable in water and air -inexpensive and easy to prepare -simple to use -environmental friendly	

Table 1.1 Comparison of enzyme catalysis, organometallic catalysis and organocatalysis[12]

These include their general air/water stablility, low cost and easy preparation, as well as potentially low toxicity and benefits in green chemistry.[12] These advantages make organocatalysts advantageous for medicinal chemistry as it does not have problem of removing metal impurities. Many types of organocatalysts have been developed, with a selection in Figure 1.2.[13]

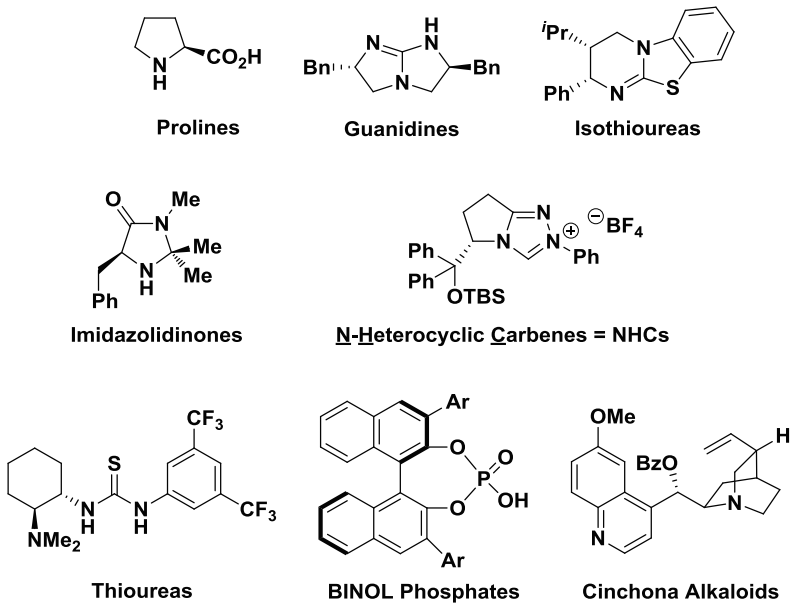
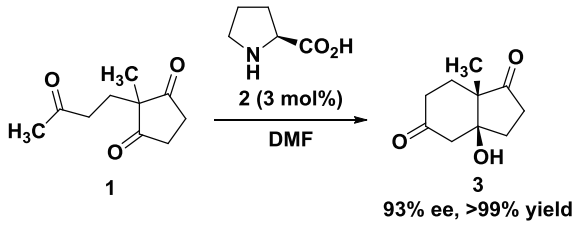


Figure 1.2 A selection of typical organocatalysts.

Before organocatalysis was widely recognised as a synthetic strategy, many individual reactions were developed in this field. Bredig and Fiske,[14] Pracejus,[15] and Wynberg[16,17] reported asymmetric organocatalytic reactions from 1912 to 1960.[13] However, at the time, these scientists only took these processes as individual transformations and the power of organocatalysis as a general method was not understood and its value as a methodology was underdeveloped. In the 1970s, one of most famous asymmetric organocatalysis aldol intramolecular reaction was discovered by Hajos, Parrish, Sauer, Eder and Wiechert (Scheme 1.1).[18]



Scheme 1.1 The Hajos –Parrish- Sauer- Eder- Wiechert symmetric aldol reaction

The Hajos-Parrish-Sauer-Eder-Wiechert reaction is an asymmetric aldol process in which an achiral triketone **1** is treated with the natural chiral compound, *L*-proline **2**, giving the Wieland-Miescher ketone product **3**, an important intermediate in steroid synthesis, in 93% ee. (Scheme 1.1) However, general application of this reaction was not fully understood until 30 years later through studies by the Barbas group.[19] They proposed the aldolase antibody catalysts operating in the aldol reaction, inspired from the Hajos-Parrish-Sauer-Eder-Wiecherft reaction, in which an enamine intermediate was prepared.[19] Thus work is especially significant as it extended the Hajos–Parrish-Sauer-Eder-Wiechert reaction, and allowed it be applied to transformations that have broader applicability, specifically the development of the intermolecular aldol reaction.[20] This publication and another from MacMillan and co-workers, on iminium catalysis allowed organocatalysis to blossom.[21]

1-2-1. Organocatalytic asymmetric reactions

Over last decade, a variety of organocatalytic strategies have been developed, that all rely upon interaction between catalyst and substrate. The nature of this interaction can be classified into two types, either covalent or non-covalent interaction pathways (Figure 1.3).[13] "Non-covalent" interactions between catalysts and substrates involve hydrogen bonding and phase-transfer catalysis. Other processes that involve the formation of covalent catalyst-substrate adducts are defined as "covalent catalysis". For example the formation of active enamine or iminium ion intermediates from secondary amine belongs to this substrate class.[13]

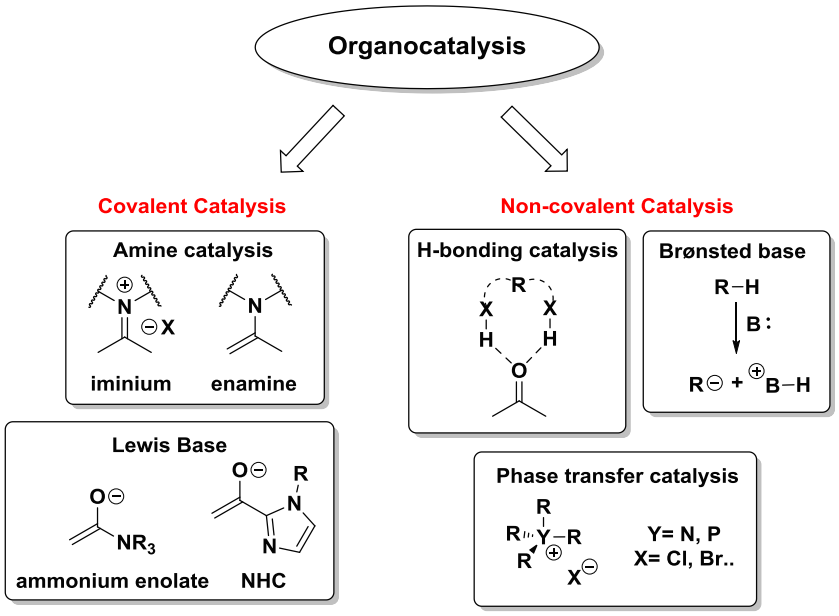


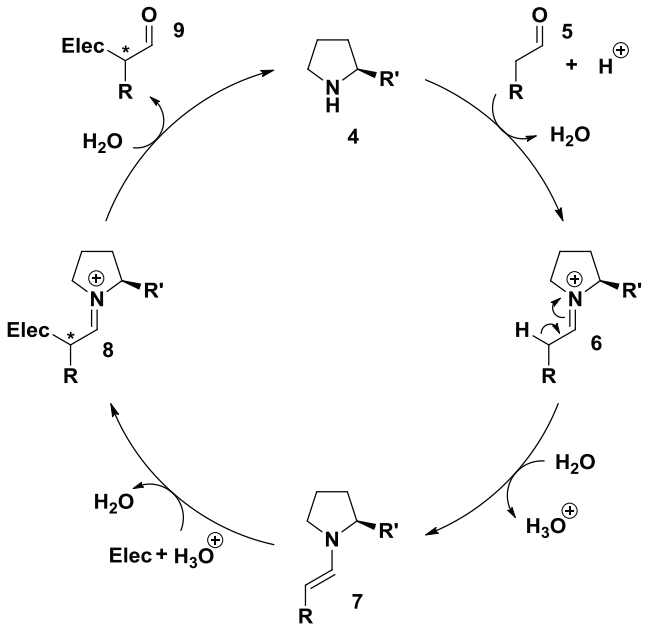
Figure 1.3 Organocatalysis with two classes of interactions

1-2-1-1. Covalent interaction cycloadditions

Enamine catalysis

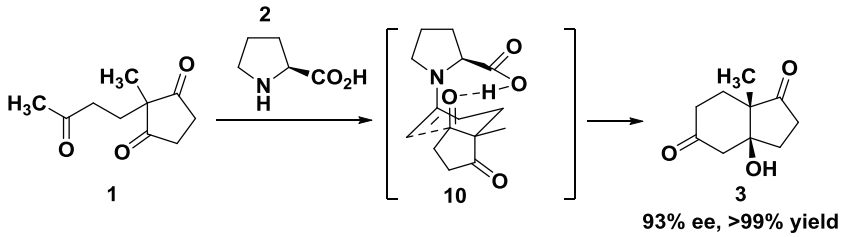
In asymmetric organocatalysis, enamine catalysis is perhaps the most widely developed method. Enamine catalysis involves the *in situ* formation of a catalytically active enamine and its subsequent reaction with an electrophile.[22] A typical enamine catalytic cycle starts from a

chiral amine catalyst **4** that activates the starting material aldehyde **5** through the formation of an iminium ion **6**. This raises the acidity of the adjacent α proton, with deprotonation leading to an active nucleophilic enamine intermediate **7**. The subsequent reaction with an electrophile reforms the iminium ion **8**, with hydrolysis releasing the chiral catalyst and a desired α- functionalized aldehyde product **9** in high ee (Scheme 1.2).



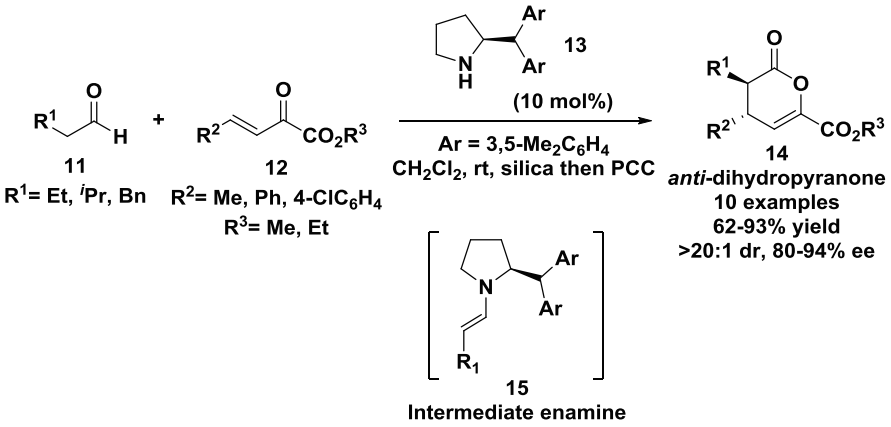
Scheme 1.2 General enamine catalytic circle with amine

An early example of this approach (Scheme 1.1), the Hajos-Parrish-Sauer-Eder-Wiechert reaction, proceeds via an enamine intermediate through a hydrogen bonded transition state **10** with high enantioselectivity (93% ee) (Scheme 1.3).[18]



Scheme 1.3. The proposed transition state of
the Hajos-Parrish-Sauer-Eder-Wiechert reaction

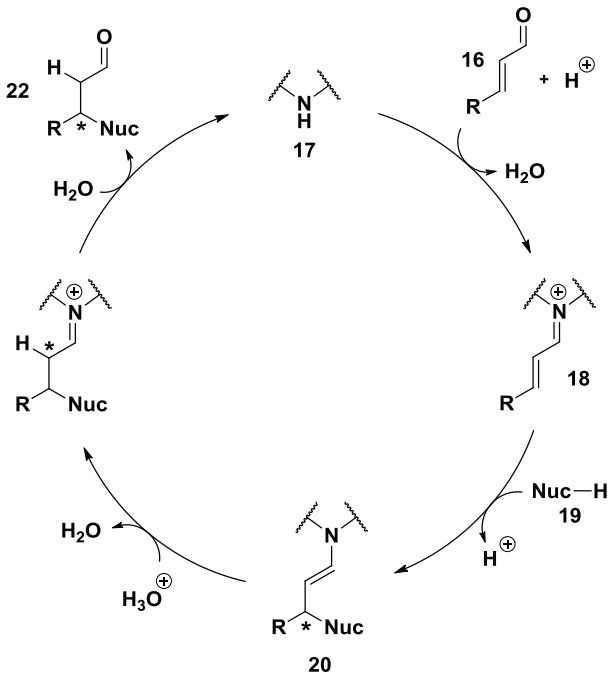
In 2003, Jørgensen reported a new one-pot procedure for the formal [4+2] cycloaddition of aldehydes **11** and enones **12** *via* enamine catalysis.[23] Aldehydes and chiral proline catalyst **13** were used to generate the intermediate enamine **15** which subsequently reacted with enones giving the *anti*-dihydropyranone products **14** in good diasteroselectivity (>20:1 dr) and high enantiocontrol (84-94% ee) (Scheme 1.4).



Scheme 1.4 The asymmetric organocatalytic [4+2] cycloaddition by Jørgensen *et al*

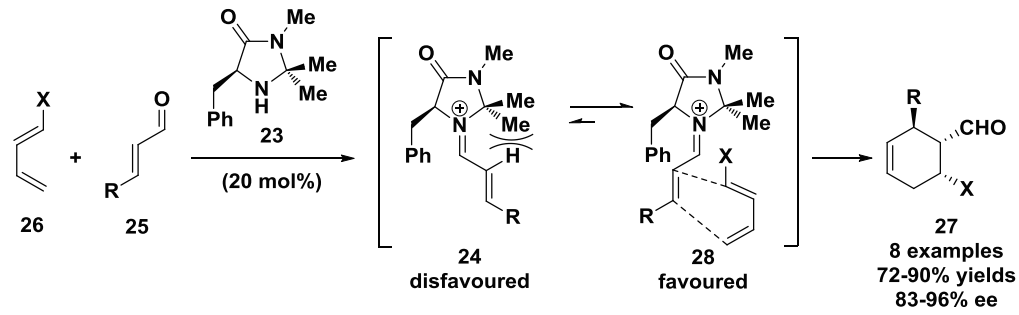
Iminium catalysis

Iminium catalysis has been well developed in various reactions such as Diels-Alder reactions, cycloadditions and conjugate additions. In such a reaction, an α,β-unsaturated ketone or aldehyde **16** condenses with a chiral secondary amine catalyst **17** to form an active iminium ion **18**.[22] The nucleophile **19** then attacks the β-carbon atom of the conjugated iminium ion intermediate **18** to form the β-functionalized enamine **20**. Finally, the catalyst and the product **22** are released by hydrolysis (Scheme 1.5).



Scheme 1.5 General iminium catalysis cycle

As an example of this approach, the first asymmetric iminium-catalyzed Diels-Alder reaction was reported by MacMillan in 2000.[21] The chiral imidazolidinone **23** was used to generate the iminium ion **24** and catalyse the reaction between α,β-unsaturated aldehydes **25** and various dienes **26**, obtaining cyclic products **27** with good enantioselectivity (83-96% ee).[21] MacMillan suggested an (*E*)-iminium ion **28** is the more favoured configuration in the reaction, as it avoids the interaction between the α-position hydrogen and methyl group on catalyst. The diene prefers to approach from the *si* face avoiding the bulky benzyl group catalyst resulting in the endo product being favoured (Scheme 1.6).



Scheme 1.6. The first asymmetric iminium-catalyzed Diels-Alder reaction by MacMillan

N-Heterocyclic carbene (NHC) catalysis

In chemistry, a carbene is a molecule that contains a neutral carbon atom with a pair of valence electrons. The carbene species used in organocatalytic reactions is a "persistent carbene" which is sTable at room temperature.[24] The most common carbene species which have been applied in organocatalytic reaction processes are thioazol- (A), triazol- (B), imidazol-(C) and imidazolin-2-ylidenes (D) (Figure 1.4).[25]

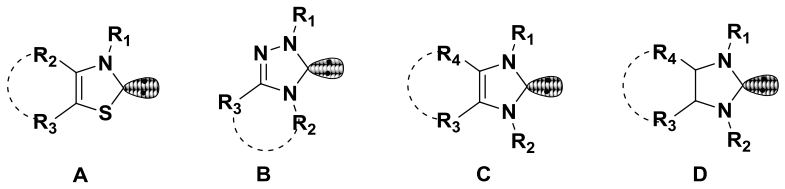
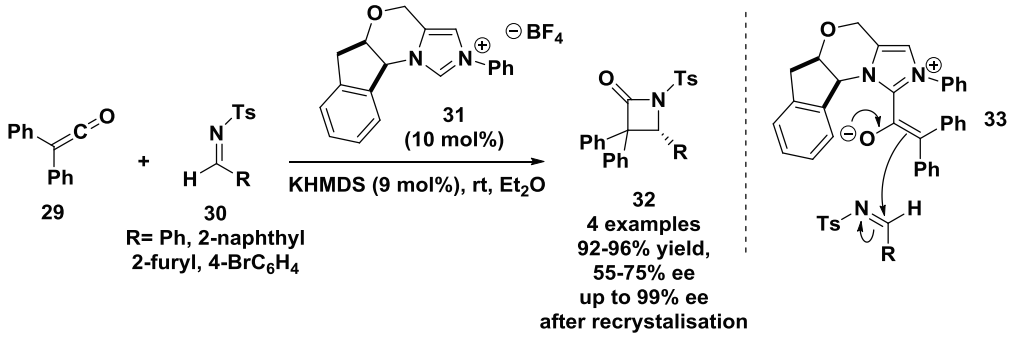


Figure 1.4 Common carbene species

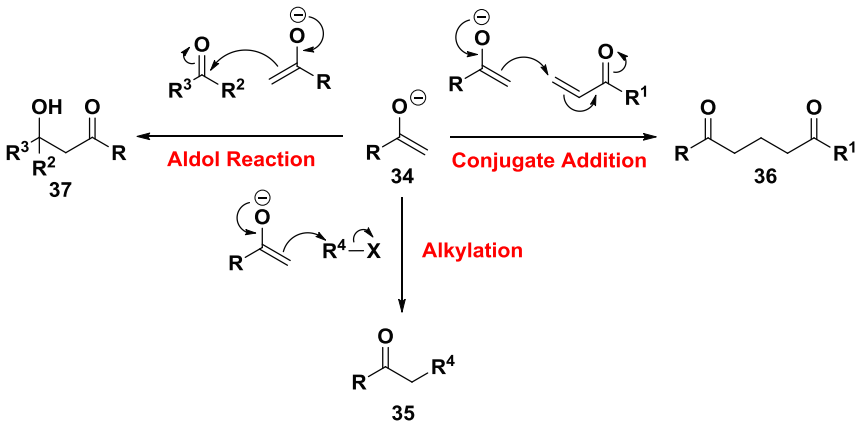
The Smith group developed a reaction procedure in which treatment of ketenes **29** with NHC catalyst **31** forms an active enolate intermediate **33**, which subsequently reacted with imines **30** in a formal [2+2] cycloaddition to form the asymmetric β-lactam products **32** with 55-75% ee which can be increased up to 99% after crystallisation (Scheme 1.7).[26]



Scheme 1.7 The synthesis of β-lactam by Smith *et al*

Ammonium enolate catalysis

In organic chemistry, the enolate is a powerful species in the C-C bond formation which can be applied in various chemical reactions, such as alkylations, conjugate additions and aldol reactions (Scheme 1.8).[27]

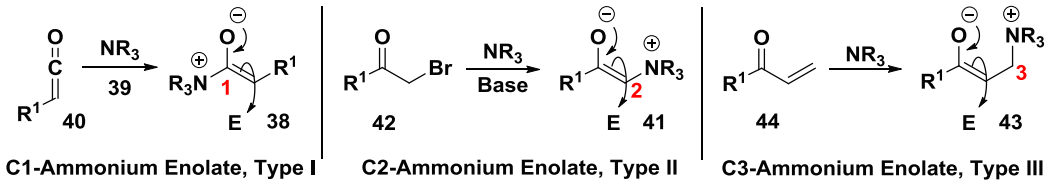


Scheme 1.8 Examples of enolate applications

While enamine catalytic processes transform aldehydes and ketones directly into α-functionalised compounds, ammonium enolates can promote functionalised enantioselective transformations of various other carbonyl containing molecules,[28] for example, ester, amide and other electron-withdrawing groups can all be prepared that cannot be achieved by enamine catalysis. Therefore, the development of chiral ammonium enolate catalysis has become an alternative solution for other catalytic reaction processes.

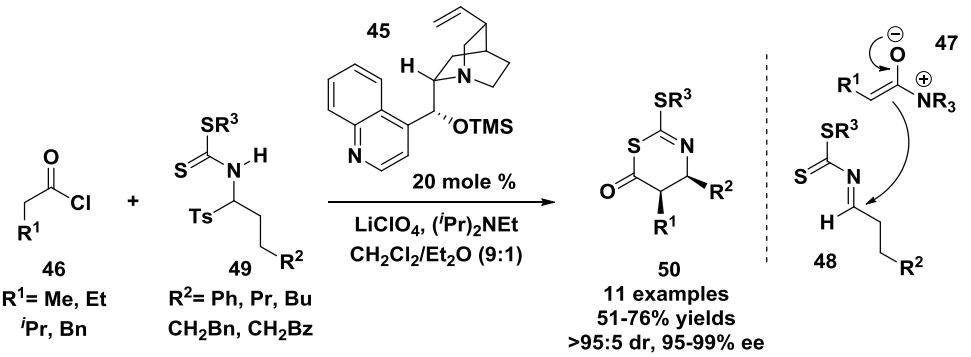
There are three common types of ammonium enolates that can be generated (Type I-III, Scheme 1.9), know as C1-, C2- and C3- ammonium enolates, in which the numbering refers to the number of atoms from enolate to ammonium. C1-ammonium enolates **38** typically result from the reaction of tertiary amine catalysts (R_3N) **39** and ketenes **40**. C2-ammonium enolates **41** can be produced through reacting tertiary amine catalysts (R_3N) with α-bromocarbonyl compounds **42** and a base. Lastly C3-ammonium enolates **43** result from 1,4-addition of a nucleophilic amine catalyst to an α,β-unsaturated carbonyl compound **44**

(Scheme 1.9).[28,29]



Schemes 1.9 Three pathways to generate ammonium enolate

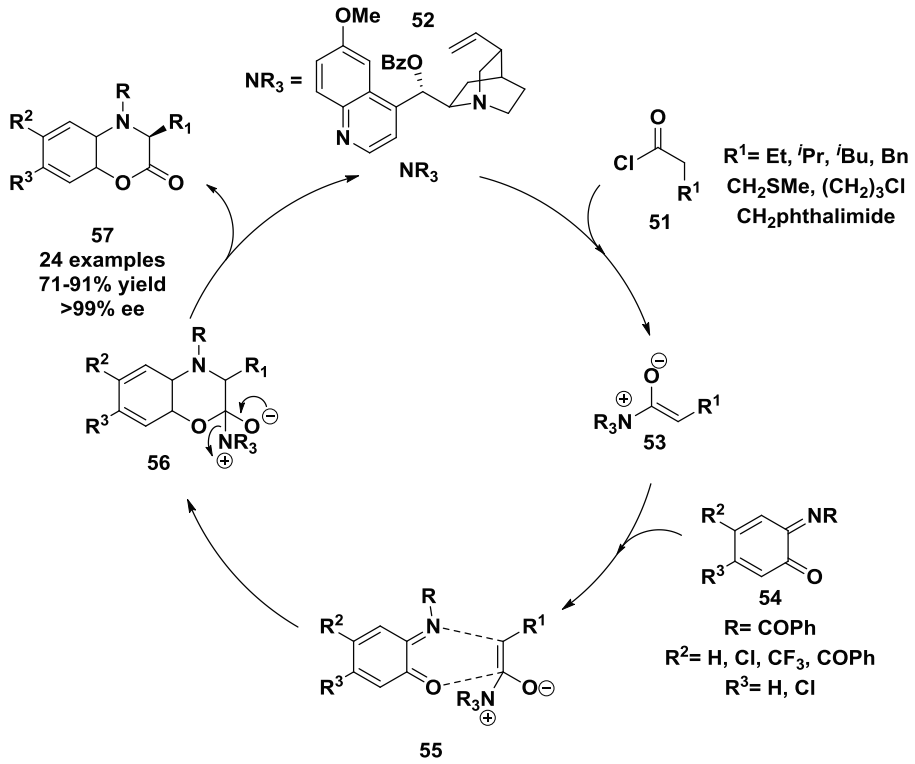
C1-ammonium enolates have been the most developed in various reactions. For example, Nelson and co-workers reported the treatment of catalytic asymmetric [4+2] cycloaddition of ketene with *N*-thioacyl imines and treated with a cinchona catalyst **45**.[30] Generation of ketenes *in situ* from an acid chloride **46** then forms an ammonium enolate intermediate **47**. Subsequently, the ammonium enolate **47** attacks the imine **48** generated *in situ* from α-amido sulfone **49** to afford the [4+2] cycloaddition product **50** with excellent diastereo- and enantiocontrol (>95:5 dr, 95-98% ee) (Scheme 1.10).



Scheme 1.10 The catalytic asymmetric [4+2] cycloaddition by Nelson *et al*

An example of enantioselective [4+2] cycloaddition reaction has been developed by Lectka *et al*.[31] Generation of a ketene *in situ* from an acid chloride **51**, followed by activation with a cinchona alkaloid derived catalyst **52** gave the active ammonium enolate intermediate **53**. The active enolate intermediate then underwent a [4+2] cycloaddition reaction with a range of

ortho-quinones, *ortho*-quinone diimides and *ortho*-quinone imides **54**. The catalyst was then regenerated and the product **57** was obtained. This approach gave good yield (58-91%) with excellent ee (90-99%) (Scheme 1.11).



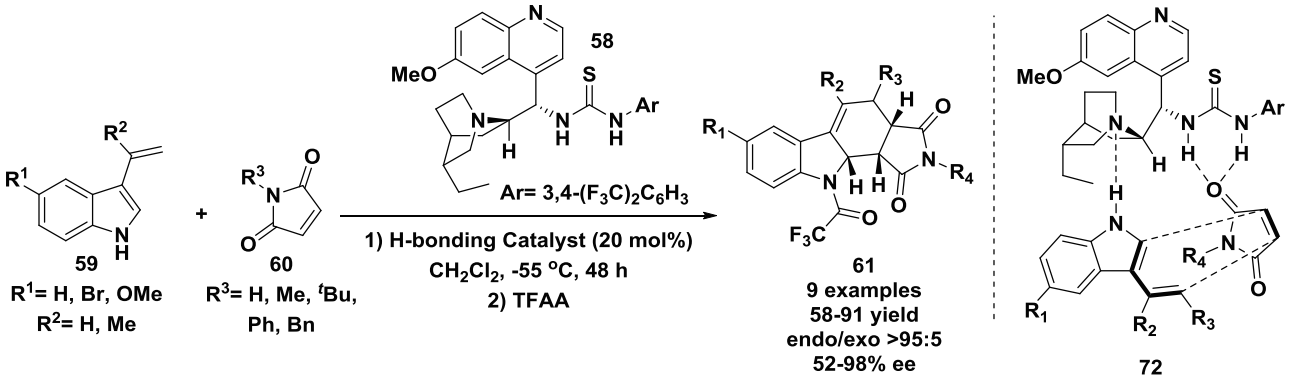
Scheme 1.11 The proposed mechanism of Lectka's approach

1-2-1-2. Non-covalent interaction reactions

Non-covalent interactions in organocatalysis mimic the interactions from natural enzymes. Compared with covalent interactions, non-covalent interactions are weaker, less directional and less distance dependent. However, this strategy can provide high level of enantioselectivity through cooperative effects.[32] Three major concepts have been reported for organocatalytic processes involving non-covalent interactions. These are H-bonding catalysis, phase transfer and "ion pair" catalysis. An example of each concept will be introduced in this section.

H-Bonding catalysis

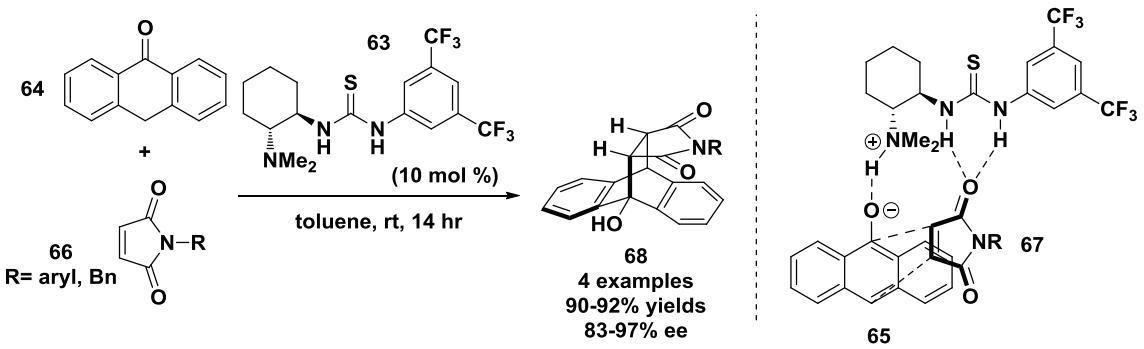
The development of H-bond donor molecules as catalysts in organic reaction has grown remarkably in the past few years. This concept uses catalysts, such as thioureas and bifunctional cinchona alkaloid derivatives, that can form hydrogen bonds with substrates to enhance the activity of organic reactions.[33] As an example, a thiourea can provide dual H-bonding in catalysis, and has gained increasing attention. For example, in Diels-Alder reactions, these H-bond donor molecules act like weak Lewis acid catalysts and enhance the rate of the reaction.[13] In 2008, Ricci and co-workers reported a new method for the organocatalytic asymmetric Diels-Alder of 3-vinylindoles (Scheme 1.12).[34] This asymmetric Diels-Alder reaction was catalysed by quinine thiourea derivative **58** with a bifunctional acid-base functionality, allowing the formation of H-bonds to both diene **59** and dienophile **60** resulting in excellent enantioselectivity of the product **61** (up to 98% ee). In the proposed transition state **62** for the reaction, H-bonding between the catalyst and the dienophile lowers the LUMO of the dienophile, while increases the HOMO of the diene (Scheme 1.12)[34].



Scheme 1.12 The organocatalytic asymmetric Diels-Alder of 3-vinylindoles by Ricci *et al*

Rios and co-workers[35] have reported the treatment of anthrones and maleimide in the presence of Takemoto's bifunctional thiourea catalyst **63.** This catalyst offers both Brønsted acid (secondary amine) and base (tertiary amine on thiourea moiety) active sites, to promote

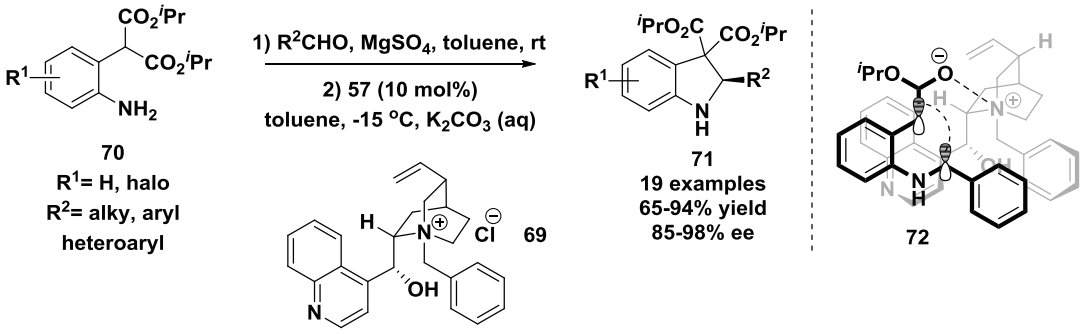
the asymmetric Diels-Alder reaction in high yield (average 90% yield) and enantioselectivity (up to 96% ee). In this reaction, anthrone **64** is proposed to form H-bonds with the chiral secondary amine **63** generated anthrone enolate **65**. Subsequent association to the maleimide **66,** which is also activated by forming dual H-bonding of **67** with the thiourea moiety of the catalyst, followed by a [4+2] cycloaddition reaction leads to formation of the product **68** in high enantioselectivity (83- 96% ee) (Scheme 1.13).



Schemes 1.13 The approach of H-bonding catalysis *via* bifunctional thiourea

Phase-transfer catalysis

A simple explanation of a reaction system employing phase-transfer catalysis is based upon a biphasic system involving an organic phase and an aqueous phase. Recently, Smith and co-workers have proposed a catalytic 6π-electrocyclisation phase-transfer reaction catalysed by cinchona alkaloid derivatives **69**.[36] The reaction was carried out by treatment of benzaldimine **70** with 10% catalyst **69** in a biphasic system of aqueous potassium carbonate in toluene to give the bicyclic product **71** with high yield (81-99%) and enantioselectivity (84-98% ee) (Scheme 1.14).

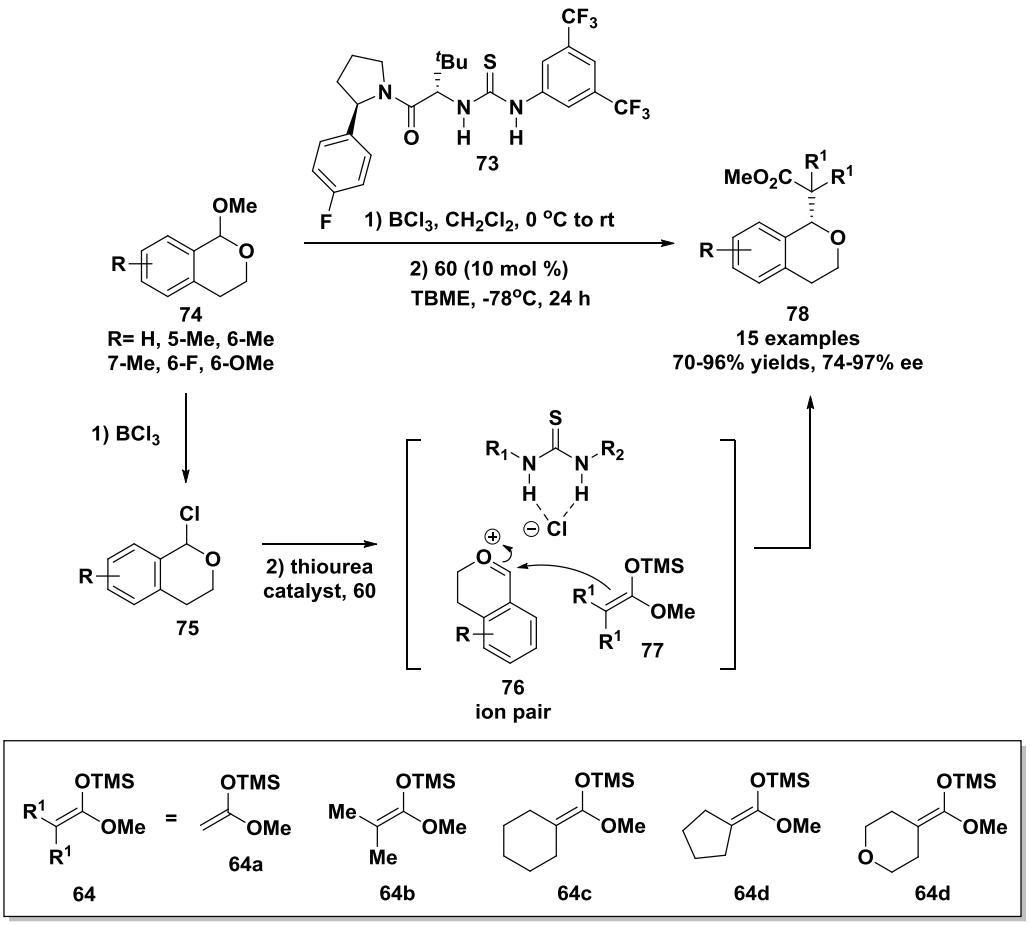


Scheme 1.14 The proposed asymmetric electrocyclisation *via* phase-transfer catalysis

The stereocontrol in this process may be rationalised by the tight-ion pair model which has been proposed for phase transfer asymmetric alkylation by Corey and co-workers.[37] The oxygen enolate anion of the substrate forms an ionic pair interaction **72** with the quaternary ammonium cation of the cinchona catalyst; one π-face of the delocalized anionic component will be blocked by the bulky catalyst. Subsequently the electrocyclisation then occurs away from the bulky catalyst *via* orbital overlap **72** which has only one face to access (Scheme 1.14).

Counterion catalysis

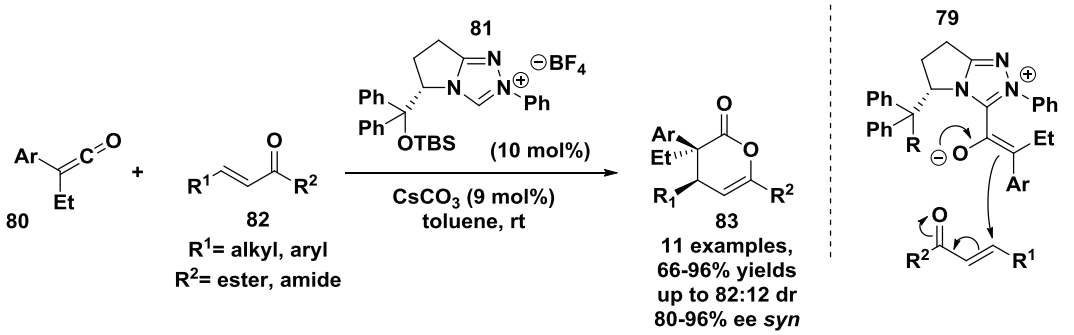
As an example of counterion catalysis, chiral thiourea catalysts form strong complexes with halide ions to generate a transient ion pair that can act as a chiral counterion making nucleophiles approach to a single face only.[12] Jacobsen and co-workers reported the transformation of asymmetric thiourea-catalyzed addition to cyclic oxocarbenium ions.[38] The principle in this reaction involves the H-bonding thiourea catalyst **73** intercepting chloride ions from chloroisochromans **75** to generate an ion pair **76**. Tetrasubstituted silyl ketene acetals **77** act as nucleophiles, and following addition to oxocarbenium ions **76**, results products **78** in high enantiopurity (70-96% yield, 74-97% ee) (Scheme 1.15).



Scheme 1.15 The Counterion catalytic approach by Jacobsen *et al*

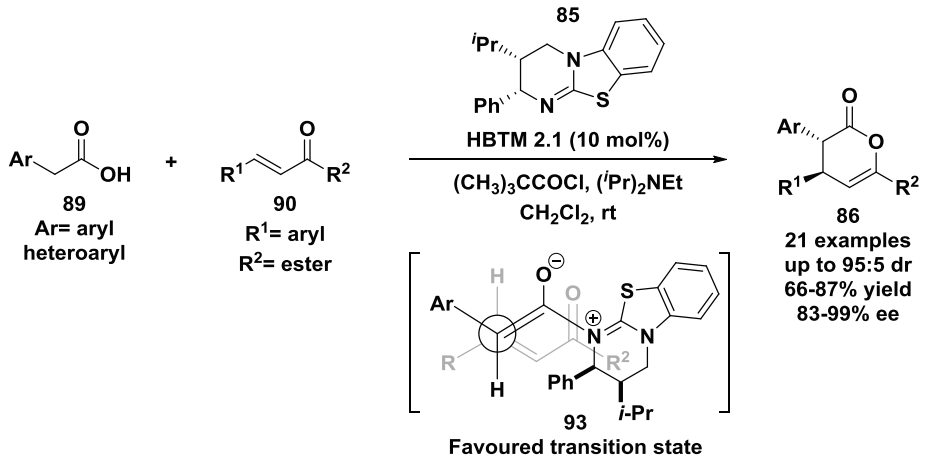
1-3. Previous work in the Smith Group

Previous research in the Smith group has successfully applied NHC catalysts to the synthesis of δ-lactones *via* an azolium enolate intermediate.[39] The method relies upon the generation of the active enolate intermediate **79** from ketenes **80** and the NHC catalyst **81**, before reaction with the α,β-unsaturated ketoester **82**. Cycloaddition, followed by regeneration of the catalyst, gave the *syn*-dihydropyranone **83** in modest dr, but good ee (up to 95%) and excellent yield (up to 99%) (Scheme 1.16).



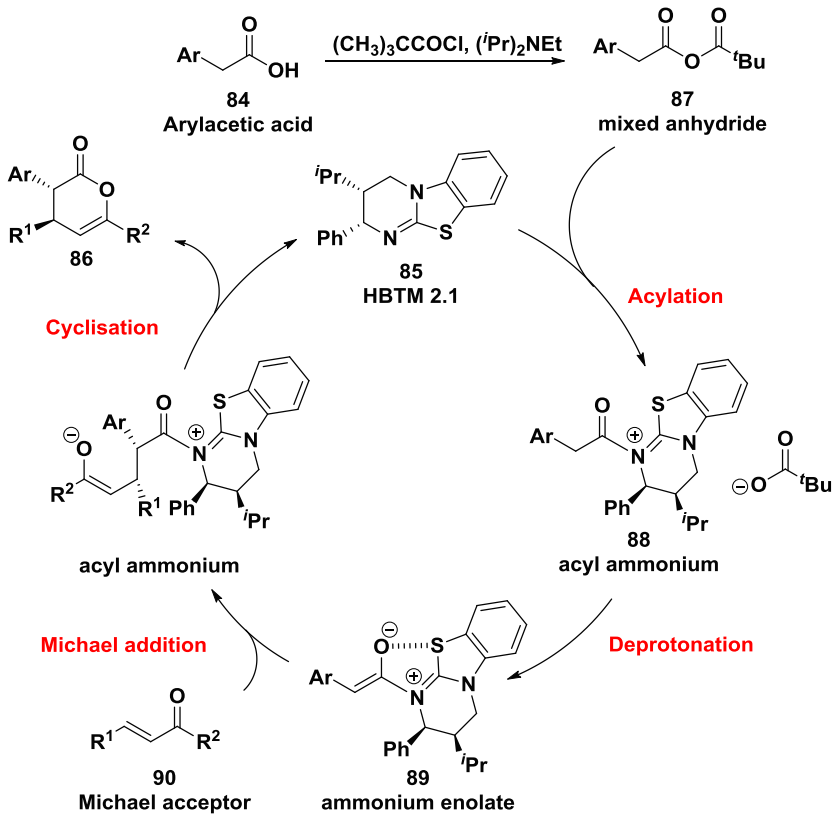
Scheme 1.16 The synthesis of *syn*-dihydropyranone in the Smith group

Although useful, the ketene involved in this process has to be purified by distillation before being used in the reaction and cannot be stored for indefinite periods. These characteristics of ketenes give them limited synthetic utility. Recently, the Smith group has reported a new pathway for catalytic asymmetric intermolecular [4+2] intermediate cycloadditions *via* the generation of an active ammonium enolate from simple, cheap and commercial available arylacetic acids **84** through reaction with a chiral isothiourea catalyst **85** (Scheme 1.17).[40] This formal [4+2] cycloaddition reaction gives *anti*-dihydropyranone **86**, through the proposed transition state **93**, with high dr (up to 98:2) and ee (up to 99%).



Scheme 1.17 The formal [4+2] cycloaddtion reaction catalysised by isothiourea

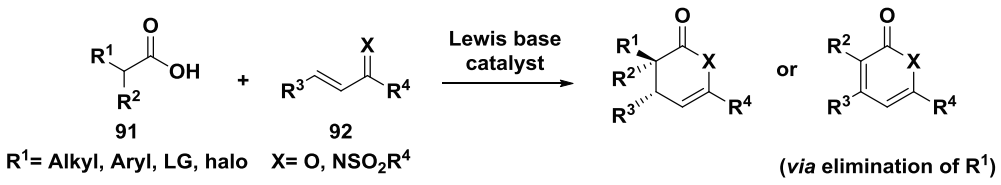
The proposed mechanism of this process relies upon the reaction of the arylacetic acid **84** with pivaloyl chloride to form the mixed anhydride **87**. *N*-Acylation of the chiral isothiourea **85** with this anhydride forms the acyl ammonium adducts **88**. Deprotonation generates the active ammonium enolate intermediate **89**, that undergoes Michael addition with ketoester acceptor **90**. Cyclisation and catalyst regeneration gives the asymmetric [4+2] cycloaddition products, *anti*-dihydropyranone **86**, and catalyst **85** (Scheme 1.18).



Scheme 1.18 The proposed mechanism of the formal [4+2] cycloaddtion reaction

1-4. The aim of this work

Building upon this previous work, the main aim of this project is to probe the reactivity of ammonium enolate intermediates *via* Lewis base catalysis, generated *in situ* from a carboxylic acid **91**, with a range different Michael acceptors such as ketoenones and α,β-unsaturated ketimines **92** in formal [4+2] cycloaddition reaction to synthesise a diverse range of either stereodefined heterocyclic products or planar heterocycles. To generate the planar heterocycles, it was envisaged that a suiTable leaving group (R^1) within the carboxylic acid would have to be identified, with the introduction of a heteroatom investigated for this purpose (Scheme 1.19).



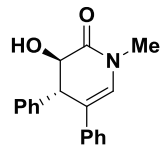
Scheme 1.19 The aim of the project

Chapter 2. Asymmetric Organocatalytic Michael Addition-Lactamisation; Access to Dihydropyridinones

2-1. Introduction

The dihydropyridinone motif is an important heterocyclic class containing a six-membered ring cyclic amide with a double bond. Compared with other six-membered heterocyclic scaffolds containing a nitrogen atom, such as pyridines, piperidines and indolizidine alkaloids, the dihydropyridinone structure has not been much explored, despite the motif being found in many natural products. For instance, homoclausenamide is a *Clausena* alkolid isolated from the leaf extract of Rutaceae *Clausena lansium* Skeels;[41] widely used in Chinese medicine for the treatment of influenza, gastrointestinal disorders and dermatological disease.[42]

Clausena lansium



Homoclausenamide

The dihydropyridinone motif is also an important subunit in pharmaceuticals,[43,44,45] moreover, it can be used as a synthon toward the synthesis of other heterocycles.[46] For example, the polysubstituted dihydropyridinone, finasteride **93** is applied in the treatment of male frontal pattern hair loss.[47] A simple spiro-dihydropyridinone **94** has been reported by Wang *et al* [48] who also disclosed its activity as an antiproliferation of leukemia cell . Dihydropyridinone **95** has also been found as a subunit in a α_{1a} adrenergic receptor anatagonist.[49] (Figure 2.1)

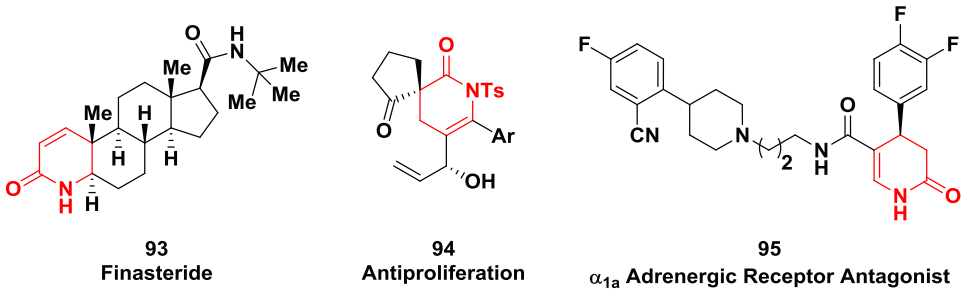


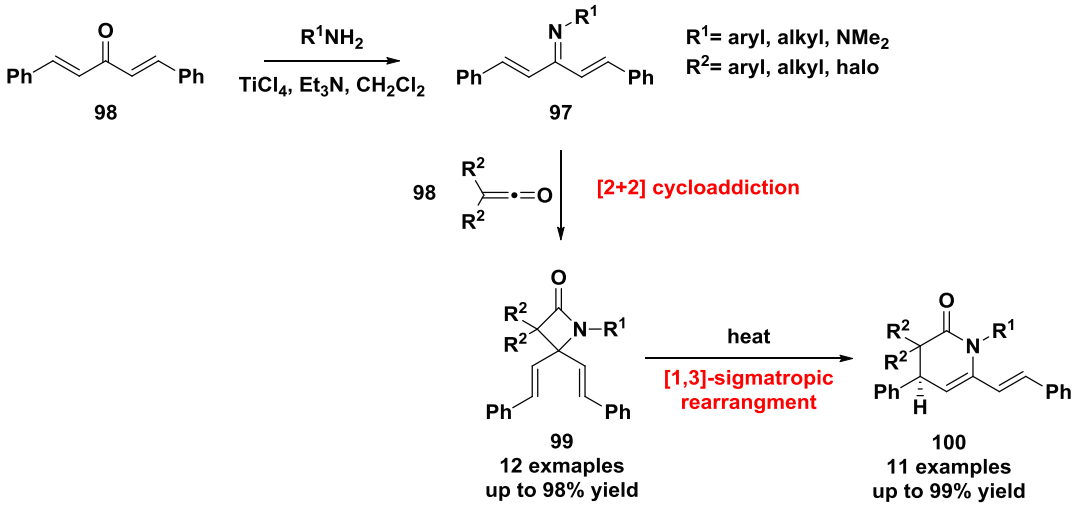
Figure 2.1 A selection of dihydropyridinone containing compounds

A range of studies on the synthesis of dihydropyridinone have been reported, including: Horner-Wadsworth-Emmons/cyclocondensation;[50,51] diene-transmissive hetero-Diels-Alder reactions;[46] radical [3+2] annulations;[52] the Nazarov intermediate cyclisation *via* Schmidt rearrangement;[53] and 6-*endo*-enamide-epoxide cyclisation.[42] Some selected examples of dihydropyridinone synthesis are shown below.

2-1-1. Previous studies of dihydropyridinone synthesis

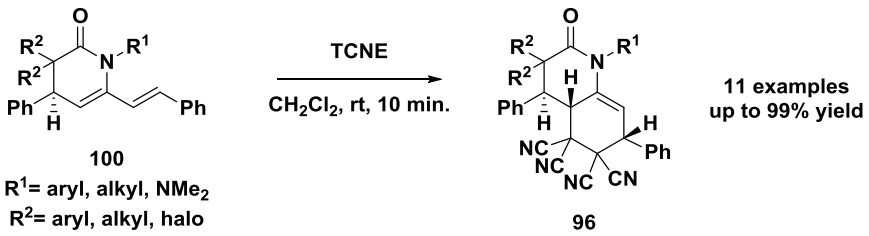
2-1-1-1. Diene-transmissive hetero-Diels-Alder reaction

The diene-transmissive hetero-Diels-Alder reaction (DTHDA) allows the synthesis of dihydropyridinones *via* two sequential cycloadditions. Compared with the diene-transmissive Diels-Alder reaction (DTDA), the DTHDA reaction contains more than one heteroatom within either a triene/polyene or a dienophile. Kobayashi and co-workers have reported the synthesis of dihydropyridinones *via* the diene-transmissive hetero-Diels-Alder reaction[46] to form hexahydroquinolinones **96**. The reaction starts with the formation of azatriene **97** from the condensation of the corresponding ketone **98** and a primary amine using $TiCl_4$ and Et_3N at 0 ˚C for 1 h. The azatriene **97** is isolated and reacted directly without any purification with ketene **98** to produce the [2+2]-cycloadduct β-lactam **99** in good yield. This undergoes a [1,3]-sigmatropic rearrangement after refluxing in toluene for 1 h to give more thermodynamically sTable dihydropyridinone **100** in excellent yield (99% in most cases.) (Scheme 2.1)



Scheme 2.1 Diene-transmissive hetero-Diels-Alder Reaction

These dihydropyridinones **100** react onwards in a second cycloaddition at room temperature with tetracyanoethylene (TCNE), giving **96** with complete diastereoselectivity in excellent yield (94-99% yield) (Scheme 2.2).

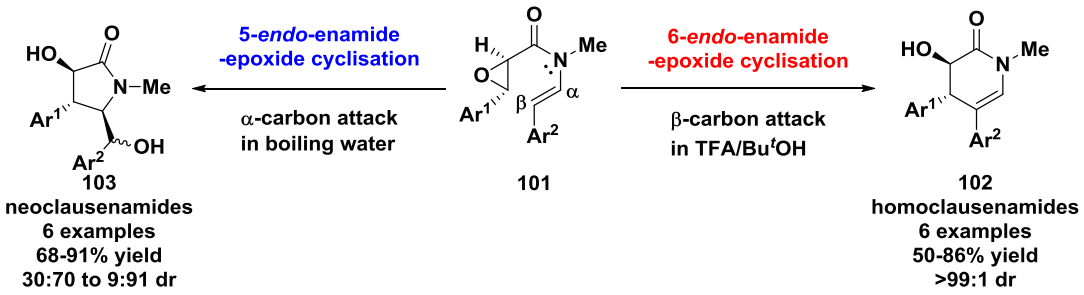


Scheme 2.2 Second cycloaddition with TCNE

2-1-1-2. Amide cyclisation

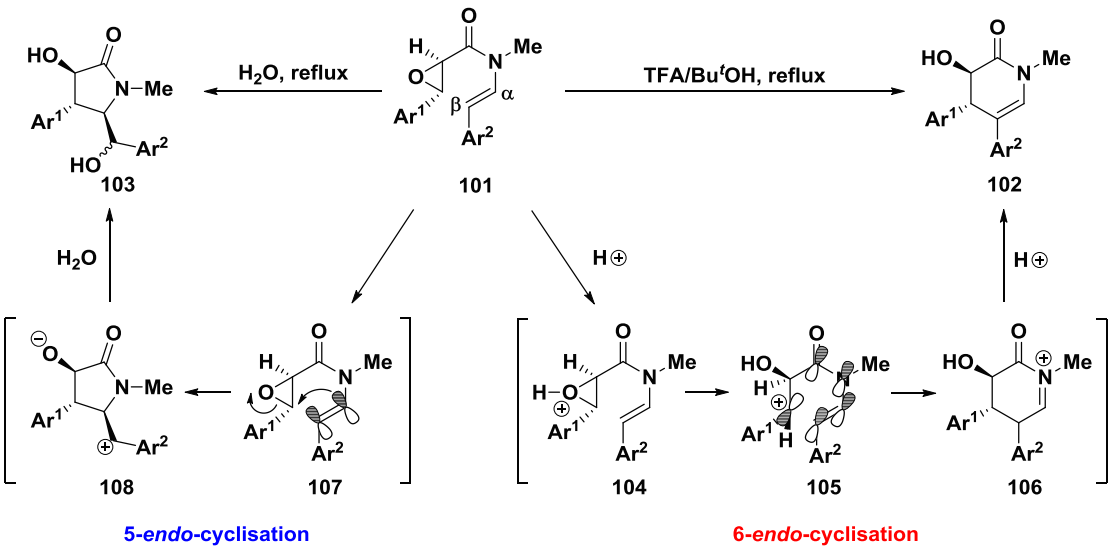
As the dihydropyridinone structure contains a carbonyl motif, double bond, and nitrogen atom, one strategy for dihydropyridinone synthesis is therefore to cyclise the amide chain. For example, Wang and co-workers have reported using a Brønsted acid mediated stereospecific intramolecular enaminic reaction to synthesize the natural product-homoclausenamide, neoclausenamide and derivatives thereof.[42,54] Depending upon the reagent used (TFA or refluxing water) the enamide **101** will give either 6-*endo*-cyclisation to form six-membered

dihydropyridinone (homoclausenamide) **102** or 5-*endo*-cyclisation to form γ-dihydropyridinone (neoclausenamide) **103** (Scheme 2.3).



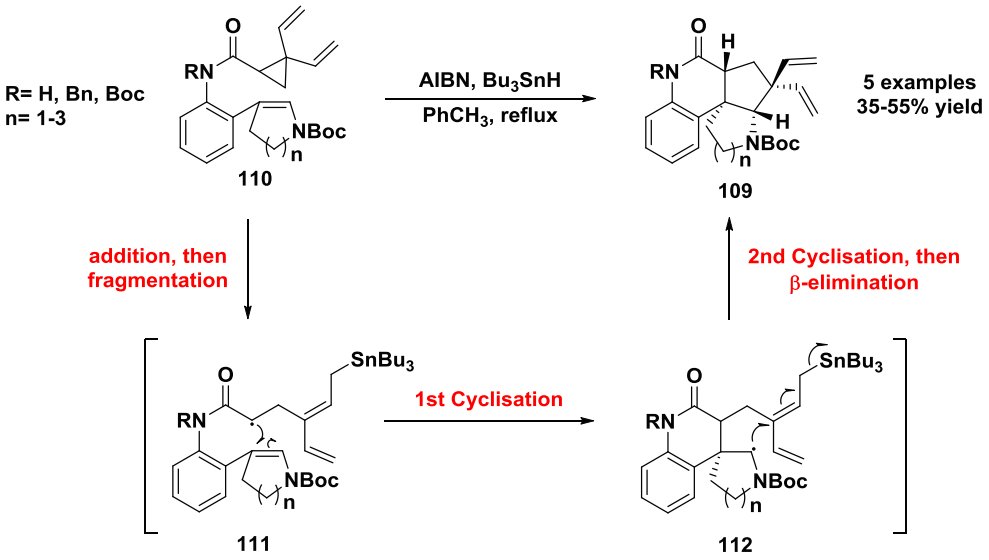
Scheme 2.3 A Brønsted acid mediated stereospecific intramolecular enaminic reaction

The proposed mechanism of this intramolecular enaminic reaction is shown in Scheme 2.4 In the present of TFA, the oxirane-containing amide **104** may be protonated and ring-opened to form carbonium intermediate **105**, which can proceed 6-*exo*-enamide-epoxide cyclisation *via* β-carbon (enaminic carbon) attack to the carbonium then form the iminium **106**. Following deprotonation gives homoclausenamides **102**. Alternatively, boiling the amide **101** in water leads to the α-carbon acting as the nucleophilic site to attack the epoxide ring. It suggests that the lone pair electron on nitrogen does not conjugate with the carbon-carbon double bond; the amino plane might be perpendicular to the carbon-carbon double bond resulting in inhibition of the delocalisation of the lone pair electron on nitrogen. This facilitates a 5-*exo*-cyclisation to give the five membered neoclausenamides **103** (Scheme 2.4).



Scheme2.4. Plausible mechanism for 6-*endo*- and 5-*endo*-enamide-epoxide cyclisation of **101**

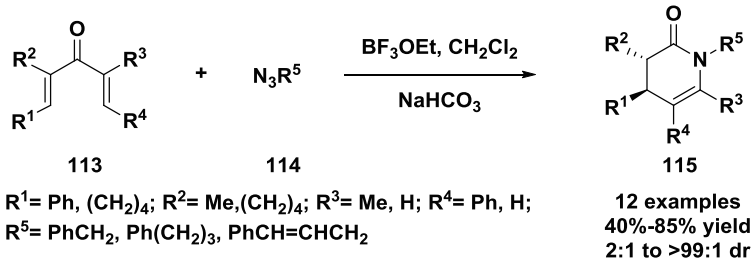
Recently, LaPorte *et al.* have developed a radical [3+2]-annulation of divinylcyclopropanes for the synthesis of analogues of the natural product meloscine.[52] The proposed formation of this dihydropyridinone **109** begins with the addition of tributyltin radical to the vinyl group of amide **110**, allowing the fragmentation of the cyclopropane ring to give the radical intermediate **111**, which triggers the 6-*endo-trig*-cyclisation to form the tricyclic intermediate **112**. Finally, a 5-*endo-trig*-cyclisation to form the second ring structure then β-elimination to remove the tin radical gives the polycyclic dihydropyridinone **109** (Scheme 2.5).



Scheme 2.5 The radical [3+2] annulation of divinylcyclopropanes

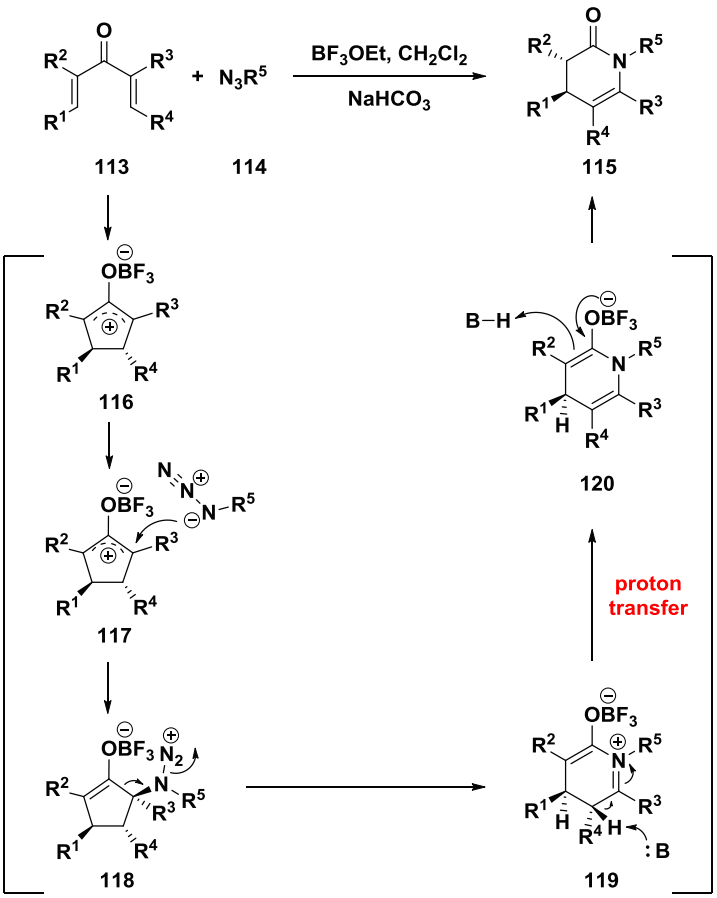
2-1-1-3. Domino electrocyclisation/azide-capture/Schmidt rearrangement of dienones

The Nazarov cyclisation is one of the most well known methodologies to form cyclopentenones *via* a Lewis acid catalysed cationic 4π-electrocyclic ring closure. This reaction contains a conrotatory 4π-electrocyclisation, according to the Woodward-Hoffmann rules. West *et al*[53] has developed a dihydropyridinone synthesis using dienones **113** to form the Nazarov intermediate *in situ* that reacts with organic azide **114**, which is well known to act as a 1,3-dipole and as a nucleophile in the presence of electron-deficient species such as carbocations. This leads to highly functional *trans*-dihydropyridinone **115** in moderate to high yields and good to excellent diastereoselectivity (Scheme 2.6).



Scheme 2.6 Intramolecular azide trapping dihydropyridinone formation

This reaction process starts with the Nazarov cyclisation to form the Nazarov intermediate **116** *in situ* with a carbocation facilitating the addition of azide **114** and subsequent Schmidt-type rearrangement. Proton transfer leads to give the major *trans*-dihydropyridinone **115** (Scheme 2.7).



Scheme 2.7 The proposed mechanism dihydropyridinone formation

Traditionally, chiral enantiopure dihydropyridinones have been prepared from original starting materials such as chiral amino acids; in the other words, they have to use the enantiopure starting materials to obtain the compounds in single enantiomeric form. The enantiopure material normally comes from nature, the chiral pool, or is prepared *via* difficult biotransformations. Besides, lots of the examples are stoichiometric rather than catalytic reactions, generating large amounts of chemical waste. Since the importance of asymmetric organic compounds has been recognised in many areas, for instance in the pharmaceutical industry and also natural product synthesis, the development of an efficient, asymmetric and catalytic dihydropyridinone synthesis with excellent stereoselectivity under mild reaction conditions is a worthwhile endeavour. To reach this target, one of the methodologies is organocatalysis; the reaction is mediated by an organocatalyst, with racemic or prochiral

starting materials to produce products in high stereoselectivity. Among many cyclisation methods, this project is particularly interested in using the formal [4+2]-aza-Diels-Alder reaction, for the synthesis of dihydropyridinone.

2-1-2. Organocatalytic enantioselective formal [4+2]-cycloaddition, formal aza-Diels-Alder reaction

The Diels-Alder reaction is classified as a [4+2]-cycloaddition and has been well recognised as a powerful tool in synthetic chemistry for the formation of six-membered rings. Traditionally, the reaction favours the interaction between electron-rich dienes and electron-poor dienophiles, although inverse electron-demand systems are known. The mechanism of Diels-Alder is believed to occur in a single concerted transformation. To distinguish the difference from the Diels-Alder reaction, stepwise [4+2]-cycloadditions containing two steps, for instance, Mannich-Michael reaction, Mannich-Friedel-Crafts and Michael-lactamisation, have been termed the formal [4+2]-cycloadditions or the formal Diels-Alder reaction. Alongside the original Diels-Alder reaction with only carbon containing dienes and dienophiles, there are hetero-Diels-Alder reactions[55,56] such as the aza-Diels-Alder reaction[56] containing a nitrogen atom in either the diene or dienophile. Aza-Diels-Alder reactions can be classified into two classes, the normal-electron demand aza-Diels-Alder (NED-aza-Diels-Alder) and the inverse-electron demand aza-Diels-Alder (IED-aza-Diels-Alder). Due to the increasing attention on the synthesis of enantiopure bioactive aza-heterocycles and their potential as valuable intermediates for natural product synthesis, catalytic aza-heterocycle synthesis in an atom-economic manner are highly sought-after. However, the development of catalytic enantioselective aza-Diels-Alder reactions has been problematic as stoichiometric amount of Lewis acid catalysts are traditionally required for the reaction. This is mainly due to the nature of the basic nitrogen atom in the diene, dienophile, the aza intermediate or even the aza-heterocyclic product

involved in the reaction that can strongly coordinate with the Lewis acid catalyst, resulting in either the slowing or even shut down of the catalytic cycle. To conceal this issue, two successful strategies have been widely applied from the literature, the first using the combination of compatible Lewis acid with chiral ligands, the second is the use of organocatalysis.

2-1-2-1. The Normal-Electron Demand Aza-Diels-Alder (NED-aza-Diels-Alder)

Based on the knowledge of frontier molecular orbital (FMO) theory, the NED-aza-Diels-Alder reaction occurs between the lowest unoccupied molecular orbital (LUMO) of dienophile and the highest occupied molecular orbital (HOMO) of diene. Hence, the reaction favours to have electron rich diene **121**, which has higher HOMO energy, with electron poor dienophile **122**, which has lower energy of LUMO (Figure 2.2).

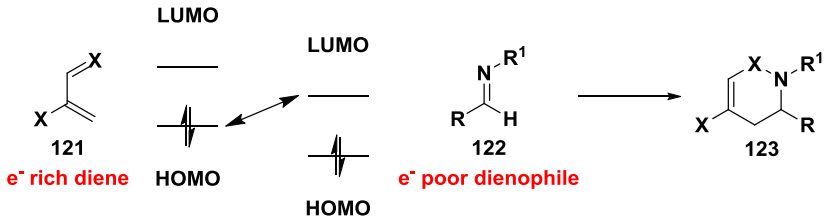


Figure 2.2 Typical NED-aza-Diels-Alder reaction

To encourage the NED-aza-Diels-Alder interaction between diene and dienophile, this interaction can be strengthened by either raising the HOMO energy of diene *via* aminocatalysis **124** or lowering the LUMO energy of dienophile through Lewis acid **125** or Brønsted acid **126** (Figure 2.3).

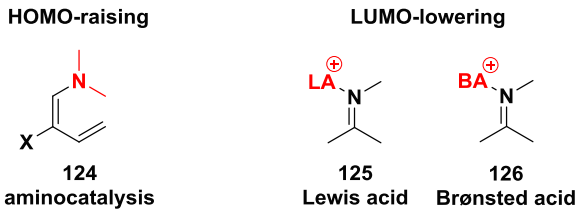
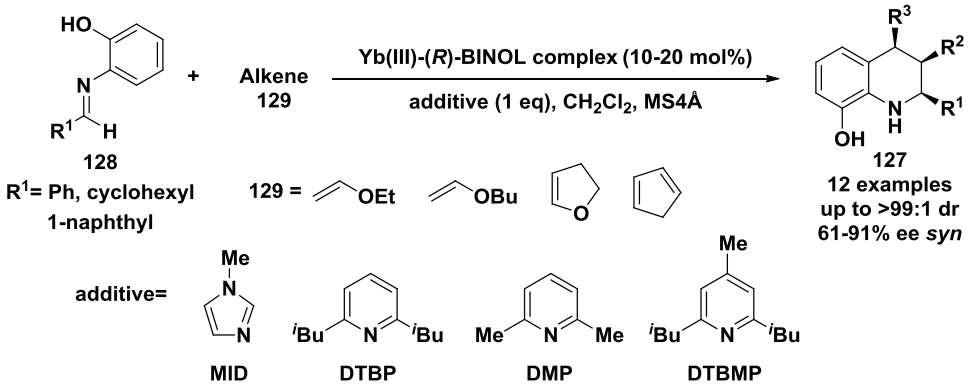


Figure 2.3 Activation modes of NED-aza-Diels-Alder reaction

LUMO-Lowering *via* chiral Lewis acid catalysis

Kobayashi *et al.* have presented the first example of a catalytic enantioselective reaction by using chiral Lewis acid complex, (*R*)-BINOL-Ytterbium(III), to form tetrahydroquinoline derivatives **127** (Scheme 2.8).[55,57]



Scheme 2.8 The synthesis of tetrahydroquinoline catalysed by (*R*)-BINOL-Ytterbium(III)

The proposed transition state model suggested by Kobayashi for the reaction is that the chiral complex prepared from $Yb(OTf)_3$, (*R*)-BINOL and DBU provides bidentate coordination to the imine and the axial chirality of (*R*)-BINOL is transfered *via* hydrogen bonding to amine components. The additive, DTBP, interacts with the phenolic hydrogen of the imine **128**, which is fixed by bidentate coordination to the metal. Due the steric hinderance of the *Si* face, the dienophile alkene **129** attacks from the *Re* face (Figure 2.4).[57]

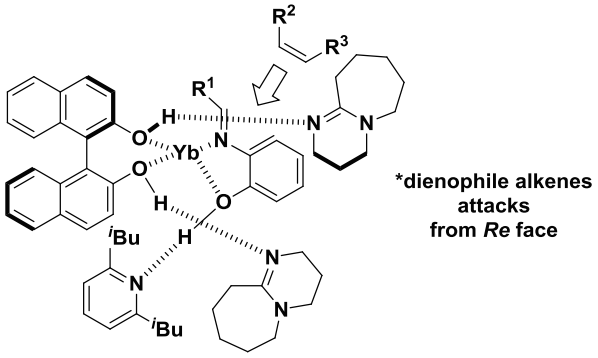
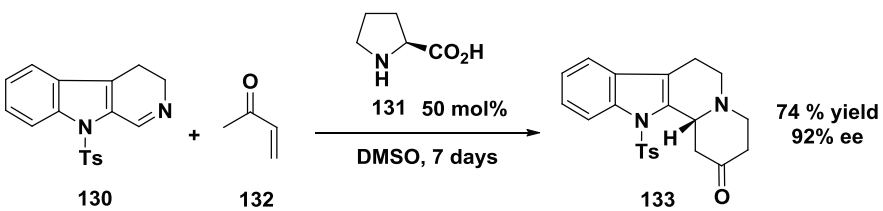


Figure 2.4 The proposed transition state by Kobayashi

However, to achieve the best results, different additives were required for different substrates. This was explained due to changes in the asymmetric environment created by (*R*)-BINOL-Ytterbium(III) with different substrates. Hence, the product scope is limited.

HOMO-Raising *via* aminocatalysis

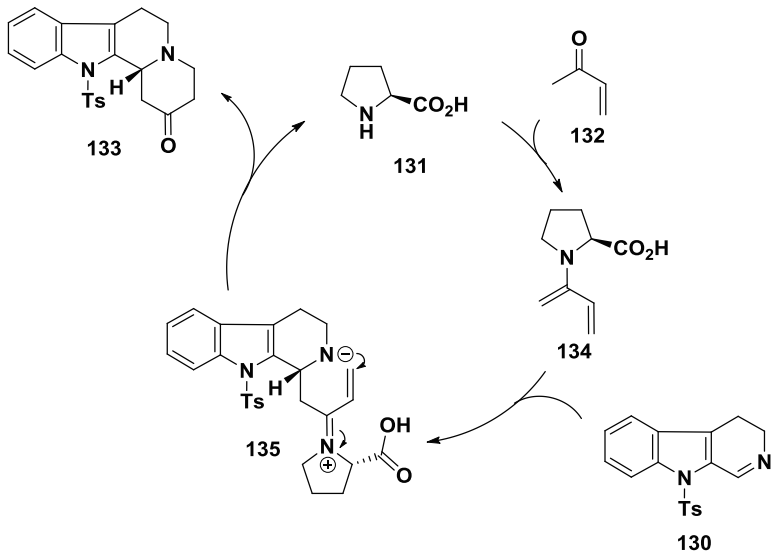
In 2003, the first direct asymmetric organocatalytic NED-aza-Diels-Alder *via* activating the diene **130** by L-proline **131** was reported by Ohsawa and co-workers.[58] They successfully applied this approach using cyclic imines **130** and α,β-unsaturated ketone **132** catalysed by L-proline to form a precursor of natural indole alkaloids **133** in good yield with excellent enantioselectivity (Scheme 2.9). However, high level of catalyst loading (50 mol %), super-stoichiometric ketone (30 eq) and also long reaction time (7 days) detract from the utility of this methodology.



Scheme 2.9 The direct proline-catalysed asymmetric aza-Diels-Alder addition

The reaction is believed to start from reacting proline **131** and ketone **132** to form the active

enamine **134**, which will react with the cyclic (Z)-imine **130** as a dienophile in a Mannich type reaction to give the iminium ion intermediate **135**. Subsequent intramolecular Michael addition is used to cyclise the ring (Scheme 2.10). Later in 2006, Ohsawa also applied this methodology successfully in the total synthesis of the alkaloid *enti*-dihydrocorynantheol.[59]



Scheme 2.10 The proposed mechanism of proline-catalysed asymmetric addition

2-1-2-2. The Inverse-Electron Demand Aza-Diels-Alder (IED-aza-Diels-Alder).

Compared with the NED-aza-Diels-Alder reaction, the inverse-electron demand aza-Diels-Alder employs the reverse concept, in that the reaction occurs between the LUMO of the diene and the HOMO of the dienophile. 1- and 2-azadienes (**136** and **137**) are suiTable reagents for this type of reaction as they act as electron deficient, having the LUMO with lower energy that will be able to react with electron rich dienophile **138** and **139** to form the nitrogen containing heterocycles **140** and **141** (Figure 2.5).

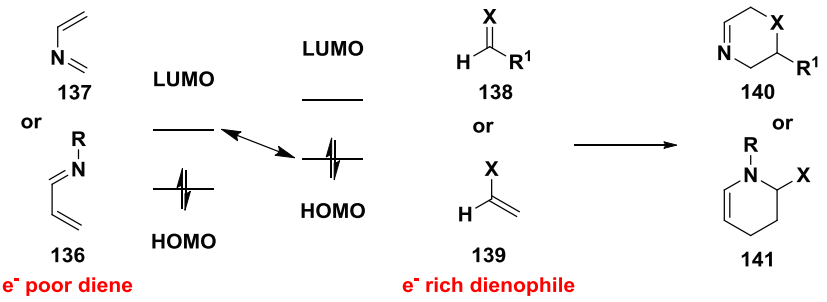


Figure 2.5 Typical IED-aza-Diels-Alder reaction

There are two classes of activation mode to promote the IED-aza-Diels-Alder reaction; the first one is lowering the LUMO energy of the diene generally *via* Lewis acid **142** or Brønsted acid catalysis **143**, the other raisies the HOMO energy of dienophile through organocatalysis, such as aminocatalysis **144**[60] and enolate chemistry **145** and **146** (Figure 2.6).[28]

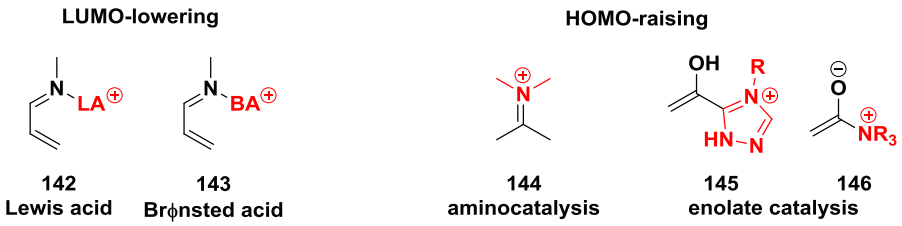
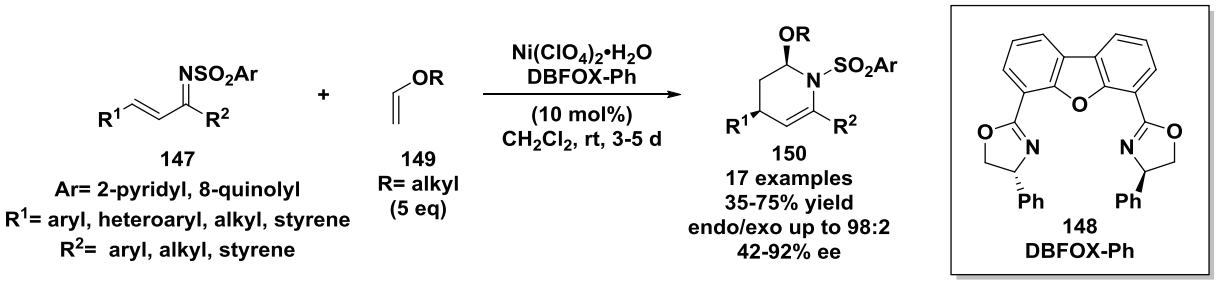


Figure 2.6 Activation modes of IED-aza-Diels-alder Reaction

Recently many studies of the dihydropyridinone functional motif synthesis have been reported using asymmetric organocatalytic formal IED-aza-Diels-Alder reaction *via* HOMO-raising activation.

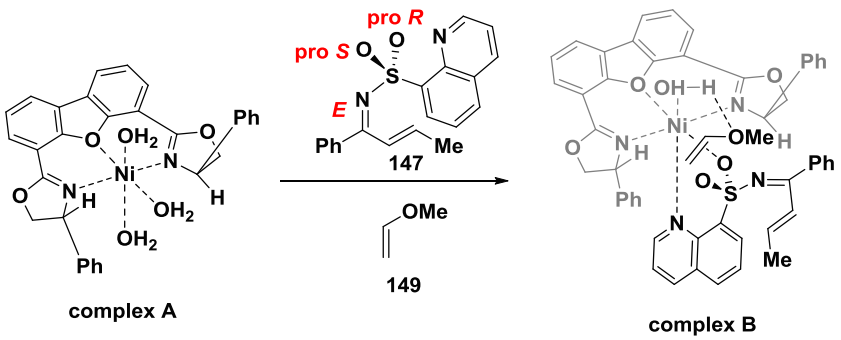
LUMO-Lowering via Chiral Lewis Acid

Carretero *et al*[61,62] have reported the first chiral Lewis acid promoted IED-aza-Diels-Alder reaction with 1-azadiene (ketimine **147**). The chiral Lewis acid combination of $Ni(ClO_4)\cdot H_2O$ and DBFOX-Ph **148** enabled ketimine **147** and vinyl ethers **140** to undergo cycloaddition to form piperidine derivatives **150** in high *endo*-selectivity (up to 98:2) and moderate to excellent enantioselectivity (Scheme 2.11). However, this method requires long reaction times and excess of the enol-ether component (5 eq).



Scheme 2.11 The piperidine formation *via* chiral Lewis acid catalysis

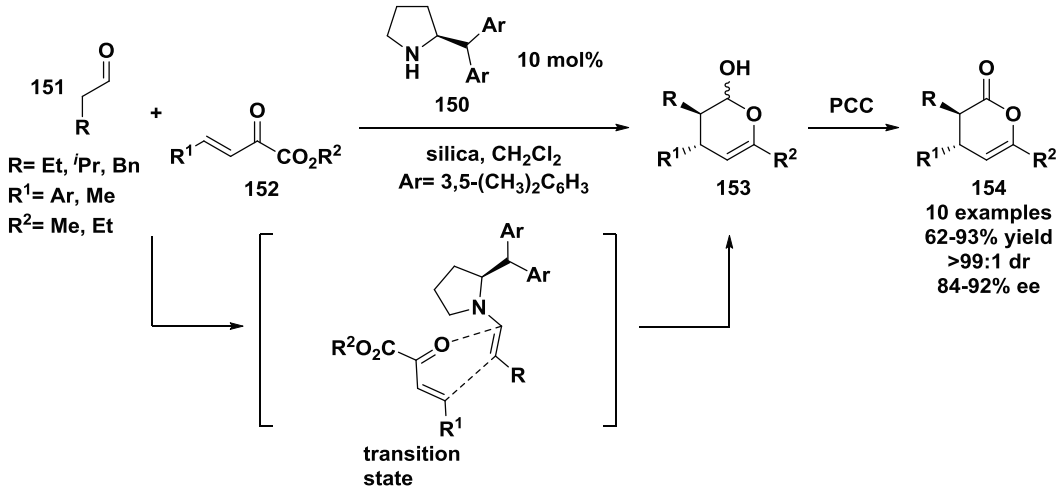
$Ni(ClO_4)\cdot H_2O$ and DBFOX-Ph **148** form the chiral Lewis acid complex A. The reactive model complex B containing the *pro S* oxygen in ketimine **147** coordinated with Ni and the *E*-configuration of ketimine force the reaction from the *Re* face of ketimine and *endo* approach of the olefin **149**, which is stabilised by a hydrogen bond with water (Scheme 2.12).[62]



Scheme 2.12 Stereochemical model for the cycloaddition

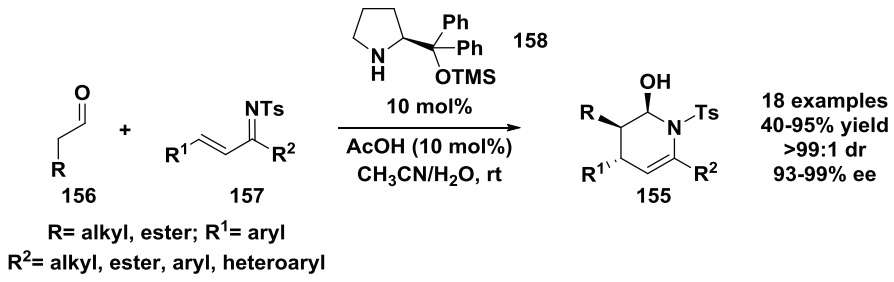
HOMO-Raising *via* aminocatalysis

In 2003, Jorgensen and co-workers[23] disclosed that L-proline derived catalysts **150** and aliphatic aldehydes **151** can generate enamine species *in situ* and can act as HOMO-raised dienophiles in IED-hetero-Diels-Alder reactions to form lactols **153**. Subsequent oxidation with PCC led to highly stereoselective formation of δ-lactones **154** (Scheme 2.13).



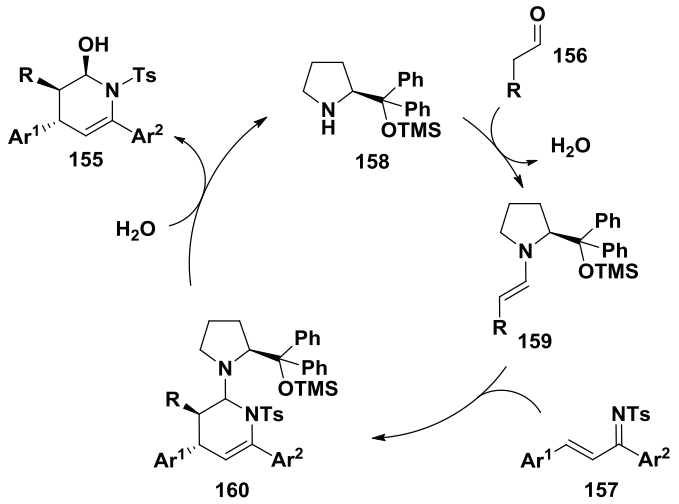
Scheme 2.13 Jorgensen's HOMO-raised active model

Inspired by Jorgensen's work, Chen *et al*[63,64] applied aminocatalysis *via* enamine intermediates to synthesise hemiaminal **155** with excellent diastereo- and enantioselectivities (Scheme 2.14).



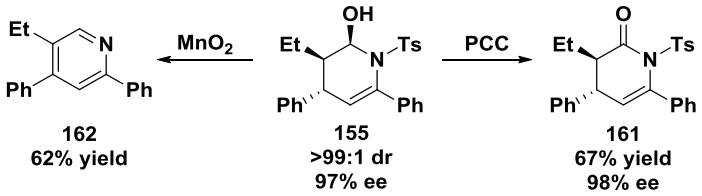
Scheme 2.14 Hemiaminal **155** synthesis by aminocatalysis

The proposed mechanism begins from the condensation of proline derived catalyst **158** with aldehyde **156** generate the HOMO-raised dienophile enamine **159**. This enamine will then undergo [4+2]-cycloaddition with electron-deficient ketimine **157** to form the complex **160**, with hydrolysis to release the catalyst and hemiaminal product **155** (Scheme 2.15). The key to success in this work is the MeCN/H_2O solvent mixture; this aids the hydrolysis process and regenerates the catalyst.



Scheme 2.15 The proposed proline catalytic cycle

The hemiaminal **155** can be oxidised with PCC into dihydropyridinone **161** with moderate yield without compromising the enantiopurity. Using different oxidation reagents, the parent hemiaminal can also be derivatised into tri-substituted pyridine **162** by treating with MnO_2 (Scheme 2.16).

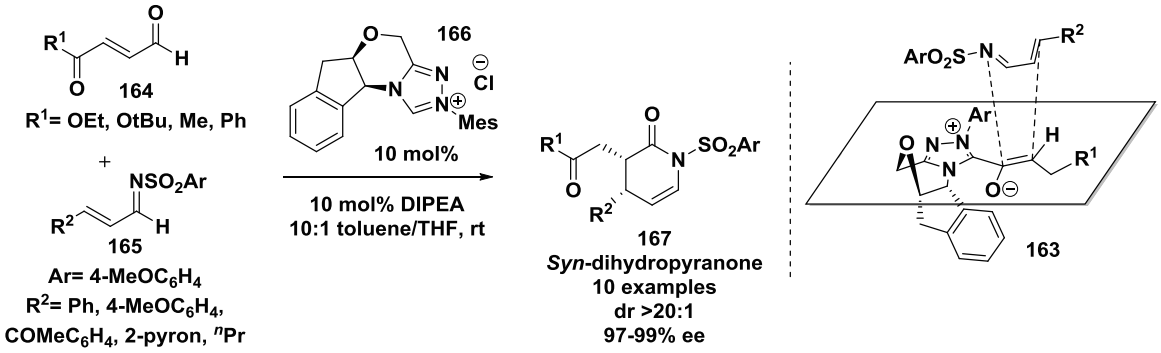


Scheme 2.16 Derivertisations of hemiaminal

2-1-3. Organocatalytic dihydropyridinone formations

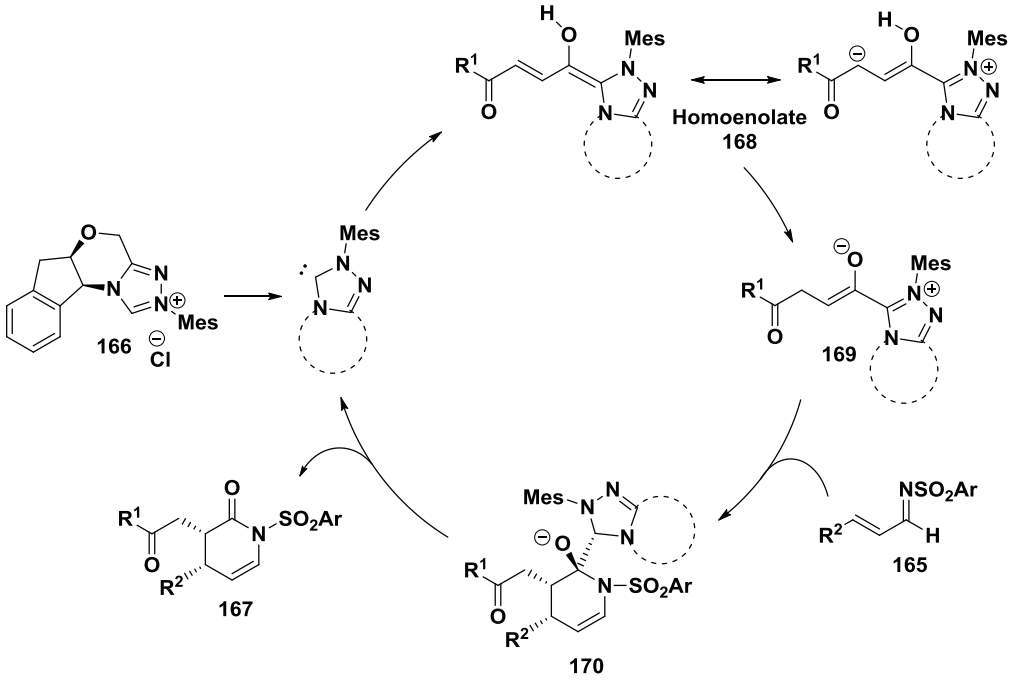
2-1-3-1. *Via* NHC catalysis

Both the approaches from the Bode[65] and Ye[66] groups have applied NHC catalysis to form an active enolate intermediate for dihydropyridinone synthesis. Carbene catalysis has been applied to various reactions such as the benzoin condensation[67] and the Stetter reaction.[25] In 2006, Bode and co-workers successfully generated azolium enolate intermediates **163** from enones **164** and used them in the first NHC catalyzed [4+2]-hetero-Diels-Alder reaction.[65] In this reaction, enone was treated with *N*-protected α,β-unsaturated imines **165** in the presence of NHC **166** to give the *syn*-dihydropyranone product **167** with high diastereo- and enantiocontrol (>20:1 dr and up to 99% ee) (Scheme 2.17).



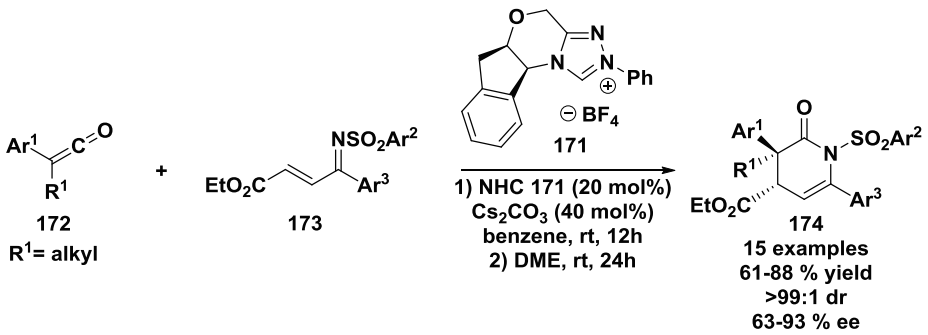
Scheme 2.17 The NHC catalyzed [4+2] cycloaddition reaction by Bode *et al*.

The proposed mechanism for this process starts from the NHC precursor **166** activated by $(^{i}Pr)_2NEt$, generating a homoenolate **168** with enone **164**, which subsequently forms active enolate **169**. Cycloaddition with the *N*-protected α,β-unsaturated imine **165** generates the [4+2]-cyclised *syn*-dihydropyranone product **167** (Scheme 2.18).



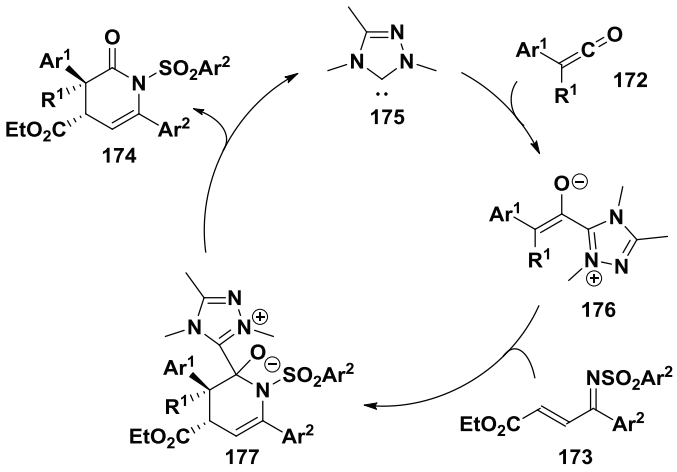
Scheme 2.18 The proposed mechanism of NHC catalyzed [4+2] cycloaddition reaction

Ye and co-workers also have developed a δ-dihydropyridinone synthesis using a NHC catalyst **171** by reacting ketenes **172** with tosyl ketimine **173** (Scheme 2.19).[66] The initial diastereoselectivity of the reaction was low (4:1 dr; *anti*:*syn*). However, stirring the crude product in DME at rt for 24 hours after the catalysis reaction was complete improved the diastereoselectivity (up to >20:1). DME played a crucial role as Cs_2CO_3 dissolves more readily in DME then benzene, allowing epimerisation of C(4) position of the *syn*-dihydropyridinone to the *anti*-dihydropyridinone over time.



Scheme 2.19 Ye's approach to the synthesis of highly enantioselective δ-dihydropyridinone

The proposed mechanism begins by generating the NHC **175** from its precursor followed by nucleophilic addition into the ketene **172** to form the enolate intermediate **176**. This undergoes an inverse-electron-demand Diels-Alder reaction to give adduct **177**. The adduct then collapses to give the dihydropyridinone product **174** and regenerate the NHC catalyst **175** (Scheme 2.20).

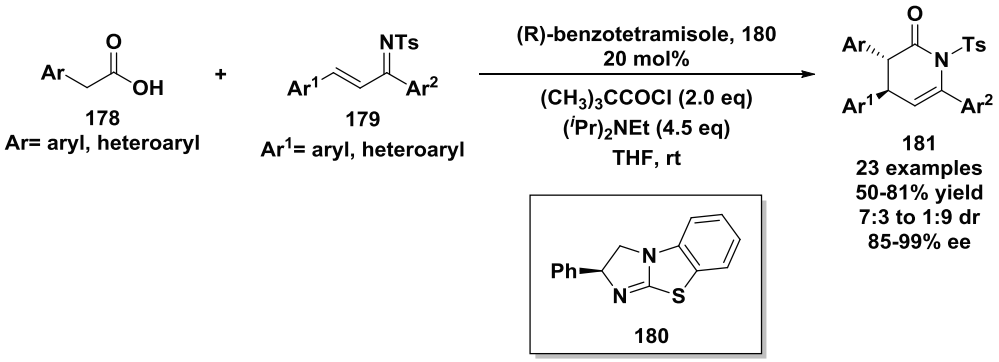


Scheme 2.20 The Proposed mechanism of Ye's approach

Both these methods have shown the utility of enolate chemistry *via* NHC catalysis, in providing the dihydropyridinone products with high diastereo- and enantioselectivies. However, ketenes are not easy to handle and are a very reactive species, which can cause other undesired side reactions and in many cases they have dimerisation problems.[25] Moreover, both methods have long reaction times, and the reaction scale was small. Hence, it is required to develop new and efficient methods which could use cheap, easy to handle starting materials with mild reaction conditions to generate the highly functionalised dihydropyridinones.

2-1-3-2. Isothiourea catalysis

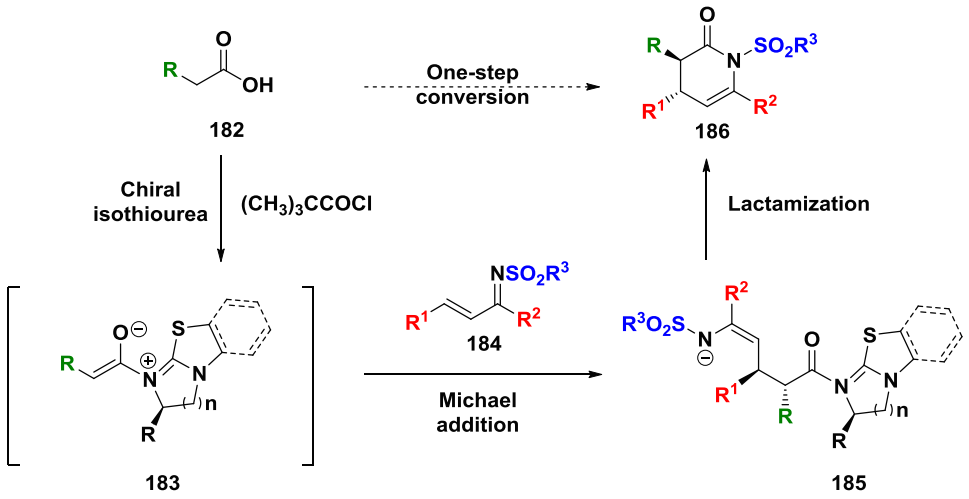
The first example of organocatalytic dihydropyridinone synthesis mediated by isothiourea catalysts has been reported by the Smith group.[68] The methodology uses cheap, commercially available and easy to handle arylacetic acids **178** as ammonium enolate precursors and ketimine **179** to generate highly functionalised *trans*-dihydropyridinone **181** (Scheme 2.21).



Scheme 2.21 Smith's approach

2-2. The aim of this work

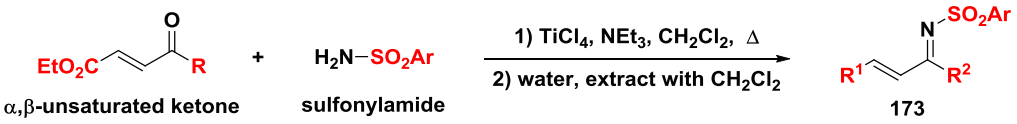
Previous work from the Smith group has developed an efficient asymmetric one-pot intermolecular Michael addition-lactonization process from carboxylic acids and α,β-unsaturated carbonyl compounds that proceeds *via* an ammonium enolate intermediate.[40] Smith and co-workers have also applied this active ammonium enolate species successfully into the asymmetric dihydropyridinone formation as shown above (Scheme 2.21). This previous work has shown only examples where arylacetic acids and tosyl substituted ketimines were used. Building upon this, the aim of this project was to probe the reactivity of these ammonium enolate intermediates with a range of α,β-unsaturated γ-ketoester ketimine acceptors, substituted with various sulfonyl groups, to form highly functionalised dihydropyridinone in a formal [4+2]-cycloaddition process (Scheme 2.22).



Scheme 2.22 This Work

2-3. Ketimine synthesis

To explore the limitation of reactivity of the ammonium enolate species, we decided to examine Michael acceptors made up of α,β-unsaturated ketimines substituted with ester groups, **173**. These have shown good reactivity in the NHC catalysed ammonium enolate chemistry by Ye and co-workers.[66] Besides, this type of ketimine can be easily synthesised by treating the commercially available α,β-unsaturated ketone with sulfonylamide, $TiCl_4$ and NEt_3. Regarding imine synthesis from the literature, the majority of methodologies treat carbonyl substrates and sulfonylamide with Lewis acids, such as $TiCl_4$ or $BF_3{\cdot}OEt_2$, with NEt_3, then purifying *via* flash column chromatography (Scheme 2.23).



Scheme 2.23 General Scheme of ketime synthesis from literature

However, these ketimines that were interesting to this project were found to be problematic by following the standard procedure reported by Ye *et al*.[66] The issue is the pure ketimines were

unable to be isolated from flash column chromatography in our hands, in contrast to what Ye *et al.* have stated in their procedure. This type of ketimine were first developed and reported by Ye[66,69] and then also used by Chen and co-workers,[70,71] however, the procedure was not clear and those reported ketimines have not been fully characterised.

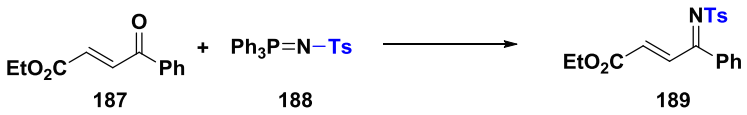
Following the procedure from the literature, the synthesis did work as expected; the ketimine product was present in the crude ^{1}H NMR spectrum. However, the major problem in this type of ketimine preparation was the purification; the ketimines were very sensitive, as they could easily hydrolyse in acidic and also basic column conditions. In our hands they did not survive silica gel column chromatography as reported in the literature. Basified silica or neutral alumina were both unsuccessful in purifying the ketimine from the crude reaction mixture and the ketimine was found to decompose on the column. This hydrolysis could be easily observed *via* 2D TLC. Kugel-Rohr distillation was attempted, resulting in decomposition into the starting enone and sulfonamide. Moreover, literature preparations removed impurities such as titanium salts by adding water into the reaction crude that could possibly accelerate the hydrolysis.

At this stage, it was clear that the flash column chromatography was not an option for obtaining the ketimine products cleanly. To avoid hydrolysis, it was necessary to develop either a new procedure avoiding using Lewis acids, which could stop forming the unwanted side products to avoid the purification, or a new purification process that could limit water hydrolysis.

2-3-1. Aza-Wittig Reaction

To achieve these goals, an Aza-Wittig reaction was applied for the preparation of ketimine acceptors **189,** ketone **187** was reacted with *N*-tosyl triphenylphosphane Wittig reagent **188**. (Table 2.1) However, the results show that the yields of this reaction are very low and changing the solvent, temperature, increasing the reaction time, or performing the reaction in a sealed microwave tube did not improve the yields. In most cases, the starting material was the only recovered material. Surprisingly, even adding a Lewis acid, $TiCl_4$, up to one equivalent, did not improve the conversion and the reaction mixture looks significantly messier from the ^1H NMR spectra.

Table 2.1 Aza-Wittig reaction optimisation



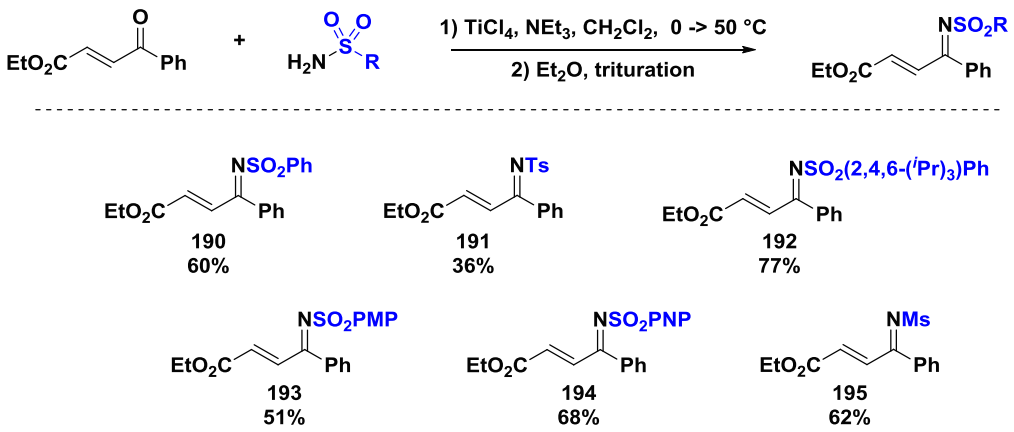
187 188 189

Entry	t (day)	$TiCl_4$ (%)	Temp. (^oC)	Solvent	Heating method	Ketimine[a]
1	1	-	85	THF	Reflux	2%
	2	-	160	toluene	Reflux	6%
	3	-	160	toluene	Sealed tube	13%
2	1	10	85	THF	reflux	-
3	1	100	85	THF	Sealed tube	-
	2	100	160	THF	Sealed tube	-
4	7	100	160	toluene	Sealed tube	7%

[a] Determined by from ^1H NMR spectroscopic analysis

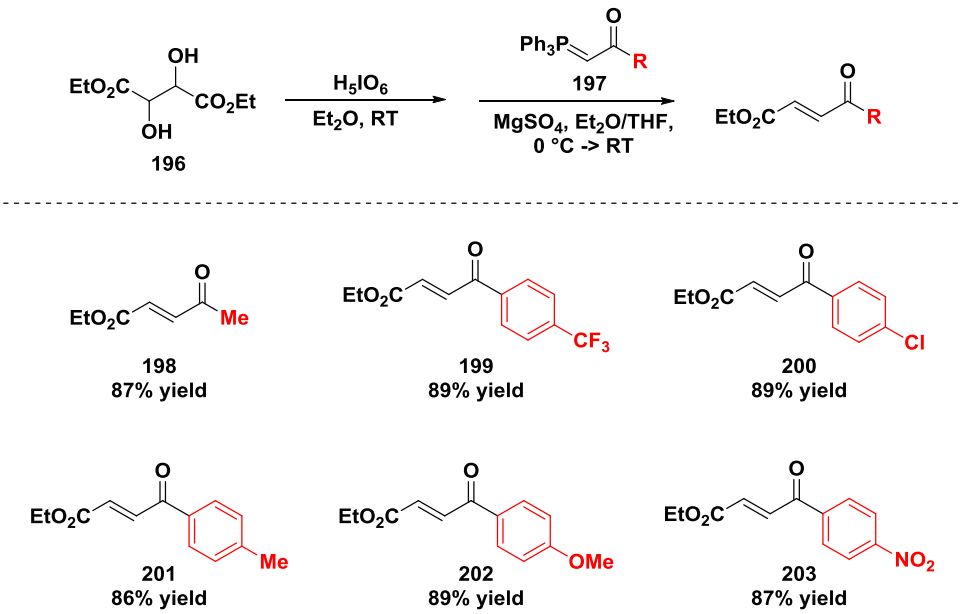
2-3-2. New purification procedure

An alternative that has been tried is to find a new purification which could limit hydrolysis from the reaction procedure (Scheme 2.23). Instead of quenching the reaction mixture with water, diethyl ether was used to precipitate impurities. The organic solvent was then removed and more diethyl ether added again, this step was repeated until there was no further precipitate was observed. This crude material was then triturated with diethyl ether at $-20^{\circ}C$ in a ice/salt/acetone bath. During the trituration, it was important to make sure all the crude was fully triturated into a crystalline solid, as the gummy impurities accelerate ketimine decomposition. Moreover, it was also found that the concentration of reaction solvent cannot be lower than 0.3 M, otherwise clean solid ketimine cannot be made. Also, using freshly re-purified enone starting materials in the ketimine synthesis improved the purification of the ketimine. Following the optimised purification, six ketimines with various sulfonyl groups including electron withdrawing (nitro) **194** and donating (alkyl, methoxy) **191-193** aryl substituents and also non-aryl (mesyl) **195**, were prepared in good yield (Scheme 2.23). Trifluoromethanesulfonamide ($H_2NSO_2CF_3$) was also applied into the ketimine preparation but there was no reaction at all, only the starting material enone returned.



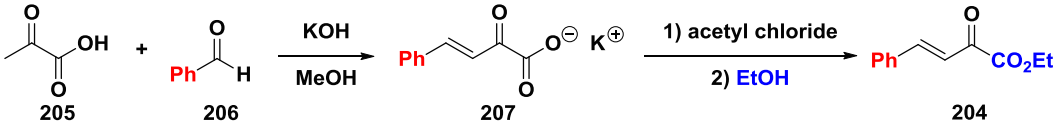
Scheme 2.23 The ketimines prepared from enones

Modified aryl substituted ketimines were also prepared, with the precursor enone synthesised through Xiao's procedure[72] from the oxidation of diethyl tartrate **196** to form aldehyde intermediate *in situ*. This undergoes highly stereoselective Wittig reaction with the corresponding 2-(triphenylphosphoranylidene)acetophenone **197**, resulting in the corresponding α,β-unsaturated enones **198-203**, only (*E*)-isomer was observed by ^{1}H NMR spectroscopy (Scheme 2.24).



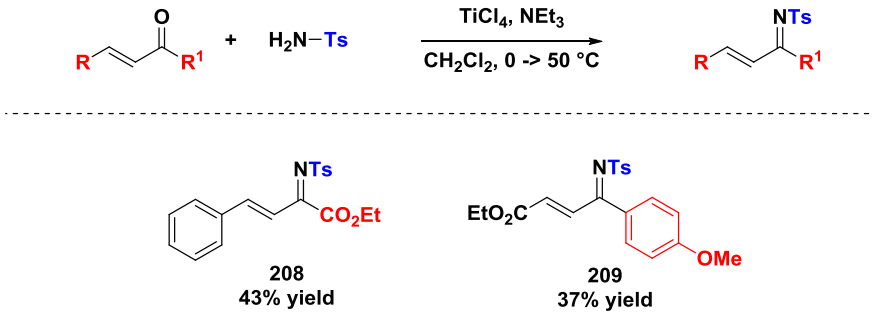
Scheme 2.24 The preparation of α,β-unsaturated enones

The enone **204** with the reversed substituents can be prepared from the previous work of Smith *et el*, by reacting pyruvic acid **205** with aryl aldehyde **206** and potassium hydroxide to obtain potassium enoate **207**, which reacts with the corresponding alcohol resulting the reversed enone **204** (Scheme 2.25).



Scheme 2.25 The preparation of enone **204** with reversed substituents

However, the substrates with methyl, aryl *p*-trifluoromethyl and aryl *p*-nitro substituted ketimines were difficult to prepare as the reaction only had maximum 50% conversion. The aryl *p*-nitro enone did not even react with benzensulfonamide by ^{1}H NMR spectroscopy. Besides, those ketimines were not sTable and decomposed easily on attempting trituration. Also, they were hydrolysed back immediately to starting material once applied to flash column chromatography. The reactions of aryl *p*-methyl, *p*-chloro and *p*-methoxyl enones with benzenesulfonamide were working fine but the crude materials were all gums even at −20˚C, and could not be triturated to solid forms in our hands. Aryl *p*-methyl, *p*-chloro substituted enones have also repeated with tosyl amides which have been prepared by Ye and Chen's group, however, none of them could be obtained in solid form. Despite these issues, the reversed enone **204** and aryl *p*-methoxyl enone **202** worked with tosyl amide and those two ketimines, **208** (43% yield) and **209** (37% yield), could be purified by flash column chromatography (Scheme 2.26).

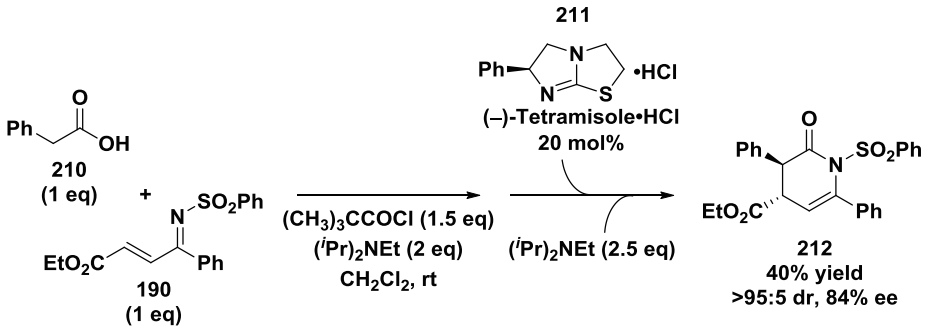


Scheme 2.26 The modified ketimines

2-4. Background reactions

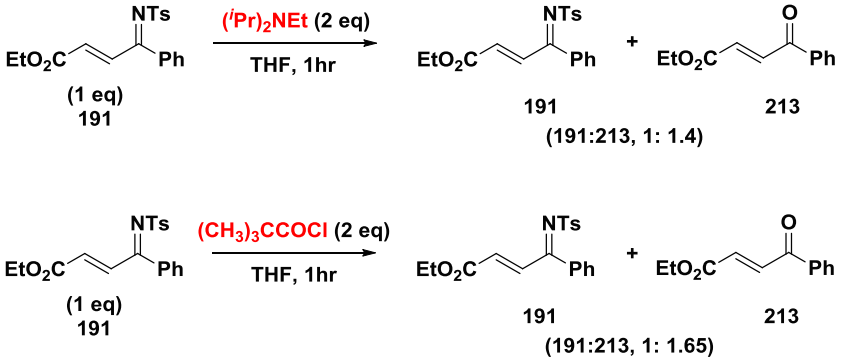
Initial studies, reacting phenylacetic acid **210** with a ketimine **190** catalysed by an isothiourea **211**, formed dihydropyridinone **212** with excellent diastereo- and enantioselectivity (>95:5 dr and 84% ee) (Scheme 2.27). The original process dissolved both phenylacetic acid and the ketimine in CH_2Cl_2 before adding pivaloyl chloride and (^{i}Pr)$_2$NEt for 30 minutes then adding

the catalyst and futher $(^{i}Pr)_2NEt$.



Scheme 2.27 Initial studies with acceptor added before the catalyst

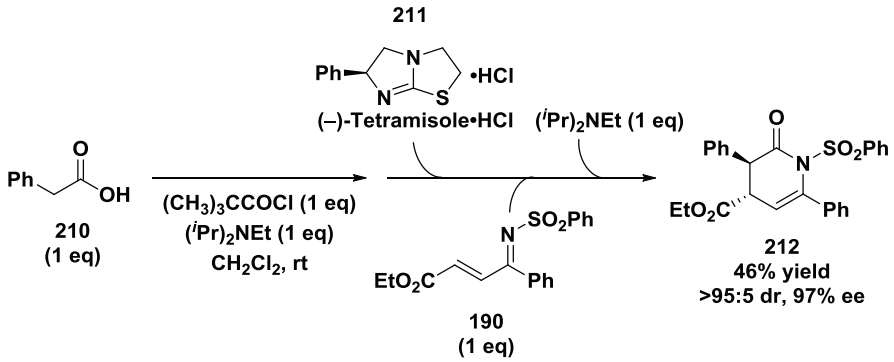
However, during the ketimine synthesis, this type of ketimine was shown to easily decompose under either acidic or basic reaction conditions. Hence, before starting the optimisation process, background reactions were examined to find out if the starting material ketimine **191** can tolerate the reaction conditions. The results showed the ketimines easily hydrolyse back into enone **213**, by stirring with pivaloyl chloride and $(^{i}Pr)_2NEt$ individually for one hour (Scheme 2.28).



Scheme 2.28 Background reactions with $(^{i}Pr)_2NEt$ and pivaloyl chloride

Due to this fact, the pivaloyl chloride and also $(^{i}Pr)_2NEt$ have to be distilled first before applied into the reactions. Moreover, the initial reaction conditions for dihydropyridinone synthesis has started from the minimum amount of agents used, with 1 eq of pivaloyl chloride and 1 eq of $(^{i}Pr)_2NEt$ used to form a mixed anhydride. After 30 minutes the mixed anhydride

is formed *in situ*, followed by adding the catalyst, ketimine and a further 1 eq of base. The new procedure avoids decomposition of the ketimine before the desired catalysis and also minimises the possible racemic background reaction which has been suggested by previous dihydropyridinone projects. Hence, this results in the increases of enantioselectivity from 84% ee to 97% ee and also improving the yield from 40% to 46%. (Scheme 2.29)

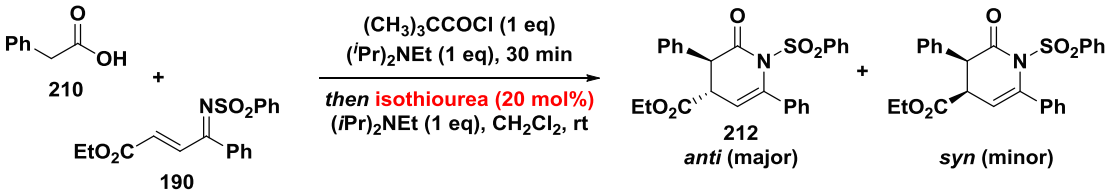


Scheme 2.29 New procedure with acceptors added after catalyst

2-5. Initial Catalyst Studies

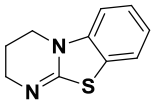
The model reaction employed phenylacetic acid with a ketimine catalysed by achiral isothiourea DHPB **214**, affording the dihydropyridinone in promising 65% yield and with excellent diastereocontrol (*anti*: *syn*, 88:12) (Table 2.2, Entry 1). Various chiral isothioureas, including HBTM 2.1 **215**, benzotetramisole (BTM) **216** and (－)-tetramisole·HCl **211**, were tested in this process. Chiral isothiourea HBTM 2.1 was the most "active" catalyst, with complete reaction in one hour, but it gave the poor diastereocontrol (75:25 dr) (Entry 2). BTM also gave equally good enantioselectivity, however, the yield was much lower and reaction was not complete after double the amount of time (Entry 3). Commercially available (－)-tetramisole·HCl gave not only the best yield (46%) but also high diastereo- and enantioselectivity (>95:5 dr and 97% ee) (Entry 4). Hence, (－)-tetramisole·HCl was chosen as the chiral catalyst for this project.

Table 2.2 Initial studies with various isothiourea catalysts

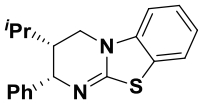


Entry	Cat.	Solvent	t (h)	Yield[a]	Pro: SM[b]	dr[b]	ee (%)
1	DHPB	THF	1	65%	>99:1	88:12	-
2	HBTM 2.1	CH_2Cl_2	1	33%	>99:1	75:25	95
3	BTM	CH_2Cl_2	6	28%	71:29	>95:5	98
4	**(−)-Tetramisole·HCl**	**CH_2Cl_2**	**3**	**46%**	**>99:1**	**97:3**	**98**

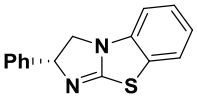
[a] isolated yield; [b] determined by ^{1}H NMR spectroscopic analysis



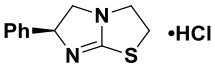
214
DHPB



215
HBTM 2.1



216
Benzotetramisole (BTM)



211
(–)-Tetramisole•HCl

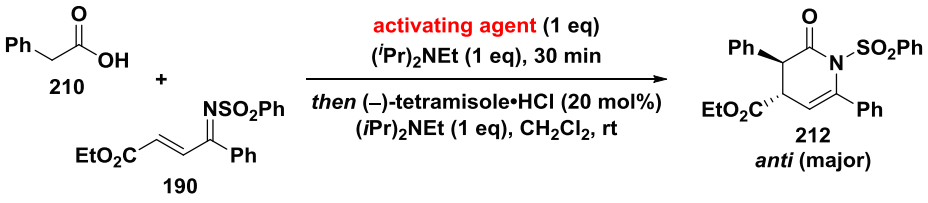
2-6. Optimisation

The initial study showed this methodology had extraordinary diastereo- and enantiocontrol when catalysed by tetramisole·HCl. However, product yield was low and the crude residues contained many unidentified species. There were a few options to improve product yield, for example, evaluating alternative activating agents, the equivalents of base used, and catalyst loading.

2-6-1. Activating Agent Screen

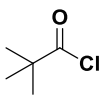
Several activating agents were tested to see which resulted in highest product yield (Table 2.3). Benzoyl chloride **218** (Entry 2) and 4-nitrobenzoyl chloride **219** (Entry 3) provided both good diastereocontrol (91:9 dr and 83:17 dr); however, compared with pivaloyl chloride, the reaction was much slower and was not complete in three hours. 4-Methoxybenzoyl chloride **220** (Entry 4) gave the same enantioselectivity as with pivaloyl chloride, however the reaction was not only much slower but also it was difficult to separate the δ-dihydropyridinone product from the mixed anhydride, formed from phenylacetic acid and 4-methoxybenzoyl chloride, hence, the isolated yield was much lower.

Table 2.3 Activating agent screen

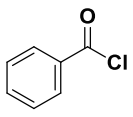


Entry	Activating agent	t (h)	Yield[a]	Pro: SM[b]	dr[b]	ee (%)
1	**Pivaloyl Chloride**	**3**	**46%**	**>99:1**	**97:3**	**98**
2	Benzoyl Chloride	3	32%	71:29	91:9	94
3	4-Nitrobenzoyl Chloride	3	29%	61:39	83:17	92
4	4-Methoxybenzoyl Chloride	16	16%	>99:1	90:10	98

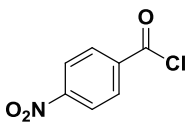
[a] isolated yield; [b] determined by ^{1}H NMR spectroscopic analysis



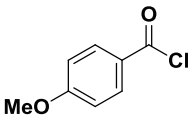
217
Pivaloyl chloride



218
Benzoyl chloride



219
4-Nitrobenzoyl chloride

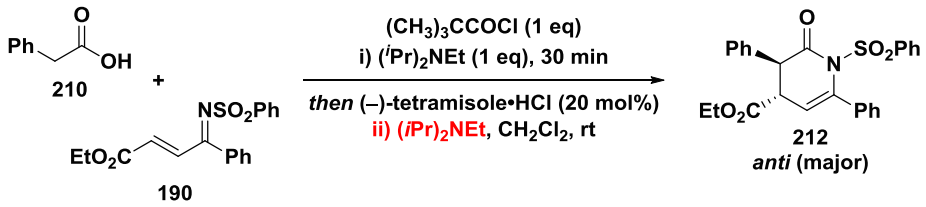


220
4-Methoxybenzoyl chloride

2-6-2. Equivalents of base screen

During the preparation of the ketimine starting material, it was found to be very sensitive and easy to be hydrolyzed under both acid and base conditions, even in water. Hence, the use of excess $(^{i}Pr)_2NEt$ should be minimised. However, the catalyst, (−)-tetramisole is used as its HCl salt and activated by base. To investigate the role of base, various amount of $(^{i}Pr)_2NEt$ were examined in the model reaction. Consequently, extra base added in second step of the reaction did not affect stereoselectivity but also did not improve the yield (Entry 5-7, Table 2.4). The addition of 1 eq each in first and second steps (Entry 1 and 2) gave the consistent result on different reaction scales (0.2 mmol and 1.0 mmol). Therefore, we chose to maintain these base equivalents.

Table 2.4 Base Equivalent Optimisation



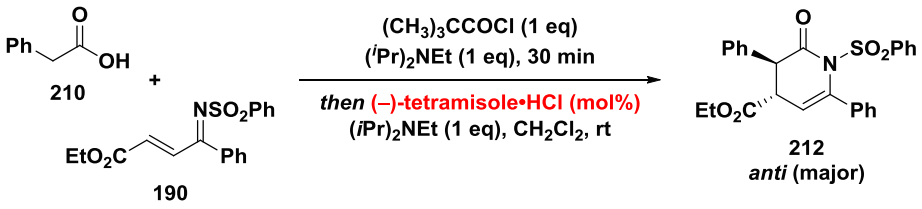
Entry	Catalyst	ii) $(^{i}Pr)_2NEt$ (eq)	Yield[a,d]	Yield[b, d]	dr[c]	ee (%)
1	(−)-Tetramisole·HCl	1	46%		96:4	97
2	**(−)-Tetramisole·HCl**	**1**		**48%**	**98:2**	**98**
3	Free base (−)-Tetra	1	62%		93:7	98
4	Free base (−)-Tetra	1		45%	-	98
5	(−)-Tetramisole·HCl	1.2	31%		98:2	98
6	(−)-Tetramisole·HCl	1.2		40%	98:2	98
7	(−)-Tetramisole·HCl	1.5	37%		-	97

[a] 0.2 mmol scale; [b] 1.0 mmol scale; - overlap with impurities, dr cannot be measured through ^{1}H NMR spectroscopic analysis; [c] determined by ^{1}H NMR spectroscopic analysis; [d] isolated yield

2-6-3. Catalyst loading screen

One of the important aims in the development of catalytic methodology is to use as little catalyst as possible. Reducing the catalyst loading to 10 mol% did not affect the enantioselectivity (98% ee), but slightly increased the diastereocontrol from 93:7 to 97:3 dr. (Table 2.5, Entry 2). However, 10 mol% catalyst loading was insufficient to complete the reaction overnight and yield was low. On the other hand, increased catalyst loading to 40 mol% gave better yield (75% yield) (Entry 3). It is worth pointing out, using 1 eq of catalyst resulted in even better diastereo- and enantioselectivities (95:5 dr, 99% ee) but it did not help with yield (67% yield) (Entry 4).

Table 2.5 Catalyst loading Screen



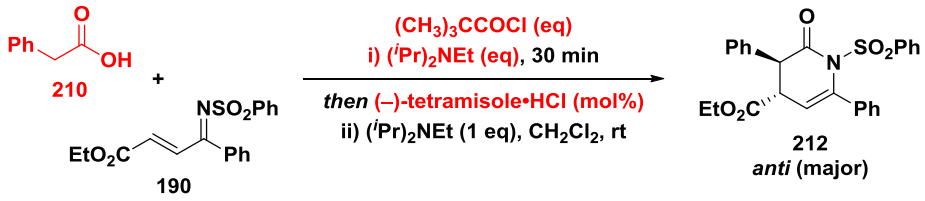
Entry	Cat (%)	T (h)	Yield[a]	Pro:SM[b]	dr[b]	ee (%)
1	**20**	**3**	**46%**	**1:0**	**97:3**	**98**
2	10	16	38%	1:0.3	97:3	98
3	40	3	75%	1:0	93:7	98
4	100	1	67%	1:0	95:5	99

[a] isolated yield; [b] determined by ^{1}H NMR spectroscopic analysis

2-6-4. Equivalents of acids screen

Next, the equivalents of phenylacetic acid used were investigated to try and improve the yield. Doubling the equivalents of carboxylic acid, pivaloyl chloride and $(^{i}Pr)_2NEt$ gave a higher yield of product (from 49% to 62%) and shorter the reaction time (from three hours to one hour) without compromising the stereocontrol (Entry 2, Table 2.6). Moreover, this reaction could be repeated under open flask conditions with bench solvent and the results remained the same with excellent diastereo- and enantiocontrol (Entry 3). However, using two equivalents of acid but using the catalyst loading of 10 mol% gave the same yield, diastereo- and enantiocontrol (Entry 4) as the conditions with one equivalent of acid and 20 mol% catalyst (Entry 1). Using 5 mol% catalyst loading did not complete the reaction overnight and gave more side-products by ^{1}H NMR spectroscopic analysis (Entry 5).

Table 2.6 Equivalents of Acids Screen



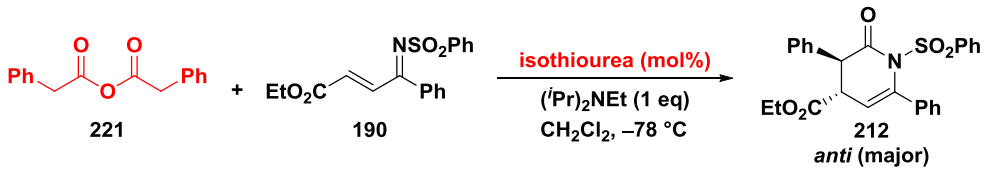
Entry	Acid (eq)	Cat (%)	$(CH_3)_3CCOCl$ (eq)	i) $(^{i}Pr)_2NEt$ (eq)	T (h)	Yield[a]	dr[b]	ee (%)
1	1	20	1	1	3	49%	98:2	97
2	2	20	2	2	1	62%	93:7	98
3*	**2**	**20**	**2**	**2**	**1**	**65%**	**92:8**	**98**
4	2	10	2	2	3	45%	97:3	95
5	2	5	2	2	16	-	-	-

*was carried under bench conditions without flame drying and used bench solvent; [a] isolated yield; [b] determined by ^{1}H NMR spectroscopic analysis

2-6-5. Pre-formed anhydride screen

The use of pre-formed homo-anhydrides was also applied to this methodology to simplify the procedure and to try and avoided undesired by-products. Using phenylacetic anhydride **221** improves the purification from flash column chromatography, however, the diastereoselectivity decreased from 97:3 to 84:16 (Table 2.7, Entry 1)**.** HBTM 2.1 was also tested as a catalyst with pre-formed anhydride at 5 mol% catalyst loading, but the diastereoselectivity dramatically decreased to 60:40, although the enantiocontrol remained high (>99% for major, 93% for minor) (Entry 2). Using one equivalent of anhydride with 5 mol% HBTM 2.1 loading gave even lower yield and diastereoselectivity (Entry 3).

Table 2.7 Pre-formed Anhydride Screen



Exp	Cat	Catalyst loading	Yield	dr	ee (%)
1	**(−)-Tetramisole·HCl**	**20%**	**62%**	**84:16**	**95**
2	HBTM 2.1	5%	56%	60:40	>99 (*ent*), 93
3[a]	HBTM 2.1	5%	28%	52:48	-

[a] experiment was carried with only 1 eq anhydride

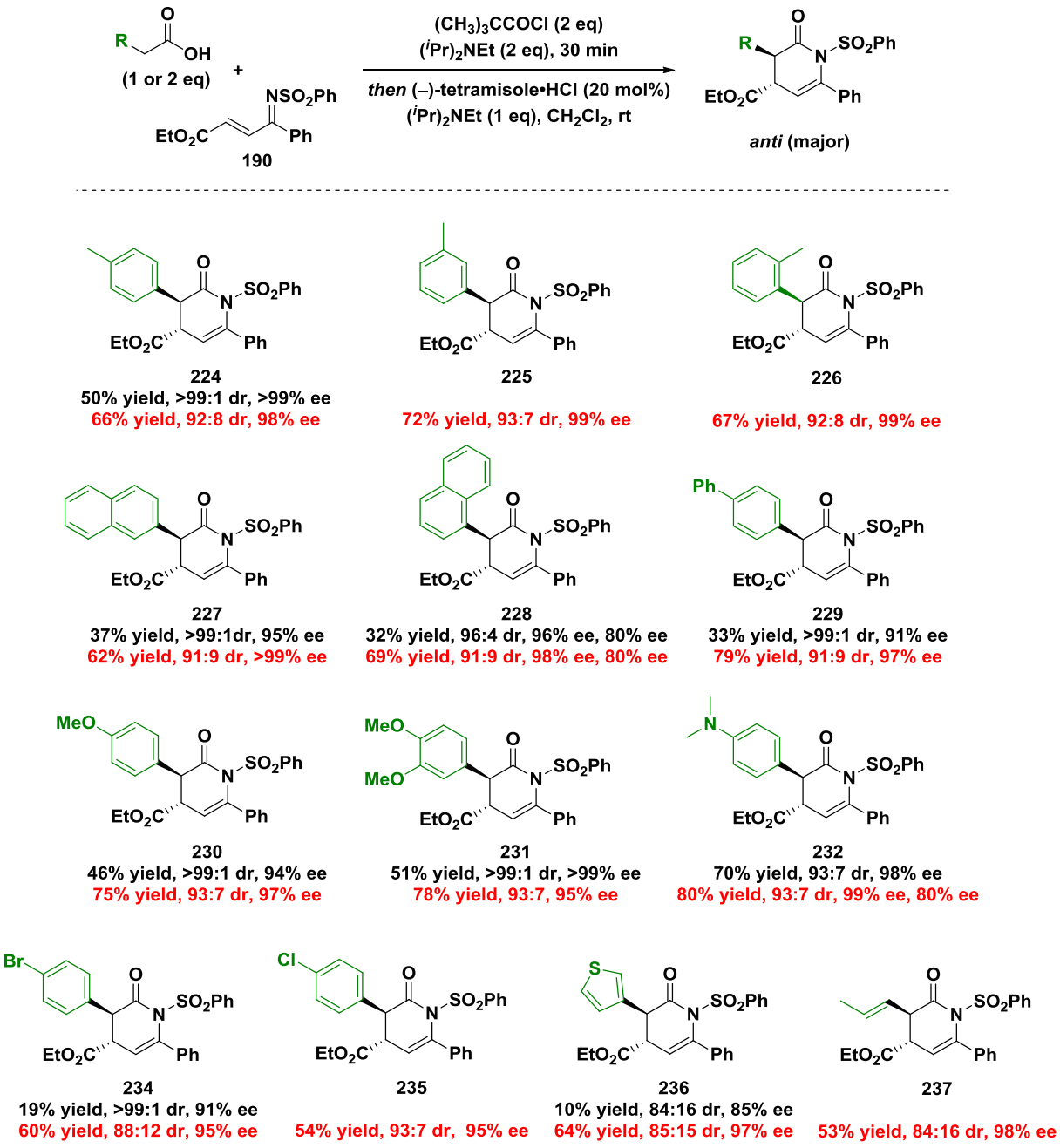
In conclusion, the best condition for this dihydropyridinone was with two equivalents each of acetic acid, pivaloyl chloride and $(^{i}Pr)_2NEt$ to generate excess mixed anhydride, followed by (−)-tetramisole·HCl (20 mol%) then one equivalent acceptor along with one futher equivalent of $(^{i}Pr)_2NEt$.

2-7. Product Scope

2-7-1. Variation of the Acid

Some selected phenylacetic acids were next applied in this methodology using both one and two equivalents of acid. Using two equivalents of acetic acid generally resulted in improved enantiocontrol; however, the diastereoselectivity was slightly lower when more acid was used in most cases. Ye *et al* (Scheme 2.19) improved diastereoselectivity by stirring the crude in DME for 24 hours with Cs_2CO_3 to facilitate the epimerisation of *syn*-dihydropyridinone to *trans*-dihydropyridinone[66]. However, treating this dihydropyridinone product under reaction condition again with DHPB and $(^{i}Pr)_2NEt$ did not improve the diastereoselectivity. Overall, using two equivalents of acid mainly improved the yield. For example, *p*-bromophenyl acetic acid and 3-thiophene acetic acid gave incomplete reactions overnight with one equivalent of acid and were difficult to purify by flash column chromatography. However, these reactions with two equivalents of acid worked well in one hour and the yields of product increased remarkably (Scheme 2.30, **234**, 19% to 60%; **236**, 10% to 64%).

Other aryl acetic acids were also successfully demonstrated in this method. For example, *p*-, *o*- and *m*-tolyl acetic acids **(224-226)** did not affect the reaction resulting in excellent yield, diastereo- and enantiocontrol. Increasing the size of the aromatic ring by applying 1-, 2-naphthalene and 4-biphenylacetic acid **(227-229)** also gave product with high diastereo- and enantiocontrol. The electron-donating substituted aryl, *p*-methoxy **230**, 3,4-dimethoxy **231**, and *p*-dimethylamino **232** worked best in this methodology. Moreover, this methodology was highly tolerant of a range of substituents such as *p*-chloro **235**, *p*-bromo **234**, and heterocyclic 3-thiophene **236**. Notably, alkenylacetic acid **237** substituents also worked well, only the diastereocontrol was slightly lower compared with other aryl substituents and the enantiocontrol still remained high (Scheme 2.30).



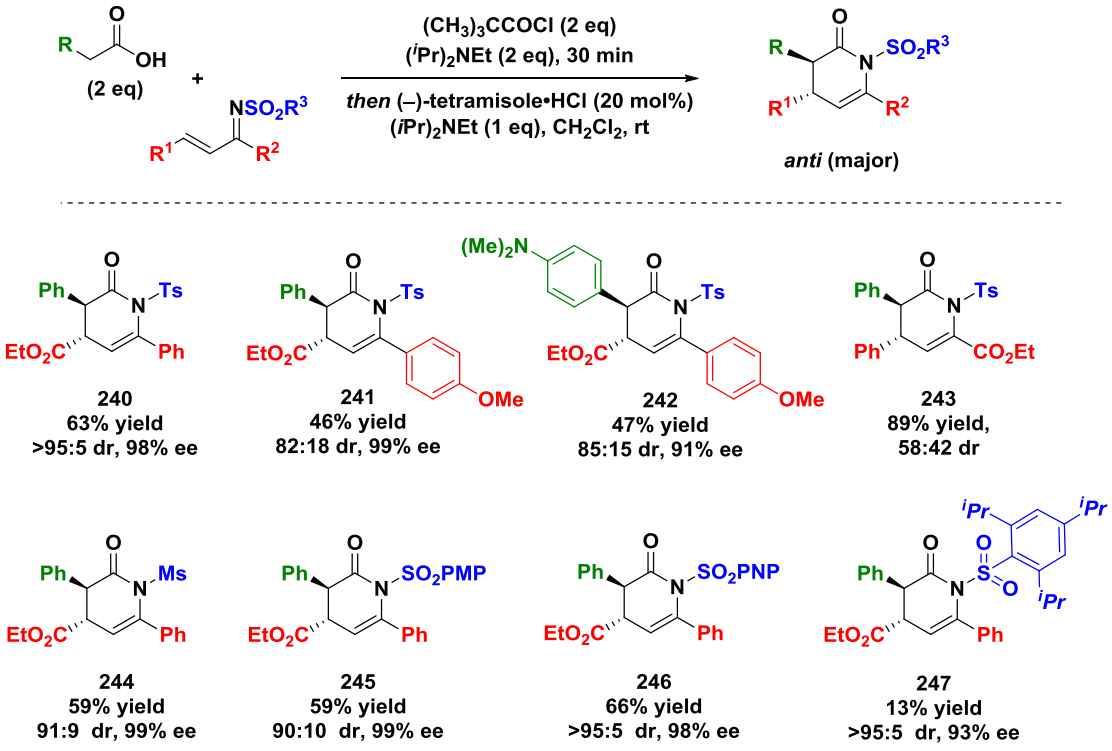
Scheme 2.30 Reaction scope: variation of acid

Red: reaction condition with 2 eq of acid, Black: reaction condition with 1 eq of acid.

However, the scope was limited to mono-substituted acetic acid. Di-substituted acetic acids gave no conversion.

2-7-2. Ketimines Scope

Various ketimines were also successfully applied to the reaction using two equivalents of acid. The ketimines with various *N*-sulfonyl groups have been examined in this reaction, which has shown sulfonyl groups such as mesyl **244**, *p*-methoxy **245**, and *p*-nitro **246**, did not compromise the stereocontrol. Moreover, the *p*-nitro sulfonyl group gave even better yield and excellent stereocontrol. The ketimine bearing with tri-isopropyl group **247** also gives good stereocontrol; however, the yield is much lower than others. This reduced yield is due to the product requiring purification *via* recrystallisation; it could not be easily purified by flash column chromatography. The ketimines with a *p*-methoxy substituted aromatic ring were also successful applied to the reaction resulting in moderate yield (**241** and **242**). The ketimine with reversed ester and phenyl substituents **243** can be tolerated in this reaction, the yield was high (89%) but the diastereoselectivity was very low (58:42). Due to the separation issue in chiral HPLC, the enantioselectivity of the reversed dihydropyridinone is still under investigation (Scheme 2.31).



Scheme2.31 Variation of ketimine

2-8. Evidence of the absolute configuration

The initial assignment of the *anti* relative configuration within the parent dihydropyridinone **212** is consistent with the observed preferential *anti*-selectivity in the related reaction of chalcone-derived ketimines promoted by isothioureas[68]. The comparison of the ^{1}H coupling constants of related *N*-tosyl dihydropyridinone **213** ($J \approx 10$ Hz, relative configuration confirmed by X-ray crystallography) and the parent dihydropyridinone **212** ($J \approx 10$ Hz) giving the similar coupling constants (Figure 2.7).

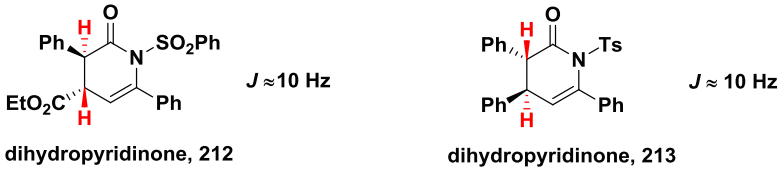


Figure 2.7 The ^{1}H coupling constants comparison of dihydropyridinones

To unambiguously identify both the relative and absolute configuration of the major diastereomer of dihydropyridinone, enantiopure dihydropyridinones **230** has been examined *via* X-ray crystallography analysis (Figure 2.8). This confirmed the absolute and relative as *anti*-(3*S*, 4*S*).

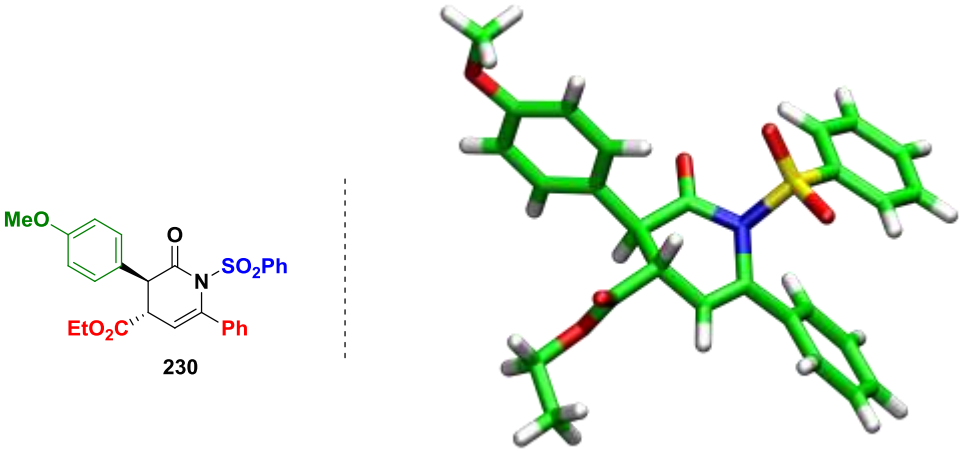
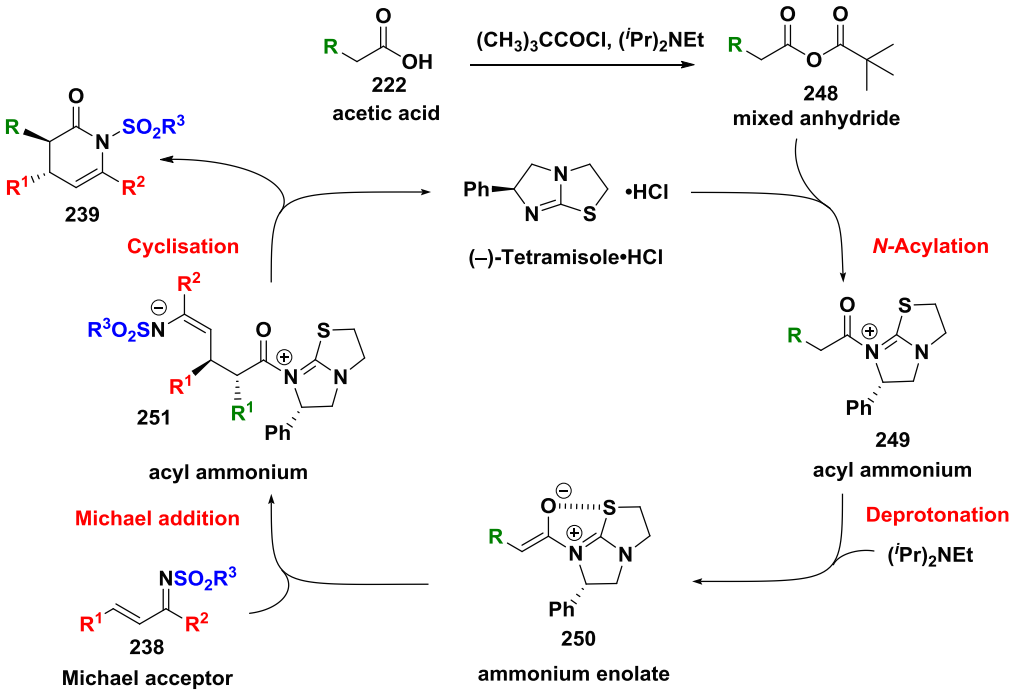


Figure 2.8 Assignment of absolute configuration

2-9. Proposed Mechanism

The proposed mechanism starts with activation of the acetic acid with pivaloyl chloride to form a mixed anhydride **248**. *N*-acylation of the chiral isothiourea **211** with this anhydride forms an acyl ammonium adduct **249**. Deprotonation generates the active (*Z*)-ammonium enolate intermediate **250**, which subsequently undergoes Michael addition with the α,β-unsaturated acceptors **238**. Then, intramolecular cyclisation and catalyst regeneration gives the dihydropyridinone product **239** (Scheme 2.32).



Scheme 2.32 The proposed mechanism

From the scope of this investigation, the results have shown high diastereo- and enantiocontrol. The results may be proposed due to several factors which have been involved in the transition state. The (Z)-ammonium enolate form allows for a favourable nonbonding interaction (n_o -> σ* C-S) between the oxygen of the enolate and the sulfur[73,74] on the isothiourea catalyst as been suggested by Birman[75] and also Romo[76] *et al*. This nonbonding interaction not only influences the flat ammonium enolate conformation but also stabilises the

transition state by locking the isothiourea catalyst in position. Therefore, the phenyl group of the isothiourea catalyst would sit in the *pseudo*-axial orientation which blocks the *Re* face, subsequently forcing the Michael acceptor to approach from the *Si* face (Figure 2.9). Hence, this methodology forms the dihydropyridinones with excellent diastereo- and enantioselectivities.

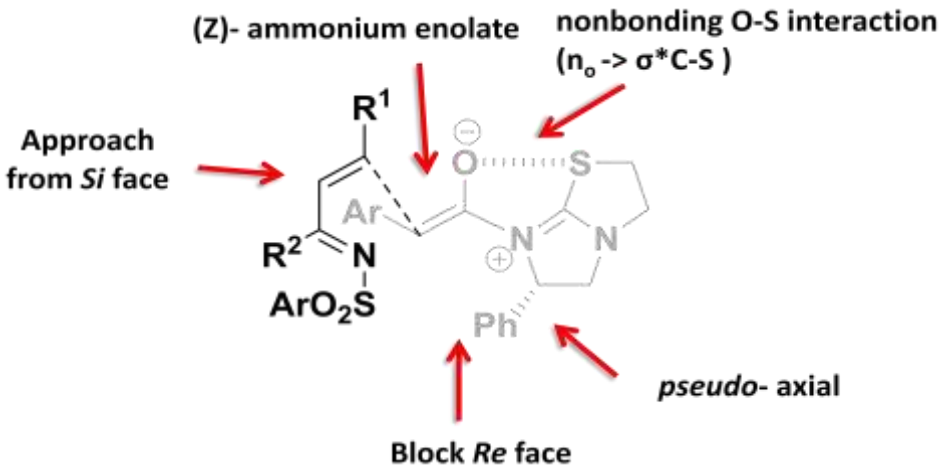


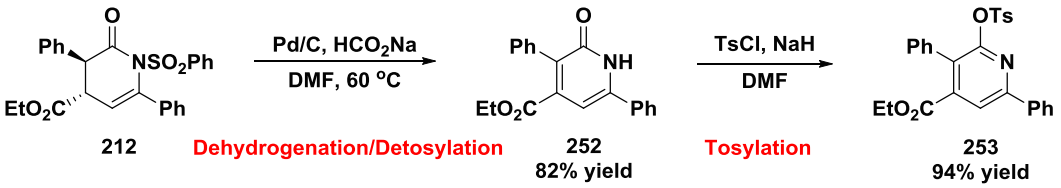
Figure 2.9 The Michael addition transition state

2-10. Derivatisation

As having prepared the dihydropyridinone successfully, we were interested in examining a range of derivatisations into functionalised products.

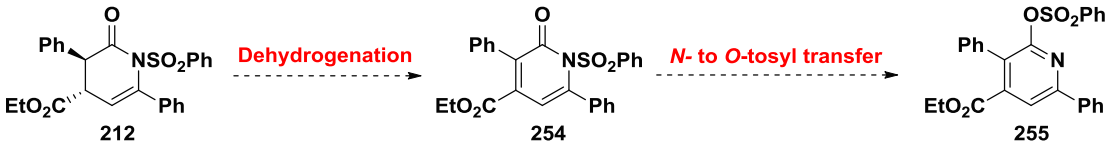
2-10-1. Dehydrogenation/desulfonylation and tetra-substituted pyridine

Dehydrogenation/desulfonylation of the model dihydropyridinone can be carried out in a one-pot reaction by treatment with palladium on carbon and sodium formate in DMF, resulting in 2-pyridone **252** in 82% yield. This pyridone could be *O*-tosylated, by the treatment with sodium hydride and tosyl chloride in DMF, to form the highly functionalised *tetra*-substituted pyridine **253** in two steps and 94% yield (Scheme 2.33).



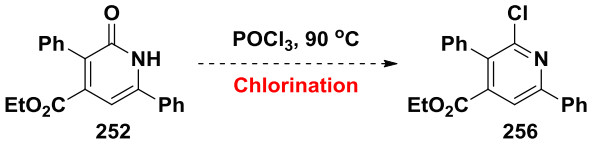
Scheme 2.33 Pyridone and pyridine synthesis

Next, dehydrogenation was investigated as it could be a pathway transferring dihydropyridinone **212** directly to pyridine **253** in one step *via* the spontaneous *N*- to *O*-tosyl transfer of intermediate pyridone **254** (Scheme 2.34). However, the model dihydropyridinone with various dehydrogenating reagents such as 10% palladium on carbon (Pd/C), magnesium dioxide (MnO_2), chloranil and DDQ unfortunately gave no reaction. This observation suggests dehydrogenation could not happen without desulfonylation first.



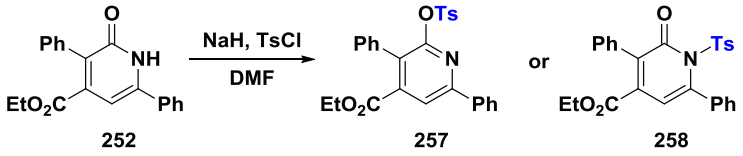
Scheme 2.34 Pyridine synthesis *via* dehydrogenation then spontaneous *N*- to *O*-tosyl transfer

This observation suggests dehydrogenation could not happen without desulfonylisation first. Pyridone **252** was also reacted with phosphorous oxychloride ($POCl_3$) to form the 2-chloro pyridine **256**, but the crude contained more than three different products which could not be isolated by flash column chromatography (Scheme 2.35).



Scheme 2.35 Chlorination

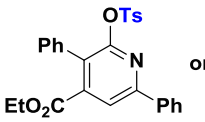
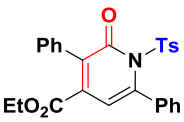
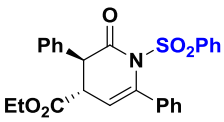
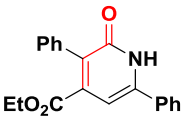
The product of tosylation of pyridine has been assigned as the *tetra*-pyridine **257**. However, formation of the isomer, *N*-tosyl pyridone **258**, was also possible (Scheme 2.36). In order to determine the structure, various spectroscopic methods were used.



Scheme 2.36 The potential product of tosylisation

Comparing with the IR data with other similar structures (Table 2.8), the model dihydropyridinone **212** and the dehydrogenation pyridone **252** all have peaks around 1710-1725 cm^{-1} due to the carbonyl C=O stretch. Pyridone also has a strong signal at 1629 cm^{-1} due to the α,β-unsaturated C=O motif. Consequently, if the tosylated product is pyridone, there should also be a strong signal around 1629 cm^{-1} for the α,β-unsaturated C=O motif; however, only a signal at 1718 cm^{-1} is observed.

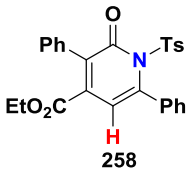
Table 2.8 The IR Data Comparisaion of Various Heterocycles.

	 **257**	 **258**	 **212**	 **252**
IR (cm^{-1})	1718		1722	1714 1629

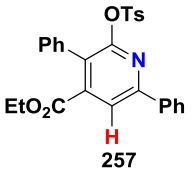
The structures were also investigated by NMR spectroscopic analysis and the structure predicted by NMR simulation. The computational calculations show pyridine **257** has lower energy (− 84.49 Kj/mol) than pyridone **258** that make the pyridine **257** more thermodynamically sTable (Table 2.9). Comparing the experimental NMR data with the

simulation NMR data from three different databases, DET, ACD and Mnova, which have been listed in Table 2.9, the ^{15}N NMR chemical shift orediction of pyridine from the databases is average 286.7 ppm, which is in close agreement to the experiment result of 286.7 ppm. On the other hand, pyridone is calculated around 202.5 ppm. The ^{1}H NMR shift of the indicated C(5) proton is 7.99 ppm by experiment which is located in the aromatic region as matched to pyridine, with an average calculated value of 7.92 ppm. The ^{13}C NMR of C(5) position of pyridine **257** is also closer to the experimental finding, with the calculated average of 120.0 ppm compared with 118.1 ppm experimentally. In all cases (^{15}N, ^{1}H and ^{13}C NMR) the simulation of pyridine isomer is closer to the experimental result, which gives the confidence in the assignment of pyridine **257**.

Table 2.9 Comparison of chemical shift calculation of pyridone 258 and pyridine 257



258



257

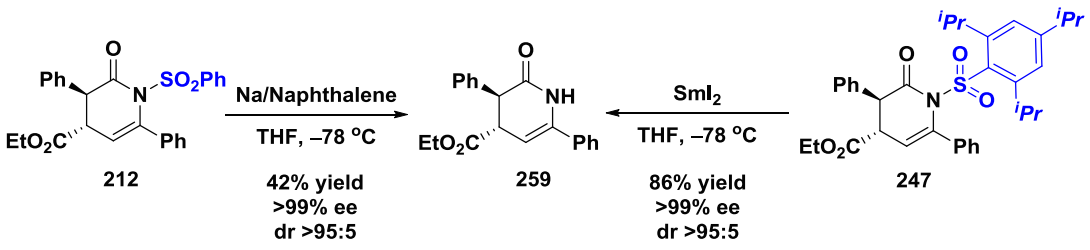
	Pyridone 258	Pyridine 257	Experimental
Rel. E[Kj/mol]	0	-84.49	
DFT- ^{15}N (ppm)	240.7	293.4	
ACD- ^{15}N (ppm)	195.8	287.9	**284.7**
Mnova- ^{15}N (ppm)	171.8	278.7	
DFT- ^{1}H, C(5)*H* (ppm)	5.80	7.87	
ACD- ^{1}H, C(5)*H* (ppm)	6.78	8.51	**7.99**
Mnova- ^{1}H, C(5)*H* (ppm)	6.37	7.39	
DFT- ^{13}C, *C*(5) (ppm)	111.9	121.4	
ACD- ^{13}C, *C*(5) (ppm)	99.7	116.5	**118.1**
Mnova- ^{13}C, *C*(5) (ppm)	112.9	122.0	

In the end, a suitable crystal of sulfonylation product **257** was obtained and has been examined *via* X-ray crystallography. This allowed the structure to be unambiguously confirmed as pyridine **257** (Figure 2.10).

Figure 2.10 Crystal structure of pyridine **257**

2-10-2. Desulfonylation

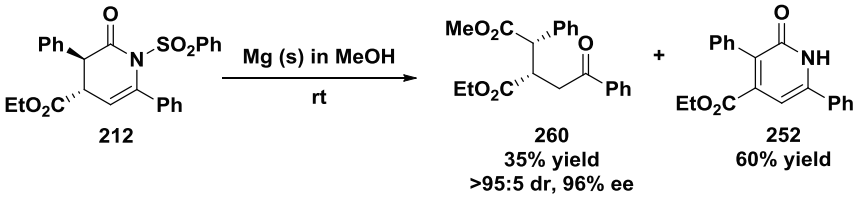
The parent dihydropyridinone can be desulfonylated *via* treatment with sodium/naphthalene at -78 ˚C to give product **259** that crystallised after flash column chromatography to give excellent >99% ee and a single diastereoisomer in 42% yield. Alternatively, samarium iodide was used to remove the triisopropylbenzensulfonyl group, giving the desulfonyl product **259** as a single diasteromer with excellent enantioselecticity and good yield (>99% ee and 86% yield) (Scheme 2.37). Both desulfonylation methods provide product **259** in excellent diastereo- and enantiopurity .



Scheme 2.37 Desulfonylation of dihydropyridinones

2-10-3. Desulfonylation and ring opening

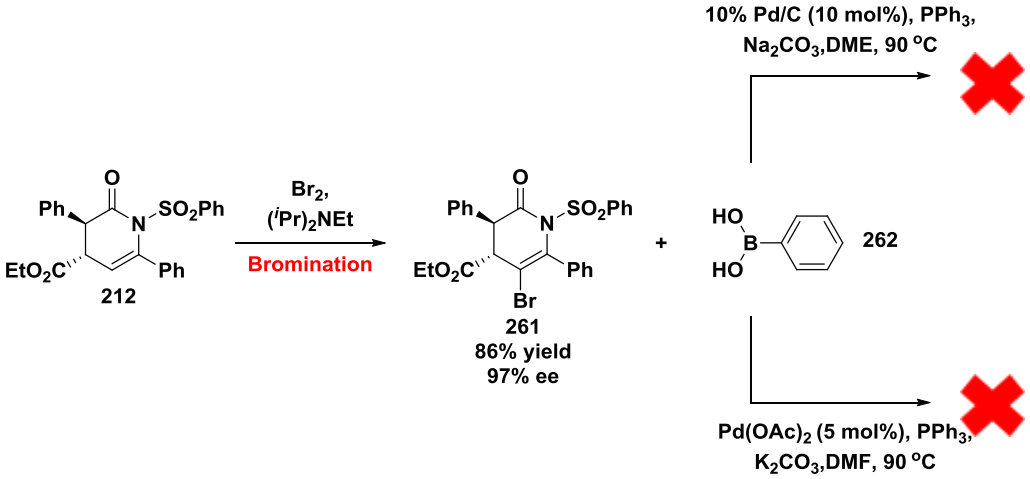
Magnesium/MeOH as a one-electron reducing agent has been applied in the literature for reductive cyclisation, conjugated double bond reduction, deprotections,[77] desulfonylations, and related process.[78] Previous studies have shown that magnesium/MeOH can also remove the sulfonyl group from the nitrogen in various ring sizes (4-7 membered ring) of cyclic amines[79–81] or from the nitrogen of amides.[82] Therefore, treatment of dihydropyridinone **212** with magnesium/MeOH resulted in formation of ketone **260** *via* desulfonylation and ring-opening, in 35% yield and 96% ee (Scheme 2.38). Pyridone **252** was also formed and able to isolate in 60% yield.



Scheme 2.38 Reduction with magnesium/MeOH

2-10-4. Bromination and Suzuki reaction

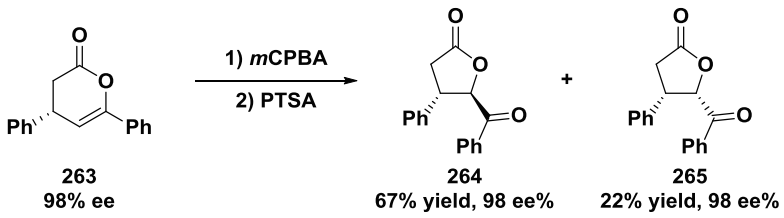
Bromination can also be demonstrated with dihydropyridinone by treatment with bromine and $(^{i}Pr)_2NEt$ to give brominated product **261** in 87% yield with 97% ee as a single diastereoisomer. We anticipated that brominated product could potentially being further modified *via* Suzuki coupling. Brominated dihydropyridinone **261** was treated with phenyl boronic acid **262** catalysed by 10 mol% Pd/C in DME and refluxed at 90 ˚C. The brominated dihydropyridinone was fully consumed by TLC analysis in two hours, however, the crude showed a complex mixture by ^{1}H NMR spectroscopic analysis and there were no sign of the desired product. The reaction was also tried using 5% $Pd(OAc)_2$ but again none of the desired product was formed and so this process was abandoned (Scheme 2.39).



Scheme 2.39 Bromination and the future Suzuki reaction

2-10-5. Epoxidation

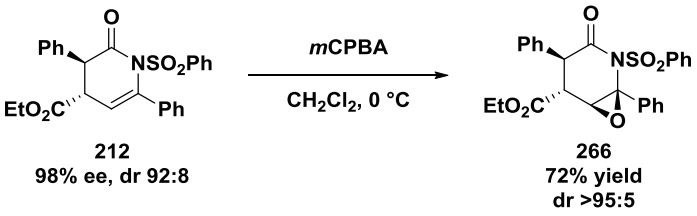
The next idea was to treat the dihydropyridinone **212** with *m*CPBA then PTSA to give the γ-lactone **264** or **265** in a one-pot reaction as the similar example which has been demonstrated by Chi and co-workers.[83] Chi showed that treatment of δ-lactone **263** with *m*CPBA then PTSA gave two separable diastereomers γ-lactone **264** and **265** without compromising enantioselectivity in good overall yield (Scheme 2.40).



Scheme 2.40 γ-Lactone formation in Chi's approach.

However, the reaction with dihydropyridinone **212** did not work as planned, although it can be oxidised to form the epoxide **266**, adding PTSA was found to decompose the epoxide product. The epoxide was sensitive to acidic conditions and it did not survive in $CDCl_3$ when used for ^1H NMR analysis. The epoxidation worked much slower than expected and the

reaction mixture had to be left at 0 ˚C for 24 hours. The epoxide **266**, which has four contiguous stereocentres, was obtained as single diastereomer with 72% yield (Scheme 2.41).



Scheme 2.41 Epoxidation

To assign the configuration of the epoxide, 2D nOe spectroscopic analysis was applied to determine the relative configuration between H^5 and H^6. The ^1H NMR spectrum of the epoxide **266** has been fully assigned for H^4 (4.02 ppm), H^5 (3.13 ppm) and H^6 (3.79 ppm) and is shown in Figure 2.11

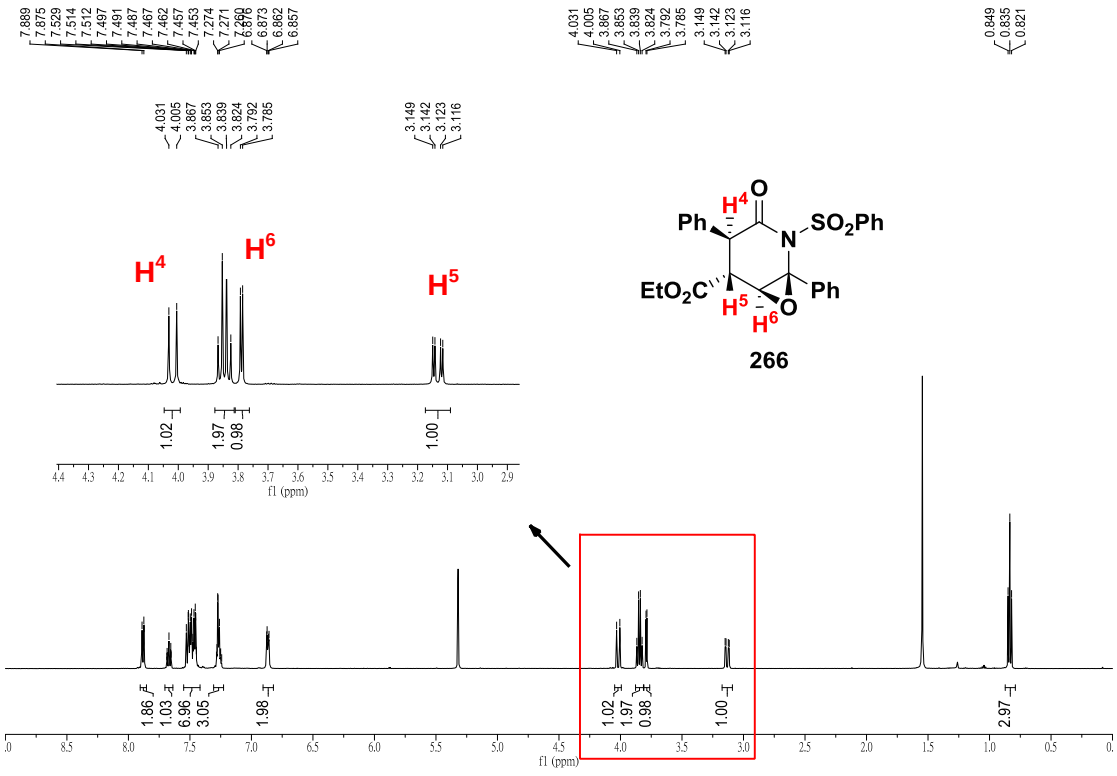


Figure 2.11 NMR spectrum of epoxide **266**

To find the relative configuration between H^5 and H^6, two nOe spectra have been performed. The first nOe spectrum irradiated H^6 peak at 3.79 ppm, and showed nOe correlation with H^4 peak, meaning H^6 and H^4 are close in space and are on the same face of the molecule (Figure 2.12). Correlation with H^5 was also observed, which would be expected from protons on adjacent carbon atoms.

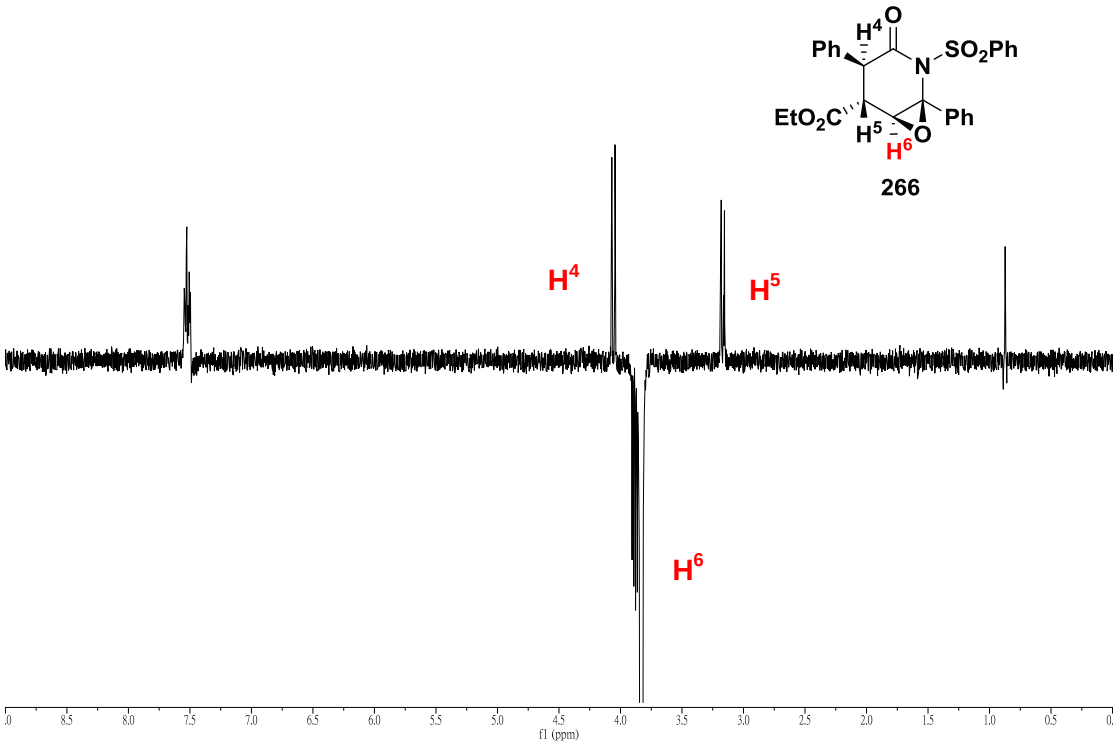


Figure 2.12 nOe analysis of epoxide with aadiated the H^6

For comparison, the second nOe spectrum has irradiated the H^4 peak at 4.02 ppm. Again, the H^6 peak has been observed, as well as the H^5 peak which is adjacent to H^4 (Figure 2.13).

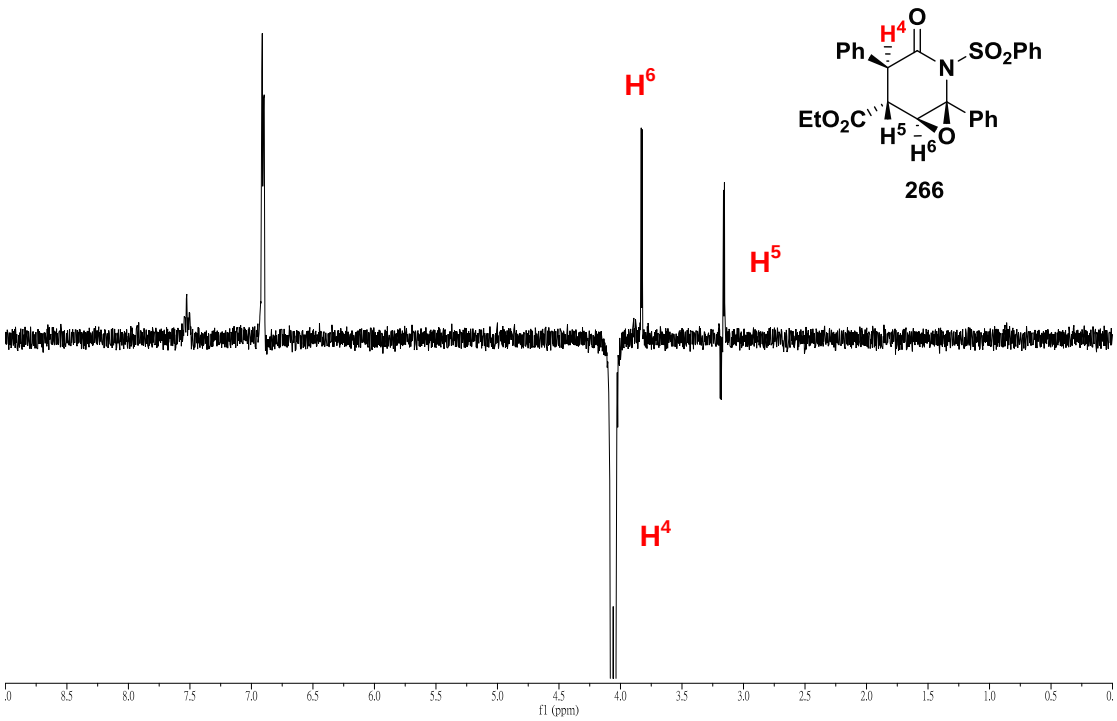


Figure 2.13 nOe analysis of epoxide **266** with the H^4 radiated

This is consistent with the epoxide ring being on the same face as the phenyl group on the *C*(4) position, and the structure has been assigned. further unambiguous evidence for this structure was obtained by X-ray crystallography, with the absolute configuration confirmed as 1*S*,4*S*,5*R*,6*S* (Figure 2.14).

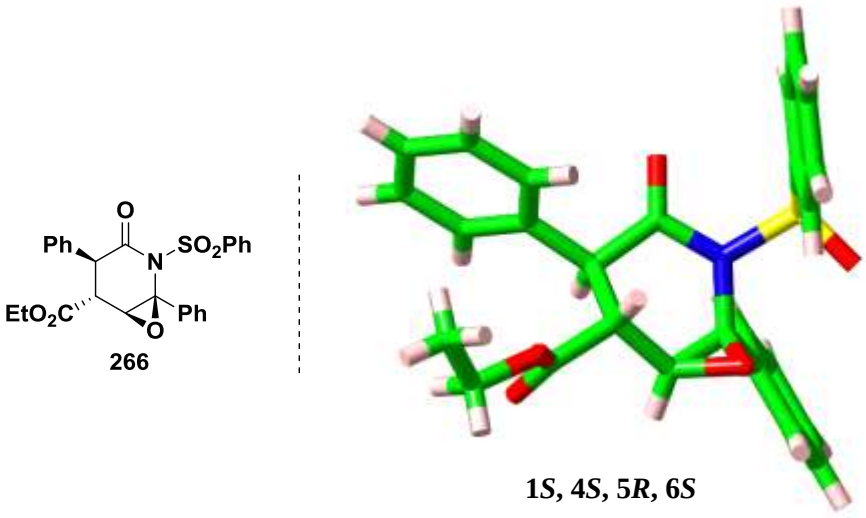
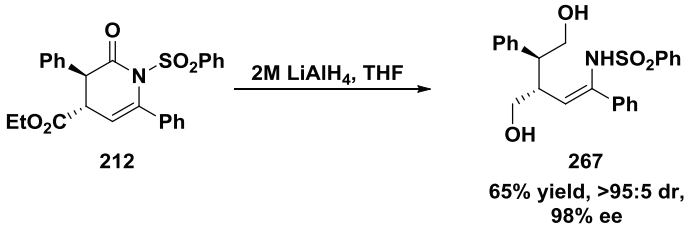


Figure 2.14 Crystal structure of epoxide

Due to the separation issues on chiral HPLC, the enantiomeric excess of epoxide could not be determined. However, the enantioselectivity of epoxide is assumed to be identical to the starting material dihydropyridinone **212** (98% ee).

2-10-6. Reduction

The model dihydropyridinone **212** contains both ketone and ester functional groups, which can be reduced by treatment with two equivalents of 2M $LiAlH_4$ in THF solution at 0 ˚C. The reduction was completed in one hour by TLC analysis. The reaction mixture was quenched with 0.1 M HCl then extracted with diethyl ether immediately. $NaBH_4$ can also provide the same result. From the crude ^1H NMR spectra, it showed both the amide and ester functional groups were reduced; however, the sulfonyl group has remained on the nitrogen. The dihydropyridinone **212** had been ring-opened to give the acyclic enamine-diol product **267** with the sulfonyl amine product and two hydroxyl groups. Flash column chromatography gave a single diastereomer of dihydroxyl *N*-sulfonyl amine **267** with 98% ee and 65% yield (Scheme 2.42). It is surprising that the *N*-sulfonyl enamine is retained in the molecule and can be isolated from the silica column without being hydrolysed. The isolated yield is good suggested the significant stability of molecule with this functionality



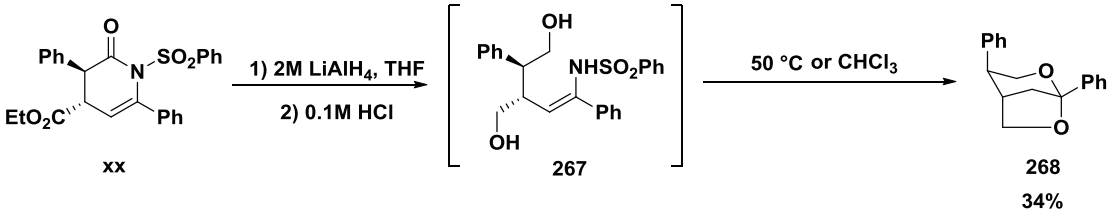
212 **267**

65% yield, >95:5 dr, 98% ee

Scheme 2.42 Reduction with $LiAlH_4$

The bicyclic ketal formation was also observed after reduction of dihydropyridinone with two equivalents of 2 M $LiAlH_4$ in THF solution at 0 ˚C. The reaction was quenched with 0.1 M

HCl, stirred for one hour and extracted with CH_2Cl_2. The dihydroxyl *N*-sulfonyl amine **267** was observed in the crude ^{1}H NMR spectra at this stage. The crude was stirred with $CHCl_3$ overnight to give the bicyclic ketal **268**. Following flash column chromatography gave a single diastereomer of bicyclic ketal in 34% yield after chromatography (Scheme 2.43).



Scheme 2.43 Bicyclic ketal formation

The key step for formation of this bicyclic ketal is stirring the reaction mixture with 0.1 M HCl for no less than an hour. Without this step, ^{1}H NMR spectrum analysis shows the presence of the dihydroxyl product **267**, which could not be cyclised through heating or stirring with chloroform. Hence, 0.1 M HCl is needed to promote cyclisation into the ketal. The relative configuration has been confirmed via X-ray crystallography (Figure 2.15).

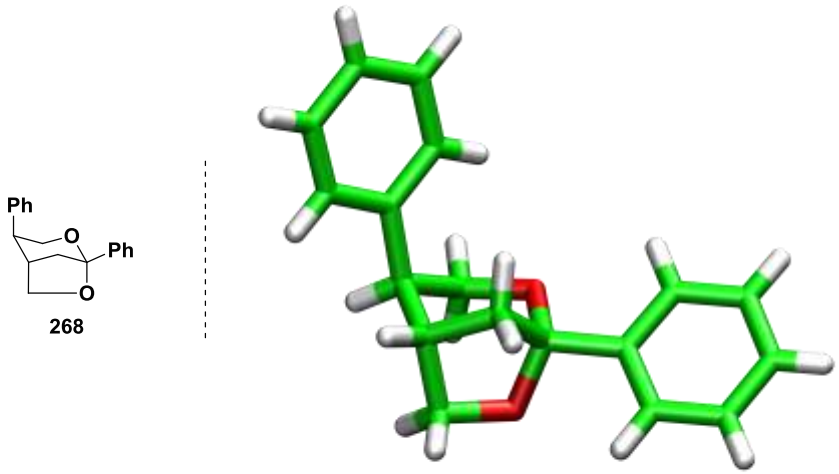
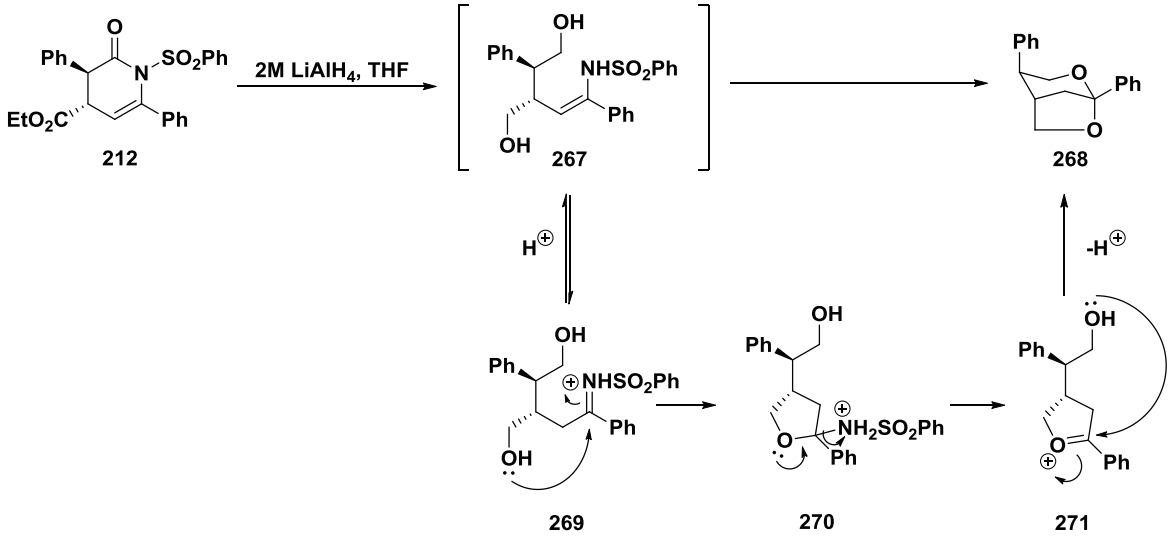


Figure 2.15 Crystal structure of bicyclic ketal

The proposed mechanism of bicyclic ketal contains two cyclisation, the five member ring closed first to eliminate the sulfonamide forming the oxonium ion that is trapped in the formation of a six membered ring to obtain the bicyclic ketal product (Scheme 2.44).

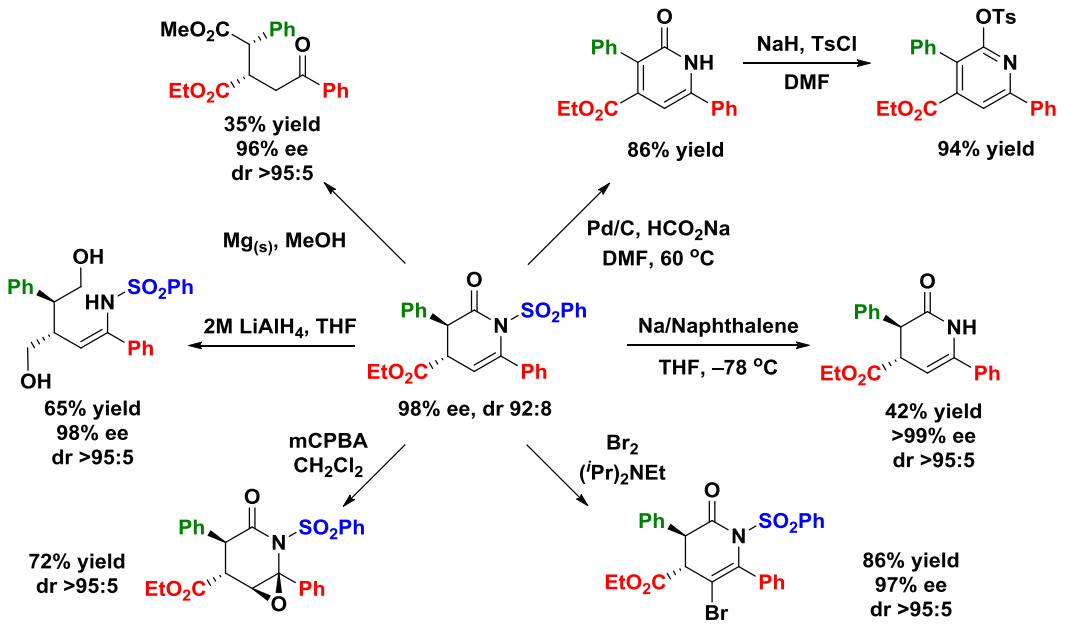


Scheme 2.44 The proposed mechanism of bicyclic ketal formation

2-11. Conclusion

In conclusion, this project has developed a one-pot methodology using cheap and easy handled acetic acids *via* isothiourea catalysis to synthesise highly functionalised dihydropyridinones with excellent diastereo- and enantioselectivities. This methodology can tolerate not only electron withdrawing and donating substituted arylacetic acid but also the alkene acetic acid. Various sulfonyl substituted ketimines also give good yield without compromising the stereocontrol.

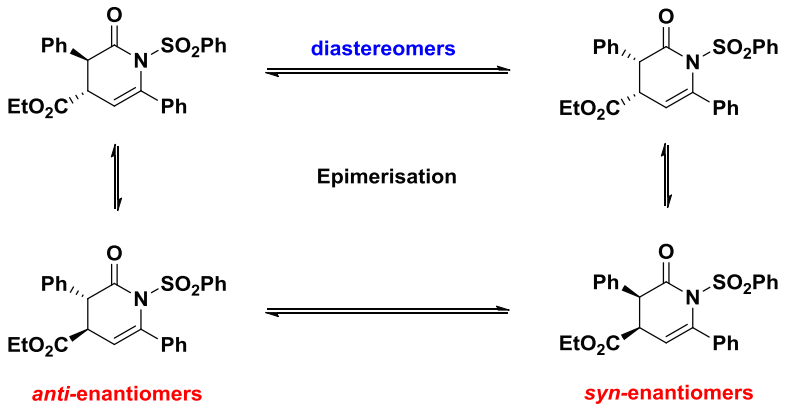
The model dihydropyridinone **212** has been successfully derivatised in a wide range of transformations, such as pyridine formation, bromination, epoxide formation, in good yield without compromising the stereochemical integrity of the products (Scheme 2.45).



Scheme 2.45 The summary of derivatisation

2-12. Future Works

During the optimisation of this process, the results of using different equivalents of starting material acetic acid affected the diastereo- and enantiocontrol noticeably. Using two equivalents of acid accelerated the reaction when compared with one equivalent of acid. The reaction time was shortened from three hours to one hour. One possibility may be the reaction conditions facilitated epimerisation, hence, lowering the diastereoselectivity (Scheme 2.46).



Scheme 2.46 Epimerisation

However, re-treating the product with (−)-tetramisole·HCl and base did not change the diastereoselectivity; instead the product started to decompose. Hence, it could be other factors from in the original reaction that affect the diastereoselectivity. Therefore, more in-depth studies of this epimerisation are required.

To date, the examples which have been demonstrated *via* isothiourea-mediated form a single *N*-heterocyclic molecule in one-pot reactions. However, there are known natural products and also synthetic products that have multi-ring structures, such as spirocyclic oxindole,[84–88] with 6-membered ring motifs, or other polycyclic structures (Figure 2.16).[89,90]

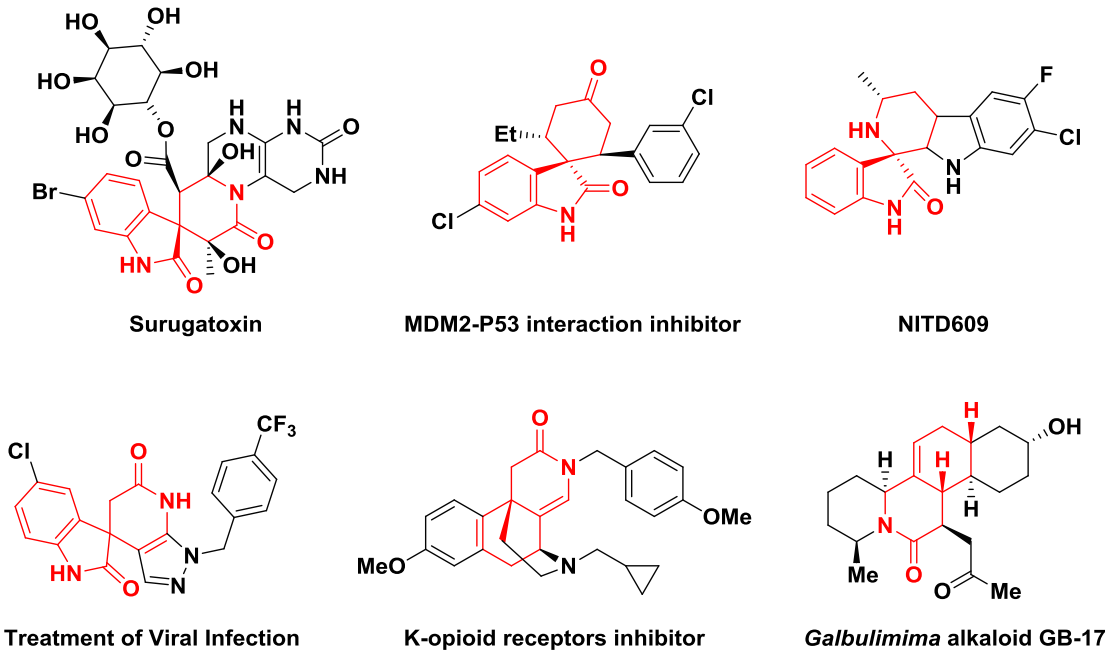
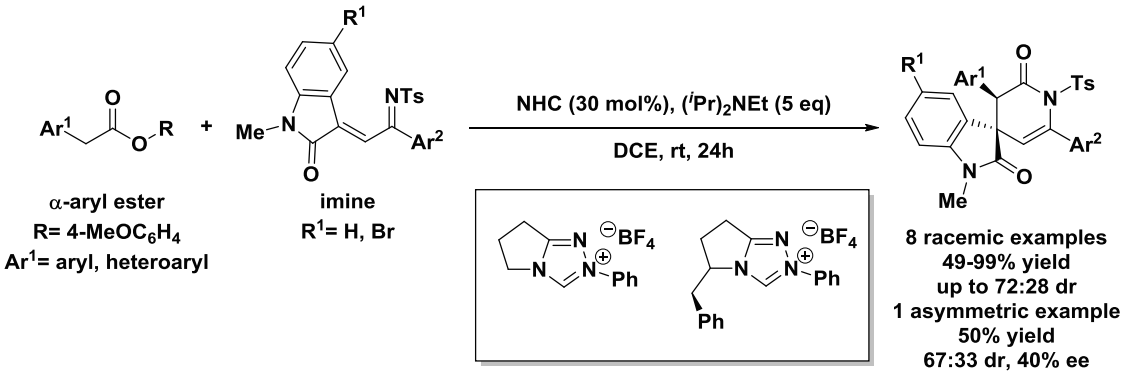


Figure 2.16. Selected natural and synthetic products with biological activities.

In 2013, Chi and co-workers has reported using α-aryl ester and unsaturated imine catalysed by NHC (in the box) to access spirocyclic oxindoles (Scheme 2.47). However, the work resulted in good yield but poor stereocontrol with mainly racemic examples. Due to the steric nature of quaternary centre, the methodology with high diastereo- and enantioselectivities still

remain challenging.



Scheme 2.47 Spirocyclic oxindoles formation *via* NHC catalysis

There are other well developed ketimines in the literature (Figure 2.17). Carrying these into the isothiourea catalysis reaction with commercially available acetic acids, theoretically, will result in highly functionalised spirocyclic oxindoles or bicyclic products in an efficient one-pot reaction (Scheme 2.48).

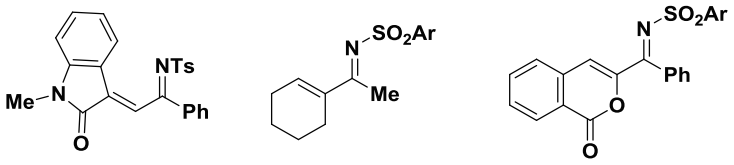
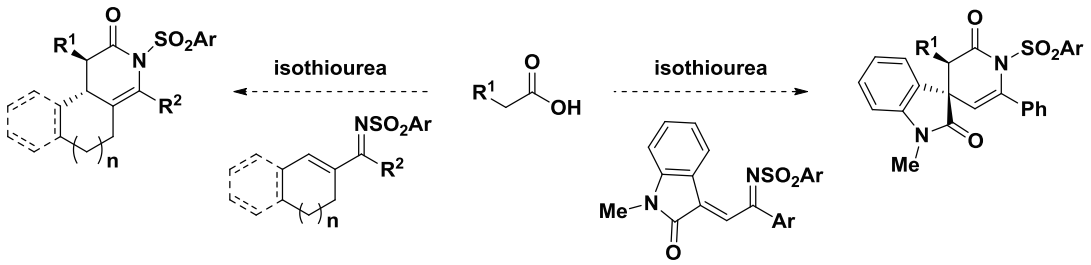


Figure 2.17 Selected potential ketimines from literatures

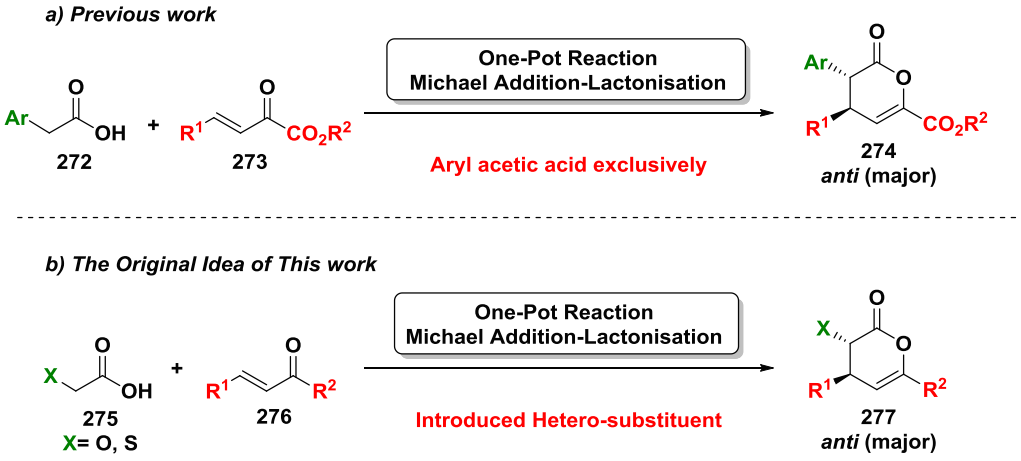


Scheme 2.48 Proposed reactions

Chapter 3. Isothiourea-Mediated Synthesis of Heterocycles

3-1. Introduction and initial aims

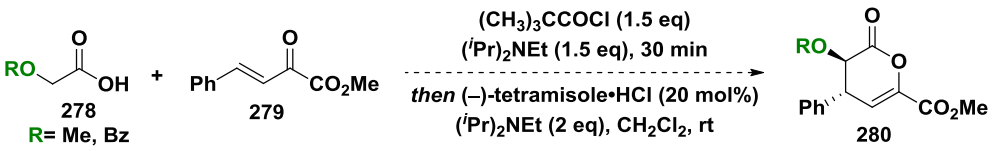
Previous work from the Smith group has developed an efficient asymmetric one-pot intermolecular Michael addition-lactonization process from aryl carboxylic acids **272** exclusively and α,β-unsaturated carbonyl compounds **273** that proceeds *via* an ammonium enolate intermediate (Scheme 3.1, a).[40] To extend this methodology, we wished to introduce heteroatom containing acetic acids **275** to further probe the activity of the ammonium enolate intermediate and lead to functional products (Scheme 3.1, b).



Scheme 3.1 Isothiourea-mediated one-pot synthesis of heterocycles

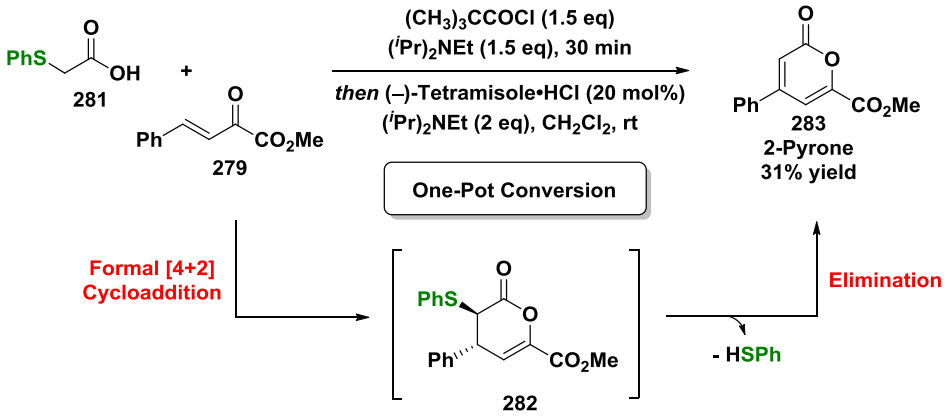
3-1-1. Initial studies

Initial studies were carried with commercially available oxygen containing acetic acids, methoxyacetic acid and benzyloxyacetic acid with α,β-unsaturated ketoester **279** using the commercial available isothiourea catalyst, (－)-tetramisole·HCl. However, under standard condition, no oxygen substituted lactone **280** was observed upon using either methoxyacetic or benzyoxylacetic acid, only unreacted starting material ketoester returned (Scheme 3.2).



Scheme 3.2 The initial studies with oxygen containing acetic acids

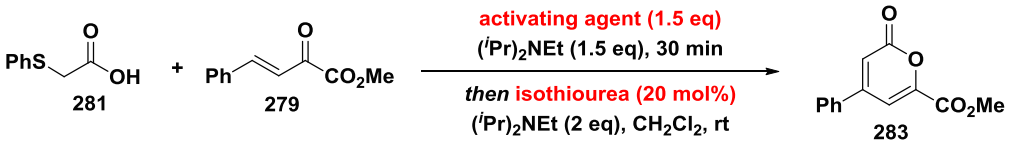
The same reaction condition has also been repeated with commercially available (phenylthio)acetic acid **281**, the sulfur substituted dihydropyridinone **282** was not observed. However, the major product isolated from these reactions was 2-pyrone **283** in 31% yield, presumably resulting from elimination of PhSH from initially formed lactone **282** (Scheme 3.3).



Scheme 3.3 The test results with (phenylthiol)acetic acid and α,β-unsaturated acceptors

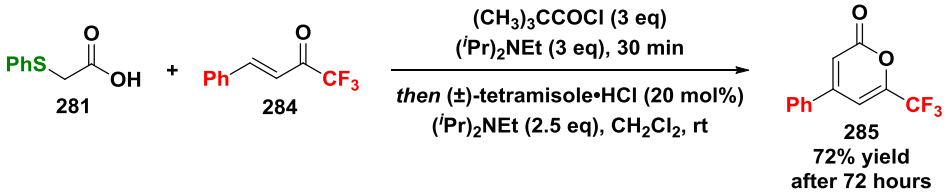
Next, (Phenylthio)acetic acid was further examined as an ammonium enolate precursor to understand and optimise the elimination process for 2-pyrone synthesis. Modification of the reaction conditions by varying the catalyst or using different activating agents such as benzoic anhydride, all lead to the same eliminated product in modest yield (26-35%, Table 3.1, Entries 1-3). These experiments demonstrated the elimination step could not be stopped due to neither using the different isothiourea catalysts nor activating agents.

Table 3.1 The Initial Studies with Ketoeaster 279



Entry	Isothiourea cat	Activating agent	t (hr)	Yield (%)
1	**(－)-Tetramisole·HCl**	**pivaloyl chloride**	**18**	**35**
2	(R)-Benzotetramisole	pivaloyl chloride	18	27
3	(－)-Tetramisole·HCl	benzoic anhydride	18	26

However, after initial attempts at optimisation with acceptor **279**, it was unable to raise the yield of pyrone **283** to a promising level. Therefore, an alternative trifluoromethyl enone **284** was tested. CF_3 group was examined and provided promising results, with 72% isolated yield of pyrone **285** obtained after 72 hours (Scheme 3.4).



Scheme 3.4 Pyrone synthesis with α,β-unsaturated trifluoromethyl enone **284**

3-1-2. Previous studies on 2-pyrone synthesis

2-Pyrones (and commonly called 2H-pyran-2-ones, 2-pyranones, α-pyrones)[91] contain a oxygen atom, a carbonyl functionality on *C*(2) and a diene motif, in other words, it is an unsaturated cyclic ester. The aromatic character of 2-pyrone allow it readily undergo electrophilic substitution, for example, sulfonations and halogenations. The aliphatic character of 2-pyrone allow it to participate in Diels-Alder reaction as a diene.[92] Thus allows the 2-pyrone motif to be used a pathway toward other aromatics. 2-Pyrone is also the common

motif found in natural products. For example, Proscilardein **288**, a cardiac glycoside classified in Bufadienolides class contains a steroid structure and 2-pyrone motif can also be obtained from the plant of genus *Scilla* and in *Dermia maritima*.[93] Compounds of the bufadienolides class have been employed as treatment for heart failure and cardiac arrhythmia and also in several different types of cancers by exhibiting cytotoxic activity (Figure 3.1).[92,93]

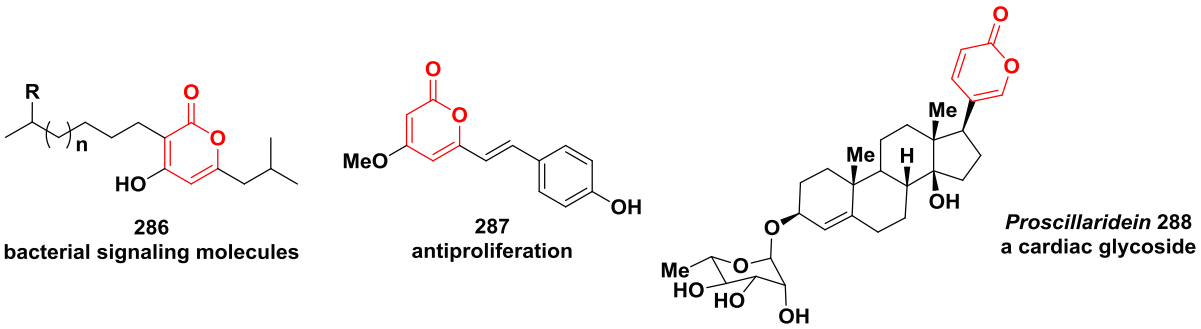


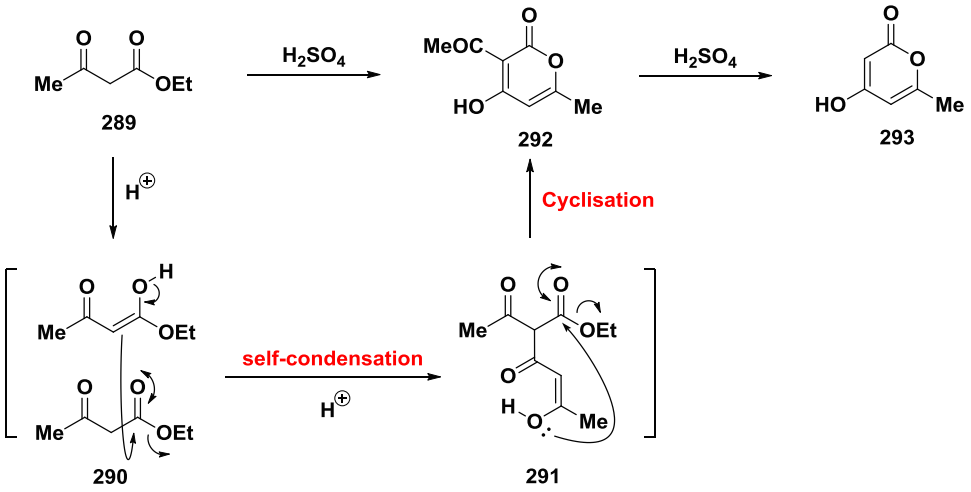
Figure 3.1 Selective 2-Pyrone Examples

2-pyrones substituted with styryl groups, such as compound **287**, isolated from ethanolic extracts of the seed of *Alpinia bleharocalyx* have demonstrated excellent activity in antiproliferation.[94] Several 2-pyrones **286** with long alkane chain at *C*(3) have recently identified as a bacterial communication signal between PluR-Ppys system in *P. luminescens*.[95]

Although various 2-pyrones containing compounds have been successfully isolated from plant origins and animal sources[92] and their bioactivities have been identified for important medical therapies, the convenient and highly functionalised synthesis of 2-pyrones is not much explored yet. The most common route to 2-pyrone synthesis is condensation/cyclisation of β-ketoester. Alternative other methods can be synthesised 2-pyrones from gold-catalysed dimerisation of propiolic acid or gold-catalysed coupling reaction then following the cyclisation.

3-1-2-1. *Via* condensation/cyclisation reaction

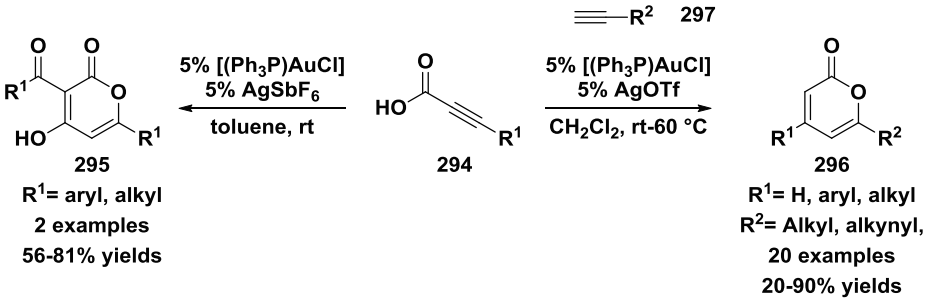
In the presence of sulfuric acid, ethyl acetoacetate **289** undergoes self-condensation to form the adduct **291** then following by cyclisation to obtain pyrone **292** The ester group can be decarboxylated by treating with more sulfuric acid afford pyrone **293** (Scheme 3.5).[92,96,97]



Scheme 3.5. The acid-catalysed condensation/cyclisation

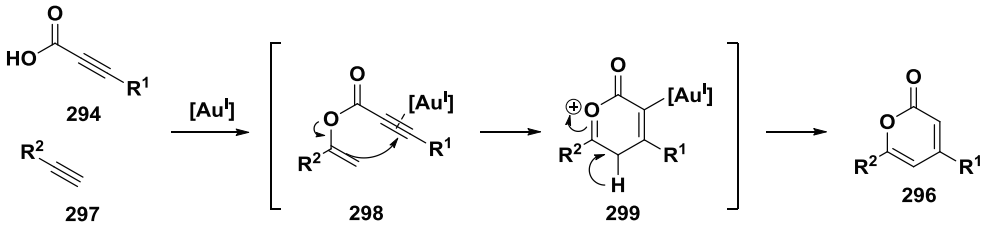
3-1-2-2. *Via* gold-catalysis

Schreiber and co-workers[98] have reported an alternative methodology to synthesise analogues of pyrone **295** and **296** from propiolic acid **294** *via* gold-catalysis. Using 5% $[(Ph_3P)AuCl]/AgSbF_6$ in the reaction condition gives the dimerisation product **295** in good yield. However, employing 5% $[(Ph_3P)AuCl]/AgOTf$ results pyrone **296** formation with low to excellent yield through gold-catalysed coupling reaction (Scheme 3.6).



Scheme 3.6 Syntheses of 2-Pyrone *via* Gold-Catalysed Coupling Reaction

This process is presumed to proceed by initial gold(I) catalysed form an intermediate **298** by an intermolecular coupling. The intermediate then undergoes a 6-*endo* type cyclisation to afford oxocarbenium intermediate **299**, which following deprotonation and proto-demetalation results in the desired product **296** (Scheme 3.7).

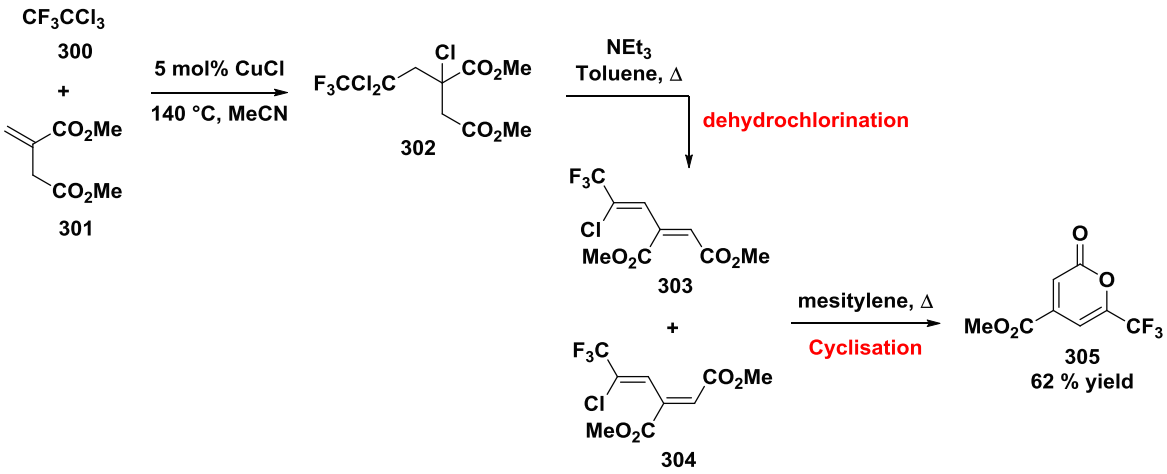


Scheme 3.7 The proposed mechanism of gold-catalysed coupling reaction

Alternative other catalytic methodologies have been reported for 2-pyrone synthesis, for example, base-catalysed Michael addition-lactonisation of 1,2-allenyl ketones by K_2CO_3,[99] rhenium-catalysed sequential addition-cyclisation of 1,3-dicarbonyl compounds *via* $ReBr(CO)_5$ [100,101] and palladium-coupling Stille reaction/heterocyclisation.[102] However, to date, organocatalysis has not been much applied in planar molecule synthesis, particularly for pyrone synthesis.

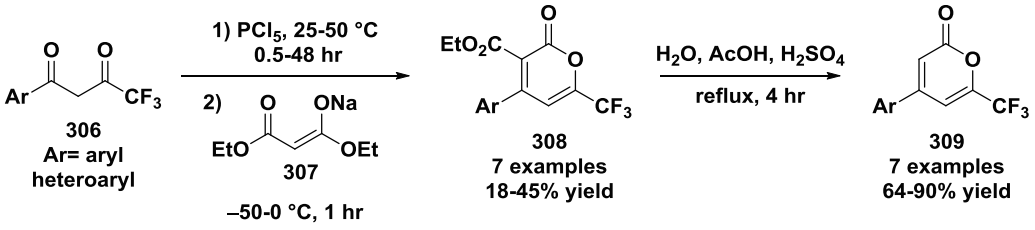
3-1-3. Synthesis of trifluoromethyl substituted 2-pyrones

From the literature, few syntheses of 2-pyrones bearing the biologically interesting CF_3 group have been developed. To prepare several CF_3-containing bioactive compounds, Martin *et al*[103] applied Cu(I)-catalytic approach for trifluoromethyl substituted 2-pyrones synthesis. Reacting **300** and dimethyl itaconate **301** at 140 ˚C generated adduct **302** and then following double dehydrochlorination by refluxed in NEt_3 resulting in two isomers **303** and **304**. These isomers can then cyclise to form 2-pyrone **305** in 62% yield (Scheme 3.8).



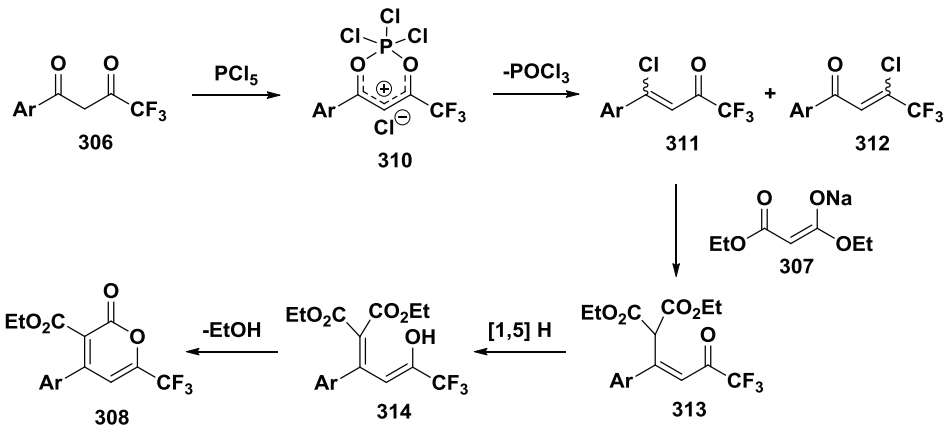
Scheme 3.8. The Cu(I)-catalytic approach for 2-pyrone synthesis.

Usachev *et al*[91,104] have also presented a synthetic route to CF_3 substituted pyrone synthesis from *in situ* prepared α,β-unsaturated enone. Diones **306** was first reacted with PCl_5 then with sodium diethyl malonate **307** resulting in pyrone **308** in low to moderate yields. Pyrone underwent decarboxylation process by refluxing in aqueous acetic acid with addition of H_2SO_4. Pyrones **309** were isolated in good yields (Scheme 3.9).



Scheme 3.9 The Synthesis of 2-Pyrone

Dione **306** was firstly chlorinated by treatment of PCl_5 to generate two α,β-unsaturated chloro ketone regioisomers **311** and **312**. α,β-Unsaturated chloro ketone **311**was more favoured to react with sodium diethyl malonate through nucleophilic addition to form intermediate **313**, which undergoes [1,5] H-transfer to generate intermediate **314**. Finally, cyclised intermediate afforded pyrone **309** (Scheme 3.10).

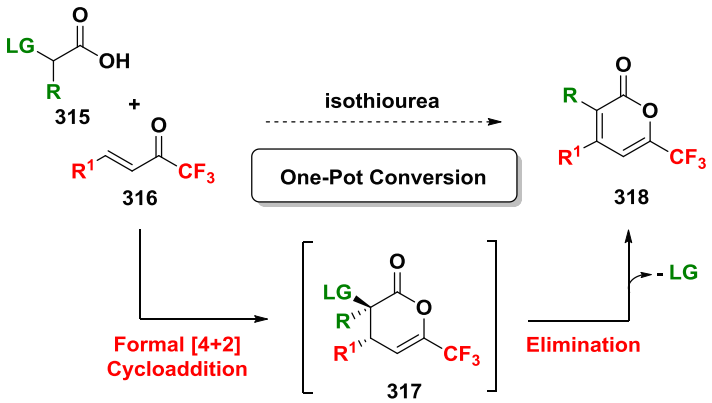


Scheme 3.10 Proposed Mechanism of Pyrone Synthesis

Both methods used similar strategies to synthesis 2-pyrone by synthesed α,β-Unsaturated intermediate *in situ*. However, it leads to form different regio-isomeric intermediates and unusually only one is favoured the other to undergo a cyclisation forming the desired pyrone product. Hence, in most cases, pyrones were obtained with low yield.

3-2. The aim of this project

Building on this discovery of pyrone formation and the interest within this motif, this project aimed to synthesise a range of planar, 2-pyrones **318**, from acetic acid deriverties bearing a potential leaving group and a CF_3-enone **316** *via* ammonium enolate chemistry (Scheme 3.11).

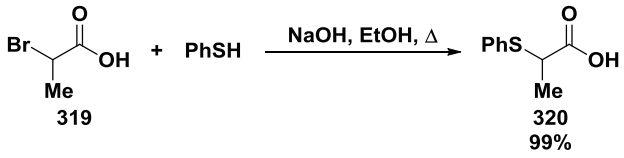


Scheme 3.11 This work

3-3. Starting material preparation

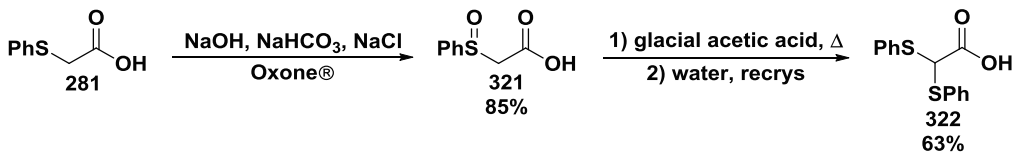
3-3-1. Acetic acid preparation

(Phenylthio)acetic acid, which has been used mainly in this project is commercially available, and applied into the reaction directly without further purification; same as bromoacetic acid, chloroacetic acid and (phenylthio)phenyl acetic acid. 2-(phenylthio)propanoic acid **320**, 2-(phenylsulfinyl)acetic acid **321** and bis(phenylthio)acetic acid **322** were prepared following by literature procedures.[105–107] 2-(phenylthio)propanoic acid **320** was prepared from refluxing 2-bromopropanoic acid, sodium hydroxide and thiophenol in ethanol overnight resulting in excellent yield (99%) (Scheme 3.12).



Scheme 3.12 Synthesis of 2-(phenylthio)propanoic acid **320**

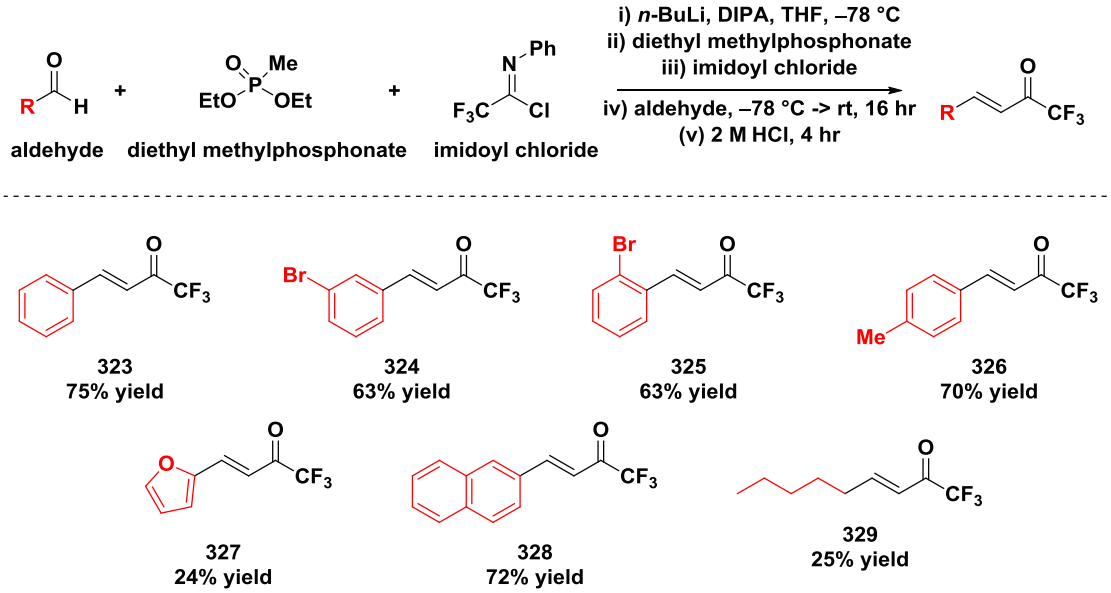
2-(phenylsulfinyl)acetic acid **321** was obtained by oxidation of (phenylthio)acetic acid in Oxone® with 85% yield, the product was pure and applied into reactions directly without any further purification. 2-(phenylsulfinyl)acetic acid could be transferred into bis(phenylthio)acetic acid **322** by refluxed in glacial acetic acid overnight. The crude was washed with water then purified through recrystallisation giving bis(phenylthio)acetic acid in 63 % yield (Scheme 3.13).



Scheme 3.13 Synthesis of 2-(phenylsulfinyl)acetic acid **321** and bis(phenythio)acetic acid **322**

3-3-2. Trifluoromethyl enone synthesis

Various trifluoromethyl enones **323-329** were prepared following the procedure of Zhang *et al.*[108] LDA was formed treating diisopropylamine with ^{n}butyl lithium and diisopropylamine in THF at −78 ˚C, subsequent addition of diethyl methylphosphonate, then nucleophilic addition to imidoyl chloride resulting in a phosphonate intermediate. This intermediate undergoes Horner-Wadsworth-Emmons reaction with different aldehydes to afford various trifluoromethyl enones (Scheme 3.14). Seven examples were prepared following this method including the parent CF_3-enone **323**, *m*- and *o*-bromo **324** and **325**, p-methyl **326**, 2-furan **327**, 2-nathphalene **328** and hexyl **329** substituted enone. *p*-nitro, *p*-bromo substituted and 2-thiophene enones were also applied in this project and were prepared by other Smith group colleagues using the same method.



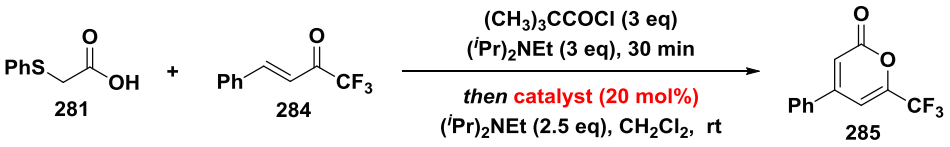
Scheme 3.14 Synthesis of trifluoromethyl enones

3-4. Optimisation

3-4-1. Catalyst screen

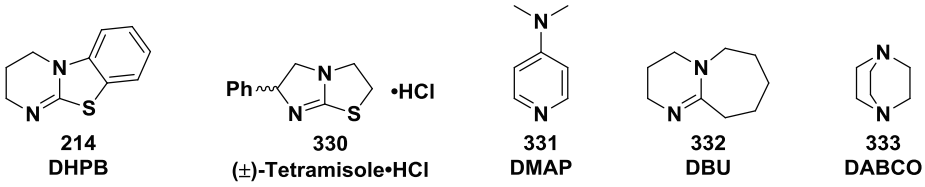
With the promising acceptor, trifluoromethyl enone, in hand, optimisation of the process began with a catalyst screen. A model reaction using (phenylthio)acetic acid **281** and phenyl trifluoromethyl enone **284** was investigated. Various isothiourea catalysts, such as achiral DHPB and commercially available racemic tetramisole·HCl, or alternative nucleophilic catalysts, such as DMAP, DBU and DABCO, were examined to assess their reactivity in this reaction. The results of this screen are shown in Table 3.2. DHPB gave the best yield (68%, Table 3.2, Entry 1). (−)-tetramisole·HCl resulted product in a moderates yield (52%, Entry 2) with remaining enone (24%). DMAP gave a lower isolated yield (34%, Entry 3), however, further investigations with DMAP were conducted, the enone was fully consumed after 24 hr by ^{1}H NMR. DBU and DABCO led to low isolated yields under the reaction conditions described (Entry 4 and 5).

Table 3.2 Catalyst Screen



Entry	Catalyst (20 mol%)	t (hr)	SM (%)[a]	Yield (%)[a]
1	**DHPB**	**24**	**-**	**68**
2	(±)-Tetramisole·HCl	24	24	52
3	**DMAP**	**27**	**-**	**34**
4	DBU	27	41	15
5	DABCO	27	61	9

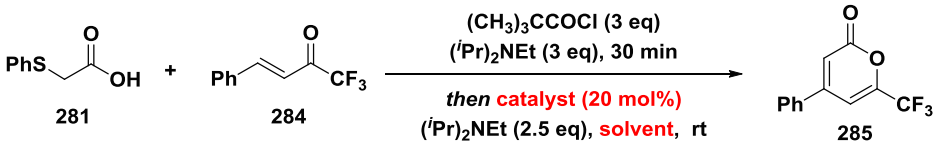
[a]yield has been measured with 1-methyl naphthalene as an internal standard through ^{1}H NMR spectroscopic analysis.



3-4-2. Solvent screen

Next, DHPB and DMAP were examined in a range of solvents, using the model substrates **281** and **284**. Pleasingly, employing DHPB in acetonitrile (MeCN) gave an excellent conversion (96%) by NMR spectroscopic analysis using 1-methyl naphthalene as an internal standard and 88% isolated yield through flash column chromatography (Table 3.3, Entry 3). The yield of the DMAP catalysed reactions was not improved by varying the solvent (Entry 4-6). Therefore, DHPB in MeCN was identified as the optimised catalyst and solvent in this 2-pyrone synthesis.

Table 3.3. Solvent screen



Entry	Catalyst	Solvent	SM (%)[a]	Yield (%)[a]	Isolated yield (%)
1	DHPB	THF	32	54	
2	DHPB	Toluene	44	46	
3	**DHPB**	**MeCN**	**-**	**96**	**88**
4	DMAP	THF	52	27	
5	DMAP	Toluene	40	35	
6	DMAP	MeCN	-	55	50

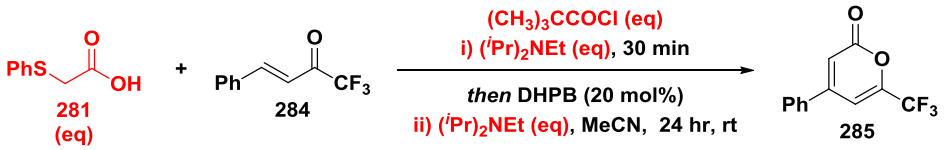
[a] yield has been measured with 1-methyl naphthalene as an internal standard through ^{1}H NMR spectroscopic analysis.

3-4-3. Acid, base and activating agent equivalent screen

So far, the reaction condition used for above screening was with the excess amount of acid (2 eq), base (3 eq *then* 2.5 eq) and additives (3 eq). The possibility of reducing these reagents was next explored and the results displayed in Table 3.4. Using 1 eq of acid resulting in low yield from 37-49% with unreacted starting material enone **284** (Entry 1-3) after 24 hours. Employing 2 eq equivalents of the acid, base and additives of the reaction improved the yield

remarkably and the starting material enone was fully consumed (Entry 4-7). However, The optimised experiments show excess acid (2 eq), base (3 eq *then* further 2.5 eq) and pivaloyl chloride (3 eq) were necessary for obtained high yield (96% by ^{1}H NMR) with 88% isolated yield (Entry 10). In addition, the purification through flash column chromatography is also much easier compared with others conditions.

Table 3.4. Acid, base and additive equivalent screen

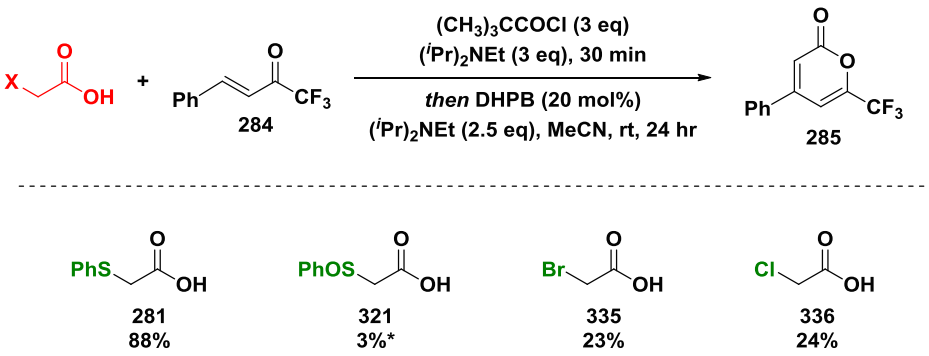


Entry	Acid (eq)	$(CH_3)_3CCOCl$ (eq)	i) $(^iPr)_2NEt$ (eq)	ii) $(^iPr)_2NEt$ (eq)	SM (%)[a]	yield (%)[a,b]
1	1	1.5	1.5	1	16	49
2	1	2	2	1	36	40
3	1	2	2	2	39	37
4[c]	1.5	2	2	2	-	(77)
5	2	2	2	1	-	72
6	2	2	2	2	-	71
7	2	3	2	2	-	81
8	2	3	3	1	trace	57
9	2	3	3	2	trace	55
10	**2**	**3**	**3**	**2.5**	**-**	**96 (88)**

[a] yield has been measured with 1-methyl naphthalene as an internal standard through ^{1}H NMR spectroscopic analysis. [b] the number in brackets refer the isolated yield. [c] no standard indicator (SI)

3-4-4. Acetic acid screen

A variety of acetic acids bearing a range of potential leaving groups were also examined with the previously optimised reaction condition. For the model pyrone **285** synthesis, both bromo- **335** and chloroacetic acid **336** gave the product in 23% and 24% isolated yields, respectively. Sulfoxide substituted acid **321** gave low conversion to pyrone **285**. (Thiophenyl)acetic acid is still the best choice for this methodology (Scheme 3.15).



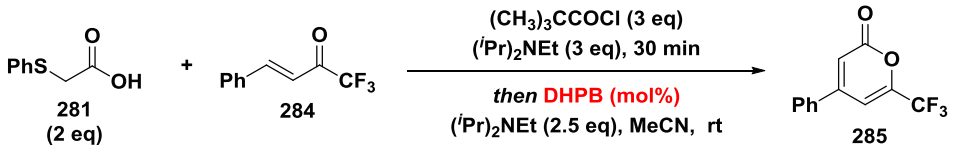
Scheme 3.15 Reaction scope: variation of acetic acids

*yield has been measured with 1-methyl naphthalene through 1H NMR spectra.

3-4-5. Catalyst loading screen

Finally, catalyst loading in this reaction was examined. Initial studies used 20 mol% DHPB and gave 88% isolated yield (Entry 1, Table 3.5). Reducing the catalyst loading to 10 mol% gave 81% isolated yield (Entry 2). Further reduction of the catalyst loading to 5 mol% resulted in also good 82% yield (Entry 3). Pleasingly, even 1 mol% and 0.1 mol% catalyst loading gave good isolated yields of 77% and 71%, respectively (Entry 4 and 5). Surprisingly, without catalyst, 59% product was obtained after 24 hours (Entry 6). However, the purification is challenging as there was more impurities in the crude mixture. DHPB plays a key role in the reaction and results in higher amounts of isolated pure product.

Table 3.5 Catalyst Loading Screen

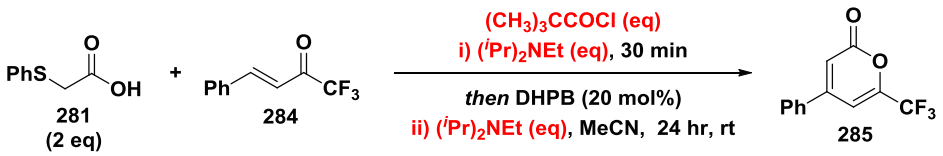


Entry	DHPB (mol%)	Isolated yield (%)
1	**20**	**88**
2	10	81
3	5	82
4	**1**	**77**
5	0.1	71
6	-	59

3-4-6. Moisture condition and scale-up

So far, the reactions were conducted in dry conditions, including using flame dried glassware and dry solvent. Carrying out the reaction in open-flask condition slightly reduced the yield, from 88% to 80% (Table 3.6 Entry 1). The absence of standard indicator, 1-methyl naphthalene, did not impact the reactivity, resulting in the excellent yield of 89% (Entry 2). The reaction was also scaled up to gram scale (6 mmol), resulting in an isolated yield of 90% (1.30 g) (Entry 3). The same scale was also applied in using less equivalents of activating agents and base, but only gave the product in 83% yield (Entry 4).

Table 3.6 Moisture condition and scale-up

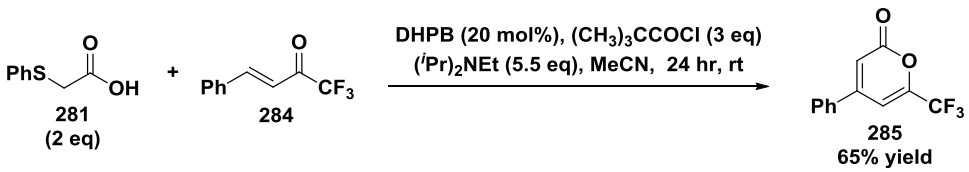


Entry	$(CH_3)_3CCOCl$ (eq)	i) $(^iPr)_2NEt$ (eq)	ii) $(^iPr)_2NEt$ (eq)	Isolated yield (%)
1[a]	3	3	2.5	80
2[b]	3	3	2.5	89
3[c]	**3**	**3**	**2.5**	**90**
4[c]	2	2	2	83

[a] Open-flask conditions. [b] without standard indicator (SI). [c] the reaction was in 1.0 mmol scale

The optimation process has shown the best condition for 2-pyrone formation is with two equivalents of (phenylthio)acetic acid, three equivalents of pivaloyl chloride and 3 equivalents of $(^iPr)_2NEt$ to generate excess mixed anhydride, followed by the addition of 1 or 20 mol% of DHPB then one equivalent of acceptor and a further 2.5 equivalents of $(^iPr)_2NEt$.

The reaction has also been attempted adding all the reagents at the outset of reaction, without activating the acetic acid with pivaloyl chloride, using 20 mol% DHPB. However, the yield decreased to 65%. Hence, performing the activation process step initially, leads to higher isolated yield of desired product (Scheme 3.16).

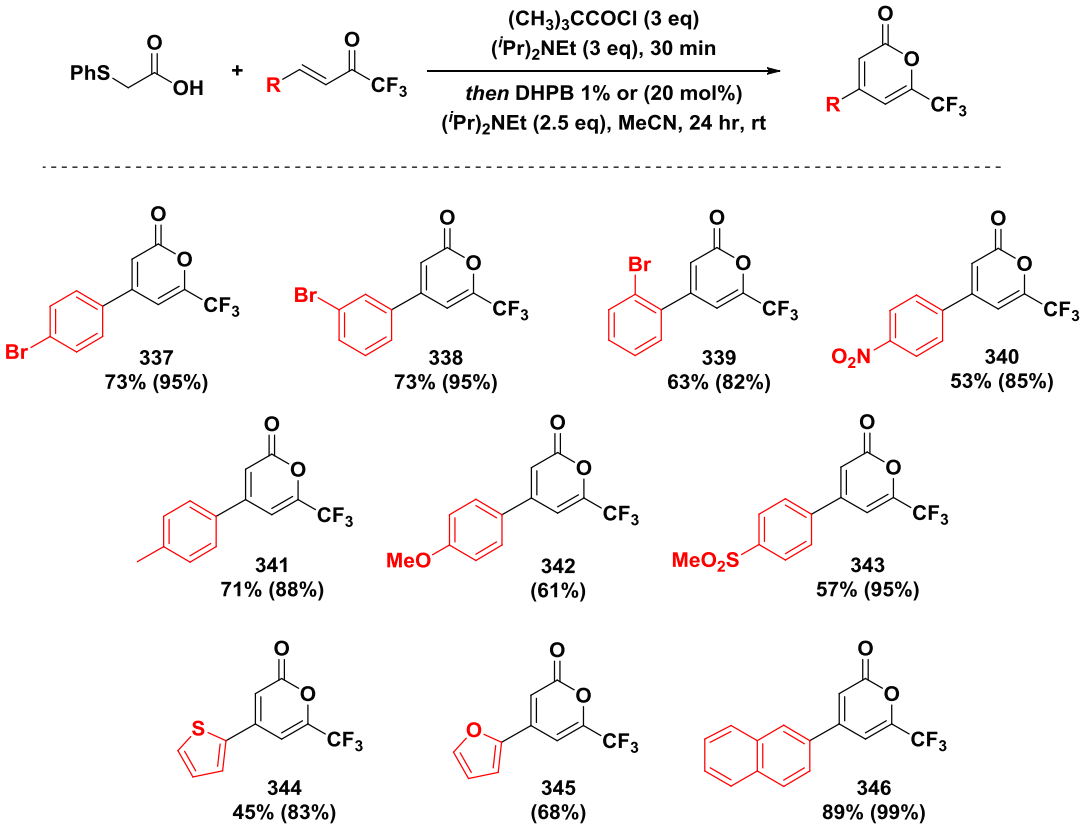


Scheme 3.16 The reaction without activating process

3-5. Product scope

3-5-1. Acceptor screen

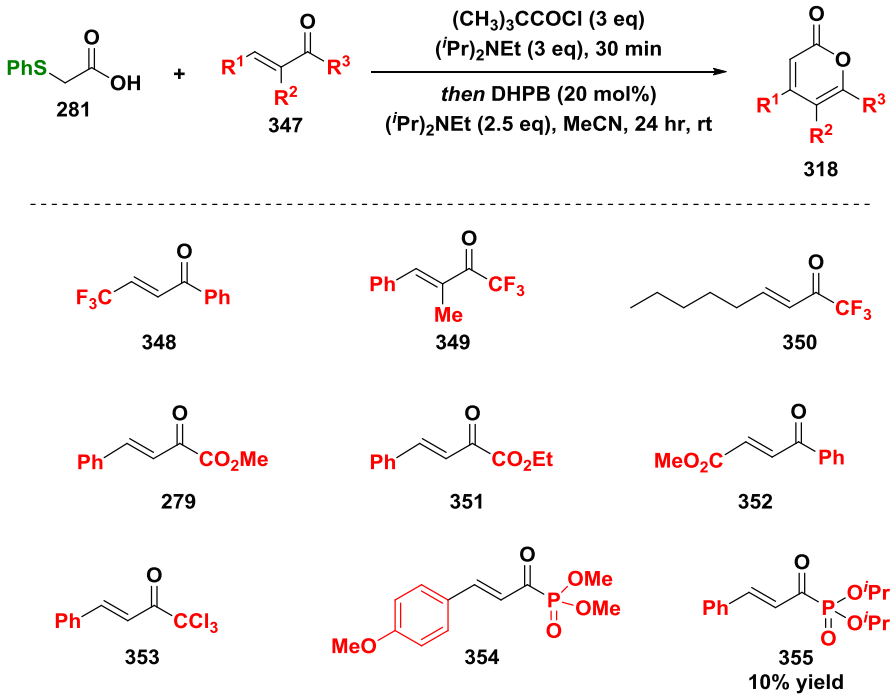
Following optimisation of this process, various trifluoromethyl enones were next studied to assess the scope and limitations of the reaction. The experiments were examined using both 1 and 20 mol% catalyst loading and results were shown in Scheme 3.17, the yield in brackets refers to the isolated yields from 20 mol% catalyst loading reaction. In general, the 20 mol% catalyst loading gave pyrone **337-346** in excellent yields (61-99% yield). This methodology tolerated a range of aromatic substituents in the enone, for example, pyrones with *o*/*m*/*p*-bromo substitution **337-339** were isolated in excellent yields. Other electron-withdrawing **340** and **343** and electron-donating substituted aryl motifs **341** and **342**, were obtained in high yield. Additionally, heteroaromatic functionalities **344** and **145** could be incorporated. In comparison with other substituents, formation of *p*-methoxy substituted pyrone **342** requires extended reaction time of 72 hours using at 20 mo% catalyst loading, while the and 2-furyl substituted pyrone **345** was also obtained with moderate yields. Catalyst loading of 1 mol% leads to good isolated yields in most cases, however, generally 10-20% lower yield than compared to the use of 20 mol% catalyst loading. The isolated yields of *p*-nitro substituted aryl **340** and 2-thiophene **344** pyrones were also dramatically reduced at 1 mol%, but good at 20 mol% catalyst loading. Pyrone with 2-nathphalene **346** was isolated in excellent yield using either 1 or 20 mol% catalyst loading (Scheme 3.17).



Scheme 3.17 Reaction Scope: Variation of Trifluoromethyl Enone

*numbers in brackets refer the isolated yields from 20 mol% catalyst loading reactions

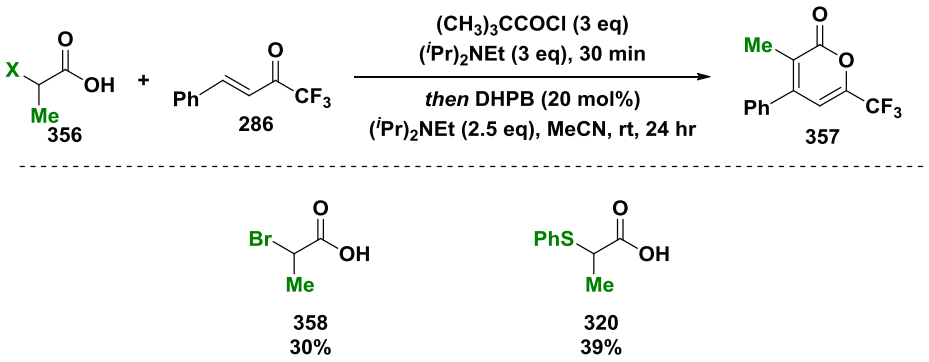
(Phenylthio)acetic acid has been applied in the isothiourea catalysed synthesis of 2-pyrone with trifluoromethyl enones. Further investigations focused on alternative Michael acceptors in related processes. Reversed trifluoromethyl and phenyl enone **348**, α-substituted trifluoromethyl enone **349** and alkanyl substituted trifluoromethyl enone **350** were submitted to the optimised reaction conditions but give no reaction (Scheme 3.18). Other substrates with various substituents have also been examined under the reaction conditions described, but only starting enone was returned. The α,β-unsaturated trichloroketone **353** is unreactive in this system. α,β-Unsaturated keto-phosphates **354** and**d 355** were also examined, however, the reactions resulted in a complex mixture, observed by crude ^{1}H NMR, and only 10 % of pyrone **355** was isolated.



Scheme 3.18 Reaction scope: variation of Michael acceptors

3-5-2. The α,α-disubstituted acetic acids

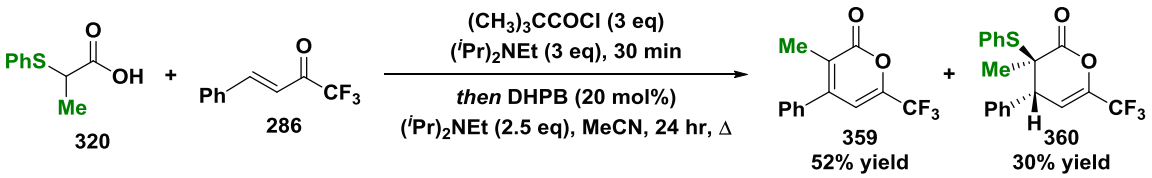
To expand the scope to include tri-substituted pyrones, α,α-disubstituted acetic acids have been examined in this methodology. Pleasingly, α,α-disubstituted acetic acids, which have been incompatible in our previous isothiourea-mediated methodologies, could also be tolerated in this system giving the tri-substituted pyrone product **357** from both 2-bromopropionic acid **358** and α,α-di(phenylthio)acetic acid **320**. The reaction with α-methyl (phenylthio)acetic acid gave better reactivity, with higher isolated yield of 39% and a much cleaner crude reaction mixture (Scheme 3.19).



Scheme 3.19 Reaction scope: variation of acetic acids

*yield has been measured with 1-methyl naphthalene through 1H NMR spectra.

The yield of the reaction with α-methyl (phenylthio)acetic acid was improved by reacting the substrate and catalyst in a sealed tube at reflux (95 ˚C). The desired pyrone product **359** was isolated in 52% yield but in addition, a single diastereomer of sulfide substituted δ-lactone **360** was also isolated from the reaction mixture in 30% yield (Scheme 3.20).



Scheme 3.20 Reaction with α-methyl (phenylthio)acetic acid

The relative configuration of racemic δ-lactone **360** was confirmed by X-ray crystallography to show the *trans*-δ-lactone with a *syn*-relationship between thiophenol substituent on *C*(3) and hydrogen on *C*(4) (Fiugure 3.2).

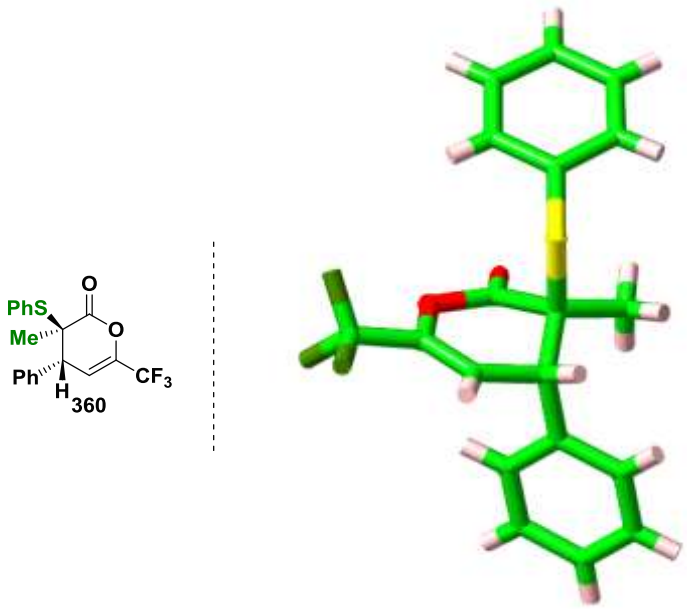
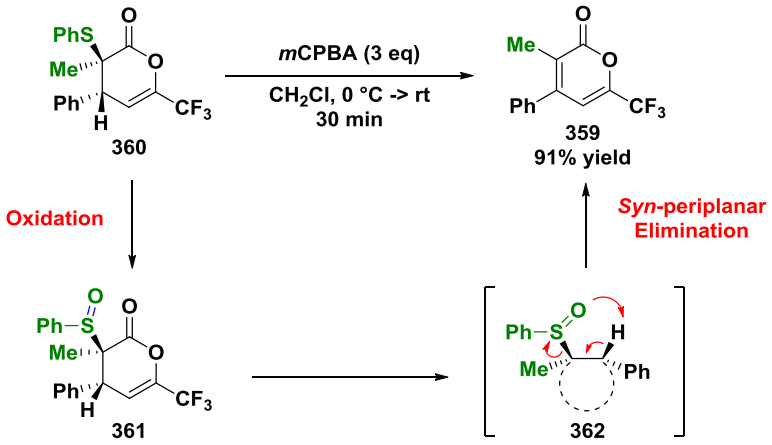


Figure 3.2 X-ray Crystal Structure of δ-lactone **360**

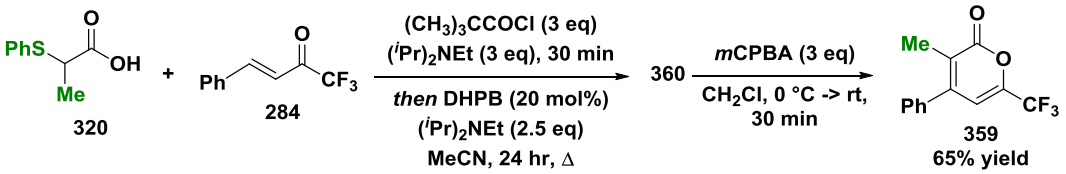
3-5-2-1. *Syn*-periplanar elimination via sulfide oxidation

Following the synthesis of *anti*-lactone **360**, *via* isothiourea catalysis, futher 1,2-*syn*-elimination to pyrone **359** was desired. To facilate the desired elimination, the δ-lactone was oxidised with *m*CPBA to form sulfoxide **361** then *in situ syn*-periplanar elimination resulted in the desired tri-substituted pyrone **359** in excellent yield, 91% (Scheme 3.21).



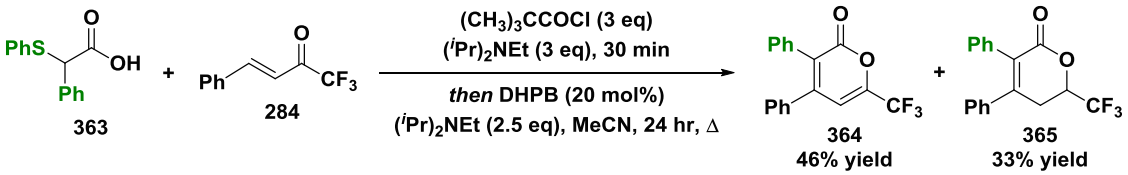
Scheme 3.21 Oxidation of Sulfide and *Syn*-periplanar Elimination

The oxidation with *m*CPBA has also been applied directly to the crude catalysis reaction mixture from α-methyl (phenylthio)acetic acid **320** and acceptor **284**, in a cascade process without any work-up and direct purification, giving the desired tri-substituted pyrone **359** in 65% yield (Scheme 3.22).



Scheme 3.22 One-Pot Tandem *Tri*-substituted Pyridine Synthesis

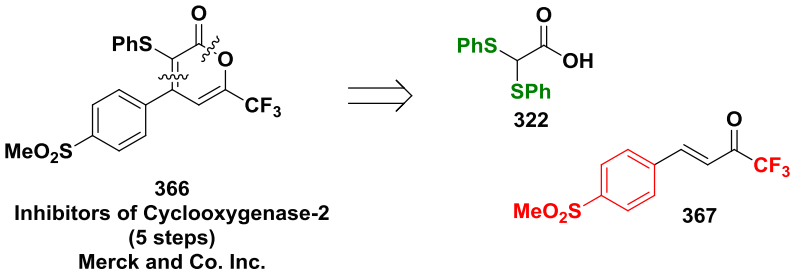
α-Phenyl (phenylthio)acetic acid **363** has also been examine in this methodology. The desired pyrone **364** was isolated in 46% yield alongside unexpected lactone **365** in 33% yield (Scheme 3.23).



Scheme 3.23 Reaction with α-phenyl (phenylthio)acetic acid

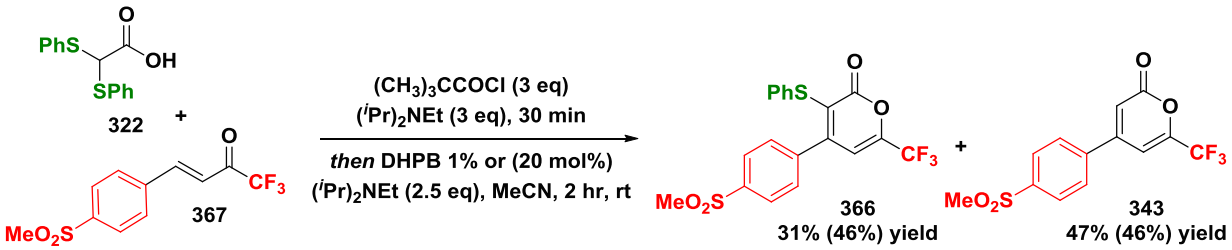
3-6. Application of methodology-synthesis of COX-2 inhibitor

To demonstrate the utility of this methodology, it was applied to the synthesis of pyrone xx, which was investigated by Merck & Co.,[109] and has biological activity as a COX-2 inhibitor. Retrosynthesis analysis suggests the potent pyrone **366** can be formed from the reaction with bis(phenylthio)acetic acid **322** and trifluoromethyl acceptor **367** (Scheme 3.24).



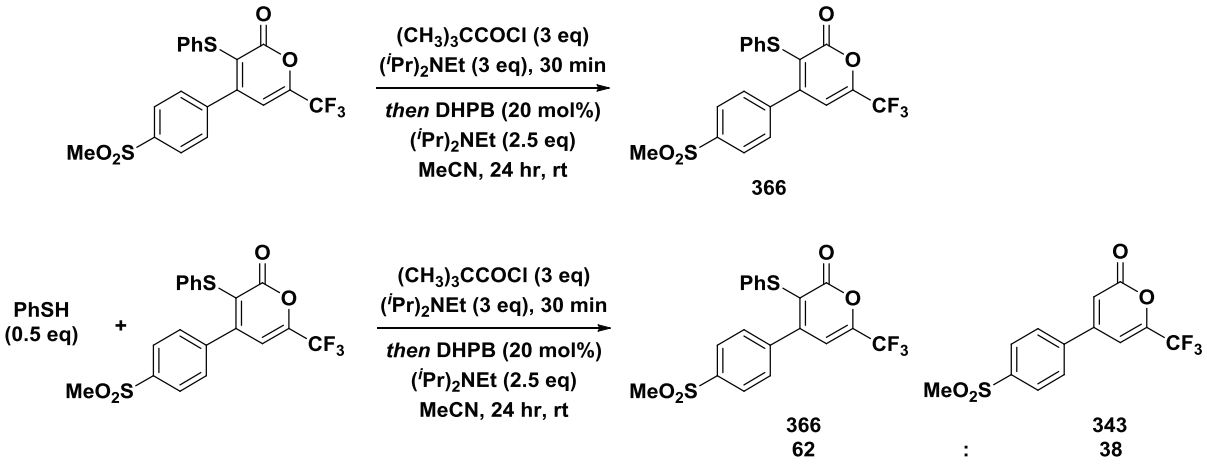
Scheme 3.24 Retrosynthetic analysis of COX-2 inhibitor **366**

The reactions with 1 or 20 mol% catalyst loading were successful; however, they gave a separable mixture containing two products (with 20 mol%, 1:1, **366** and **343**; with 1 mol%, 31:47, **366** and **343**), the target pyrone **366** and also the undesired desulfurised pyrone **343** (Scheme 3.25).



Scheme 3.25 The synthesis of COX-2 inhibitor **366**

Presumably, the desulfurisation occurs due to the thiophenol generated during the reaction. To investigate this further, control experiments were studied. Product **366** was resubmitted to the standard reaction conditions for 24 hours, returning only pyrone **366**. Another experiment re-treated pyrone **366** in the same condition with the addition of 0.5 eq of thiophenol, resulting in both pyrone **366** and **343** in a 62:38 ratio by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Scheme 3.26).



Scheme 3.26 The control experiments with pyrone **366**

Attempts to prevent the undesired desulfurisation unfortunately did not improve the isolated yield of product pyrone **366**, such as the addition of dibenzyl disulfide.

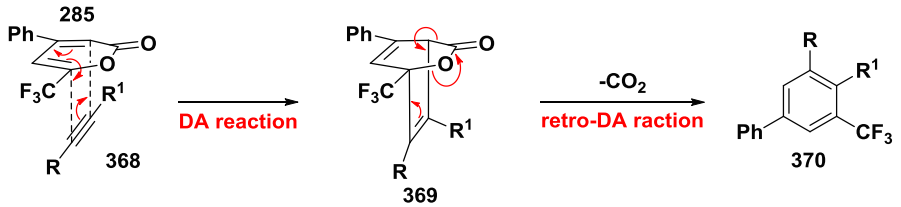
3-7. Derivatisation

To exemplify the used of pyrones in synthesis, their derivatisation to a range of aromatic/heteroaromatic building blocks was investigated.

3-7-1. Formation of aromatics

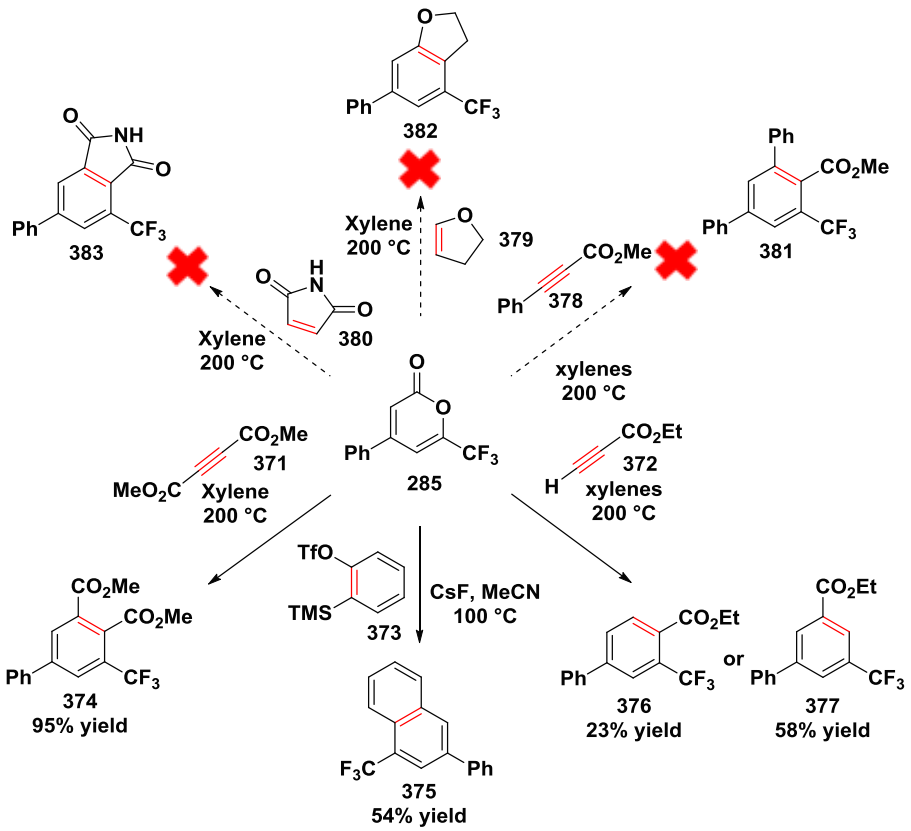
via Diels-Alder /retro-Diels-Alder reaction of 2-pyrone

The general proposed mechanism of making aromatics from a pyrone utilities as a diene in a Diels-Alder reaction with the various dienophile. This forms a bicyclic intermediate **369,** that undergoes a retro-Diels-Alder reaction and loss of CO_2 to give various aromatic product **370** (Scheme 3.27).



Scheme 3.27 The general proposed mechanism of aromatics formation

The parent pyrone **285** was treated with various dienophiles such as dimethyl acetylenedicarboxylate (DMAD) **371**, ethyl propiolate **372** and benzyne precursor **373** to generate benzene **374-377** and naphthalene **375** derivatives *via* Diels-Alder /retro Diels-Alder reaction. The low polarity of naphthalene **375**, resulted in challenging purification and a reduced isolated yield. These type of reactions were generally carried out in a sealed tube in refluxing xylene at 200 ˚C for 72 hours. Ethyl propiolate gave a mixture of two regioisomers (68:38, **377** and **376**), that were separable by flash column chromatography. Further attempted examples used methyl phenyl propiolate **378**, as well as cyclic dienophiles, such as maleimide **380** and 2,5-dihydrofuran **379**, were also examined, however, no reaction was observed in these cases, with only starting material returned (Scheme 3.28).

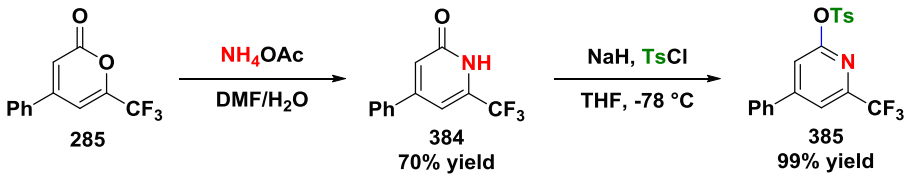


Scheme 3.28 The examples of DA/retro-DA reaction

3-7-2. Aza-heterocycle synthesis

3-7-2-1. Pyridone 384 and pyridine 385

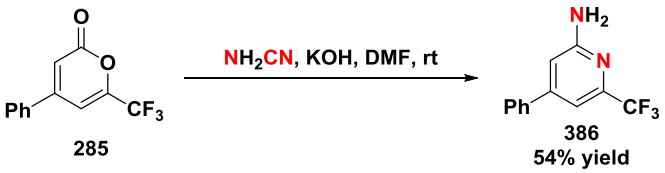
2-Pyrones have previously been used as a synthon for aza-heterocycle synthesis, for example, pyridone[104,110] and pyridine.[111–113] Treatment with pyrone **285** with ammonium acetate in refluxing in aqueous DMF generated pyridone **384** in good yield, 70%.[104] Pyridone **384** was then treated with NaH and TsCl to give tri-substituted pyridine **385**, in excellent yield, 99% (Scheme 3.29).[114]



Scheme 3.29 Pyridine synthesis through 2-pyrone

3-7-2-2. Synthesis of 2-amino pyridine 386

The parent pyrone **285** was also transformed into 2-amino pyridine **386** resulted in 54% yield by treatment with with cyanamide in DMF (Scheme 3.30).[112]

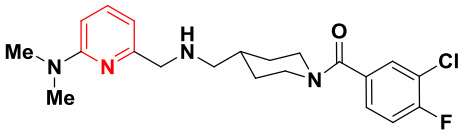


Scheme 3.30 Synthesis of 2,4,6-Subtituted Pyridine Synthesis

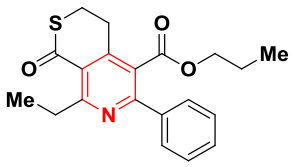
Having utilised this methodology for the synthesis of 2-pyrone, its applicability for the synthesis of pyridine was evaluated.

3-8. Pyridine synthesis

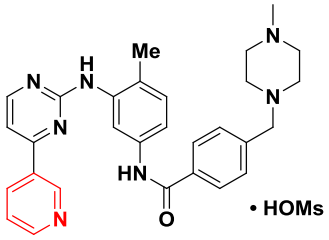
Pyridine is a six-membered aromatic ring containing a nitrogen atom. The first pyridine, picoline, was isolated by Anderson in 1846 from the pyrolysis of bone oil. The pyridine was formed from the condensation of a simple aldehyde and ketone with ammonia which is believed to be formed from the decomposition of glycerol and nitrogenous materials.[115] However, the correct structure was only reported 20 years later by Körner in 1869 and Dewar in 1871.[115] The pyridine motif has raised lot of attention in the last 50 years from many synthetic chemists as many pyridine-containing compounds have been employed as bioactive agents in pharmaceutical chemistry for various medicinal treatments, such as human immunodeficiency virus (HIV) and chronic myelogenous leukaemia (Figure 3.3).[115,116]



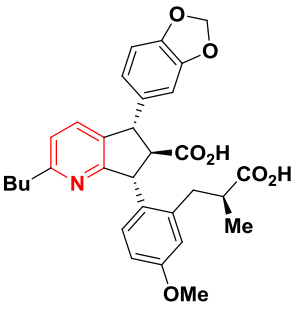
5-HT Receptor Agonist
(Antidepressant)



A_3 Adenosine Receptor Antagonist
(Antiinflammatory Antiasthmastic)



Imatinib Mesylate
(Chronic Myelogenous Leukaemia)



Endothelin Receptor Agonist
(Heart Failure, Hypertension)

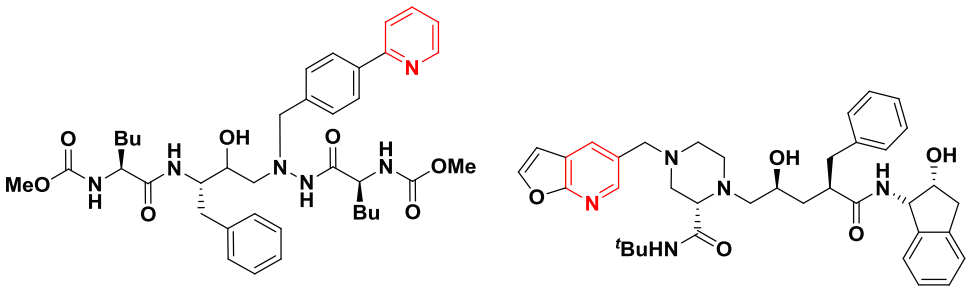
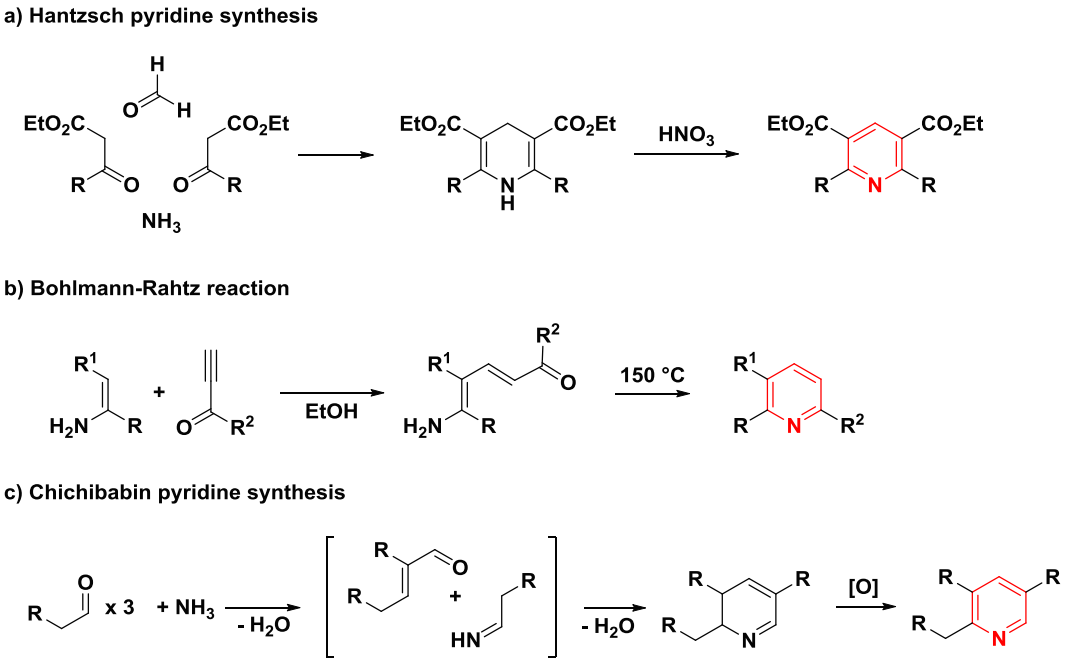


Figure 3.3 A Selection of Bioactive Molecules Containing Pyridines

To form the core pyridine structure, common methods employ the condensation of amine and carbonyl compounds or thermal [2+2+2] cycloaddition. However, to access highly functionalised substituted pyridines is more challenging. There are many classic methodologies such as muticomponent reaction (MCR),[117] Hantzsch pyridine synthesis,[116,118,119] Bohlmann-Rahtz reaction[120–125] and Chichibabin pyridine synthesis,[126–129] that are well known (Scheme 3.31).

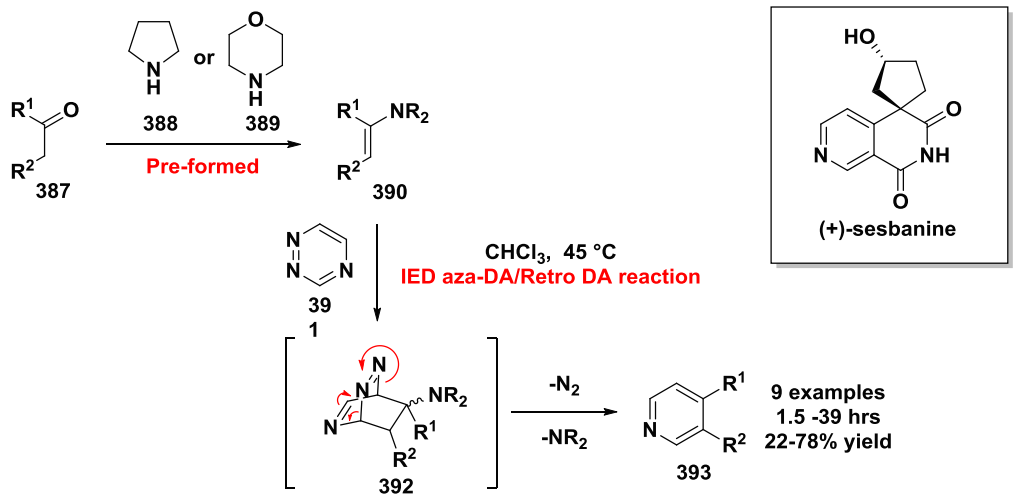


Scheme 3.31 General mechanism of standard pyridine synthesis

One of the alternatives is to derivatise from nitro-pyridine series[130] or oxazoles.[131] Metal catalysis, such as copper,[103,132,133,134] gold[132,133], rhodium,[135] ruthenium[136,137] are quite well developed for pyridine synthesis, particularly in [2+2+2] cycloaddition pyridine synthesis.[138,139] Recently, Yoshikai *et al*.[140] have reported a copper/iminium dual-catalysis system. However, based on the best knowledge, the first organocatalytic pyridine synthesis has been reported in 1982 by Boger *et al.*[141,142]

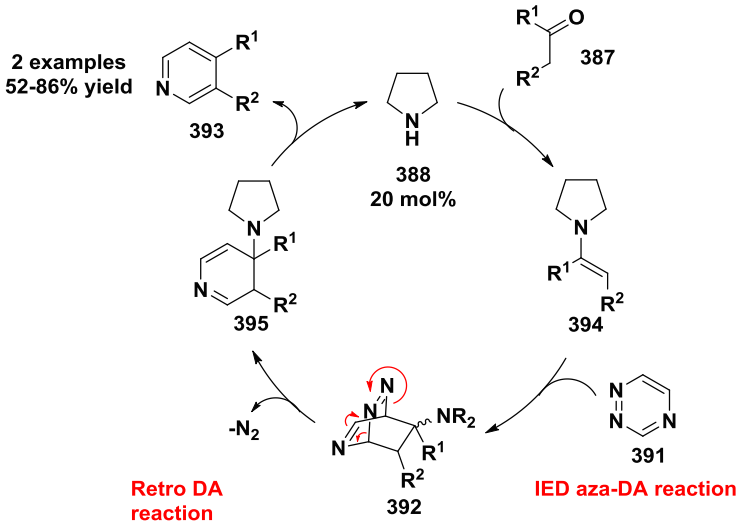
3-8-1. The first pyridine synthesis example of organocatalysis

The original idea was to develop short synthetic routes for natural alkaloids, such (+)-*sesbanine*- a potential cytotoxic alkaloid, and also the other antitumor and antibiotic agents *Sesbania drummondii*.[143,144] Initially, Boger and co-workers found that reacting electron-rich olefins, such as the pre-formed enamine **390**, with 1,2,4-triazine **391** resulted in a thermal cycloaddition process *via* inverse electron demand aza-Diels-Alder reaction (IED aza-DA reaction). Intermediate **392** is initially formed, followed by a retro Diels-Alder reaction process eliminating nitrogen gas to obtain pyridine **393** with excellent regiocontrol (Scheme 3.31). This study also showed that pyrrolidine enamine have better reactivity in this process then morpholino enamine.[141]



Scheme 3.31 Thermal cycloaddition for pyridine synthesis from pre-formed enamines

However, to circumvent enamin preparation, Boger and co-workers successfully formed enamine intermediate **394** *in situ* using achiral pyrrolidine as catalyst (20 mol%) to form pyridine **393**.[142] The key to the success of this method is the addition of activated 4 Å molecular sieves as to catalyse and complete the enamine formation that helps to regenerate the pyrrolidine then complete the catalytic cycle (Scheme 3.32).



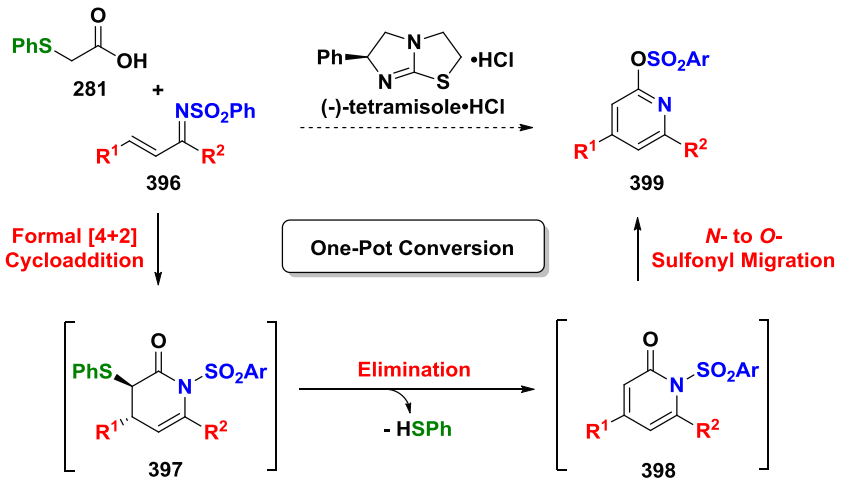
Scheme 3.32 One-pot organocatalytic pyridine synthesis

However, at the outset of this project, there were no general routes for the organocatalytic synthesis of functionalised pyridines.

3-9. The aim of this work

The previous isothiourea-mediated pyrone synthesis has shown that (phenylthio)acetic acid could be used to trigger thiophenol elimination from an *in situ* prepared lactone. Based on the same idea, this work examined the ketimines for the same reaction condition through a formal [4+2] cycloaddition then thiophenol elimination to result in pyridone **398**. Regarding literature examples[145–148], the *N*-sulfonyl substituted pyridines were found to spontaneously undergo *N*- to *O*- sulfonyl migration at room temperature or under heating. Hence, the

intermediate pyridone **398** was expected to undergo subsequent an *N*- to *O*- sulfonyl migration giving a functionalised *tri*-substituted pyridine **399** in a one-pot reaction (Scheme 3.33). The 2-sulfonyl group has the potential for having further installation ofkm H, aryl, heteroaryl, alkyl and amino substituents *via* various cross-coupling strategies or S_NAr processes. To the best of our knowledge, this represents the first example of catalytic isothiourea mediated pyridine synthesis.



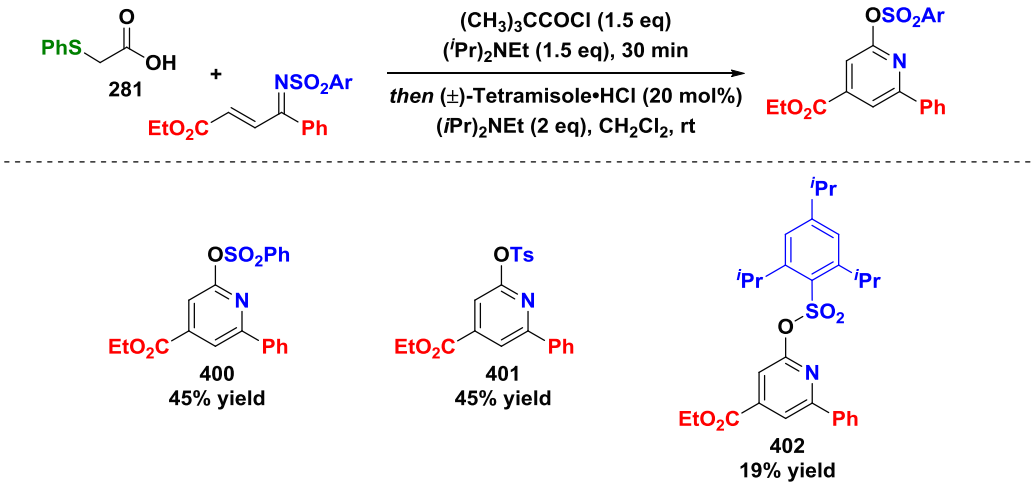
Scheme 3.33 One-pot isothiourea mediated pyridine synthesis

(Thiophenyl)acetic acid using in this project is commercially available and the preparation of the acceptor ketimines **190-192** has been discussed in chapter 3.

3-10. Initial results and discussion

Initial work aimed to assess the scope of *N*-sulfonyl substituent on this process. Under the reaction conditions described in Scheme 3.34 various size sulfonyl substituted ketimines **190**, **191** and **195** have examined. Benezensulfonyl and tosyl ketimine gave the same isolated yield (45%). However, the triisopropylsulfonyl substituted ketimine only gave the pyridine in 19%. The crude was observed by ^{1}H NMR contained a mixture of pyridone intermediate and

pyridine product. Unfortunately, the isolation of the pyridone failed.



Scheme 3.34 Various sulfonyl groups scope

3-11. Confirmed constitution

To confirm the constitution of pyridine product, various analytical techniques were applied. ^{1}H NMR spectroscopic analysis showed the signal of C(5)*H* is 8.21 ppm, which is located in the aromatic region matching the result, which has been discovered from the pyridine analogue **257** in the dihydropyridinone project (7.99 pm), in Chapter 2. Furthermore, IR data only has the carbonyl C=O stretch at 1724 cm^{-1}, showing the structure is not like the pyridone containing the α,β-unsaturated C=O motif. Unambiguous evidence to prove the constitution of pyridine **400** was finally identified by a suiTable crystal structure examined *via* X-ray crystallography (Figure 3.4).

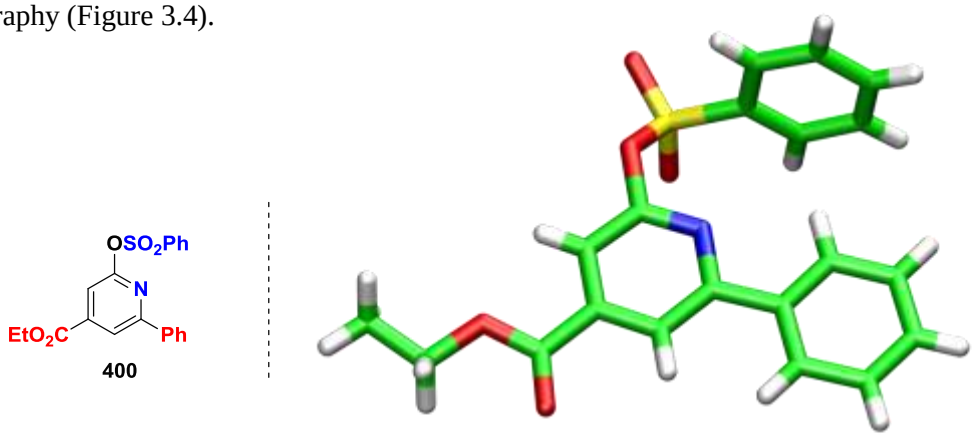
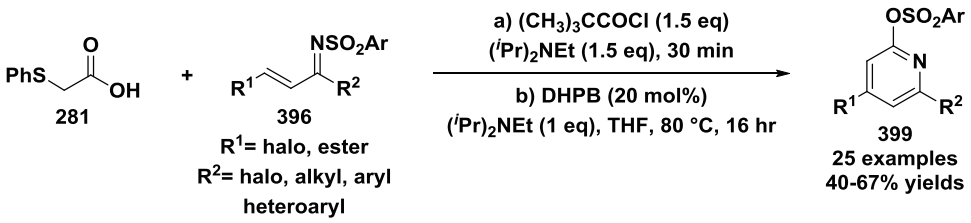


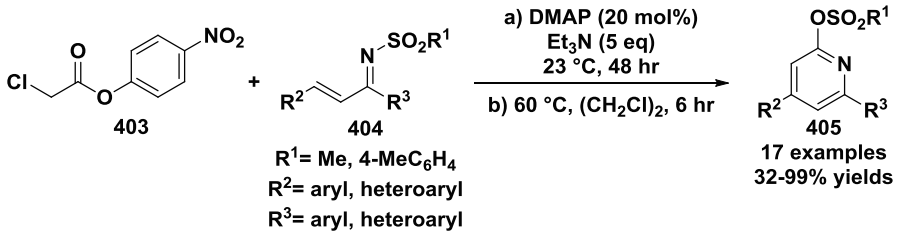
Figure 3.4 Crystal Structure of Pyridine **400**

After these initial studies, this project formed the basis of another PhD student' research.[149] The further optimised studies have shown the *N*- to *O*-sulfonyl migration can be accelerated *via* heating the reaction mixture at 70 ˚C fully converting pyridone into pyridine (Scheme 3.35). Furthermore, a cross-over control reaction proved that the *N*- to *O*-sulfonyl migration is an intramolecular process.[149]



Scheme 3.35 Isothiourea-mediated one-pot pyridine synthesis from Smith group

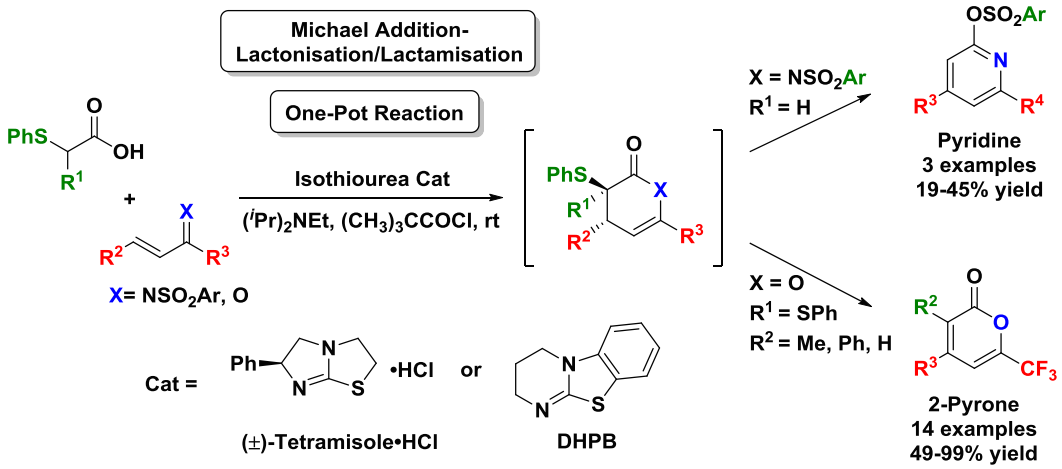
Following the publication of this work, Chi and co-workers reported a DMAP-catalysed one-pot pyridine synthesis from α-chloro acetic ester with unsaturated ketimines (Scheme 3.36).[150]



Scheme 3.36 Chi's approach of DMAP-catalysed one-pot pyridine synthesis

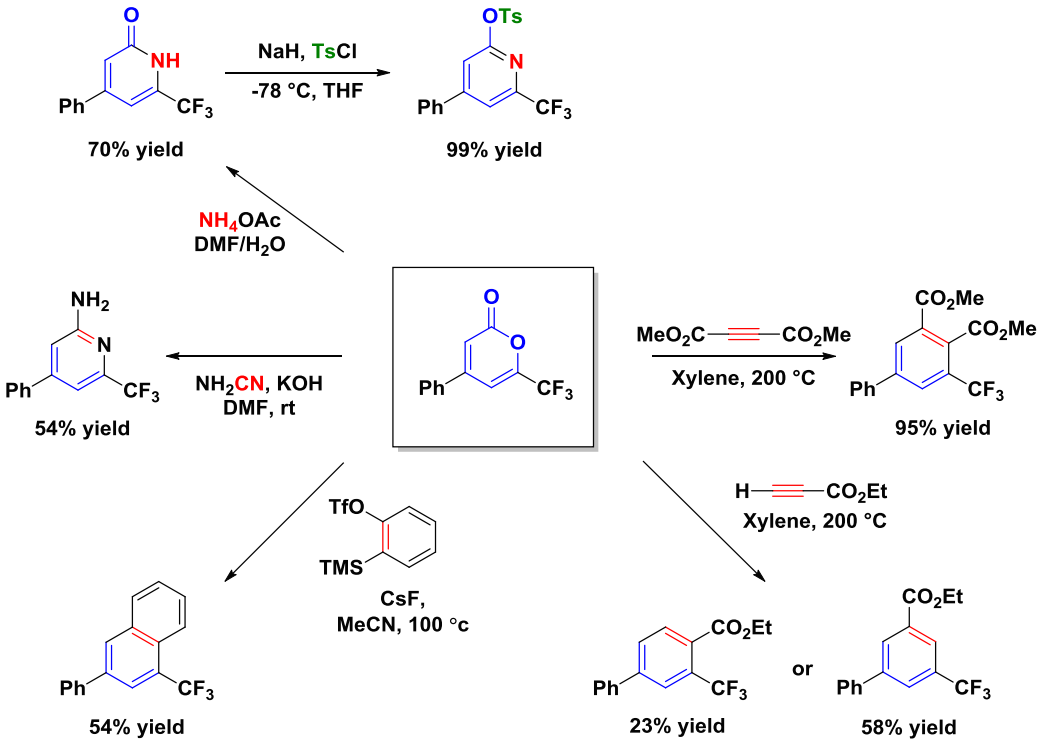
3-12. Conclusion

In conclusion, (thiophenyl)acetic acid react, under Lewis base catalysis, with a range of electron deficient enone Michael acceptors to generate planar, pyridine and pyrone, *via* isothiourea-mediated Michael addition/cyclisation/thiophenol elimination cascade protocol in a one-pot reaction (Scheme 3.37).



Scheme 3.37 One-Pot Isothiourea-Mediated Plan Molecule Synthesis

This methodology has been utilised in the synthesis of COX-2 inhibitor **366** with good overall yield. The parent pyrone has been employed in a series of further manipulations and is readily derivertised into a wide range of valuable aromatics/heteroaromatics with good yields (Scheme 3.38).

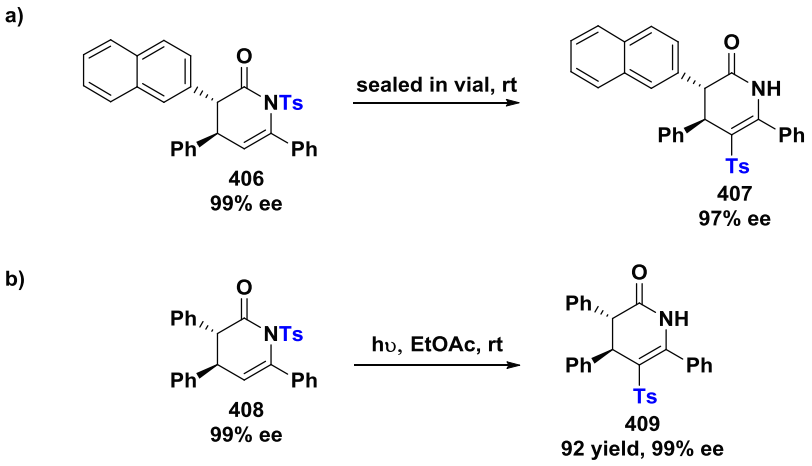


Scheme 3.38 The summary of pyrone derivatisation

Chapter 4. *N*- to *C*- Sulfonyl Migration *via* Photoisomerisation

4-1. Introduction

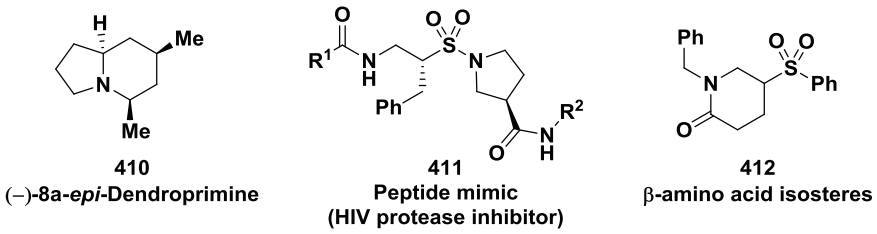
Previous work within the Smith group identified an interesting *N*- to *C*-sulfonyl migration. Upon storage in sealed vial expose to air and light for prolonged periods of time, *N*-Ts dihydropyridinone **406** undergoes *N*- to *C*-sulfonyl migration into product **407** without loss in enantioselectivity (Scheme 4.1, a). The same rearrangement could also be promoted through heating **408** in ethyl acetate at reflux for 72 hours. However, subjecting dihydropyridinone **408** to UV light induced efficient photoisomerisation forming **409** in 92% yield without compromising the enantiopurity (Scheme 4.1, b).[68]



Scheme 4.1 Previous observations from the Smith group

This novel *N*- to *C*-sulfonyl migration process *via* photoisomerisation has not been explored in detail and further investigation into the scope and limitation of this reaction are needed. Studies into the mechanism of the *N*- to *C*-sulfonyl migration would also be of interest. The product 5-sulfonyl dihydropyridinone are also of interest as they have the potential for further derivatisation.[151–153] Previously, 5-sulfonyl dihydropyridinone were demonstrated as intermediates in the synthesis of racemic indolizidine alkaloid analogue

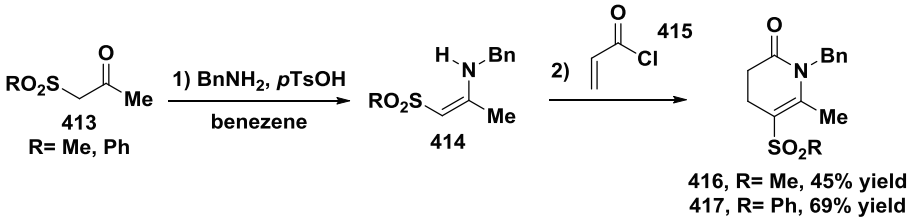
(8a-*epi*-dendroprimine **410**)[154] and peptide mimic **411** which were specifically designed as a inhibitor of HIV protease (Scheme 4.2).[155]



Scheme 4.2 Target molecules synthesised from 5-sulfonyl dihydropyridinones

4-1-1. Alternative literature on the formation of 5-sulfonyl dihydropyridinones

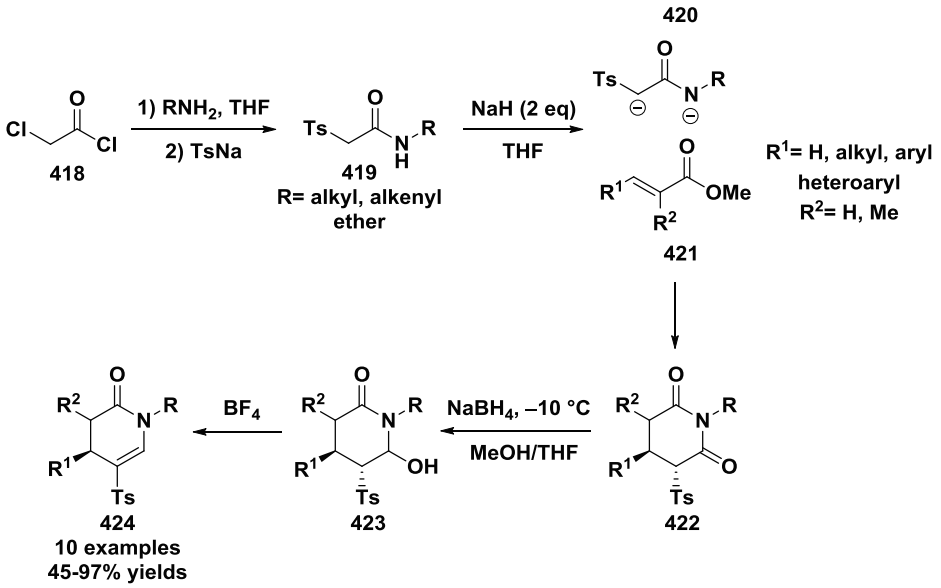
Stille *et al*. reacted $BnNH_2$ and ketone **413** bearing an electron-withdrawing substituent (SO_2Ph and SO_2Me) with *p*TsOH in benzene to form enamine **414** *in situ*. Subsequently, aza-annulation with acryloyl chloride **415** results in the formation of 5-sulfonyl dihydropyridinones **416** and **417** in good yields (Scheme 4.3).[155] The electron-withdrawing sulfonyl group is the key to the reaction as it favours the β-enamino form of the ketimine, encouraging the aza-annulation process.



Scheme 4.3 Synthesis of 5-sulfonyl dihydropyridinone
via enamine condensation/aza-annulation

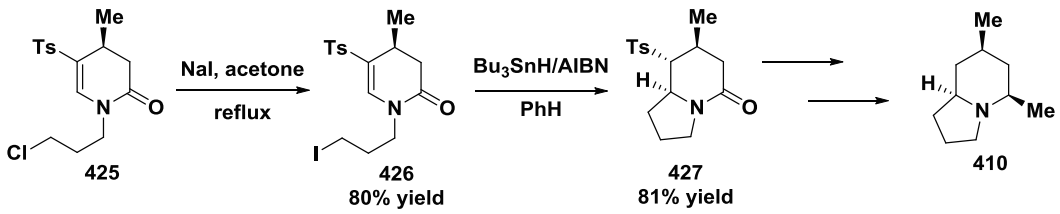
Tai and co-workers also developed a stepwise reaction to generate glutarimides **422**.[154,156] The reaction starts by treating chloroacetyl chloride **418** with a primary amine and sodium *p*-toluenesulfinate to form *p*-toluenesulfonyl acetamide **419**. Deprotonation of *p*-toluenesulfonyl acetamide with 2 eq sodium hydride results in formation of dianion **420**,

which then readily reacts with variety of α,β-unsaturated esters **421** to afford glutarimides **422**. The imide moiety was reduced with sodium borohydride forming δ-lactam **423**. Finally, lactam was dehydrated with boron trifluoride in the presence of anhydrous magnesium sulfate resulting in dihydropyridinones **424** in good to excellent yields (up to 97%) (Scheme 4.4).



Scheme 4.4 Synthesis of 5-sulfonyl dihydropyridinones

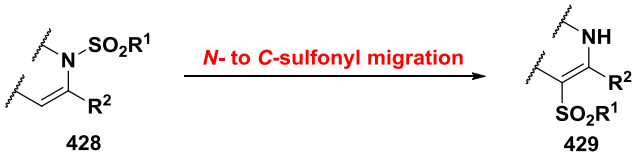
5-sulfonyl dihydropyridinone **425** was applied in the synthesis of racemic indolizidine alkaloid analogue, 8a-*epi*-dendroprimine **410**. Firstly, **425** was treated with NaI in acetone at reflux to form intermediate **426**, which underwent intramolecular cyclisation with Bu_3SnH/AIBN giving the indolizidine carbon skeleton of **427** that was elaborated in the further synthesis of 8a-*epi*-dendroprimine **410** (Scheme 4.5).



Scheme 4.5. Synthesis of 8a-*epi*-dendroprimine **410** from 5-sulfonyl dihydropyridinone **427**

4-1-2. The N- to C- Sulfonyl Migration

To the best of our knowledge, *N*- to *C* sulfonyl migration has not been previously reported in cyclic non-aromatic ring structures. However, related reactions have been reported for both acyclic and and aromatic systems and have been termed 1,3-sulfonyl migration, 1,3-sulfonyl shift and *ortho*-isomerisation (Scheme 4.6).



Scheme 4.6. General Scheme of *N*- to *C* sulfonyl migration in sulfonamides

From the literature, *N*- to *C* sulfonyl migration can be promoted by either photochemical or thermal reactions and these approaches are discussed in the following section.

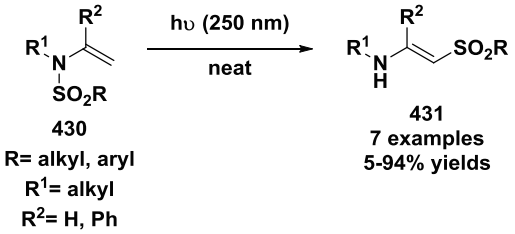
4-1-2-1. Photochemistry

The general term photochemistry is used to describe the use of light to promote chemical reactions by absorption of either ultraviolet (wavelength from 100-400 nm), visible light (400-700 nm) or infrared radiation (700-2500 nm). Compared with thermal chemical reactions, photochemical reactions can help to overcome large activation barriers and can also be used to promote reactions that are inaccessible by thermal processes, for example some [2+2] cycloaddition processes.

N- to *C*-Sulfonyl Photoisomerisation Reaction

In 1959, Stacey *et al*. reported a photoisomerisation under UV light at 250 nm to convert vinylsulfonamides **430** into 2-sulfonylvinylamines **431** (Scheme 4.7).[157] Aryl sulfonylamides such as SO_2Ph and tosyl gave isomerisation products in good yields (68-94%). Unfortunately,

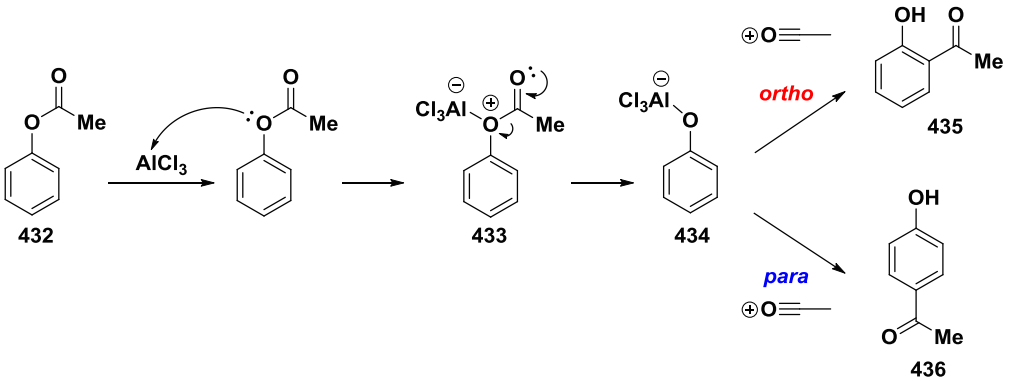
alkyl sulfonylamides only result in 5-10% yields of the photoisomerisation products. Furthermore, the reaction could be inhibited by small amounts of Et_3N, 1,2-ethanedithiol, thiophenol, butyraldehyde or styrene, and is not catalysed by either pyridine or *p*-toluenesulfonic acid, which all suggest that the isomerisation is not an ionic reaction but is radical in nature.



Scheme 4.7 The photochemical isomerisation of sulfonamides

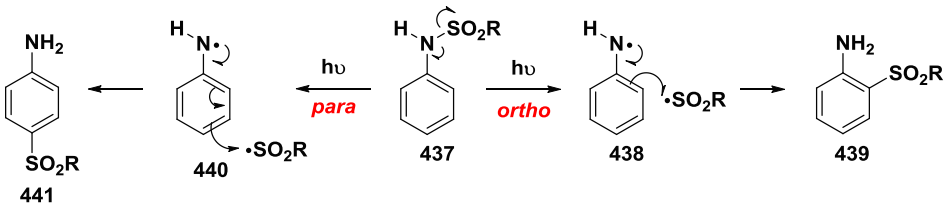
Photo-Fries Rearrangement

The Fries rearrangement is an *ortho*, *para*-selective isomerisation transforming a phenolic ester **432** into a hydroxyl aryl ketone catalysed by a Lewis acid such as $AlCl_3$ under thermal conditions. The reaction involves an acyl group migration onto an aromatic ring.[158] The regioselectivity can be affected by variation in the reaction conditions such as temperature and solvent (Scheme 4.8).



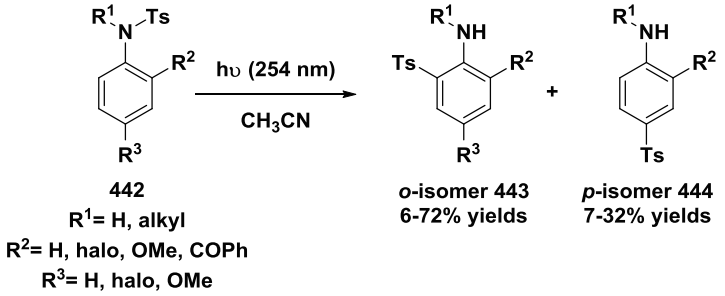
Scheme 4.8 General mechanism of the Fries rearrangement

Photo-Fries rearrangements are promoted by light and are thought to proceed by a radical mechanism. Irradiating the *N*-sulfonyl aniline **437** under UV light generates sulfonyl radical and aniline radical. These two radicals can recombine at the *ortho* position or *para* position resulting in two regioisomers **439** and **441** (Scheme 4.9). There are a few literature reports of the photo-Fries rearrangement with *N*- to *C*-sulfonyl migration in aromatics such as benzenes,[159,160] indoles[161] and carbazoles.[162]



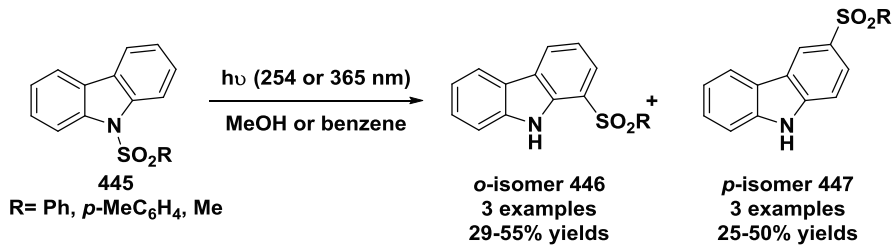
Scheme 4.9 General proposed mechanism of photo-Fries rearrangement

For example, Park and co-workers have demonstrated a photo-Fries rearrangement of *N*-tosylamides.[160] Irradiating *N*-tosyl amides **442** at 254 nm in acetonitrile resulted in photoisomerisation into anilines **443** and **444**. The regioselectivity of the method could be improved by blocking the *para* position with a substituent (Scheme 4.10). However, the yields were generally low in most cases.



Scheme 4.10 A Photo-Fries Rearrangement of *N*-Tosylamides

Photo-Fries rearrangement of carbazoles with various sulfonyl groups has been reported by Chakaborty *et al*.[162] The carbazoles **445** were irradiated with UV light at 254 and 365 nm either in methanol or benzene (Scheme 4.11). The wavelength at 365 nm gave shorter reaction times and slightly increased yields. The aryl sulfonyl substituent favoured forming the *para*-isomer **447** (*ortho*: *para*, 3:4), whereas, the mesyl sulfonyl group more favoured the *ortho*-isomer **446** (*ortho*: *para*, 4:3).

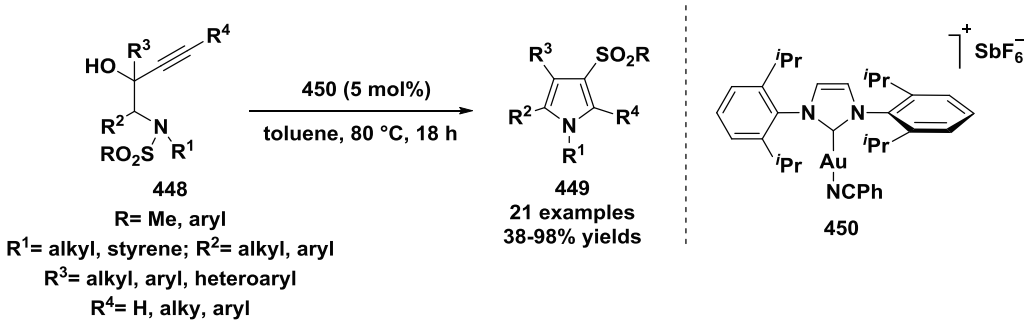


Scheme 4.11 Photo-Fries Rearrangement of Carbazoles with Various Sulfonyl Groups

In most cases, photo-Fries rearrangement gives a mixture of two regioisomer of products with low yield and poor regioselectivity. Hence, this reaction procedure is not readily applied in large-scale synthetic procedures.

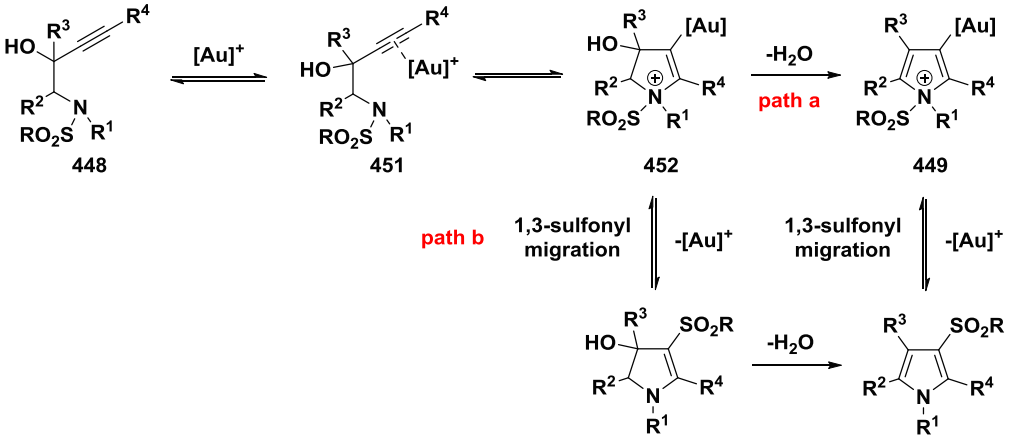
4-1-2-2. Catalytic 1,3-Sulfonyl Migration

In addition to photo-induced procedures, *N*- to *C*-sulfonyl migration can be promoted by organometallic chemistry.[163–165] Recently, Chan and co-workers have developed a gold-catalysed domino aminocyclisation/1,3-sulfonyl migration of 1,7-enyne benzoates **448** (Scheme 4.12).[165]



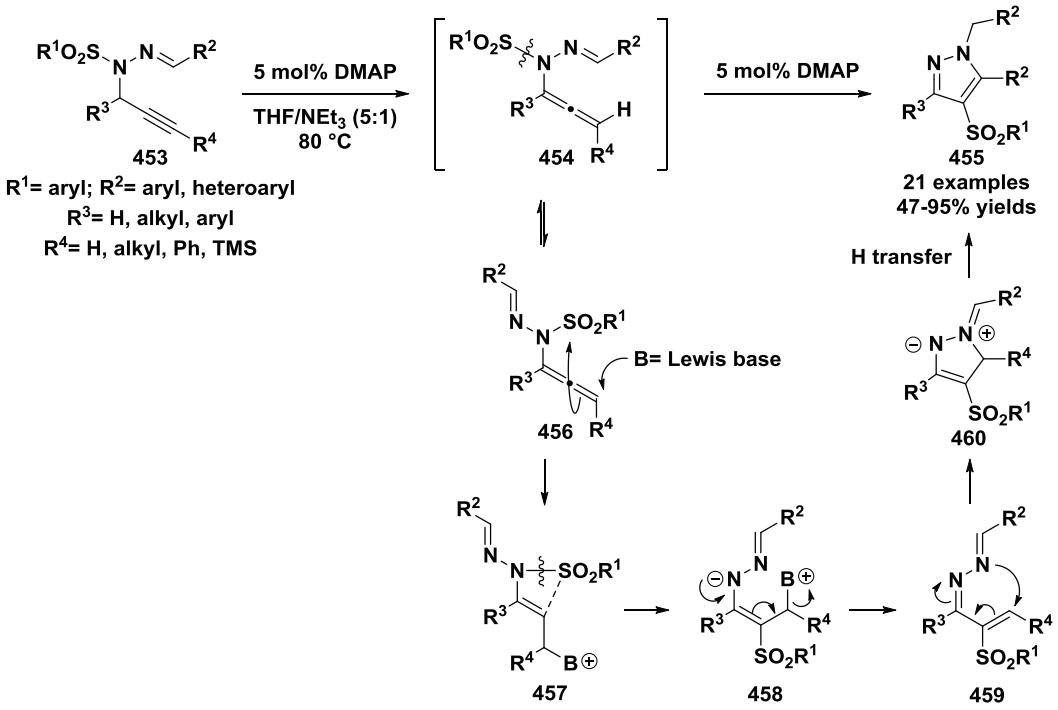
Scheme 4.12 Gold-Catalysed Cycloisomerisation of 1,7-enyne benzoates

This gold-catalysed cycloisomerisation could involve the activation of 1,7-enyne benzoates by coordinating gold catalyst **450** with the alkyne moiety to give gold(I) intermediate **451**, which undergoes the intramolecular aminocyclisation forming complex **452**. Then, complex **452** can undergo either dehydration following by 1,3-sulfonyl migration into product **449** (Scheme 4.13, path a) or 1,3-sulfonyl migration then dehydration (path b). A crossover experiment demonstrated that the 1,3-sulfonyl migration is an intramolecular process (Scheme 4.13).



Scheme 4.13 The Proposed Mechanism of Gold-Catalysed Cycloisomerisation

A novel 1,3-sulfonyl migration has also been demonstrated using Lewis base catalysis. Zhan *et al*. employed DMAP as catalyst for synthesis of mutisubstituted pyrazoles from propargylic hydrazones **453** (Scheme 4.14).[166] This method examined various sulfonyl groups and a wide scope providing good to excellent yields (47-95%). A crossover experiment of propargylic amides suggested this 1,3-sulfonyl migration is an intramolecular process. The proposed mechanism starts with isomerisation of the alkyne moiety of propargylic amide **453** into the allenic sulfonamide **454**. Nucleophilic addition of DMAP to the terminal sp^2 carbon of the allene **456** pushes electron density onto the sulfonylamide to afford intermediate **457**, which undergoes 1,3-sulfonyl migration resulting in **458**. Elimination of the Lewis base catalyst gives α,β-unsaturated imine **459**, which then undergoes intramolecular Michael addition to generate the zwitterionic cyclic intermediate **460**. Finally, proton transfer affords the observed pyrazole products **455**.

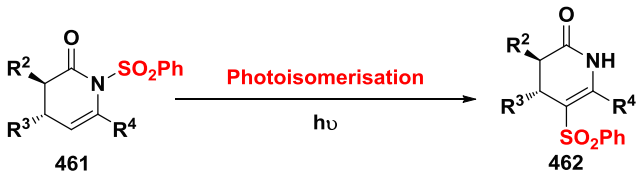


Scheme 4.14 DMAP-Catalysed Synthesis of Multisubstituted Pyrazole

Compared with photoisomerisation, catalytic thermal methodologies not only provide more precise 1,3-sulfonyl migration without regioselectivity issues but also generally provide a wide range of scope and good yields. Hence, the photo-induced *N*- to *C*-sulfonyl migration discovered from Smith group is particularly interesting as it provides specific isomerisation products in excellent yield and it is also the first example of *N*- to *C*-sulfonyl migration of non-aromatic cyclic substrates containing stereocentres.

4-2. The aim of this work

Building on the discovery of the *N*- to *C*-sulfonyl migration from previous work within the group, this project aimed to study the limitation of this rearrangement and also to investigate the mechanism of the photo-induced migration process (Scheme 4.15).



Scheme 4.15 The Proposed *N*- to *C*-sulfonyl migration

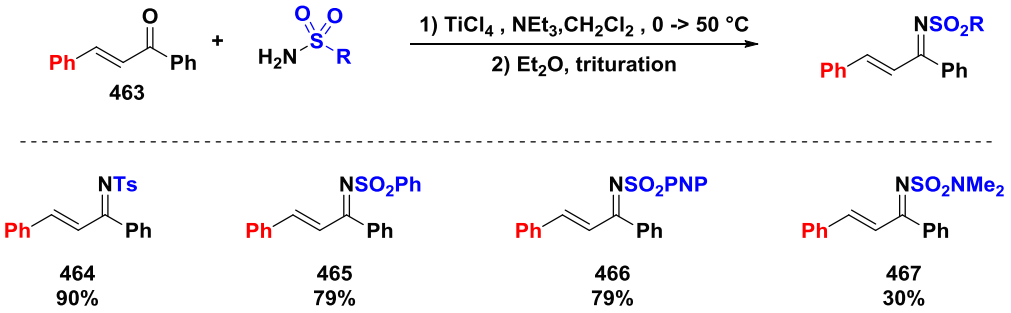
We envisaged using a range of *N*-sulfonyl dihydropyridinones synthesised using the isothiourea-catalysed Michael-addition lactamisation protocol developed previously (chapter 2) and subjecting them (R^3= ester) to photoisomerisation conditions. Moreover, to probe the scope and limitation of this reaction by varied in *N*-substituent and substitution (R^3 and R^4).

4-3. Starting Material Preparation

4-3-1. Ketimines with Various R^3 and N-Substituent

A series of ketimine was synthesised from the reaction of chalcone **463** with sulfonamides using $TiCl_4$ and Et_3N in CH_2Cl_2 (Scheme 4.16). The ketimine product **464-466** could mostly

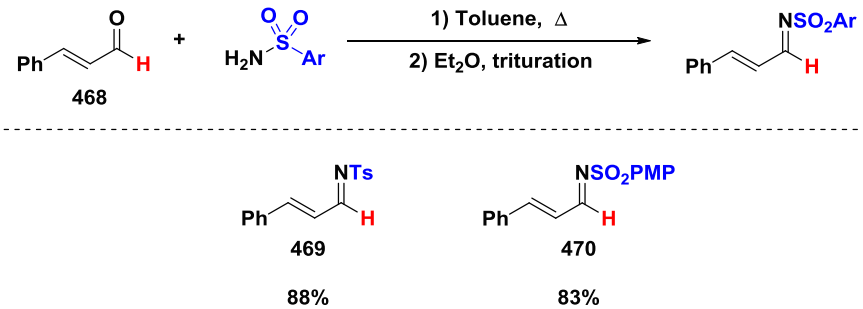
be purified by trituration in diethyl ether, giving pure products in good yield without the need for further purification. Only ketimine **467** bearing *N*-SO_2NMe_2 substituent needed to be purified through flash chromatography, which accounts for the lower isolated yield.



Scheme 4.16 Ketimines Prepared from Chalcones.

4-3-2. Aldimine Synthesis

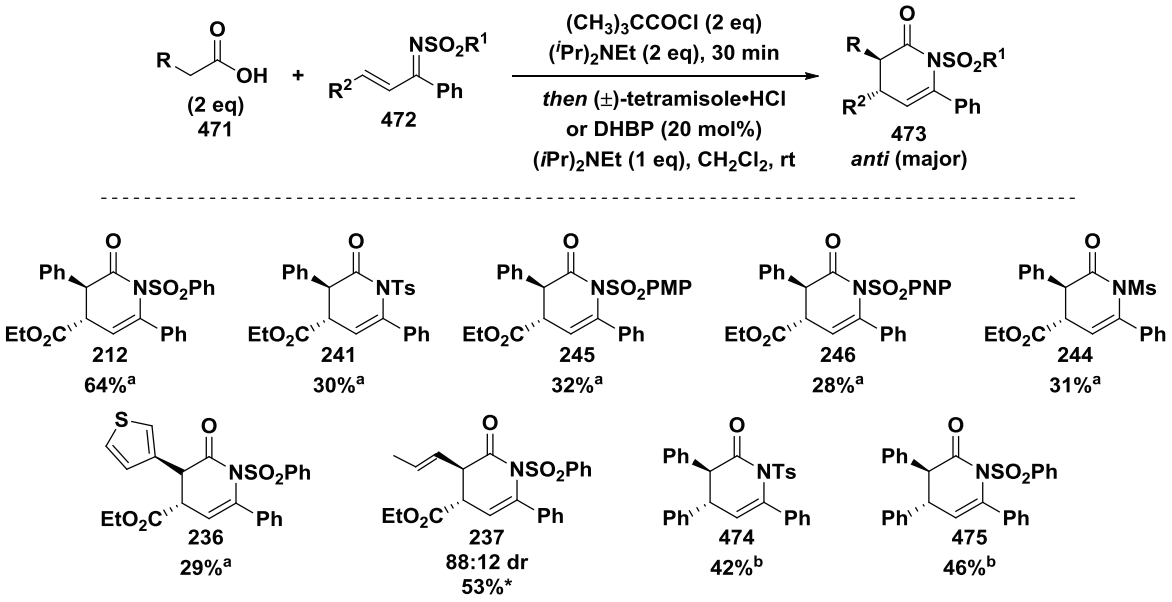
Aldimines **469** and **470** were also synthesised by heating cinnamoyl aldehyde **468** with sulfonylamides at reflux in toluene under Dean-Stark conditions. The products precipitated from the reaction mixture by quenching with diethyl ether allowing aldimines **469** and **470** to be obtained in excellent yield on a gram scale (88% and 83%) (Scheme 4.17).



Scheme 4.17 Synthesis of *N*-sulfonyl aldimines

4-3-3. Dihydropyridinone Synthesis

Dihydropyridinones with a C(4) ester substituent, were prepared following the isothiourea-mediated methodology from aryl and alkyl acetic acids and ketimines catalysed by (±)-tetramisole·HCl previously discussed.[167] Aryl substituted dihydropyridinone **474** and **475** were prepared under the same reaction condition, using DHPB as a catalyst. All the dihydropyridinones were purified through recrystallisation from diethyl ether to give the *anti*-diastereomers (>95:5 dr) form. Dihydropyridinone **237** was prepared using (−)-tetramisole·HCl and was purified by column chromatography to give product with 88:12 dr (Scheme 4.18).



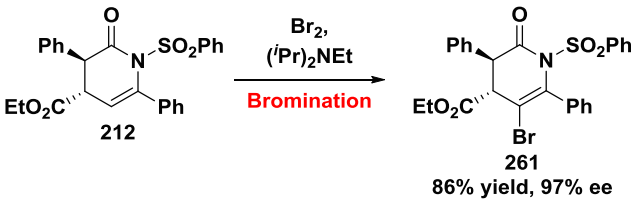
Scheme 4.18. Dihydropyridinones Preparation

[a]catalysed by (±)-tetramisole·HCl; [b]catalysed by DHPB;

*catalysed by (−)-tetramisole·HCl and purified through flash column chramotography

4-3-3-1. Effect of C(5) Substituent

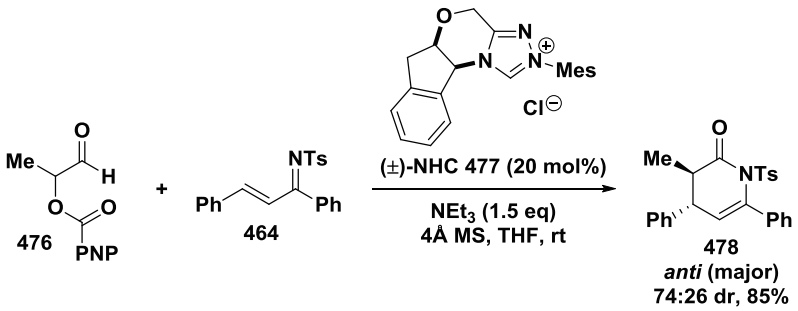
The 5-bromo dihydropyridinone **261** was prepared by treating dihydropyridinone **212** with bromine and $(^{i}Pr)_2NH$ in CH_2Cl_2, following the bromination procedure that as reported in chapter 2 (Scheme 4.19).[167]



Scheme 4.19 Synthesis of 5-bromo dihydropyridinone **261**

4-3-3-2. Dihydropyridinone with Alkyl Substituent on C(3)

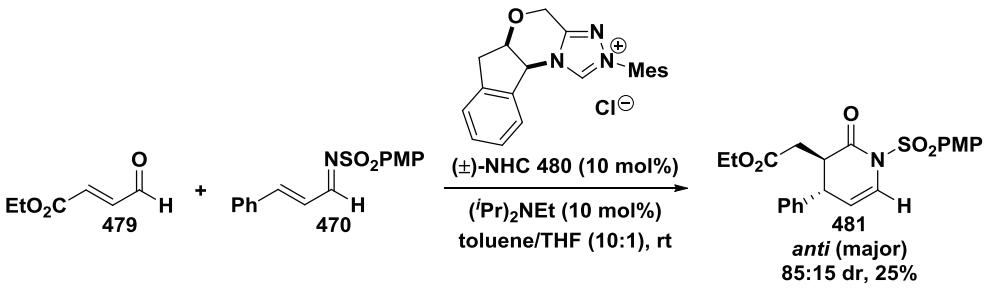
3-Methyl dihydropyridinone **478** was synthesed using an NHC-redox catalysis procedure previously developed within the group.[168] α-Aroyloxyaldehyde **476** was reacted with ketimine **464** catalysed by racemic triazolium NHC catalyst **477**. The crude was purified through flash column chramotography giving the desired *anti* major product **478** in 85% yield with 74:26 dr (Scheme 4.20).



Scheme 4.20 Dihydropyridinone Preparation *via* NHC-redox catalysis

4-3-3-3. Dihydropyridinone with H Substituent on C(6)

Following Bode's NHC approach,[169] treatment of α,β-unsaturated aldehyde **479** and aldimine **470** catalysed by racemic triazolium NHC catalyst **480** afford *anti* major dihydropyridinone **481** in 25% with 85:15 dr (Scheme 4.21).

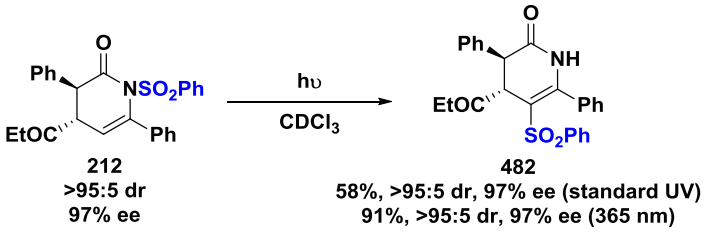


Scheme 4.21 Dihydropyridinone Preparation *via* Bode's Approach

4-4. Initial Studies

The *N*- to *C*-sulfonyl migration was initially observed during the preparation of the C(4) ester substituted dihydropyridinones. The isomerisation occurred when product **230** was concentrated under reduced pressure with the bath at 40 ˚C. Moreover, *p*-OMe aryl substituted dihydropyridinones such as **241** and **242** were even more reactive as sulfonyl migration was observed in $CDCl_3$ during NMR spectroscopic analysis.

Ester substituted dihydropyridinone **212** was initially examined under the same photochemical reaction conditions as previously found.[68] Therefore, dihydropyridinone **212** was dissolved in $CDCl_3$ and irradiated with a standard UV lamp for 24 hours. This promoted *N*- to *C*- sulfonyl migration, allowing product **482** to be isolated in 58% yield with no loss in diastereo and enantioselectivity (Scheme 4.22). However, the crude reaction mixture contained unidentified side products and therefore the yield was lower than expected.



Scheme 4.22 Initial Study with Chiral Dihydropyridinone **212**

The standard broad spectrum UV lamp output wavelength mainly at 365 nm but also gives strong wavelengths at 405 nm and also 435 nm,[170] which may cause the formation of undesired side products. The UV light resource was therefore replaced by a black light lamp that has a sharp wavelength at 365 nm only. In this case, the reaction was much cleaner giving the desired product in 91% yield, again with no loss in stereoselectivity.

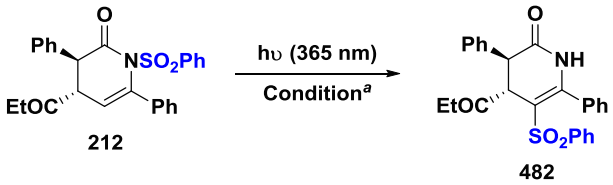
4-5. Control Experiments

4-5-1. Acid, temperature and light screen

The initial studies indicated that this *N*- to *C*-sulfonyl transfer can be triggered by a number of potential factors including mild acid (in $CDCl_3$), thermally (refluxing), or by light (UV). In order to investigate factors affecting efficient product formation, several control experiments were carried out. Firstly, dihydropyridinone **212** was placed in an NMR tube in $CDCl_3$ and was covered in foil to eliminated UV light. After 16 hour at rt. ^{1}H NMR analysis indicated that there was 37% conversion transferred into product **482**. After 40 hours, the ratio of dihydropyridinone **212** to product **482** increased to 51:49, but no further increase in product was observed after 112 hours (Table 4.1, Entry 1). Next, the reaction mixture was placed in bench chloroform and covered in foil eliminated UV light before being heated to 50 ˚C for 16 hours. ^{1}H NMR analysis showed a **212**: **482** ratio of 50:50, that proving that the transformation can be accelerated thermally in chloroform (Entry 2). In comparison, the sulfonyl transformation could be more efficiently performed under UV irradiation with product **482** formed in an excellent 91% isolated yield (Entry 3). Replacing the bench NMR solvent with $CDCl_3$ that was basified using solid K_2CO_3 completely shut down the reaction (Entry 4), while heating the reaction mixture to 50 ˚C led to no product being observed (Entry 5). However, the sulfonyl transfer did occur in basified $CDCl_3$ under UV irradiation and ^{1}H NMR analysis showed that starting material was fully consumed, resulting in the isolation of **482** in 90% yield (Entry 6). These results show that photo-irradiation with UV light at 365nm

is the most efficient way of promoting *N*- to *C*-sulfonyl migration. However the isomerisation also occurs under thermal conditions in the presence of bench $CDCl_3$, which is likely to be mildly acidic.

Table 4.1 Control Experiments- Acid, Temperature and Light



Entry	UV	T (˚C)	t (h)	SM (%)[b]	Pro (%)[b]
1[c]	off	rt	16	63	37
	off	rt	40	51	49
	off	rt	112	50	50
2	off	50	16	47	53
	off	50	40	47	53
3	on	30	16	6	94(91)[e]
4[d]	off	rt	16	100	-
5[d]	off	50	16	100	-
6[d]	on	30	16	4.5	90

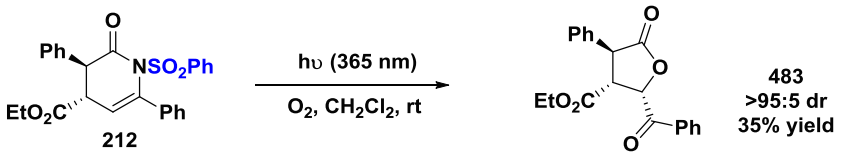
[a] conditions: reactions have been carried with racemic dihydropyridinone (>95:5 dr), in $CDCl_3$ in a NMR tube. [b] yield measured with 1-methyl naphthalene as internal standard by ^1H NMR spectroscopic analysis. [c] $CDCl_3$ used directly from bottle. [d] $CDCl_3$ basified with K_2CO_3 before used. [e] isolated yield

4-5-2. Scale-up

An interesting observation was made upon scaling-up the photoisomerisation procedure during optimisation. The reactions were mostly performed in NMR tubes with fairly on small scale (0.1 mmol). To enable to scale up, the reaction was performed in a round bottomed flask (RBF). However, irradiating **212** in $CDCl_3$ in a RBF did not give the expected product **482** but highly functionalised lactone **483** in 25% yield, the configuration was confirmed by *X*-ray crystallography. Hence, on scale-up reaction transfer to RBF required degassed $CDCl_3$.

4-5-3. Lactone Synthesis via Photolysis

Repeating the scaled-up photoisomerisation of dihydropyridinone **212** under an oxygen atmosphere allow resulted in formation of lactone **483**, which was isolated in 35% yield as confirmed by ^{1}H NMR analysis (Scheme 4.23)



Scheme 4.23 Lactone Formation under an O_2 atmosphere

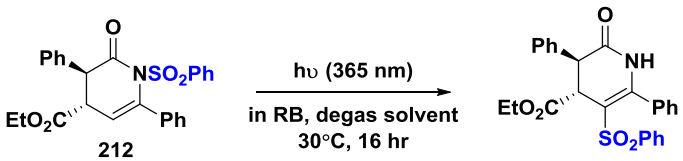
The formation of lactone suggests there is an oxygen source in the reaction. Compared with the reaction carried out in an NMR tube, the RBF has increased surface area in contacting with air. Dihydropyridinone was treated with methylene blue in methanol and red light (wavelength= 620-750 nm), which generate highly reactive singlet oxygen; however, no product was observed. This project was not followed further.

4-6. Optimisation-Solvent Screen

Various solvents were examined in this photoisomerisation reaction using enantiomerically pure dihydropyridinone **212** to determine the best solvent. Methanol gave only 9% conversion into product **482** after 16 hours by ^{1}H NMR analysis (Table 4.2, Entry 1). Ethyl acetate gave slight improvement resulting in 48% isolated yield without affecting the products enantiopurity (98% ee) (Entry 2). THF worked well, affording product **482** in 68% isolated yield and 97% ee. Using either CH_2Cl_2 or $CHCl_3$ gave completed conversion in 16 hours forming product **482** in 84% and 71% isolated yield, respectively (Entry 4 and 5). The yield was not affected by diluting the reaction in CH_2Cl_2 (Entry 6). The reaction was scale-up using racemic dihydropyridinone **212** (0.4 mmol) performing the reaction in a round-bottomed flask

in both CH_2Cl_2 and $CHCl_3$. Pleasingly, both reactions worked well, forming product **482** in excellent yield in both cases, and CH_2Cl_2 was chosen as the optimial solvent for further investigations. While performing the scale-up reaction it was also observed that trace impurities on the reaction glassware could affect the reaction yield. Therefore, all glassware was thoroughly cleaned in a KOH base bath and washed with water before use.

Table 4.2 Optimisation-Solvent Screen



Entry	Solvent	V (mL)	SM (%)[a]	Pro (%)[a]	Yield (%)[b]	ee (%)
1	MeOH	1	64	9	-	-
2	EtOAc	1	18	51	48	98
3	THF	1	11	78	68	97
4	CH_2Cl_2	1	-	85	84	98
5	$CHCl_3$	1	-	-	71	98
6	CH_2Cl_2	2	-	-	87	98
7[c,e]	CH_2Cl_2	4	-	98	95	N/A
8[c,d,e]	$CHCl_3$	4	-	97	95	N/A

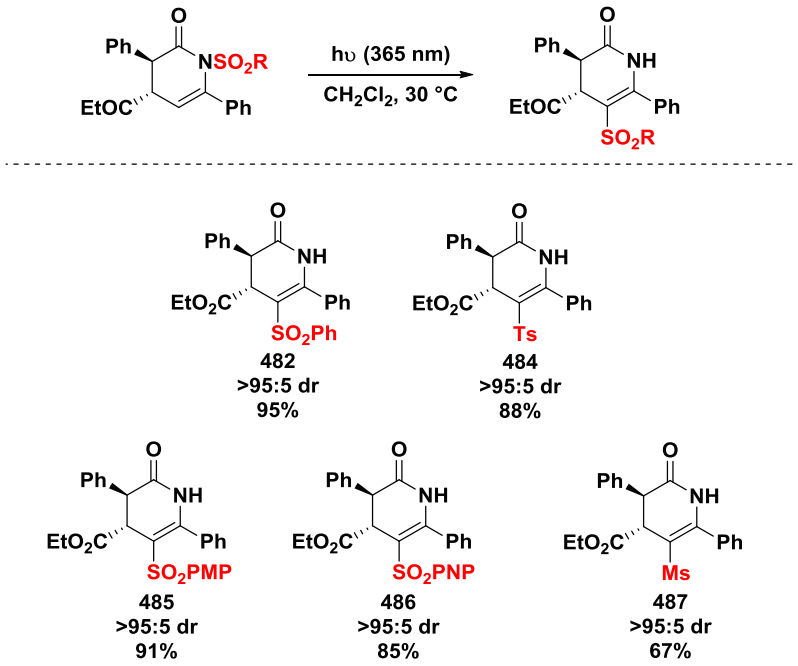
[a] yield measured with 1-methyl naphthalene as internal standard by ^{1}H NMR spectroscopic analysis.[b] isolated yield. [c] 0.4 mmol scale. [d] the glassware has been cleaned in a KOH bath overnight before used; [e]racemic **212** used

4-7. Scope

4-7-1. Variation of sulfonyl groups

With an optimised procedure in hand, the scope of this process was tested. A range of *N*-sulfonyl dihydropyridinones was subjected to the optimised photoisomerisation conditions. The methodology tolerates various different sulfonyl substituents including SO_2Ph and Ts, which give the isomerised products **482** and **484** in 95% and 88% yields, respectively. Aryl sulfonyl group containing both electron-donating (*p*-MeO) and electron-withdrawing (*p*-NO_2)

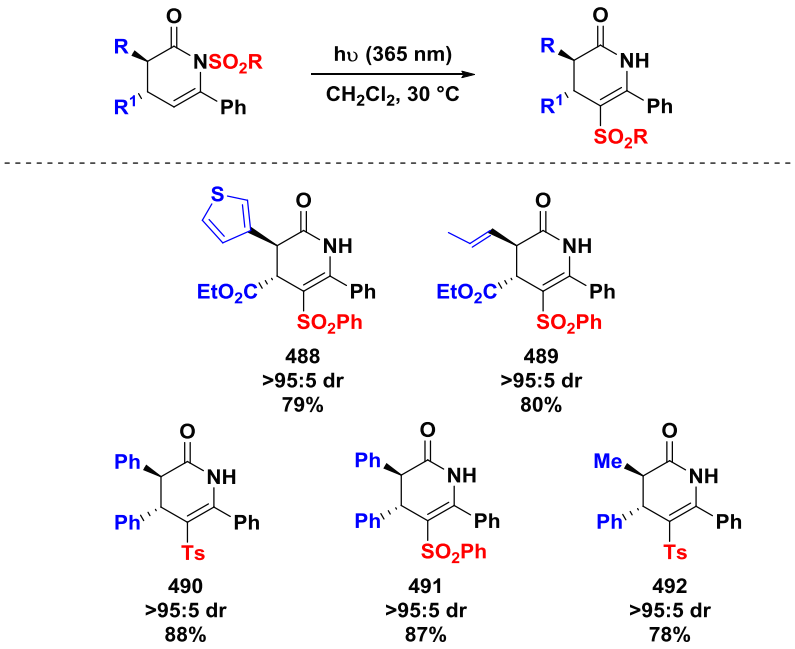
substituents also worked well, giving the products **485** and **486** in high yields. The *N*-mesyl substituted dihydropyridinone gave product **487** in a reduced isolated yield of 67%, with the remaining material isolated as un-reacted starting material (Scheme 4.24). All products retain high diastereoselectivity (>95:5 dr) and there is no epimerisation was observed.



Scheme 4.24 Variation of Sulfonyl Group

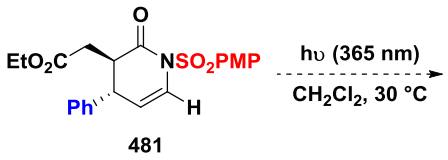
4-7-2. Variation of Ring Substituents

Dihydropyridinones with various substituent on *C*(3) and *C*(4) were investigated under the previously optimised conditions. Replaced the aryl group on *C*(3) with a 2-thiophene substituent, gave product **488** in a good 79% yield. An alkyl group could also be tolerated, giving **489** in good isolated yield (80%). Dihydropyridinones **474** and **475** with three aryl substituents also work well with product **490** and **491** formed in 88% and 87% yield, respectively (Scheme 4.25).



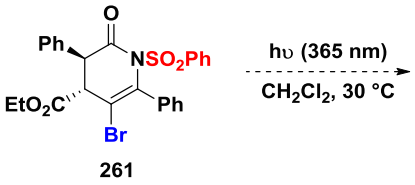
Scheme 4.25 Variation of Ring Substituents

Dihydropyridinone **481** without a C(6) substituent was also examined in this photoisomerisation. Surprisingly, in this case, no reaction was observed and only starting material was returned. This suggests that an aryl C(6) substituent may be important for the *N*- to *C*-sulfonyl migration process (Scheme 4.26).



Scheme 4.26 Reaction without C(5) substituent.

As expected, blocking the C(5) position with a bromine substituent prevented the photoisomerisation process with starting material **481** returned unchanged (Scheme 4.27).



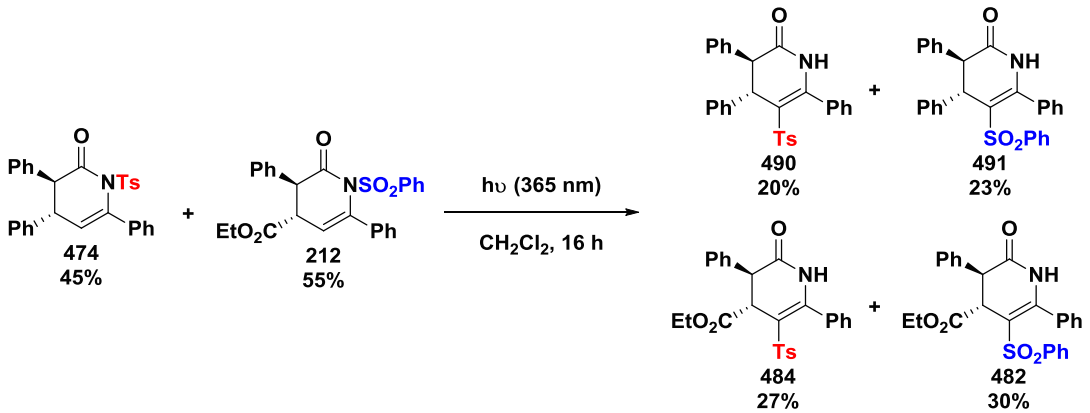
Scheme 4.27 Reaction with 5-Bromo Dihydropyridinone **261**

4-8. Mechanism Studies

To investigate the mechanism of this *N*- to *C*-sulfonyl migration process a number of experiments were performed.

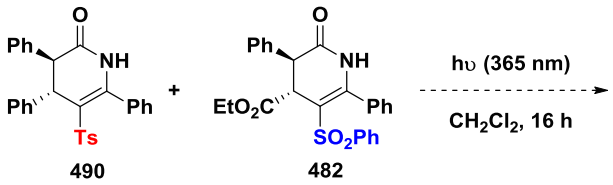
4-8-1. Crossover Reaction

Firstly, a crossover experiment was performed to probe whether the process is intra- or intermolecular in nature. Dihydropyridinones **474** and **212** (45:55) were irradiated at 365 nm in CH_2Cl_2 for 16 hours. Analysis of the crude ^1H NMR showed the formation of all four possible C-sulfonyl products, **482**, **484** and **490**-**491**, in approximately equal amounts, consistent with an intermolecular step at some point in the reaction mechanism (Scheme 4.28).



Scheme 4.28 Crossover Reaction of **474** and **212**

Irradiating a 1:1 mixture of *C*-sulfonyl products **490** and **482** under the standard reaction conditions did not lead to any further crossover, and two *C*-sulfonyl products **490** and **482** were returned unchanged (Scheme 4.29). This suggests that the products are sTable to photolysis and do not undergo further photo-induced processes.



Scheme 4.29 Product Crossover Reaction

These two crossover experiments indicate that the *N*- to *C*- sulfonyl migration reaction is intermolecular, as all four possible products were obtained from a crossover experiment in an approximate statistical mixture.

4-8-2. Proposed Mechanism

A plausible mechanism of this photoisomerisation reaction involves the homolysis of the N-S bond upon UV photolysis at 365 nm. The UV/Vis spectrum of dihydropyridinone **212** showed absorption maximium at 261.9 nm and a small maximium at 366.8 nm (Figure 4.1).

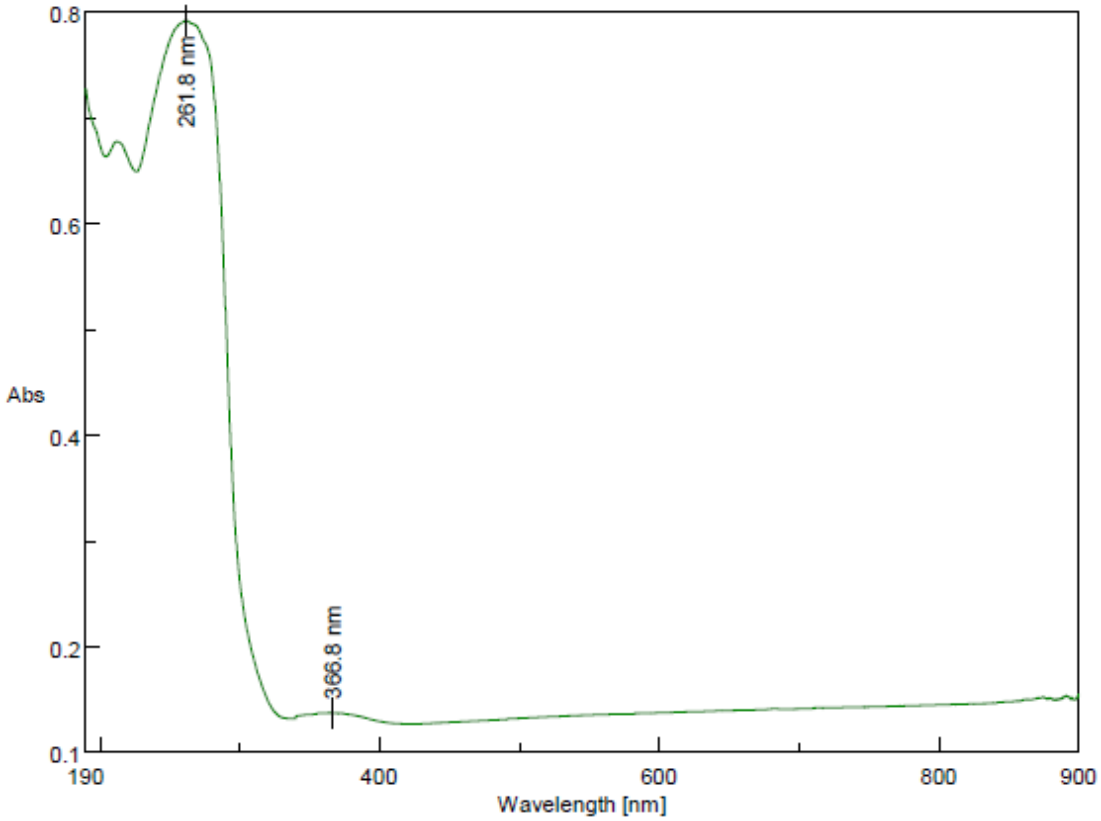
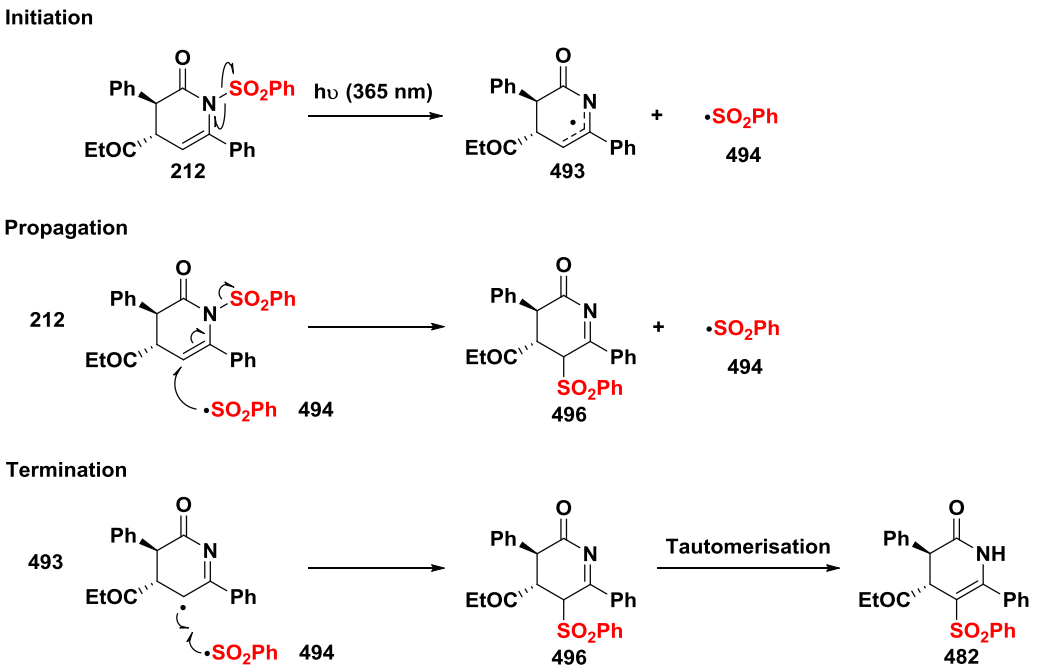


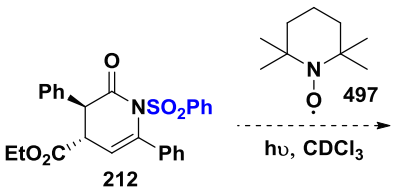
Figure 4.1 The UV/Vis spectrum of dihydropyridinone **212**

The strong absorption at 365 nm radiation indicates that the dihydropyridinone **212** may be excited under the reaction conditions. A plausible radical mechanism for this photoisomerisation process is shown in Scheme 4.30. It is proposed that the reaction could be initiated by the homolysis of the N-S bond of dihydropyridinone **212** to generate sulfonyl radical **494** and radical **493**. The radical process can be propagated by the reaction of sulfonyl radical **494** with dihydropyridinone **212** at C(5) position to form intermediate **496** and generate more sulfonyl radical **494**. The reaction can be terminated by radical recombination of **494** and **493** at C(5) position to form intermediate **496** that can subsequently tautomerise into product **482**. This mechanism is consistent with the crossover experiments described previously (Scheme 4.28) as sulfonyl radical **494** reacts is proposed to react in an intermolecular fashion with remaining dihydropyridinone during the propagation step.



Scheme 4.30 The Proposed Mechanism

In an attempt to confirm the presence of radical intermediates, the photoisomerisation of dihydropyridinone **212** was repeated with the addition of one equivalent of TEMPO as a radical scavenger. In the case, no product formation was observed and the starting material was recovered unchanged (Scheme 4.31).



Scheme 4.31 The Reaction with TEMPO

4-8-3. EPR Experiment

To further investigate the possibility of radical formation, a sample of dihydropyridinone **212** was irradiated analysed by EPR spectroscopy in collaboration with Professor John Walton.

Treatment of dihydropyridinone was examined by EPR spectroscopy in ^{t}Butyl benezene (^{t}BuPh) and radiated at 250 nm at room temperature (295 K) with sources after 1 minute and 40 minutes giving interesting data on the species in solution. The experimental *g*-factor and

the hyperfine splitting (hft) of the initial species in spectrum (a) and the major component in (b) are very close to the parameters from the literature for the benzenesulfonyl radical, ·SO_2Ph. (Lit[171]: *g*-factor = 2.0045, $a(2H_m)$ = 1.18, $a(1H_p)$ = 0.55, $a(2H_o)$ = 0.35 G) (Figure 4.2). This is positive evidence supporting the formation of benzenesulfonyl radical **494** during the photolysis. In addition the EPR signal is isotropic that confirms radical **494** disconnected from dihydropyridinone xx and is freely mobile in the solution.

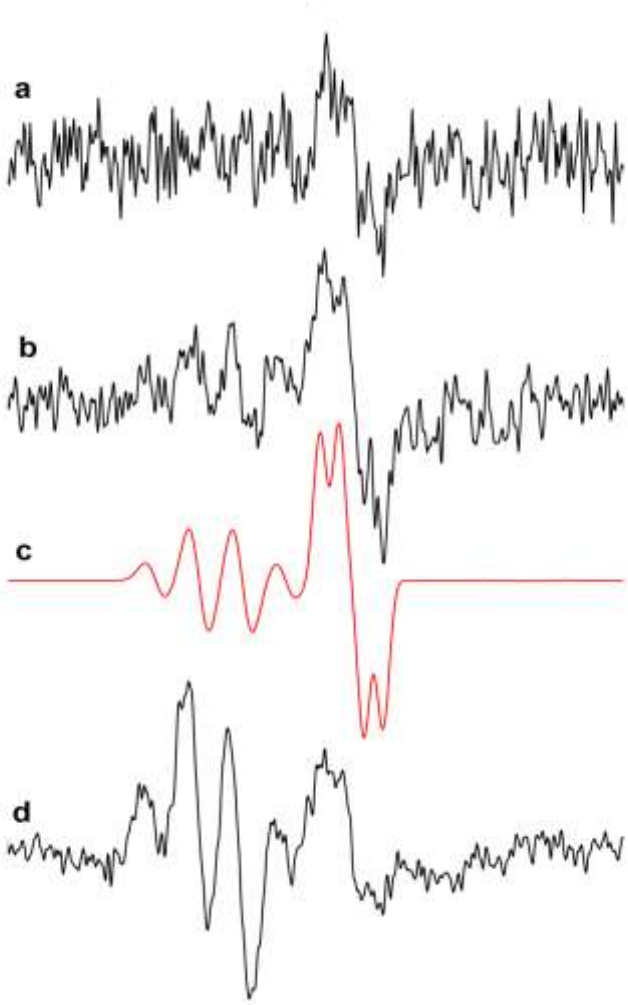


Figure 4.2 EPR Spectra During Continuous Photolysis of a Solution of Dihydropyridinone **212** in ^{t}BuPh at 295 K.

(a) 1 scan after 1 min UV irradiation; (b) 40 scans after ~ 15 min UV irradiation; (c) Computer simulation; (d) 70 scans after ~ 60 min UV irradiation.; Best fit of spectrum (b) (R = 0.900) was obtained with the following parameters: Major radical: 77 %, lw = 0.54 G, *g*-factor = 2.0044, $a(2H_m)$ = 1.18, $a(1H_p)$ = 0.55, $a(2H_o)$ = 0.35 G; Minor radical: 23% , lw = 0.0.6 G, *g*-factor= 2.0090, $a(3H)$ = 2.51 G

As photolysis was continued, a second radical was generated and dominated in the spectrum (d) after 60 minutes. Compared with the experimental hfs and computational hft from the related structure of aza-ally radical **498**, the results suggested the second radical is not **493** (Figure 4.3).

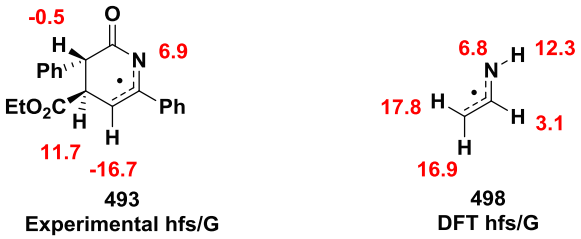


Figure 4.3 Experimental and DFT computed hfs of radicals related to **493**

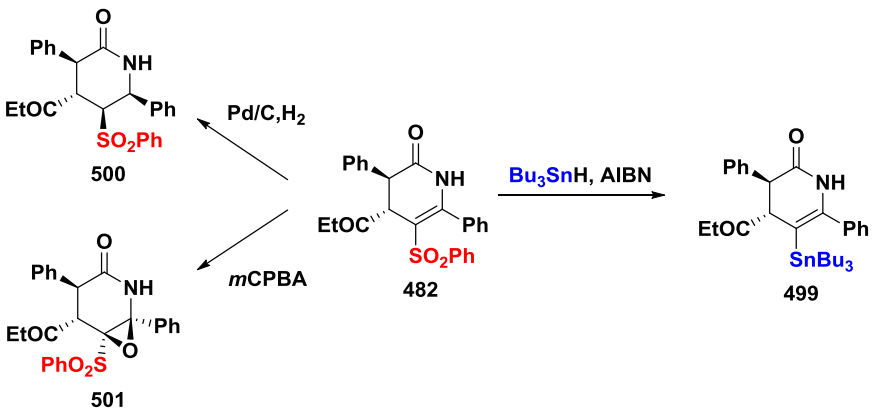
The *g*-factor of the second radical is unusually large (*g*= 2.0090), which is consistent with it not being located in carbon or nitrogen. The literature suggests that the radical is benzenesulfinyl radical, ·SOPh. (lit[172]: *g*-factor = 2.0091, $a(2H_m)$ = 0.7, $a(1H_p)$ = 2.4, $a(2H_o)$ = 2.4 G). Although the small hfs from meta-H atom is resolved in spectrum (d), otherwise, the other correspondence are close. Spectrum (b) and simulation spectrum (c) contains both sulfonyl and sulfinyl radicals and are closely matched to the related radical from literature.[173] The sulfinyl radical could possibly be generated from the sulfonyl radical or from either starting material dihydropyridinone **212** or photoisomerisation product **482**. although none of these products have been observed in the photoisomerisation in solution.

4-9. Conclusion

In summary, a novel *N*- to *C*-sulfonyl migration promoted by UV light was developed and a range of dihydropyridinones with various sulfonyl, aryl and alkyl substituents were successfully isomerised. This method uses mild reaction conditions and generally gave high yields without loss of the diastereo- or enantioselectivity of the dihydropyridinone products tested. Mechanistic studies indicate that *N*- to *C*-sulfonyl migration is a radical process promoted by UV absorption at 365 nm and crossover studies indicate there is an intermolecular step in the reaction process.

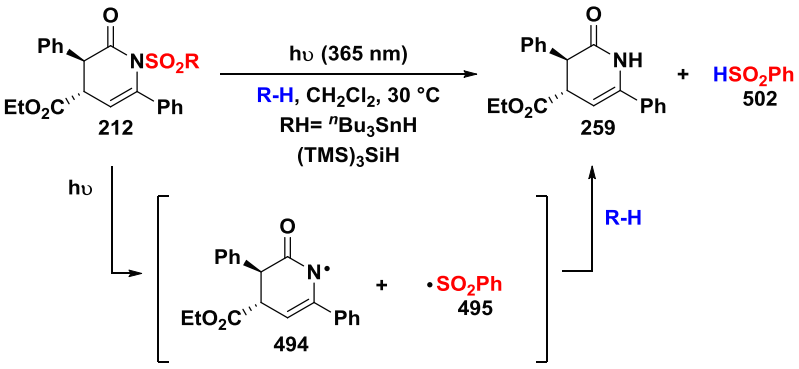
4-10. Future Work

The synthetic utility of the *C*-sulfonyl products could be investigated. For example, literature precedent indicated that treating *C*-sulfonyl alkenyl with organometallic reagents results in alkyl substitution. Treatment with Bu_3SnH/AIBN may lead to formation of alkenyl tin product **499**, which could be further utilised in cross-coupling reaction.[153] The alkene moiety of dihydropyridinone **482** can be functionalised *via* hydrogenation by a treatment with Pd/C/H_2 creating two new stereocenters; or reacted with mCPBA forming an expoxide **501** (Scheme 4.32).



Scheme 4.32 Potential derivatisation examples

EPR analysis of photoisomerisation showed evidence of formation of benzenesulfonyl radical **494**. According to previous reports, $^{n}Bu_3SnH$[174] and $(TMS)_3SiH$[175] can be used as a benzensulfonyl radical scavenger to form phenylsulfinic acid **502**, which is sTable and water soluble. This could be used in combination with the optimised photoisomerisation conditions to form desulfonylation products **259** (Scheme 4.33).



Scheme 4.33 The potential Photodesulfonylation

Conclusion

This thesis has demonstrated the organocatalytic ammonium enolate chemistry principally applied to ketimine acceptors using isothiourea catalysts. For example, the synthesis of dihydropyridinones resulted in excellent stereoselectivity (94-99% ee and 84:16 dr to >95:5 dr). The dihydropyridinone product was successfully transferred into several potential products *via* bromination, dehydrogenation and reduction without compromising the stereoselectivity. A one-pot highly efficient planar heterocycle synthesis catalysed by isothioureas was developed resulting in the formation of highly functionalised pyridines and pyrones. This methodology was then extended to the preparation of the patent COX-2 inhibitor **366** (see Scheme 3.25). The pyrone product was also utilised as a diene in forming various aromatics such as benzene and naphthalene *via* Diels-Alder/retro-Diels-Alder reactions.

The intermolecular 1,3-sulfonyl migration of these asymmetric dihydropyridinones was performed by photoisomerisation. The scope covered with a range of sulfonyl groups and the mechanism has been studied by cross-over experiments and EPR analysis indicating a radical mechanism.

Future Work

To date, organocatalytic ammonium enolate chemistry has shown the potential for the synthesis on enantiopure heterocycle products with high stereocontrol. This project has demonstrated it can also apply to planar heterocycle synthesis. The next step for organocatalytic ammonium enolate chemistry could be to develop the synthesis for multi-ring structure (see Figure. 2.16), creating for quaternary carbon centre formation and subsequent application in natural product synthesis.

Chapter 5. Experimental

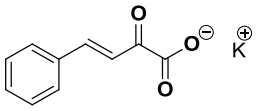
5-1.General information

Anhydrous CH_2Cl_2 was obtained from an Mbraun SPS-800 system. Pet. ether is defined as petroleum ether 40–60 ℃. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature (rt) refers to 20–25 ℃. Temperatures of 0 °C and −78 °C were obtained using ice/water and CO_2(s)/ acetone baths, respectively. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution and heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated. Melting points were recorded on an Electrothermal 9100 apparatus. Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 ℃. HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasedser, LC-20AT liquid chromatography, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25–40 ℃. Separation was achieved using a Chiralcel OD-H column or Chiralpak AD-H, and IA, columns. Authentic racemic samples of chiral products were synthesised using achiral DHPB **214** or racemic tetramisole·HCl **211**. Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer as thin films using Pike MIRacle ATR accessory. Analysis was carried out using Shimadzu IR solution v1.50 and only characteristic peaks are reported. ^{1}H and ^{13}C{1 H} spectra were acquired on either a Bruker Avance 300 {δ_H (300 MHz), δ_C (75 MHz), δ_F (282 MHz)}, a Bruker Avance II 400 {δ_H (400 MHz), δ_C (101 MHz), δ_F (376 MHz)} or a Bruker Ultrashield 500 {δ_H (500 MHz), δ_C (126 MHz), δ_F (471 MHz)} spectrometer at ambient temperature in the deuterated solvent stated. Chemical

shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants, *J*, are quoted in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; dd, doublet of doublets; dq, doublet of quartets; ddd, doublet of doublet of doublets; ddt, doublet of doublet of triplets; td, triplet of doublets; tt, triplet of triplets; tdd, triplet of doublet of doublets; m, multiplet; bs., broad singlet. Mass spectrometry (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) at the EPSRC National Mass Spectrometry Service Centre, Swansea.

5-2. Preparation of potassium salts 207

Potassium (*E*)-2-oxo-4-phenylbut-3-enoate, **207**

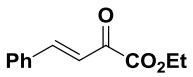


Following the procedure outline by Smith *et al*.,[40] to a solution of pyruvic acid (3.58 ml. 50 mmol, 1 eq), benzaldehyde (5.09 ml, 50 mmol, 1 eq) and MeOH at 0 °C was added a solution of KOH (4.20 g, 75.0 mmol, 1.5 eq) in MeOH (15 ml). The first equvalent of the KOH solution was added dropwise over 30 min. the last third was added as one portion and the reaction stirred at 40 °C for 1 hr then rt overnight. The precipitate was collected by filtration, washed twice with cold MeOH, once with ether and dried under vacuum gave potassium salt **207** (9.3 g, 84%), and was used without further purification.

mp. 246-248 °C; {Lit.[40] 248 °C }; **^{1}H** (400 MHz D_2O) δ_H: 6.80 (1H, d, *J* 16.5, C(3)*H*), 7.37-7.46 (1H, m, Ar*H*), 7.59-7.65 (3H, m, C(4)*H* & Ar*H*). Data consistent with literature.[40]

5-3. Preparation of α,β- unsaturated ketoesters

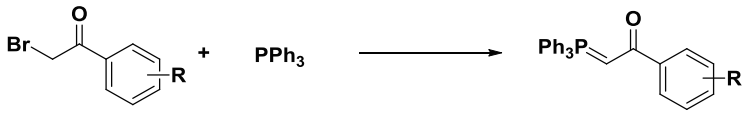
(*E*)-ethyl 2-oxo-4-phenylbut-3-enoate, **204**



Following the procedure outline by Meng *et al*.,[176] acetyl chloride (34.4 ml, 483 mmol, 11.5 eq) and potassium salt **207** (9.0 g, 42 mmol) were added to the ethanol (300 ml) at 0 ^{o}C for 30 minutes then warmed to rt then heating at reflux overnight. Concentration in vacuo gave a solid which was dissolved in water and extracted with CH_2Cl_2. The combined organics were washed with sat. aq. $NaHCO_3$, water and brine being dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude reaction mixture. Purified by flash column chromatography gave **204** as yellow oil (4.4 g, 50%).; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 1.41 (3H, *J* 7.1, CH_2CH_3), 4.40 (2H, *J* 7.1, CH_2CH_3), 7.34 (1H, *J* 16.1, C(4)*H*), 7.40-7.48 (3H, m, Ar*H*), 7.64 (2H, dd, *J* 1.9, 7.4, Ar*H*), 7.87 (1H, *J* 16.1, C(3)*H*). Data consistent with literature.[40]

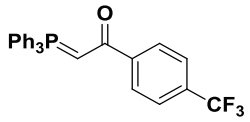
5-4. Data for Phosphoranes

General procedure A- *preparation of phosphorane **197***



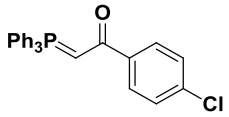
Following the procedure outline by Smith *et al*.,[40] the corresponding 2-bromoethanone (1.0 eq) and triphenylphosphine (1.0 eq) were refluxed in dry THF for 4 hrs. Once the completion, the reaction mixture was allowed to cool down to rt and the phosphonium salt was filtered and washed with Et_2O. The phosphonium salt was re-dissolved in water/CH_2Cl_2 and 2 M. aq. NaOH was added. The mixture was stirred overnight at rt and then extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding phosphorane.

1-(4-(trifluoromethyl)phenyl)-2-(triphenylphosphoranylidene)ethanone, **S1**



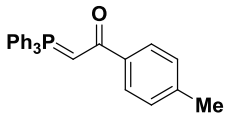
Following general procedure A: 2-bromo-1-(4-trifluoromethyl)phenylethanone (8.0 g, 30.0 mmol), triphenylphosphine (7.87 g , 30 mmol) in dry THF (150 ml) gave **S1** (12.7 g, 94%); **mp.** 172-174 ^{o}C {Lit.[40] 195 ^{o}C }; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 4.45 (1H, d, *J* 21, C(2)*H*), 7.43- 7.54 (6H, m, Ar*H*), 7.54- 7.63 (5H, m, Ar*H*), 7.65- 7.77 (6H, m, Ar*H*), 8.08 (2H, d, *J* 8.0, Ar*H*). Data consistent with literature.[40]

1-(4-chlorophenyl)-2-(triphenylphosphoranylidene)ethanone, **S2**



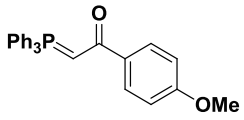
Following general procedure A: 2-bromo-4'-chloroacetophenone (7.0 g, 30.0 mmol), triphenylphosphine (7.87 g , 30 mmol) in dry THF (150 ml) gave **S2** (11.6 g, 93%); **mp.** 186-188 ^{o}C {Lit.[40] 195-197 ^{o}C }; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 4.39 (1H, d, *J* 23.7, C(2)*H*), 7.30 (2H, d, *J* 8.5, Ar*H*), 7.42- 7.52 (6H, m, Ar*H*), 7.54- 7.57 (3H, m, Ar*H*), 7.64- 7.77 (6H, m, Ar*H*), 7.90 (2H, d, *J* 8.5, Ar*H*). Data consistent with literature.[40]

1-(p-tolyl)-2-(triphenylphosphoranylidene)ethanone, **S3**



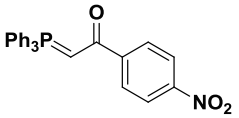
Following general procedure A: 2-bromo-4'-methylacetophenone (6.39 g, 30.0 mmol), triphenylphosphine (7.87 g , 30 mmol) and dry THF (150 ml) gave **S3** (9.8 g, 83%); **mp.** 172-174 ^{o}C {Lit.[40] 179-181 ^{o}C }; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 4.41 (1H, d, *J* 24.7, C(2)*H*), 7.16 (2H, d, *J* 8.0, C(2)*H*), 7.43- 7.50 (6H, m, *Ph*), 7.52- 7.58 (3H, m, *Ph*), 7.67- 7.77 (6H, m, Ph), 7.88 (2H, d, *J* 8.0, *Ph*). Data consistent with literature.[40]

1-(4-methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone, **S4**



Following general procedure A: 2-bromo-4'-methoxylacetophenone (6.87 g, 30.0 mmol), triphenylphosphine (7.87 g , 30 mmol) and dry THF (150 ml) gave **S4** (11.6 g, 94%); **mp.** 144-146 ^{o}C {Lit.[40] 140 ^{o}C }; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 4.41 (1H, d, *J* 24.7, C(2)*H*), 7.16 (2H, d, *J* 8.0, C(2)*H*), 7.43- 7.50 (6H, m, Ar*H*), 7.52- 7.58 (3H, m, Ar*H*), 7.67- 7.77 (6H, m, Ar*H*), 7.88 (2H, d, *J* 8.0, Ar*H*). Data consistent with literature.[40]

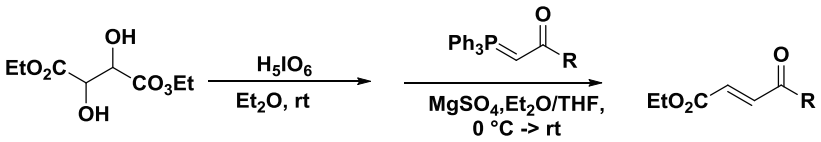
1-(4-nitrophenyl)-2-(triphenylphosphoranylidene)ethanone, **S5**



Following general procedure A: 2-bromo-4'-methoxylacetophenone (7.32 g, 30.0 mmol), triphenylphosphine (7.87 g , 30 mmol) and dry THF (150 ml) gave **S5** (12.1 g, 94%); **mp.** 150-152 ^{o}C {Lit.[40] 162-164 ^{o}C }; **^{1}H NMR** (300 MHz $CDCl_3$) δ_H 4.50 (1H, d, *J* 23.0, C(2)*H*) , 7.50- 7.53 (6H, m, Ar*H*), 7.58- 7.63 (3H, m, Ar*H*), 7.68- 7.74 (6H, m, Ar*H*), 8.08 (2H, d, *J* 8.6, Ar*H*), 8.20 (2H, d, *J* 8.6, Ar*H*). Data consistent with literature.[40]

5-5. Data for α,β- unsaturated ketones (198-203)

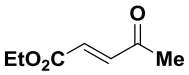
General procedure B- *preparation of α,β-unsaturated ketones*



Following the procedure outline by Xiao *et al.*,[72] periodic acid dehydrate (10 mmol, 1 eq.) was added into a stirred solution of diethyl tartrate (10 mmol, 1 eq.) in dry Et_2O (20 ml) at RT. After 3 hrs, the suspension was filtered and the solid was wash with 25 ml dry THF. Magnesium sulphate (3.0 g) was added to the organic phase and the reaction mixture was then

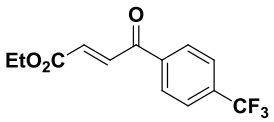
cooled in the ice bath for 30 mins. The corresponding 2-(triphenylphosphoranylidene)acetophenone (15 mmol, 1.5 eq.) was add and then warmed up to rt. Once completion, the mixture was filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: EtOAc = 15:1) to afford the desired product.

(*E*)-ethyl 4-oxopent-2-enoate, **198**



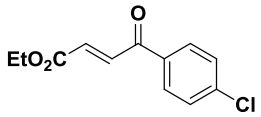
Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 ml), then added 1-(triphenylphosphoranylidene)-2-propanone (4.78 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **198** (1.86 g, 13.0 mmol, 87%), as yellow liquid.; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 1.26 (3H, d, *J* 7.1, C*H*$_3$) , 2.30 (3H, s, -*Me*), 4.20 (2H, q, *J* 7.1, -C*H*$_2$), 6.58 (1H, d, *J* 16.2, -C*H*), 6.95 (1H, d, *J* 16.2, -C*H*); Data consistent with literature.[177]

(*E*)-ethyl 4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-enoate, **199**



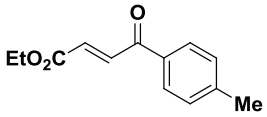
Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 ml), then added **S1** (6.73 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **199** (3.63 g, 13.3 mmol, 89%), as as yellow solid; **mp.** 152-154 ^oC ; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.35 (3H, d, *J* 7.1, C*H*$_3$) , 4.31 (2H, q, *J* 7.1, -C*H*$_2$), 6.91 (1H, d, *J* 15.6, -C*H*), 7.78 (2H, d, *J* 8.8, Ar*H*), 7.89 (1H, d, *J* 15.6, -C*H*), 8.09 (2, d, *J* 8.8, Ar*H*)

(*E*)-ethyl 4-(4-chlorophenyl)-4-oxobut-2-enoate, **200**



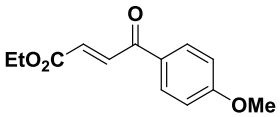
Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 ml), then added **S2** (6.21 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **200** (3.19 g, 13.4 mmol, 89%), as yellow solid.; **mp.** 52-54 ^oC {Lit.[178] 64-65 ^oC }; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.34 (3H, d, *J* 7.1, C*H*$_3$) , 4.29 (2H, q, *J* 7.1, -C*H*$_2$), 6.88 (1H, d, *J* 15.5, -C*H*), 7.48 (2H, d, *J* 8.5, Ar*H*), 7.85 (1H, d, *J* 15.5, -C*H*), 7.93 (2H, d, *J* 8.5, Ar*H*); Data consistent with literature.[72]

(*E*)-ethyl 4-oxo-4-(p-tolyl)but-2-enoate, **201**



Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 ml), then added **S3** (5.92 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **201** (2.83 g, 13.0 mmol, 86%), as yellow liquid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.34 (3H, d, *J* 7.1, C*H*$_3$) , 2.43 (3H, s, -*Me*), 4.29 (2H, q, *J* 7.1, -C*H*$_2$), 6.86 (1H, d, *J* 15.6, -C*H*), 7.30 (2H, d, *J* 7.9, Ar*H*), 7.86-7.95 (3H, m, -C*H* & Ar*H*); Data consistent with literature.[72]

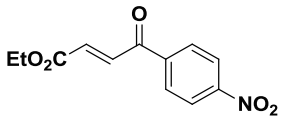
(*E*)-ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate, **202**



Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 ml), then added **S4** (6.16 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **202** (3.12 g, 13.3 mmol, 89%), as yellow

solid.; **mp.** 40 °C {Lit.[178] 37-38 °C }; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.1, C*H*$_3$) , 3.90 (3H, s, -O*Me*), 4.30 (2H, q, *J* 7.1, -C*H*$_2$), 6.87 (1H, d, *J* 15.5, -C*H*), 6.98 (2H, d, *J* 9.0, Ar*H*), 7.92 (1H, d, *J* 15.5, -C*H*), 8.01 (2H, d, *J* 9.0, Ar*H*); Data consistent with literature.[72]

(*E*)-ethyl 4-(4-nitrophenyl)-4-oxobut-2-enoate, **203**



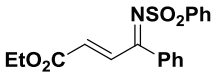
Following general procedure B, the reaction of periodic acid dehydrate (2.28 g, 10 mmol) and diethyl tartrate (2.06 g, 1.71 mL, 10 mmol) in dry Et_2O (20 mL), then added **S5** (6.38 g, 15 mmol), after purification (Et_2O : petrol 5:95) gave **203** (3.24 g, 13.0 mmol, 87%), as yellow solid.; **mp.** 138-140 °C {Lit.[178] 71-72 °C }; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.1, C*H*$_3$), 4.31 (2H, q, *J* 7.1, -C*H*$_2$), 6.92 (1H, d, *J* 15.5, -C*H*), 7.86 (1H, d, *J* 15.6, -C*H*), 8.14 (2H, d, *J* 9.0, Ar*H*), 8.35 (2H, d, *J* 8.9, Ar*H*); Data consistent with literature.[72]

5-6. Data for ketimines

General procedure C- *preparation of ketimine*

A flame-dried flask containing a stirrer bar was charged with the requisite sulfonamide (1 eq.), ethyl 3-benzoylacrylate (1 eq.) and CH_2Cl_2 (ca. 0.2 M). The resulting solution was stirred and cooled to 0 ℃ before Et_3N (2 eq.) was added followed by $TiCl_4$ (1 eq.) dropwise. The reaction mixture was allowed to warm to rt, a reflux condenser fitted to the flask, and the reaction heated at reflux overnight. The solvent was removed *in vacuo*, the titanium salts precipitated with Et_2O and the suspension filtered. The filtrate was concentrated *in vacuo*, the residue cooled in an ice/acetone/salt bath (~ −20 ℃), and triturated with a small amount of Et_2O (ca. 5 mL g^{-1}) with stirring. The resultant solid was collected by filtration and washed with further portions of cold Et_2O. The solid was dried in vacuo to leave the pure ketimines.

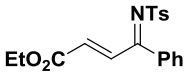
(2*E*,4*Z*) Ethyl -4-phenyl-4-((phenylsulfonyl)imino)but-2-enoate , **190**



Following general procedure C, the reaction of (*E*)-ethyl 3-benzoylacrylate 13 (1.84 mL, 10 mmol), benzenesulfonamide (1.57 g, 10.0 mmol), NEt_3 (2.8 mL, 20 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) in CH_2Cl_2 (30 mL) gave the title compound **190** after trituration as white crystals (2.04 g, 6.0 mmol, 60%).

mp. 51-52 °C {lit.[66] mp. 52 °C }; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.0, -CH_2CH_3), 4.30 (2H, q, *J* 6.3, -CH_2CH_3), 6.24 (1H, d, *J* 16.2, C(2)*H*), 7.44 (2H, t, *J* 7.7, Ar*H*), 7.51-7.56 (3H, m, Ar*H*), 7.62 (1H, t, *J* 7.4, Ar*H*), 8.03 (2H, s, Ar*H*), 8.24 (1H, d, *J* 16.1, C(3)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 14.3 (-CH_2CH_3), 61.7 (-CH_2CH_3), 127.5, 128.8, 129.1, 130.3, 133.2, 133.6, 136.8, 140.7, 164.7 (*C*(1)), 175.0 (*C*(4)); Data consistent with literature.[66]

(2*E*,4*E*)-Ethyl -4-phenyl-4-(tosylimino)but-2-enoate, **191**



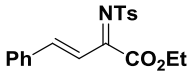
Following general procedure C, the reaction of ethyl 3-benzoylacrylate (1.84 mL, 10 mmol), *p*-toluenesulfonamide (1.68 g, 10.0 mmol), NEt_3 (2.8 mL, 20 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) in CH_2Cl_2 (30 mL) gave the title compound **191** after trituration

(1.22 g, 3.4 mmol, 34%) as white crystals.

mp. 53-54 °C; **ν_{max}** (ATR): 2938, 1714, 1545, 1304, 1157, 1094; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 6.8, -CH_2CH_3), 2.44 (3H, s, -*Me*), 4.30 (2H, q, *J* 6.6, -CH_2CH_3), 6.22 (1H, d, *J* 16.2, C(2)*H*), 7.34 (2H, d, *J* 7.9, Ar*H*), 7.43 (2H, t, *J* 7.6, Ar*H*), 7.56 (1H, t, *J* 7.4, Ar*H*), 7.72 (2H, s, Ar*H*), 7.84-7.96 (2H, br s, Ar*H*), 8.24 (1H, d, *J* 16.1, C(3)*H*); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ_C 14.2 (-CH_2CH_3), 21.1, 61.7 (-CH_2CH_3), 126.6, 127.6, 128.7, 129.7, 132.7, 133.9, 135.9, 136.5 (*C*-CO), 137.8 (NSO_2ArC(1)), 144.7 (NSO_2ArC(4)), 164.7 (*C*(1)), 174.4

(*C*(4)); **HRMS (ESI+)** C19H20NO4S ([M+H]+), found 358.1107 requires 358.1108 (− 0.2 ppm)).

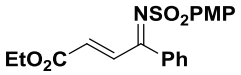
(2*E*,3*E*)-Ethyl-4-phenyl-2-(tosylimino)but-3-enoate, **208**



The starting ketone, (E)-ethyl 2-oxo-4-phenylbut-3-enoate, was prepared according the procedure outlined by Smith *et al*.[149] Following general procedure C, the reaction of the ketone **204** (2.0 g, 9.8 mmol), *p*-toluenesulfonamide (1.68 g, 9.8 mmol), NEt_3 (2.8 mL, 19.6 mmol) and $TiCl_4$ (1.1 mL,9.8 mmol) in CH_2Cl_2 (30 mL) gave **208** after purification by flashchromatography (EtOAc–pet. ether, 1 : 5) as a brown oil (1.51 g, 4.2 mmol, 43%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.48 (3H, t, *J* 7.1, -CH_2CH_3), 2.43 (3H, s, -*Me*), 4.55 (2H, q, *J* 7.1, -CH_2CH_3), 6.82 (1H, d, *J* 16.5, C(2)*H*), 7.29-7.56 (8H, m, Ar*H* and C(3)*H*), 7.90 (2H, d, *J* 8.3, Ar*H*). Data consistent with literature.[149]

(2*E*,4*E*)-Ethyl 4-(((4-methoxyphenyl)sulfonyl)imino)-4-phenylbut-2-enoate, **193**

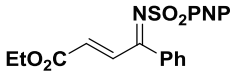


Following general procedure C, the reaction of (*E*)-ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), 4-methoxybenzenesulfonamide (0.94 g, 5.0 mmol), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (15 mL), gave the title compound **193** after trituration (0.95 g, 2.5 mmol, 50%) as an orange solid.

mp. 76-78 °C; **ν_{max}** (ATR): 2985, 1716, 1552, 1494, 1311, 1255, 1184, 1143, 1089, 1002, 975; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.35 (1H, t, *J* 6.4, -CH_2CH_3), 3.38 (3H, s, -OCH_3), 4.18-4.40 (2H, m, -CH_2CH_3), 6.21 (1H, d, *J* 16.2, C(2)*H*), 7.00 (2H, d, *J* 8.3, C(4)Ar*C*(3)*H*), 7.43 (2H, t, *J* 7.5, C(4)Ar*C*(3)*H*), 7.56 (1H, t, *J* 7.2, C(4)Ar*C*(4)*H*), 7.363-7.80 (2H, m, NSO_2ArC(3)*H*), 7.97 (2H, d, *J* 3.7, NSO_2Ar*C*(2)*H*), 8.25 (1H, d, *J* 17.4, *C*(3)*H*); **^{13}C{^{1}H} NMR** (126 MHz,

$CDCl_3$) δ_C 14.3 (-CH_2*C*H_3), 55.8 (-O*C*H_3), 61.7 (-*C*H_2CH_3), 114.2 (C(4)Ar*C*(3)), 128.7 (C(4)Ar*C*(2)), 129.7 (NSO_2Ar*C*(2)), 130.3 (NSO_2Ar*C*(3)), 132.3 (NSO_2Ar*C*(1)), 132.9 (*C*(3)), 133.4 (C(4)Ar*C*(4)), 136.0 (C(4)Ar*C*(1)), 136.9 (*C*(2)), 160.8 (NSO_2Ar*C*(4)), 163.4 (*C*(1)), 170.3 (*C*(4)); **HRMS (ESI+)**: $C_{19}H_{20}NO_5S$ $[M+H]^+$ found 374.1054, requires 374.1057 (−0.7 ppm).

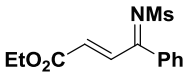
(2*E*,4*E*)-Ethyl-4-(((4-nitrophenyl)sulfonyl)imino)-4-phenylbut-2-enoate, **194**



Following general procedure C the reaction of (*E*)-ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), 4-nitrobenzenesulfonamide (1.01 g, 5.0 mmol), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (15 mL), gave the title compound **194** after trituration as a yellow solid (1.32 g, 3.4 mmol, 68%).

mp. 84-86 °C; ν_{max} (ATR): 3115, 2978, 1724, 1519, 1294, 1271, 1184, 1161, 1147, 1091, 1029, 983; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.35 (1H, t, *J* 7.1, -CH_2C*H*$_3$), 4.18 (2H, q, *J* 7.1, -C*H*$_2CH_3$), 6.32 (1H, d, *J* 16.1, C(2)*H*), 7.47 (2H, d, *J* 7.8, C(4)Ar*C*(3)*H*), 7.61 (1H, t, *J* 7.5, C(4)Ar*C*(4)*H*), 7.65-7.80 (2H, m, C(4)Ar*C*(2)*H*), 8.22 (3H, d, *J* 8.5, NSO_2ArC(2)*H* and C(3)*H*), 8.39 (2H, d, *J* 8.8, NSO_2Ar*C*(3)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.3 (-CH_2*C*H_3), 61.9 (-*C*H_2CH_3), 124.4 (NSO_2Ar*C*(3)), 128.8 (NSO_2Ar*C*(2)), 129.0 (C(4)Ar*C*(3)), 130.4 (C(4)Ar*C*(2)), 134.0 (C(4)Ar*C*(4)), 134.1 (*C*(2)), 135.3 (C(4)Ar*C*(1)), 146.4 (NSO_2Ar*C*(1)), 150.4 (NSO_2Ar*C*(4)), 164.5 (*C*(1)), 176.6 (*C*(4)); **HRMS (ESI+)**: $C_{18}H_{17}N_2O_6S$ $[M+H]^+$ found 389.0802, requires 389.0802 (−0.0 ppm).

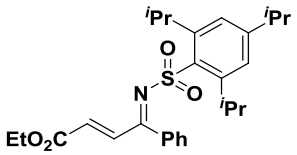
(2*E*,4*E*)-Ethyl-4-((methylsulfonyl)imino)-4-phenylbut-2-enoate, **195**



Following general procedure C, the reaction of ethyl 3-benzoylacrylate (0.92 mL, 5.0 mmol), methanesulfonamide (0.48 g, 5.0 mmol), NEt_3 (1.39 mL, 10.0 mmol) and $TiCl_4$ (0.55 mL, 5.0 mmol) in CH_2Cl_2 (30 mL), gave the title compound **195** after trituration as an orange solid (0.87 g, 3.1 mmol, 62%)

mp. 76-78 °C; ν_{max} (ATR): 2991, 1718, 1639, 1579, 1554, 1442, 1365, 1309, 1292, 1269, 1184, 1134, 1026, 970; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.32 (3H, t, *J* 7.1, -CH_2CH_3), 3.26 (3H, s, -SO_2CH_3), 4.28 (2H, q, *J* 7.1, -CH_2CH_3), 6.25 (1H, d, *J* 16.2, C(2)*H*), 7.47 (2H, t, *J* 7.8, C(4)ArC(3)*H*), 7.60 (1H, t, *J* 7.1, C(4)ArC(4)*H*), 7.76 (2H, d, *J* 7.2, C(4)ArC(2)*H*), 8.13 (1H, d, *J* 16.2, C(3)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 14.1 (-CH_2CH_3), 43.0 (SO_2CH_3), 61.6 (-CH_2CH_3), 128.8 (C(4)Ar*C*(3)), 130.1 (C(4)Ar*C*(2)), 133.4 133.3 (C(4)Ar*C*(4)), 133.5 (*C*(2)), 135.7 (C(4)Ar*C*(1)), 136.2 (*C*(3)), 164.5 (*C*(1)), 175.3 (*C*(4)); **HRMS (ESI+)** $C_{13}H_{16}NO_4S$ ($[M+H]^+$), found 282.0792, requires 282.0795 (− 0.9 ppm)).

(2*E*,4*E*)-Ethyl-4-phenyl-4-(((2,4,6-triisopropylphenyl)sulfonyl)imino)but-2-enoate, **192**

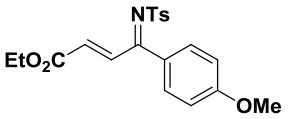


Following general procedure C, the reaction of (*E*)-ethyl 3-benzoylacrylate (7.3 mL, 40.0 mmol), 2,4,6-triisopropylbenzenesulfonamide (11.34 g, 40.0 mmol), NEt_3 (11.2 mL, 80.0 mmol) and $TiCl_4$ (4.4 mL, 5.0 mmol) in CH_2Cl_2 (120 mL), gave the title compound **192** after trituration as a white solid (14.50 g, 30.8 mmol, 77%).

mp. 104-106 °C; ν_{max} (ATR): 2964, 1720, 1622, 1150, 939; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.25 (18H, t, *J* 6.9, -$CH(CH_3)_2$), 1.31 (3H, t, *J* 7.1, -CH_2CH_3), 2.90 (1H, hept, *J* 6.8, NSO_2ArC(4)C*H*), 4.20-4.29 (4H, m, -CH_2CH_3 and NSO_2ArC(2)C*H*), 6.09 (1H, d, *J* 16.3,

C(2)*H*), 71.6 (2H, s, NSO2ArC(3)*H*), 7.42 (2H, t, *J* 7.1, C(4)ArC(3)*H*), 7.49-61 (1H, m, C(4)ArC(4)*H*), 7.76 (2H, d, *J* 6.1, C(4)ArC(2)*H*), 8.05 (1H, d, *J* 16.1, C(3)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 14.3 (-CH_2CH_3), 23.8 (-CH(CH_3)$_2$), 24.8 (-CH(CH_3)$_2$), 30.2 (SO_2ArC(2)*C*H), 34.4 (SO_2ArC(4)*C*H), 61.6 (-CH_2CH_3), 123.7 (NSO2Ar*C*(3)), 128.8 (C(4)Ar*C*(3)) , 130.3 (C(4)Ar*C*(2)), 132.4 (*C*(2)) 133.3 (C(4)Ar*C*(4)), 134.2 (C(4)Ar*C*(1)), 136.2 (NSO2Ar*C*(1)), 136.7 (*C*(3)), 150.0 (NSO2Ar*C*(2)), 153.3 (NSO2Ar*C*(4)), 164.6 (*C*(1)), 173.8 (*C*(4)); **HRMS (ESI+)** $C_{19}H_{20}NO_4S$ ($[M+H]^+$), found 358.1107 requires 358.1108 (- 0.2 ppm)).

(2*E*,4*E*)-Ethyl-4-(4-methoxyphenyl)-4-(tosylimino)but-2-enoate, **209**



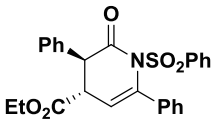
Following general procedure C with a modified work up, the reaction of (*E*)-ethyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate (0.77 g, 3.3 mmol), *p*-toluenesulfonamide (0.57 g, 3.3 mmol), NEt_3 (0.92 mL, 6.6 mmol) and $TiCl_4$ (0.36 mL, 3.3 mmol) in CH_2Cl_2 (17 mL) was followed by aqueous work up. The reaction mixture was quenched with water (30 mL) and extracted with EtOAc (×3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL min^{-1}, hexane–EtOAc (75 : 25 2CV, 57 : 43 7CV)] to give the title compound **209** (1.08 g, 2.8 mmol, 85%) as a thick yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 6.7, OCH_2CH_3), 2.43 (3H, s, NTsCH_3), 3.85 (3H, s, ArOCH_3), 4.29 (2H, q, *J* 6.9, OCH_2CH_3), 6.18 (1H, d, *J* 16.2, C(2)*H*), 6.90 (2H, d, *J* 8.2, NSO_2Ar*H*), 7.32 (2H, d, *J* 7.5, C(4) Ar*H*), 7.75 (2H, d, *J* 7.0, NSO_2Ar*H*), 7.89 (2H, d, *J* 7.4, C(4)Ar*H*), 8.01–8.21 (1H, m, C(3)*H*). Data consistent with literature.[66]

5-7. Data for Dihydropyridinones

General procedure D: one-pot isothiourea-mediated dihydropyridinone synthesis

A flask containing a stirrer bar was charged with CH_2Cl_2 (to give 0.4 M acid], aryl acetic acid (2 eq.), (^{i}Pr)$_2$NEt (2 eq.) and cooled to 0 ℃. Pivaloyl chloride (2 eq.) was added and the reaction stirred for 30 minutes. (−)-Tetramisole·HCl **211** (20 mol%) was added followed by the ketimine (1 eq.) and additional (^{i}Pr)$_2$NEt (1 eq.) in CH_2Cl_2 (to give 0.4 M of ketimine). The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction was quenched with 0.1 M HCl (~ 20 mL/mmol acid), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × eq. vol.). The combined organics were dried over $MgSO_4$, the solvent removed in vacuo on a rotary evaporator (<30 ℃ bath temp.), and the residue purified by flash chromatography in the solvent system stated.

(3*S*,4*S*)-Ethyl-2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **212**

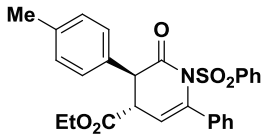


Following general procedure D, the reaction of phenylacetic acid (1.36 g, 10.0 mmol), (^{i}Pr)$_2$NEt (1.73 mL, 10.0 mmol) and pivaloyl chloride (1.23 mL, 10.0 mmol) in CH_2Cl_2 (25 mL), followed by (−)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol%), ketimine **190** (1.72 g, 5.0 mmol), (^{i}Pr)$_2$NEt (0.87 mL, 5.0 mmol) and CH_2Cl_2 (50 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **212** (1.48 g, 3.2 mmol, 64%, 92 : 8 dr) as a white solid.

mp. 128-129 ˚C; $[\alpha]_D^{22}$ +32.9 (*c* 0.55, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 20:80 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 13.2 min, t_R (3*R*, 4*R*): 33.1 min, 98% ee; ν_{max} (ATR): 2970, 1722, 1448, 1155, 989 **^{1}H NMR** (400 MHz, $CDCl_3$) *major*

diastereomer δ_H 1.04 (3H, t, *J* 7.1, -CH_2CH_3), 3.75 (1H, dd, *J* 9.6, 4.8, C(4)*H*), 4.02 (2H, qq, *J* 7.5, 3.7, -CH_2CH_3), 4.10 (1H, d, *J* 9.6, C(3)*H*), 5.87 (1H, d, *J* 4.8, C(5)*H*), 7.01 (2H, dd, *J* 6.4, 2.4, C(3)ArC(3)*H*), 7.26-7.27 (3H, m, C(3)ArC*H*), 7.38-7.40 (5H, m, C(6)Ar*H*), 7.50 (2H, t, *J* 7.9, NSO_2ArC(3)*H*), 7.65 (1H, t, *J* 7.4, NSO_2ArC(4)*H*), 7.95 (2H, d, NSO_2ArC(2)*H*); *minor diastereomer (selected)* δ_H 1.15 (1H, t, *J* 7.1, -CH_2CH_3), 6.15 (1H, d, *J* 4.9, C(5)*H*); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 13.9 (-CH_2CH_3), 45.1 (*C*(4)), 54.0 (*C*(3)), 61.6 (-CH_2CH_3), 115.9 (*C*(5)), 126.1 (C(6)Ar*C*), 128.0 (C(3)Ar*C*), 128.5 (C(6)Ar*C*), 128.6 (C(3)Ar*C*), 128.6 (C(6)Ar*C*), 128.7 (NSO_2ArC(3)), 128.8 (C(6)Ar*C*), 129.4 (NSO_2Ar*C*(2)), 134.0 (NSO_2Ar*C*(4)), 135.3 (C(3)Ar*C*(1)), 136.6 (C(6)Ar*C*(1)), 139.2 (NSO_2Ar*C*(1)), 141.3 (*C*(6)), 170.9 (C(4)*C*O), 172.2 (*C*(2)); **HRMS** (ESI^+): $C_{26}H_{24}NO_5S$ ($[M+H]^+$), found 462.1373, requires 462.1370 (0.7 ppm)).

(3*S*,4*S*)-Ethyl-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(p-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **224**

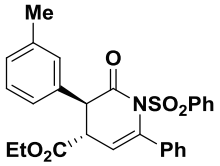


Following general procedure D, the reaction of *p*-tolylacetic acid (60.1 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole ·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **224** (63.2 mg, 0.13 mmol, 66%, 94 : 6 dr) as a white solid.

mp. 100-102 ˚C; $[\alpha]_D^{22}$ +31.1 (*c* 0.54, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 20:80 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 55.2 min, 98% ee; ν_{max} (ATR): 2933, 1730, 1516, 1355, 1159, 929; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.06 (3H, t, *J* 7.1, -CH_2CH_3), 2.29 (3H, s, -C*H*$_3$), 3.72 (1H, dd, *J* 9.7, 4.8,

C(4)*H*), 3.97-4.07 (3H, m, C(3)*H* and -C*H*$_2$CH$_3$), 5.84 (1H, d, *J* 4.8, C(5)*H*), 6.88 (2H, d, *J* 8.1, C(3)Ar*C*(2)*H*), 7.07 (2H, d, *J* 7.9, C(3)Ar*C*(3)*H*), 7.31-7.42 (5H, m, C(6)Ar*H*), 7.49 (2H, t, *J* 7.4, NSO$_2$Ar*C*(3)*H*), 7.64 (1H, t, *J* 7.4, NSO$_2$Ar*C*(4)*H*), 7.94 (2H, d, NSO$_2$Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.17 (1H, t, *J* 7.1, -CH$_2$C*H*$_3$), 2.38 (3H, s, -C*H*$_3$), 3.93 (1H, t, *J* 9.7, 4.8, C(4)*H*), 4.26 (1H, d, *J* 5.5, C(3)*H*), 5.84 (1H, d, *J* 4.8, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, CDCl$_3$) *major diastereomer* δ_C 14.2 (-CH$_2$*C*H$_3$), 21.2 (-*C*H$_3$), 45.2 (*C*(4)), 53.7 (*C*(3)), 61.7 (-*C*H$_2$CH$_3$), 116.0 (*C*(5)), 126.2 (C(6)Ar*C*), 128.5 (C(6)Ar*C*), 128.6 (C(3)Ar*C*(2)), 128.7 (C(6)Ar*C*), 128.9 (NSO$_2$Ar*C*(3)), 129.5 (NSO$_2$Ar*C*(2)), 129.6 (C(3)Ar*C*(3)), 132.3 (C(3)Ar*C*(1)), 134.1 (NSO$_2$Ar*C*(4)), 136.7 (C(6)Ar*C*(1)), 137.9 (C(3)Ar*C*(4)), 139.2 (NSO$_2$Ar*C*(1)), 141.3 (*C*(6)), 170.9 (C(4)*C*O), 172.2 (*C*(2)); **HRMS** (ESI$^+$): $C_{27}H_{26}NO_5S$ ([M+H]$^+$), found 476.1524, requires 476.1526 (−0.5 ppm)).

(3*S*,4*S*)-Ethyl-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(m-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **225**

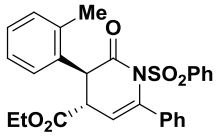


Following general procedure D, the reaction of *m*-tolylacetic acid (60.1 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH$_2$Cl$_2$ (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH$_2$Cl$_2$ (2.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et$_2$O–pet. ether, 1 : 4) gave **225** (69.6 mg, 0.15 mmol, 72%, 93 : 7 dr) as a white solid.

mp. 134-136 °C; $[\alpha]_D^{20}$ +27.9 (*c* 0.64, CH$_2$Cl$_2$); Chiral HPLC (Chiralpak IA, 10:90 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 22.7 min, t_R (3*R*, 4*R*): 62.7 min, 99% ee; ν_{max} (ATR): 2922, 1726, 1516, 1359, 1155, 887; **^{1}H NMR** (500 MHz, CDCl$_3$) *major*

diastereomer δ_H 1.05 (3H, t, *J* 7.1, -CH_2CH_3), 2.26 (3H, s, -CH_3), 3.72 (1H, dd, *J* 9.5, 4.9, C(4)*H*), 3.98-4.07 (3H, m, C(3)*H* & -CH_2CH_3), 5.84 (1H, d, *J* 4.9, C(5)*H*), 6.79 (1H, d, *J* 7.8, C(3)Ar*C*(6)*H*), 7.05 (1H, d, *J* 7.6, C(3)Ar*C*(4)*H*), 7.14 (1H, t, *J* 7.6, C(3)Ar*C*(5)*H*), 7.33-7.42 (5H, m, C(6)Ar*H*), 7.50 (2H, t, *J* 7.9, NSO_2Ar*C*(3)*H*), 7.65 (1H, t, *J* 7.4, NSO_2Ar*C*(4)*H*), 7.94 (2H, d, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.17 (1H, t, *J* 7.1, -CH_2CH_3), 2.22 (3H, s, -CH_3), 3.90-3.95 (1H, m, C(4)*H*), 4.25 (1H, d, *J* 5.5 Hz, C(3)*H*), 6.13 (1H, d, *J* 4.7, C(5)*H*); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ_C 14.0 (-CH_2CH_3), 21.5 (-CH_3), 45.2(*C*(4)), 53.9 (*C*(3)), 61.7 (-CH_2CH_3), 115.8 (*C*(5)), 125.6 (C(3)Ar*C*(6)), 126.1 (C(6)Ar*C*)), 128.6 (NSO_2Ar*C*(3)), 128.6 (C(6)Ar*C*), 128.7 (C(3)Ar*C*(5)), 128.9 (C(3)Ar*C*(4)), 129.3 (C(3)Ar*C*(2)), 129.5 (NSO_2Ar*C*(2)), 134.1 (NSO_2Ar*C*(4)), 135.3 (4C(3)Ar*C*(1)), 136.7 (C(6)Ar*C*(1)), 138.4 (C(3)Ar*C*(3)), 139.2 (NSO_2Ar*C*(1)), 141.3 (*C*(6)), 170.8 (C(4)*C*O), 172.0 (*C*(2)); **HRMS (ESI+)**: $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1522, requires 476.1526 (−0.9 ppm).

(3*S*,4*S*)-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(o-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **226**

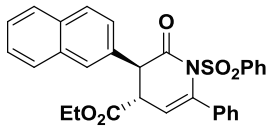


Following general procedure D, the reaction of o-tolylacetic acid (60.1 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole ·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **226** (63.9 mg, 0.13 mmol, 67%, 93 : 7 dr) as a white solid.

mp. 78-80 °C; $[\alpha]_D^{20}$ +45.8 (*c* 0.55, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 10:90 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 16.3 min, t_R (3*R*, 4*R*): 56.5 min,

99% ee; ν_{max} (film, cm-1): 2922, 1726, 1516, 1359, 1155, 887; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.00 (1H, t, *J* 7.1, -CH_2CH_3), 2.25 (3H, s, -CH_3), 3.85 (1H, dd, *J* 10.9, 4.3, C(4)*H*), 4.00 (2H, q, *J* 7.1, -CH_2CH_3), 4.31 (1H, d, *J* 10.9, C(3)*H*), 5.90 (1H, d, *J* 4.3, C(5)*H*), 6.80 (1H, d, *J* 7.8, C(3)Ar*C*(3)*H*), 7.09 (1H, td, *J* 7.8, C(3)Ar*C*(4)*H*), 7.12- 7.20(2H, m, C(3)Ar*C*(5)*H* and C(3)Ar*C*(6)*H*), 7.37-7.48 (5H, m, C(6)Ar*H*), 7.51 (2H, td, *J* 7.6, 1.7, NSO_2Ar*C*(3)*H*), 7.67 (1H, t, *J* 7.1, 1.2, NSO_2Ar*C*(4)*H*), 7.97 (2H, d, *J* 8.6, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.09 (1H, t, *J* 7.1, -CH_2CH_3), 2.43 (3H, s, -CH_3), 4.58 (1H, d, *J* 6.3, C(3)*H*), 6.17 (1H, d, *J* 5.5, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 13.9 (-CH_2CH_3), 19.8 (-CH_3), 44.4(*C*(4)), 51.3 (*C*(3)), 61.7 (-CH_2CH_3), 116.5 (*C*(5)), 126.2 (C(6)Ar*C*)), 126.6 (C(3)Ar*C*(4)), 128.2 (C(3)Ar*C*(5)), 128.5 (C(3)Ar*C*(3)), 128.6 (C(6)Ar*C*), 128.7 (C(6)Ar*C*), 128.9 (C(3)Ar*C*(4)), 129.0 (NSO_2Ar*C*(3)), 129.5 (NSO_2Ar*C*(2)), 130.9 (C(3)Ar*C*(6)), 133.0 (C(3)Ar*C*(1)), 134.2 (NSO_2Ar*C*(4)), 136.6 (C(6)Ar*C*(1)), 137.0 (C(3)Ar*C*(3)), 139.2 (NSO_2Ar*C*(1)), 141.3 (*C*(6)), 170.1 (C(4)*C*O), 172.2 (*C*(2)); **HRMS (ESI+)**: $C_{27}H_{26}NO_5S$ $[M+H]^+$ found 476.1520, requires 476.1526 (−1.3 ppm).

(3*S*,4*S*)-Ethyl-3-(naphthalen-2-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **227**

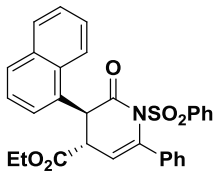


Following general procedure D, the reaction of 2-naphthaleneacetic acid (74.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91 : 9 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **227** (63.7 mg, 0.12 mmol, 62%, 92 : 8 dr) as a white solid.

mp. 178-180 ˚C; $[\alpha]_D^{22}$ +17.3 (*c* 0.55, CH_2Cl_2); Chiral HPLC (Chiralpak AD-H, 30:70 IPA:

hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 18.6 min, t_R (3*R*, 4*R*): 30.8 min, 97% ee; ν_{max} (ATR): 2978, 1774, 1446, 1359, 1166, 1124, 1097, 1012; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 0.95 (1H, t, *J* 7.1, -CH_2CH_3), 3.86 (1H, dd, *J* 9.9, 4.7, C(4)*H*), 3.96 (2H, qq, *J* 10.8, 7.1-CH_2CH_3), 4.26 (1H, dd, *J* 9.9, C(3)*H*), 5.84 (1H, d, *J* 5.2, C(5)*H*), 7.05 (1H,dd, *J* 8.5, 1.9, C(3)ArC(3)*H*), 7.34-7.57 (10H, m, Ar*H*), 7.62-7.83 (4H, m, Ar*H*), 7.97 (2H, dd, *J* 6.8, 1.2, NSO_2Ar*C*(1)*H*); *minor diastereomer (selected)* δ_H 1.14 (1H, t, *J* 7.1, -CH_2CH_3), 4.11 (2H, dtt, *J* 10.9, 7.1, -CH_2CH_3), 4.46 (1H, dd, *J* 5.6, C(3)*H*), 6.19 (1H, d, *J* 5.2, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.0 (-CH_2CH_3), 45.2 (*C*(4)), 54.3 (*C*(3)), 61.7 (-CH_2CH_3), 116.0 (*C*(5)), 126.0 (Ar*C*), 126.2 (Ar*C*), 126.4 (C(3)Ar*C*), 127.8 (Ar*C*), 128.2 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.0 (Ar*C*), 129.6 (Ar*C*), 132.8 (C(3)Ar*C*(2)), 133.0 (C(3)Ar*C*), 133.3 (C(3)Ar*C*), 134.2 (NSO_2Ar*C*(4)), 136.7 (C(6)Ar*C*(1)), 139.2 (NSO_2Ar*C*(1)), 141.4 (*C*(6)), 170.8 (C(4)*C*O), 172.0 (*C*(2)); **HRMS** (ESI^+): $C_{30}H_{26}NO_5S$ ($[M+H]^+$), found 512.1522, requires 512.1526 (−0.8 ppm)).

(3*S*,4*S*)-Ethyl-3-(naphthalen-1-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **228**



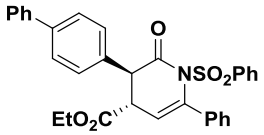
Following general procedure D, the reaction of 1-naphthaleneacetic acid (74.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91 : 9 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave lactam **228** (70.8 mg, 0.14 mmol, 69%, 92 : 8 dr) as a white solid.

mp. 176-178 ˚C; $[\alpha]_D^{22}$ −14.7 (*c* 0.58, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 10:90 IPA:

hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 ˚C) t_R (3*S*, 4*S*): 30.7 min, t_R (3*R*, 4*R*): 98.1 min, 97% ee; ν_{max} (film, cm-1): 2978, 1721, 1446, 1166, 931; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 0.95 (1H, t, *J* 7.1, -CH_2CH_3), 3.89-4.06 (3H, m, C(4)*H* and -CH_2CH_3), 4.91 (1H, d, *J* 8.6, C(3)*H*), 5.84 (1H, d, *J* 5.2, C(5)*H*), 7.12-7.20 (1H, m, C(3)Ar*H*), 7.33-7.36 (1H, m, C(3)Ar*H*), 7.39- 7.50 (5H, m, C(6)Ar*H*), 7.50-7.56 (2H, t, *J* 7.4, NSO_2Ar*C*(2)*H*), 7.66-7.72 (1H, m, NSO_2Ar*C*(3)*H*), 7.72-7.76 (1H, m, C(3)Ar*H*),7.80 (1H, d, *J* 8.3, C(3)Ar*H*), 7.87 (1H, dd, *J* 6.8, 2.7, C(3)Ar*H*), 7.99 (2H, dd, *J* 6.8, 1.2, NSO_2Ar*C*(1)*H*); *minor diastereomer (selected)* δ_H 5.18 (1H, d, *J* 6.0, C(3)*H*), 6.21 (1H, d, *J* 5.6, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 13.8 (-CH_2CH_3), 44.6 (*C*(4)), 531.3 (*C*(3)), 61.7 (-CH_2CH_3), 115.8 (*C*(5)),

123.2 (C(3)Ar*C*), 125.2 (C(3)Ar*C*), 125.9 (C(6)Ar*C*), 126.2 (C(6)Ar*C*), 126.7 (C(3)Ar*C*), 126.8 (C(3)Ar*C*(7)), 128.6 (C(6)Ar*C*), 128.6 (C(6)Ar*C*), 128.9 (C(3)Ar*C*), 129.1 (C(3)Ar*C*), 129.3 (C(3)Ar*C*), 129.6 (*Ar*), 131.0 (C(3)Ar*C*(2)), 131.7 (C(3)Ar*C*(1)), 134.2 (NSO_2Ar*C*(4)), 136.7 (C(6)Ar*C*(1)), 139.0 (NSO_2Ar*C*(1)), 141.4 (*C*(6)), 170.9 (C(4)*C*O), 171.9 (*C*(2)); **HRMS** (ESI^+): $C_{30}H_{26}NO_5S$ ($[M+H]^+$), found 512.1526, requires 512.1523 (−0.6 ppm)).

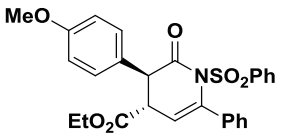
(3*S*,4*S*)-Ethyl-3-([1,1′-biphenyl]-4-yl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **229**



Following general procedure D, the reaction of 4-biphenylacetic acid (84.8 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **229** (82.2 mg, 0.15 mmol, 76%, 92 : 8 dr) as a white solid.

mp. 72-74 °C; $[\alpha]_D^{22}$ +16.2 (*c* 0.73, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 10:90 IPA: hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 59.4 min, t_R (3*R*, 4*R*): 77.6 min, 97% ee; ν_{max} (ATR): 2978, 1730, 1489, 1448, 1369, 1170, 1112, 1087, 916; **^{1}H NMR** (400 MHz $CDCl_3$) *major diastereomer* δ_H 1.06 (3H, t, *J* 7.1, -CH_2CH_3), 3.79 (1H, dd, *J* 9.9, 4.7, C(4)*H*), 4.03 (2H, q, *J* 7.1, -CH_2CH_3), 4.13 (1H, d, *J* 9.9, C(3)*H*), 5.89 (1H, d, *J* 4.7, C(5)*H*), 7.08 (2H, d, *J* 8.2, C(3)ArC(3)*H*), 7.27-7.57 (14H, m, Ar*H*), 7.66 (1H, t, *J* 15.0, 1.1, NSO_2ArC(4)*H*), 7.96 (2H, dd, *J* 8.5, 1.0, NSO_2ArC(2)*H*); *minor diastereomer (selected)* δ_H 1.18 (3H, t, *J* 7.1, -CH_2CH_3), 3.97 (1H, t, *J* 5.3, C(4)*H*), 4.33 (1H, d, *J* 5.4, C(3)*H*), 6.02-6.35 (1H, m, C(5)*H*);**^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.0 (-CH_2CH_3), 45.3(*C*(4)), 53.9 (*C*(3)), 61.8 (-CH_2CH_3), 116.1 (*C*(5)), 126.2 (Ar*C*), 127.2 (Ar*C*), 127.6 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 128.9 (Ar*C*), 129.0 (Ar*C*), 129.1 (C(3)Ar*C*(3)), 129.5 (NSO_2Ar*C*(2)), 134.2 (NSO_2Ar*C*(4)), 134.4 (C(3)Ar*C*(1)), 136.6 (C(6)Ar*C*(1)), 139.2 (NSO_2Ar*C*(1)), 140.6 (C(3)*C*), 141.1 (C(3)*C*), 141.4 (*C*(6)), 170.9 (C(4)*C*O, 172.1 (*C*(2)); **HRMS (ESI+)** $C_{32}H_{28}NO_5S$ ($[M+H]^+$), found 538.1683, requires 538.1677 (−1.1 ppm)).

(3*S*,4*S*)-Ethyl-3-(4-methoxyphenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **230**

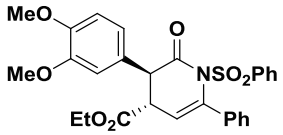


Following general procedure D the reaction of 4-methoxyphenylacetic acid (66.4 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 2 : 3) gave **230** (75.5 mg, 0.15 mmol, 74%, 92 : 8 dr) as a white solid.

mp. 152-154 ˚C; $[\alpha]_D^{22}$ +28.9 (*c* 0.54, CH_2Cl_2); Chiral HPLC, (Chiralpak AD-H, 20:80 IPA:

Chexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 25.5 min, t_R (3*R*, 4*R*): 42.8 min, 98% ee; ν_{max} (ATR): 2960, 1732, 1716, 1514, 1165, 920; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 1.06 (3H, t, *J* 7.1, -CH_2CH_3), 3.71 (1H, dd, *J* 10.0, 4.6, C(4)*H*), 3.76 (3H, s, -OCH_3), 3.97-4.06 (3H, m, C(3)*H* and -CH_2CH_3), 5.86 (1H, d, *J* 4.6, C(5)*H*), 6.76-6.84 (2H, m, C(3)Ar*C*(3)*H*), 6.88-6.96 (2H, m, C(3)Ar*C*(2)*H*), 7.31-7.43 (5H, m, C(6)Ar*H*), 7.46-7.54 (2H, m, NSO_2Ar*C*(3)*H*), 7.65 (1H, m, NSO_2Ar*C*(4)*H*), 7.90-7.97(2H, m, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.17 (3H, t, *J* 7.1, -CH_2CH_3), 3.91 (1H, dd, *J* 5.2, C(4)*H*), 3.76 (3H, s, -OCH_3), 4.11 (2H,dtt, *J* 10.8, 7.2, 3.7, -CH_2CH_3), 4.23 (1H, d, *J* 5.6, C(3)*H*), 6.19 (1H, d, *J* 4.9, 0.6, C(5)*H*), 6.72-6.76 (2H, m, C(3)Ar*C*(3)*H*), 7.06-7.11 (2H, m, C(3)Ar*C*(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 14.1 (-CH_2CH_3), 45.4 (*C*(4)), 53.6 (*C*(3)), 53.5 (*C*(5)), 61.7 (-CH_2CH_3), 114.2 (C(3)Ar*C*(3)), 116.2 (*C*(5)), 126.2 (C(6)Ar*C*), 127.3 (C(3)Ar*C*(1)), 128.6 (C(6)Ar*C*), 128.6 (C(6)Ar*C*), 128.9 (NSO_2Ar*C*(3)), 129.5 (NSO_2Ar*C*(2)), 134.1 (NSO_2Ar*C*(4)), 136.7 (C(6)Ar*C*(1)), 139.2 (NSO_2Ar*C*(1)), 141.2 (*C*(6)), 159.4 (C(3)Ar*C*(4)), 171.0 (C(4)*C*O) 172.3 (*C*(2)); **HRMS (ESI+)** $C_{27}H_{26}NO_6S$ ($[M+H]^+$), found 492.1473, requires 492.1475 (−0.5 ppm)).

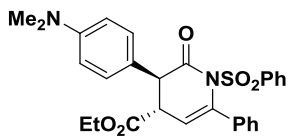
(3*S*,4*S*)-Ethyl-3-(3,4-dimethoxyphenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **231**



Following general procedure D, the reaction of 3,4-dimethoxyphenylacetic acid (78.4 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 93 : 7 dr. Purification by flash chromatography (Et_2O–pet. ether, 2 : 3) gave **231** (81.0 mg, 0.16 mmol, 78%, 97 : 3 dr) as a white solid.

mp. 126-128 ˚C; $[\alpha]_D^{22}$ +32.6 (*c* 0.53, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 30:70 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 38.0 min, t_R (3*R*, 4*R*): 53.5 min, 98ee; ν_{max} (ATR): 2937, 1782, 1593, 1516, 1448, 1367, 1298, 1224, 1143, 1087, 1026, 979; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 1.08 (3H, t, *J* 7.1, -CH_2CH_3), 3.72 (1H, dd, *J* 9.8, 4.8, C(4)*H*), 3.75 (3H, s, C(3)Ar(3)OCH_3), 3.83 (3H, s, C(3)Ar(4)OCH_3), 3.94-4.11 (3H, m, C(3)*H* and -CH_2CH_3), 5.86 (1H, d, *J* 4.7, C(5)*H*), 6.50 (1H, d, *J* 1.9, C(3)Ar*C*(2)*H*), 6.58 (1H, dd, *J* 8.2, 2.0, C(3)Ar*C*(6)*H*), 6.75 (1H, d, *J* 8.3, C(3)Ar*C*(5)*H*), 7.35-7.40 (5H, m, C(6)Ar*H*), 7.40 (2H, t, *J* 7.9, NSO_2Ar*C*(3)*H*), 7.64 (1H, t, *J* 7.5, NSO_2Ar*C*(4)*H*), 7.95 (2H, d, *J* 7.4, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.16 (1H, t, *J* 7.1, -CH_2CH_3), 3.66 (3H, s, C(3)Ar(3)OCH_3), 3.79 (3H, s, C(3)Ar(4)OCH_3), 4.22 (1H, d, *J* 5.1, C(3)*H*), 6.15-6.20 (1H, m, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.1 (-CH_2CH_3), 45.3 (*C*(4)), 53.7 (*C*(3)), 56.0 (OCH_3), 61.7 (-CH_2CH_3), 111.2 (C(3)Ar*C*(5)), 111.6 (C(3)Ar*C*(2)), 116.0 (*C*(5)), 121.1 (C(3)Ar*C*(6)), 126.1 (C(6)Ar*C*), 127.7 (C(3)Ar*C*(1)), 128.6 (NSO_2Ar*C*(3)), 128.7 (C(6)Ar*C*), 129.0 (C(6)Ar*C*), 129.5 (NSO_2Ar*C*(2)), 134.1 (NSO_2Ar*C*(4)), 136.7 (C(6)Ar*C*(1)), 139.3 (NSO_2Ar*C*(1)), 141.3 (*C*(6)), 148.9 (C(3)Ar*C*(4)), 149.0 (C(3)Ar*C*(3)), 170.9 (C(4)*C*O), 172.2 (*C*(2)); **HRMS** (ESI^+): $C_{28}H_{31}NO_7S$ ([M+ NH_4]$^+$), found 539.1842, requires 539.1846 (−0.8 ppm)).

(3*S*,4*S*)-Ethyl-3-(4-(dimethylamino)phenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **232**

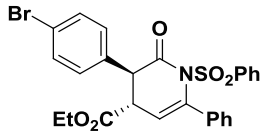


Following general procedure D, the reaction of 4-(dimethylamino) phenylacetic acid (71.7 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude

residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 2 : 3) gave **232** (80.3 mg, 0.16 mmol, 80%, 93 : 7 dr) as a white solid.

mp. 178-180 ˚C; $[\alpha]_D^{22}$ +30.6 (*c* 0.51, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 10:90 IPA: hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 55.2 min, 99% ee; ν_{max} (ATR): 2933, 1730, 1516, 1355, 1159, 929; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.09 (3H, t, *J* 7.1, -CH_2CH_3), 2.90 (6H, s, $N(CH_3)_2$), 3.68 (1H, dd, *J* 9.4, 5.0, C(4)*H*), 3.95-4.08 (3H, m, C(3)*H* and -CH_2CH_3), 5.85 (1H, d, *J* 5.0, C(5)*H*), 6.59 (2H, d, *J* 8.8, C(3)Ar*C*(3)*H*), 6.85 (2H, d, *J* 8.7, C(3)Ar*C*(2)*H*), 7.36-7.40 (5H, m, C(6)Ar*H*), 7.45-7.53 (2H, m, NSO_2Ar*C*(3)*H*), 7.64 (1H, tt, *J* 7.1, 1.2, NSO_2Ar*C*(4)*H*), 7.94 (2H, d, *J* 8.5, 1.2,NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.18 (3H, t, *J* 7.1, -CH_2CH_3), 2.86 (6H, s, $N(CH_3)_2$), 3.89-3.93 (1H, m, C(4)*H*), 4.07-4.16 (2H, m, -CH_2CH_3), 4.20 (1H, d, *J* 5.8, C(3)*H*), 6.15 (1H, dd, *J* 4.6, 0.8, C(5)*H*), 6.53 (2H, d, *J* 8.9, C(3)Ar*C*(3)*H*), 7.00 (2H, d, *J* 8.8, C(3)Ar*C*(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 14.1 (-CH_2CH_3), 40.6 ($N(CH_3)_2$), 45.4 (*C*(4)), 53.3 (*C*(3)), 61.6 (-CH_2CH_3), 112.7 (C(3)Ar*C*(2)), 116.2 (*C*(5)), 122.7 (C(3)Ar*C*(1)), 126.2 (C(6)Ar*C*), 128.6 (C(6)Ar*C*), 128.6 (C(6)Ar*C*), 128.8 (NSO_2Ar*C*(3)), 129.3 (NSO_2Ar*C*(2)), 129.5 (C(3)Ar*C*(3)), 134.0 (NSO_2Ar*C*(4)), 136.9 (C(6)Ar*C*(1)), 139.4 (NSO_2Ar*C*(1)), 141.2 (*C*(6)), 150.3 (C(3)Ar*C*(4)), 171.1 (C(4)*C*O), 172.5 (*C*(2)); **HRMS** (ESI^+): $C_{28}H_{29}N_2O_5S$ ($[M+H]^+$), found 505.1786, requires 505.1792 (−1.1 ppm)).

(3*S*,4*S*)-Ethyl-3-(4-bromophenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **234**

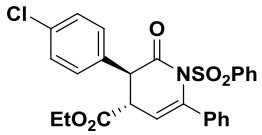


Following general procedure D, the reaction of 4-bromophenylacetic acid (86.0 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0

mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 2 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **234** (64.6 mg, 0.13 mmol, 60%, 94 : 6 dr) as a white solid.

mp. 140-142 °C; $[\alpha]_D^{22}$ +31.1 (*c* 0.54, CH_2Cl_2); ν_{max} (ATR): 2976, 1726, 1710, 1448, 1168, 925; Chiral HPLC, (Chiralpak IA, 30:70 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 30.4 min, t_R (3*R*, 4*R*): 45.8 min, 95% ee; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.07 (1H, t, *J* 7.1, -CH_2CH_3), 3.72 (1H, dd, *J* 10.5, 4.2, C(4)*H*), 3.94-4.09 (3H, m, C(3)*H* and -CH_2CH_3), 5.85 (1H, d, *J* 4.5, C(5)*H*), 6.87 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.32-7.44 (7H, m, C(3)ArC(3)*H* and C(6)Ar*H*), 7.46-7.55 (2H, m, NSO_2ArC(3)*H*), 7.66 (1H, tt, *J* 7.1, 1.2, NSO_2ArC(4)*H*), 7.93 (2H, d, *J* 8.5, NSO_2ArC(2)*H*); *minor diastereomer (selected)* δ_H 1.17 (1H, t, *J* 7.1, -CH_2CH_3), 3.90 (1H, t, *J* 5.4, C(4)*H*), 4.13 (2H, qt, *J* 7.1, 3.7, -CH_2CH_3), 4.22 (1H, d, *J* 5.4, C(3)*H*), 6.12 (1H, dd, *J* 5.2, 0.8, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.0 (-CH_2CH_3), 45.1(*C*(4)), 53.6 (*C*(3)), 61.9 (-*C*H_2CH_3), 115.9 (*C*(5)), 122.3 (C(3)Ar*C*(4)), 126.2 (C(6)ArC), 128.7 (C(6)ArC), 128.7 (C(6)ArC), 129.1 (NSO_2ArC(3)), 129.5 (NSO_2ArC(2)), 130.5 (C(3)Ar*C*(2)), 132.0 (C(3)Ar*C*(3)), 134.3 (NSO_2ArC(4)), 134.4 (C(3)Ar*C*(1)), 136.4 (C(6)Ar*C*(1)), 139.1 (NSO_2ArC(1)), 141.4 (C(6)), 170.6 (C(4)*C*O), 171.7 (*C*(2)); **HRMS (ESI+)** $C_{26}H_{23}NO_5S$ ([M+H]$^+$), found 540.0473, requires 540.0475 (−0.3 ppm)).

(3*S*,4*S*)-Ethyl-3-(4-chlorophenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **235**

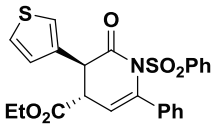


Following general procedure D, the reaction of 4-chlorophenylacetic acid (68.2 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0

mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 3 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **235** (53.5 mg, 0.11 mmol, 54%, 94 : 6 dr) as a white solid.

mp. 136-138 °C; $[\alpha]_D^{22}$ +33.3 (*c* 0.55, CH_2Cl_2); ν_{max} (ATR): 2978, 1724, 1683, 1448, 1367, 1168, 1087, 921; Chiral HPLC, (Chiralpak IA, 30:70 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 26.6 min, t_R (3*R*, 4*R*): 42.0 min, 95% ee; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.06 (1H, t, *J* 7.1, -CH_2CH_3), 3.72 (1H, dd, *J* 10.5, 4.2, C(4)*H*), 3.94-4.09 (3H, m, C(3)*H* and -CH_2CH_3), 5.86 (1H, d, *J* 4.5, C(5)*H*), 6.93 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.25 (2H, d, *J* 8.5, C(3)ArC(3)*H*), 7.35-7.39 (5H, m, C(6)Ar*H*), 7.46-7.54 (2H, m, NSO_2ArC(3)*H*), 7.66 (1H, tt, *J* 7.1, 1.2, NSO_2ArC(4)*H*), 7.93 (2H, dd, *J* 8.5, 1.2, NSO_2ArC(2)*H*); *minor diastereomer (selected)* δ_H 1.17 (1H, t, *J* 7.1, -CH_2CH_3), 3.90 (1H, t, *J* 5.4, C(4)*H*), 4.12 (2H, tq, *J* 7.2, 3.5, -CH_2CH_3), 4.24 (1H, d, *J* 5.4, C(3)*H*), 6.12 (1H, dd, *J* 5.2, 0.8, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 14.0 (-CH_2CH_3), 45.1(*C*(4)), 53.6 (*C*(3)), 61.9 (-CH_2CH_3), 116.0 (*C*(5)), 126.2 (C(6)Ar*C*), 128.7 (C(6)Ar*C*), 128.7 (NSO_2ArC(3)), 129.1 (C(3)ArC(3)), 129.1 (C(6)ArC), 129.5 (NSO_2ArC(2)), 130.2 (C(3)Ar*C*(2)), 133.9 (C(3)Ar*C*(4)), 134.2 (C(3)Ar*C*(1)), 134.3 (NSO_2ArC(4)), 136.4 (C(6)Ar*C*(1)), 139.1 (NSO_2ArC(1)), 141.4 (C(6)), 170.7 (C(4)*C*O), 171.8 (*C*(2)); **HRMS (ESI+)** $C_{26}H_{23}NClO_5S$ ([M+H]$^+$), found 496.0981, requires 496.0980 (0.2 ppm)).

(3*S*,4*S*)-Ethyl-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **236**



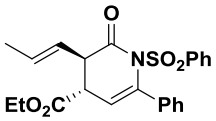
Following general procedure D, the reaction of 3-thiophenylacetic acid (56.9 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL),

followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **190** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 85 : 15 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **236** (59.7 mg, 0.13 mmol, 64%, 92 : 8 dr) as a white solid.

mp. 112-114 ˚C; $[\alpha]_D^{22}$ +29.3 (*c* 0.59, CH_2Cl_2); Chiral HPLC, (Chiralpak IA, 20:80 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 40.3, t_R (3*R*, 4*R*): 72.1, 97% ee; ν_{max} (ATR): 2924, 1728, 1448, 1357, 1303, 1219, 1165, 1120, 1083, 1056, 1029, 1001, 842; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.14 (3H, t, *J* 7.1, -CH_2CH_3), 3.68 (1H, dd, *J* 8.1, 5.5, C(4)*H*), 4.08 (2H, qq, *J* 7.4, 3.6, -CH_2CH_3), 4.24 (1H, dd, *J* 8.1, C(3)*H*), 5.85 (1H, d, *J* 5.5, C(5)*H*), 6.77 (1H, dd, *J* 5.0, 1.3, C(3)Ar*C*(5)*H*), 7.03 (1H, ddd, *J* 2.9, 1.3, 0.6, C(3)Ar*C*(2)*H*), 7.23-7.26 (1H, m, C(3)Ar*C*(4)*H*), 7.34-7.37 (5H, m, C(6)Ar*H*), 7.43-7.54 (2H, m, NSO_2Ar*C*(3)*H*), 7.64 (1H, tt, *J* 7.4, 1.2, NSO_2Ar*C*(4)*H*), 7.92 (2H, dd, *J* 8.5, 1.2, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 3.90 (1H, dd, *J* 4.7, C(4)*H*), 4.40 (1H, dd, *J* 4.7, C(3)*H*), 6.18 (1H, d, *J* 4.7, 0.8, C(5)*H*), 6.91 (1H, dd, *J* 5.0, 1.3, C(3)Ar*C*(5)*H*), 7.08 (1H, ddd, *J* 3.0, 1.2, 0.6, C(3)Ar*C*(2)*H*), 7.19 (1H, dd, *J* 5.1, 2.9, C(3)Ar*C*(4)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 14.1 (-CH_2CH_3), 44.6 (*C*(4)), 49.2 (*C*(3)), 61.8 (-CH_2CH_3), 115.3 (*C*(5)), 123.6 (C(3)Ar*C*(4)), 126.1 (C(6)Ar*C*), 126.5 (C(3)Ar*C*(5)), 126.9 (C(3)Ar*C*(2)), 128.6 ((*C*(9)), 128.6 (C(6)Ar*C*), 128.9 (C(6)Ar*C*), 129.4 (NSO_2Ar*C*(2)), 134.1 (NSO_2Ar*C*(4)), 134.9 (C(3)Ar*C*(1)), 136.6 (C(6)Ar*C*(1)), 139.1(NSO_2Ar*C*(1)), 141.4 ((*C*(6)), 170.7 ((C(4)*C*O)), 171.0 (*C*(2)); **HRMS** (ESI$^+$): $C_{24}H_{22}NO_5S$ ([M+ H]$^+$), found 468.0934, requires 468.0933 (−0.2 ppm)).

The racemic reaction was repeated using ketimine **190** (172.0 mg, 0.5 mmol) and (±)-tetramisole·HCl (24.0 mg, 0.1 mmol, 10 mol %) under the above conditions, then recrystallisation (Et_2O) giving **236** (68.7 mg, 0.15 mmol, 29%). Spectral data of **236** identical to the above.

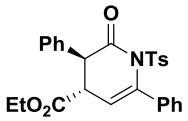
(3*R*,4*S*)-Ethyl-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-((E)-prop-1-en-1-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **237**



Following general procedure D, the reaction of (*E*)-pent-3-enoic acid (82 μL, 0.8 mmol), (^{i}Pr)$_2$NEt (140 μL, 0.8 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (2.0 mL), followed by (−)-tetramisole·HCl (19.2 mg, 0.08 mmol, 20 mol%), ketimine **190** (137.2 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and CH_2Cl_2 (4.0 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 9) gave **237** (89.5 mg, 0.21 mmol, 53%, 88 : 12 dr) as a white solid.

mp. 56-58 ˚C; $[\alpha]_D^{22}$ +67.0 (*c* 0.53, CH_2Cl_2); Chiral HPLC, (Chiralpak OD-H, 5:95 IPA: hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 ˚C) t_R (3*S*, 4*R*): 15.8 min, t_R (3*R*, 4*S*): 19.5 min, 98% ee; ν_{max} (ATR): 2976, 1732, 1448, 1367, 1170, 1085, 1026, 926; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.25 (3H, t, *J* 7.1, -CH_2CH_3), 1.66 (3H, dd, *J* 6.3, 1.4, C(3)CHCHCH_3), 3.37 (1H, dd, *J* 8.4, 5.4, C(4)*H*), 3.47 (1H, t, *J* 8.2, C(3)*H*), 4.15 (2H, qd, *J* 7.1, 1.4, -CH_2CH_3), 5.30 (1H, ddq, *J* 15.1, 8.1, 1.5, C(3)C*H*), 5.64 (1H, m, C(3)CHC*H*) , 5.80 (1H, d, *J* 5.4, C(5)*H*), 7.30-7.38 (5H, m, C(6)Ar*H*), 7.44-7.51 (2H, m, NSO_2Ar*C*(3)*H*), 7.62 (1H, tt, *J* 7.0, 1.2, NSO_2Ar*C*(4)*H*), 7.90 (2H, dt, *J* 8.6, 1.5, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.25 (3H, t, *J* 7.1, -CH_2CH_3), 1.61-1.64 (3H, m, C(3)CHCHCH_3), 3.54 (1H, dd, *J* 7.8, 4.8, C(4)*H*), 3.61 (1H, t, *J* 5.0, C(3)*H*), 6.04 (1H, d, *J* 5.2, 0.8, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.3 (-CH_2CH_3), 18.2 (C(3)CHCHCH_3), 43.7 (*C*(4)), 51.5 (*C*(3)), 61.7 (-CH_2CH_3), 115.7 (*C*(5)), 123.8 (C(3)*C*HCHCH$_3$) 126.1 (C(6)Ar*C*), 128.5 (C(6)Ar*C*), 128.6 (NSO_2Ar*C*(3)), 128.8 (C(6)Ar*C*), 129.4 (NSO_2Ar*C*(2)), 132.1 (C(3)CH*C*HCH$_3$), 134.1 (NSO_2Ar*C*(4)), 136.9 (C(6)Ar*C*(1)), 139.2 (NSO_2Ar*C*(1)), 141.2 (*C*(6)), 170.9 (C(4)*C*O), 171.8 (*C*(2)); **HRMS** (ESI^{+}): $C_{23}H_{24}NO_5S$ ([M+H]$^{+}$), found 426.1368, requires 426.1370 (− 0.4 ppm)).

(3*S*,4*S*)-Ethyl-2-oxo-3,6-diphenyl-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **240**

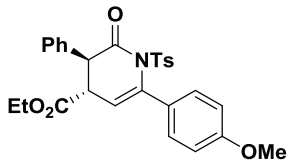


Following general procedure D, the reaction of phenylacetic acid (1.36 g, 10.0 mmol), (^{i}Pr)$_2$NEt (1.73 mL, 10.0 mmol) and pivaloyl chloride (1.23 mL, 10.0 mmol) in CH_2Cl_2 (25 mL), followed by (−)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol%), ketimine **191** (1.79 g, 5.0 mmol), (^{i}Pr)$_2$NEt (0.87 mL, 5.0 mmol) and CH_2Cl_2 (50 mL), for 1 h gave a crude residue of 92 : 8 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **240** (1.47 g, 3.1 mmol, 62%, 93 : 7 dr) as a white solid. Further recrystallisation (Et_2O) gave **240** as a single diastereoisomer (0.80 g, 1.68 mmol, 33%) as a white solid.

mp. 129-130 °C; $[\alpha]_D^{20}$ +50.2 (*c* 0.49, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 30:70 IPA : hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 20.0 min, t_R (3*R*, 4*R*): 40.6 min, >99% ee; ν_{max} (film, cm-1): 2978, 1726, 1363, 1166, 927; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 1.08 (3H, t, *J* 7.1, -CH_2CH_3), 2.49 (3H, s, -CH_3), 3.79 (1H, dd, *J* 9.6, 4.8, C(4)*H*), 4.05 (2H, qq, *J* 7.0, 3.7, -CH_2CH_3), 4.13 (1H, d, *J* 9.6, C(3)*H*), 5.89 (1H, d, *J* 4.8, C(5)*H*), 7.06 (2H, dd, *J* 6.9, 2.2, C(3)Ar*C*(3)*H*), 7.30-7.33 (8H, m, Ar*H*), 7.40-7.45 (2H, d, *J* 9.0, NSO_2Ar*C*(2)*H*), 7.87 (2H, d, *J* 9.0, NSO_2Ar*C*(3)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.0 (-CH_2CH_3), 21.9 (-CH_3), 45.3 (*C*(4)), 54.1 (*C*(3)), 61.7 (-CH_2CH_3), 115.8 (*C*(5)), 126.2 (Ar*C*), 128.1 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 129.6 (Ar*C*), 135.5, 136.4, 136.8, 141.4, 145.3, 170.9 (C(4)*C*O), 172.0 (*C*(2)); **HRMS (ESI+)**: $C_{29}H_{26}NO_5S$ ([M+H]$^+$), found 476.1526, requires 476.1526 (— 0.0 ppm)).

The racemic reaction was repeated using ketimine **191** (1.79 g, 5 mmol) and (±)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol %) under the above conditions, then recrystallisation (Et_2O) giving **240** (0.72 mg, 1.5 mmol, 30%). Spectral data of **240** identical to the above.

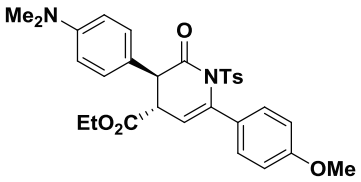
(3*S*,4*S*)-Ethyl-6-(4-methoxyphenyl)-2-oxo-3-phenyl-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **241**



Following general procedure D, the reaction of phenylacetic acid (55 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (49 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **209** (77 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 24 h gave a crude residue of 90 : 10 dr. Purification by flash chromatography (Et_2O–pet. ether, 40 : 60) gave **241** (59 mg, 0.12 mmol, 58%, 90 : 10 dr) as a white solid.

mp. 132-134 °C; $[\alpha]_D^{20}$ +32.5 (*c* 0.52, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 30:70 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 14.1 min, t_R (3*R*, 4*R*): 22.4 min, 99% ee; ν_{max} (ATR): 2929, 1718, 1606, 1501, 1361, 1161, 926; **^{1}H NMR** (500 MHz, CD_2Cl_2) *major diastereomer* δ_H 1.02 (3H, t, *J* 7.1, -CH_2CH_3), 2.45 (3H, s, NSO_2ArC(4)CH_3) 3.64 (1H, dd, *J* 9.8, 4.8, C(4)*H*), 3.82 (3H, s, -OCH_3), 3.97 (2H, q, *J* 7.1, -CH_2CH$_3$), 4.02 (1H, d, *J* 9.9, C(3)*H*), 5.75 (1H, d, *J* 4.8, C(5)*H*), 6.88-6.91 (4H, m, C(3)ArC(3)*H* & C(6)ArC(3)*H*), 7.23-7.24 (3H, m, C(3)ArC(2)*H* & C(3)ArC(4)*H*), 7.33-7.35 (4H, m, NSO_2ArC(2)*H* & C(6)ArC(2)*H*), 7.76-7.79 (2H, m, NSO_2ArC(3)*H*); *minor diastereomer (selected)* δ_H 1.55 (3H, t, *J* 7.1, -CH_2CH_3), 2.45 (3H, s, NSO_2ArC(4)CH_3), 4.22 (1H, d, *J* 5.3, C(3)*H*), 6.00-6.06 (1H, m, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ_C 14.2 (-CH_2CH_3), 22.0 (-NSO_2ArC(4)CH_3), 45.4(*C*(4)), 53.8 (-OCH_3), 55.4 (*C*(3)), 62.0 (-CH_2CH_3), 114.2 (C(6)Ar*C*(2)), 114.7 (*C*(5), 127.7.6 (C(3)Ar*C*(4)), 128.3 (C(6)Ar*C*(1)), 129.0 (C(3)Ar*C*), 129.7 (NSO_2Ar*C*), 136.2 (C(3)Ar*C*(1)), 141.3 (*C*(6)), 146.1 (NSO_2Ar*C*(4)), 154.0 (NSO_2Ar*C*(1)), 160.6 (C(6)Ar*C*(4)), 171.2 (C(4)*C*O), 172.3 (*C*(2)) **HRMS (ESI+)**: $C_{28}H_{28}NO_6S$ ([M+H]$^+$), found 506.1625, requires 506.1632 (−1.4 ppm).

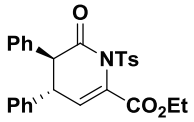
(3*S*,4*S*)-Ethyl-(4-(dimethylamino)phenyl)-6-(4-methoxyphenyl)-2-oxo-1-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **242**



Following general procedure D, the reaction of 4-(dimethylamino) phenylacetic acid (71.7 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **209** (77.5 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 95 : 5 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **242** (52.0 mg, 0.095 mmol, 47%, 88 : 12 dr) as a white solid.

mp. 144-146 °C; $[\alpha]_D^{20}$ +23.8 (*c* 0.55, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 30:70 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 16.7 min, t_R (3*R*, 4*R*): 19.9 min, 91% ee; ν_{max} (ATR): 2926, 1728, 1610, 1512, 1361, 1247, 1165, 1087, 1027, 812; **^{1}H NMR** (500 MHz, CD_2Cl_2) *major diastereomer* δ_H 1.08 (3H, t, *J* 7.1, -CH_2CH_3), 2.47 (3H, s, $NSO_2ArC(4)CH_3$), 2.89 (6H, s, -$N(CH_3)_2$), 3.60 (1H, dd, *J* 9.5, 5.0, C(4)*H*), 3.84 (3H, s, -OCH_3), 3.92 (1H, d, *J* 9.5, C(3)*H*), 4.01 (2H, qd, *J* 7.1, 3.9, -CH_2CH_3), 5.76 (1H, d, *J* 5.0, C(5)*H*), 6.57 (2H, d, *J* 8.8, C(3)ArC(3)*H*), 6.75 (2H, d, *J* 8.7, C(3)ArC(2)*H*), 6.82-6.98 (2H, m, C(6)ArC(3)*H*), 7.25-7.43 (4H, m, $NSO_2ArC(3)H$ and C(6)ArC(2)*H*), 7.79 (2H, d, *J* 8.4, $NSO_2ArC(2)H$); *minor diastereomer (selected)* δ_H 2.86 (6H, s, -$N(CH_3)_2$), 5.99 (1H, d, *J* 4.7, 0.7, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, CD_2Cl_2) δ_C 14.3 (-CH_2CH_3), 22.0 (-$NSO_2ArC(4)CH_3$), 40.3 (-$N(CH_3)_2$), 45.4(*C*(4)), 53.5 (*C*(3)), 55.8 (-OCH_3), 61.9 (-CH_2CH_3), 114.2 (C(6)Ar*C*(3)), 114.9 (*C*(5), 123.2 (C(3)Ar*C*(1)), 127.7.6 (C(6)Ar*C*(2)), 129.5 (C(3)Ar*C*(2)), 129.6 ($NSO_2ArC(2)$), 129.7 ($NSO_2ArC(3)$), 130.1 (C(6)Ar*C*(1)), 136.9 ($NSO_2ArC(1)$, 141.1 (*C*(6)), 145.9 ($NSO_2ArC(4)$), 150.7 (C(3)Ar*C*(4)), 160.5 (C(6)Ar*C*(4)), 171.4 (C(4)*C*O), 172.9 (*C*(2)); **HRMS (ESI+)**: $C_{30}H_{33}N_2O_6S$ ([M+H]$^+$), found 549.2017, requires 549.1054 (−1.2 ppm).

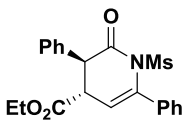
Ethyl (4*S*,5*S*)-6-oxo-4,5-diphenyl-1-tosyl-1,4,5,6-tetrahydropyridine-2-carboxylate, **243**



Following general procedure D, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol%), ketimine **208** (71.6 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 59 : 41 dr. Purification by flash chromatography (Et_2O–petrol, 1 : 4) gave **243** (37.9 mg, 0.08 mmol, 40%, 54 : 46 dr) as a white solid

mp. 118–120 °C; **ν_{max}** (ATR): 2987, 1724, 1597, 1363, 1170, 1085, 1028; **^{1}H NMR** (300 MHz, $CDCl_3$,) *both diastereoisomers* δ_H: 1.37–1.43 (3H, m, OCH_2CH_3), 2.44 (3H, s, NTsCH_3), 3.85 (1H, d, *J* 10.2, C*H*), 4.03 (1H, d, *J* 5.8, C*H*), 4.08 (2H, q, *J* 5.3, 4.5, OCH_2CH_3), 4.28–4.52 (3H, m, OCH_2CH3 and C*H*), 6.54–6.63 (1H, m, Ar*H*), 6.65 (1H, d, *J* 4.2, Ar*H*), 6.69 (1H, d, *J* 6.0, Ar*H*), 6.85 (1H, dd, *J* 7.9, 1.5, Ar*H*), 6.87–6.94 (1H, m, Ar*H*), 7.00 (1H, dd, *J* 7.4, 5.8, Ar*H*), 7.04–7.13 (2H, m, Ar*H*), 7.12–7.25 (7H, m, Ar*H*), 7.32 (2H, t, *J* 8.2, Ar*H*), 8.11 (2H, d, *J* 8.4, Ar*H*), 8.14–8.23 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, CD_2Cl_2) δ_C: 13.9, 21.5, 44.1, 44.5, 55.9, 57.2, 62.2, 126.9, 127.5, 127.6, 127.7, 127.8, 127.9, 127.9, 128.5, 128.5, 128.8, 128.8, 128.9, 129.3, 129.3, 129.4, 129.5 129.6, 129.9, 131.9, 132.8, 133.2, 135.4, 135.7, 138.8, 145.8, 170.2, 170.9; **HRMS** (ESI+): $C_{27}H_{26}NO_5S$ ([M+H]+) found 476.1527, requires 476.1526 (+0.2 ppm).

(3*S*,4*S*)-Ethyl-1-(methylsulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **244**

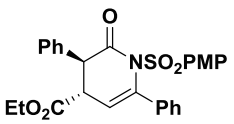


Following general procedure D, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **195** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 91 : 9 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **244** (47.1 mg, 0.12 mmol, 59%, 92 : 8 dr) as a white solid.

mp. 131-132 °C; $[\alpha]_D^{20}$ −6.3 (*c* 0.51, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 5:95 IPA : hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 41.5 min, t_R (3*R*, 4*R*): 45.0 min, 99% ee; ν_{max} (ATR): 2916, 1708, 1653, 1496, 1446, 1344, 1165, 1151, 1118, 960; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 1.18 (1H, t, *J* 7.1, -CH_2CH_3), 3.46 (3H, s, -CH_3), 3.78 (1H, t, *J* 6.3, C(4)*H*), 4.14 (2H, q, *J* 7.1, -CH_2CH_3), 4.26 (1H, d, *J* 6.3, C(3)*H*), 5.76 (1H, d, *J* 6.2, C(5)*H*), 7.20-7.48 (10H, m, Ar*C*); *minor diastereomer (selected)* δ_H 3.50 (3H, s, -C*H*$_3$), 3.81-3.87 (1H, m, C(4)*H*), 6.06 (1H, d, *J* 6.2, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.1 (-CH_2CH_3), 43.9 (-*C*H$_3$), 44.9 (*C*(4)), 53.2 (*C*(3)), 62.0 (-*C*H_2CH_3), 114.3 (*C*(5)), 125.5 (Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.8 (Ar*C*), 129.9 (Ar*C*),129.1 (Ar*C*), 135.0 (C(3)Ar*C*(1)), 137.0 (C(6)Ar*C*(1)), 141.2 (*C*(6)), 171.2 (C(4)*C*O), 173.0 (*C*(2)); **HRMS (ESI+)**: $C_{21}H_{22}NO_5S$ $[M+H]^+$ found 400.1216, requires 400.1213 (0.7 ppm).

The racemic reaction was repeated using ketimine **195** (0.141 g, 0.5 mmol) and (±)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol %) under the above conditions, then recrystallisation (Et_2O) giving **244** (62 mg, 0.16 mmol, 31%). Spectral data of **244** identical to the above.

(3*S*,4*S*)-Ethyl-1-((4-methoxyphenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **245**

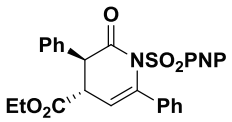


Following general procedure D, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **193** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 95 : 5 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **245** (58.2 mg, 0.12 mmol, 59%, 90 : 10 dr) as a white solid.

mp. 114-115 °C; $[\alpha]_D^{20}$ +18.1 (*c* 0.52, CH_2Cl_2); Chiral HPLC (Chiralpak AD-H, 30:70 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 17.5 min, t_R (3*R*, 4*R*): 55.6 min, 99% ee; ν_{max} (ATR): 2976, 1720, 1593, 1531, 1496, 1446, 1365, 1303, 1261, 1161, 1087, 1024, 979; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.04 (3H, t, *J* 7.1, -CH_2CH_3), 3.74 (1H, dd, *J* 9.7, 4.8, C(4)*H*), 3.89 (3H, s, -OCH_3), 4.01 (2H, qd, *J* 7.1, 1.7, -CH_2CH_3), 4.08 (1H, d, *J* 9.7, C(3)*H*), 5.83 (1H, d, *J* 4.8, C(5)*H*), 6.93 (2H, dq, *J* 9.1, 2.4, 1.9, NSO_2Ar*C*(3)*H*), 7.01-7.07 (2H, m, C(3)Ar*C*(2)*H*), 7.26-7.30 (3H, m, C(3)Ar*CH*), 7.34-7.42 (5H, m, C(6)Ar*CH*), 7.87 (2H, dq, *J* 9.1, 2.4, 1.9, NSO_2Ar*C*(2)*H*); *minor diastereomer (selected)* δ_H 1.14 (3H, t, *J* 7.1, -CH_2CH_3), 4.28 (1H, d, *J* 5.6, C(3)*H*), 6.13 (1H, dd, *J* 4.8, 0.8, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 14.0 (-CH_2CH_3), 45.2 (*C*(4)), 54.1 (*C*(3)), 55.9 (-OCH_3), 61.7 (-CH_2CH_3), 113.7 (NSO_2Ar*C*(3)), 115.7 (*C*(5)), 126.1 (C(6)Ar*C*)), 128.1 (C(3)Ar*C*), 128.5 (C(6)Ar*C*), 128.7 (C(3)Ar*C*), 128.9 (C(3)Ar*C*(4)), 129.8 (C(6)Ar*C*), 130.5 (NSO_2Ar*C*(1)), 131.9 (NSO_2Ar*C*(2)), 135.5 (C(3)Ar*C*(1)), 136.8 (C(6)Ar*C*(1)), 141.3 (*C*(6)), 164.1 (NSO_2Ar*C*(4)), 170.9 (C(4)*C*O), 172.0 (*C*(2)); **HRMS (ESI+)**: $C_{27}H_{26}NO_6S$ $[M+H]^+$ found 492.1470, requires 492.1475 (−1.1 ppm).

The racemic reaction was repeated using ketimine **193** (0.187 g, 0.5 mmol) and (±)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol %) under the above conditions, then recrystallisation (Et_2O) giving **245** (77.6 mg, 0.16 mmol, 32%). Spectral data of **245** identical to the above.

(3*S*,4*S*)-Ethyl-1-((4-nitrophenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **246**



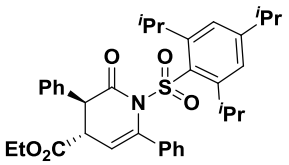
Following general procedure D, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **194** (68.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of 95 : 5 dr. Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **246** (67 mg, 0.13 mmol, 66%, >95 : 5 dr) as a white solid.

mp. 178-180 °C; $[\alpha]_D^{20}$ +4.46 (*c* 0.65, CH_2Cl_2); Chiral HPLC (Chiralpak IA, 30:70 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 14.8 min, t_R (3*R*, 4*R*): 25.4 min, 98% ee; ν_{max} (ATR): 3066, 1728, 1521, 1373, 1348, 1261, 1172, 1147, 1107, 1083, 1026, 931; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 1.12 (3H, t, *J* 7.1, -CH_2CH_3), 3.79 (1H, dd, *J* 7.8, 5.6, C(4)*H*), 4.07 (2H, qd, *J* 7.8, 2.8, -CH_2CH_3), 4.15 (1H, d, *J* 5.6, C(3)*H*), 5.84 (1H, d, *J* 5.6, C(5)*H*), 7.13 (1H, dd, *J* 7.5, 1.8, C(3)Ar*C*(3)*H*), 7.28-7.44 (8H, m, Ar*H*), 8.10 (2H, d, *J* 9.0, NSO_2Ar*C*(2)*H*), 8.30 (2H, d, *J* 9.0, NSO_2Ar*C*(3)*H*); *minor diastereomer (selected)* δ_H 1.16 (3H, t, *J* 7.1, -CH_2CH_3), 3.91-3.85 (1H, m, C(4)*H*), 4.27 (1H, d, *J* 5.5, C(3)*H*), 6.15 (1H, d, *J* 5.4, C(5)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.1 (-CH_2CH_3), 44.9 (*C*(4)), 53.7 (*C*(3)), 62.0 (-CH_2CH_3), 116.2 (*C*(5)), 123.7 (NSO_2Ar*C*(3)), 126.3 (C(3)Ar*C*(2)), 128.4 (C(3)Ar*C*(3)), 128.7 (C(6)Ar*C*)), 129.1 (C(6)Ar*C*)), 129.3 (C(6)Ar*C*)),

131.0 ($NSO_2ArC(2)$), 135.0 (C(3)Ar*C*(1)), 136.2 (C(6)Ar*C*(1)), 141.1 (*C*(6)), 144.4 ($NSO_2ArC(4)$), 150.8 ($NSO_2ArC(4)$), 170.7 (C(4)*C*O), 172.0 (*C(*2)); **HRMS (ESI+)**: $C_{26}H_{23}N_2O_7S$ $[M+H]^+$ found 507.1213, requires 507.1220 (−1.5 ppm).

The racemic reaction was repeated using ketimine **194** (0.194 g, 0.5 mmol) and (±)-tetramisole·HCl (0.24 g, 1.0 mmol, 20 mol %) under the above conditions, then recrystallisation (Et_2O) giving **246** (71.6 mg, 0.14 mmol, 28%). Spectral data of **246** identical to the above.

(3*S*,4*S*)-Ethyl-2-oxo-3,6-diphenyl-1-((2,4,6-triisopropylphenyl)-sulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **247**

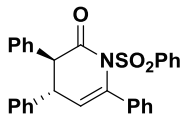


Following general procedure D, the reaction of phenylacetic acid (54.5 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (70 μL, 0.4 mmol) and pivaloyl chloride (50 μL, 0.4 mmol) in CH_2Cl_2 (1.0 mL), followed by (−)-tetramisole·HCl (9.6 mg, 0.04 mmol, 20 mol%), ketimine **192** (93.9 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (35 μL, 0.2 mmol) and CH_2Cl_2 (2.0 mL), for 1 h gave a crude residue of >95 : 5 dr. Recrystallisation (Et_2O) gave **247** (15.4 mg, 0.03 mmol, 13%, >95 : 5 dr) as a white solid.

mp. 215-216 °C; $[\alpha]_D^{20}$ +110 (*c* 0.15, CH_2Cl_2); Chiral HPLC (Chiralpak AD-H, 5:95 IPA : hexane, flow rate 1.5 mL min^{-1}, 254 nm, 40 °C) t_R (3*S*, 4*S*): 3.44 min, t_R (3*R*, 4*R*): 3.66 min, 93% ee; ν_{max} **(**film, cm^{-1}) 2960, 1734, 1715, 1599, 1172, 938; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 0.96 (3H, t, *J* 7.1, -CH_2CH_3), 1.27 (6H, d, *J* 6.6, 6.5, -$CH(CH_3)_2$), 1.29-1.37 (12H, m, -$CH(CH_3)_2$), 2.96 (1H, hept, *J* 6.9, $NSO_2ArC(4)CH(CH_3)_2$), 3.72 (1H, dd, *J* 12.9, 3.4, C(4)*H*), 3.95 (2H, q, *J* 7.1, -CH_2CH_3), 4.04 (1H, d, *J* 12.9, C(3)*H*), 4.18 (2H, p, *J*

6.6, $NSO_2ArC(2)CH(CH_3)_2$), 5.80 (1H, d, *J* 3.4, C(5)*H*), 6.71-6.84 (2H, m, C(3)ArC(2)*H*), 7.17- 7.23 (5H, m, Ar*H*), 7.39-7.47 (3H, m, Ar*H*), 7.61-7.63 (2H, m, C(6)ArC(2)*H*); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ_C 13.9 ($-CH_2CH_3$), 23.7 ($-CH(CH_3)_2$), 23.8 ($-CH(CH_3)_2$), 25.0 ($-CH(CH_3)_2$), 25.4 ($-CH(CH_3)_2$), 30.0 ($NSO_2ArC(2)CH(CH_3)_2$), 34.4 ($NSO_2ArC(4)CH(CH_3)_2$), 46.0 (*C*(4)), 53.3 (*C*(3)), 61.5 ($-CH_2CH_3$), 114.8 (*C*(5)), 123.8 ($NSO_2ArC(3)$), 126.2 (C(6)Ar*C*(2)), 127.8 (Ar*C*), 128.4 (Ar*C*), 129.0 (Ar*C*), 129.2 (Ar*C*), 133.7 ($NSO_2ArC(1)$), 135.5 (C(3)Ar*C*(1)), 137.1 (C(6)Ar*C*(1)), 142.1 (*C*(6)), 152.4 ($NSO_2ArC(2)$), 154.2 ($NSO_2ArC(4)$), 171.0 (*C*(2)), 171.2 (C(4)*C*O)); **HRMS (ESI+)**: $C_{35}H_{41}N_1O_5Na_1S_1$ ([M+ Na]$^+$), found 610.2603 requires 610.2592 (−1.2 ppm).

(3*S*,4*S*)-3,4,6-triphenyl-1-(phenylsulfonyl)-3,4-dihydropyridin-2(1H)-one, **475**

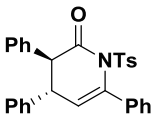


Following general procedure D, the reaction of phenylacetic acid (0.55 g, 4.0 mmol), (^{i}Pr)$_2$NEt (0.70 mL, 4.0 mmol) and pivaloyl chloride (0.50 mL, 4.0 mmol) in CH_2Cl_2 (10 mL), followed by DHPB (76.1 mg, 0.4 mmol, 20 mol%), ketimine **465** (0.70 mg, 2.0 mmol), (^{i}Pr)$_2$NEt (0.35 mL, 2.0 mmol) and CH_2Cl_2 (20 mL) for 1 h. Purification by flash chromatography (CH_2Cl_2) then recrystallisation (Et_2O) gave the title compounds **475** as a white solid (0.42 g, 0.92 mmol, 46%, 94:6 dr).

mp. 182-184 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 3.92 (1H, d, *J* 10.7, C(3)*H*), 4.04 (1H, dd, *J* 10.7, 4.2, C(4)*H*), 6.07 (1H, d, *J* 4.2, C(5)*H*), 6.80-6.82 (2H, m, C(4)Ar*C*(2)*H*), 7.03-7.05 (2H, m, C(3)Ar*C*(2)*H*), 7.13-7.19 (6H, m, Ar*H*), 7.35-7.44 (5H, m, Ar*H*), 7.49 (2H, td, *J* 7.9, 1.7, $NSO_2ArC(3)H$), 7.63-7.66 (1H, m, $NSO_2ArC(4)H$), 7.97-7.99 (2H, m, $NSO_2ArC(2)H$); *minor diastereomer (selected)* δ_H 4.11 (1H, d, *J* 5.9, C(3)*H*), 4.27 (1H, t, *J* 5.6, C(4)*H*), 6.02 (1H, d, *J* 4.6, C(5)*H*), 6.66-6.70 (2H, m, Ar*H*), 6.84-6.87 (2H, m, Ar*H*), 8.01 (2H,dd, *J* 8.5, 1.2, $NSO_2ArC(2)H$); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) *major*

diastereomer δ_C 45.3 (*C*(4)), 59.1 (*C*(3)), 123.1 (*C*(5)), 126.2 (Ar*C*), 127.3 (Ar*C*), 127.5 (Ar*C*), 127.9 (C(3)Ar*C*(2)), 128.5 (Ar*C*), 128.6 (Ar*C*), 128.7 (NSO_2ArC(2)), 128.8 (Ar*C*), 128.9 (C(4)Ar*C*(2)), 129.5 (NSO_2Ar*C*(2)), 134.0 (NSO_2Ar*C*(4)), 136.4 (C(3)Ar*C*(1)), 137.1 (C(6)Ar*C*(1)), 139.4 (NSO_2Ar*C*(1)), 140.0 (C(4)Ar*C*(1)), 140.2 (*C*(6)), 173.2 (*C*(2)); **HRMS** (ESI^+): $C_{29}H_{23}NO_3SNa$ ($[M+Na]^+$), found 488.1282, requires 488.l1291 (−1.8 ppm)).

(3*S*,4*S*)-3,4,6-triphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one, **474**



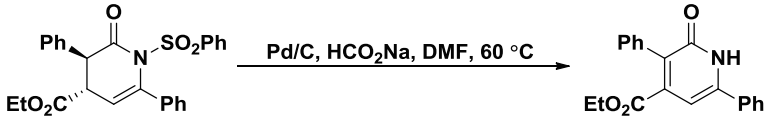
Following general procedure D, the reaction of phenylacetic acid (0.55 g, 4.0 mmol), (^{i}Pr)$_2$NEt (0.70 mL, 4.0 mmol) and pivaloyl chloride (0.50 mL, 4.0 mmol) in CH_2Cl_2 (10 mL), followed by DHPB (76.1 mg, 0.4 mmol, 20 mol%), ketimine **464** (0.72 mg, 2.0 mmol), (^{i}Pr)$_2$NEt (0.35 mL, 2.0 mmol) and CH_2Cl_2 (20 mL) for 1 h. Purification by flash chromatography (CH_2Cl_2) then recrystallisation gave the title compound **474** as a white solid (0.40 g, 0.83 mmol, 42%, >95:5 dr).

mp. 88-90 ˚C (Lit.[68] 58-62˚C); **^{1}H NMR** (500 MHz, $CDCl_3$) *major diastereomer* δ_H 2.46 (3H, s, -C*H*$_3$), 3.90 (1H, d, *J* 10.6, C(3)*H*), 4.04 (1H, dd, *J* 10.6, 4.2, C(4)*H*), 6.02 (1H, d, *J* 4.2, C(5)*H*), 6.81-6.83 (2H, m, C(4)Ar*C*(2)*H*), 7.03-7.05 (2H, m, C(3)Ar*C*(2)*H*), 7.13-7.19 (6H, m, Ar*H*), 7.28 (2H, d, *J* 8.1, Ar*H*), 7.37-7.39 (3H, m, Ar*H*), 7.42-7.44 (2H, m, Ar*H*), 7.85 (2H, d, *J* 8.4, NSO_2Ar*C*(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) *major diastereomer* δ_C 21.9 (-*C*H$_3$), 45.3 (*C*(4)), 59.1 (*C*(3)), 122.9 (*C*(5)), 127.3 (Ar*C*), 127.5 (Ar*C*), 127.9 (C(3)Ar*C*(2)), 128.5 (Ar*C*), 128.6 (Ar*C*), 128.7 (NSO_2ArC(2)), 128.8 (Ar*C*), 128.9 (C(4)Ar*C*(2)), 129.2 (Ar*C*), 129.6 (NSO_2Ar*C*(2)), 136.5 (NSO_2Ar*C*(1)), 136.5 (C(3)Ar*C*(1)), 137.2 (C(6)Ar*C*(1)), 140.0 (C(4)Ar*C*(1)), 140.2 (*C*(6)), 146.2 ((NSO_2Ar*C*(4)), 173.2 (*C*(2)); Data consistent with literature.[68]

5-8. Data for Derivatisation of Dihydropyridinone

5-8-1. Dehydrogenation/Desulfonylation

Ethyl 2-oxo-3,6-diphenyl-1,2-dihydropyridine-4-carboxylate, **252**

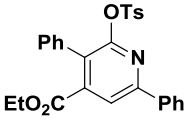


A solution of dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq.) and HCOONa (34.0 mg, 0.5 mmol, 5 eq.) in DMF (0.5 mL) was treated with 10% Pd/C (12 mol%) and stirred at 60 ℃ for 24 h. The reaction was allowed to cool to rt, diluted with water (5 mL), filtered through Celite® , and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2–MeOH, 19 : 1) to give **252** (27.6 mg, 0.086 mmol, 86%) as a white solid.

mp: 182-184 ℃{Lit:[179] 214 ℃ (EtOAc)}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 0.95 (3H, t, *J* 7.1, -CH_2CH_3), 4.07 (2H, q, *J* 7.1, -CH_2CH_3), 6.77 (1H, s, C(5)*H*), 7.37-7.41 (7H, m, Ar*H*), 7.46 (2H,d, *J* 6.9, C(6)ArC(4)*H*), 7.78 (2H,d, *J* 7.7 C(6)ArC(2)*H*), 12.17 (1H, br s, -N*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 13.7 (-CH_2CH_3), 62.0 (-CH_2CH_3)), 104.7 (*C*(5)) 126.7 (C(6)Ar*C*(2)), 128.1 (Ar*C*), 128.2 (Ar*C*), 129.4 (Ar*C*), 129.6 (Ar*C*), 130.7 (C(6)Ar*C*(4)), 132.4 (C(6)Ar*C*(1)), 134.4 (C(3)Ar*C*(1)), 143.5 (*C*(3)), 146.0 (*C*(4)), 163.9 (*C*(2)), 165.7 (*C*(6)), 167.5 (C(4)*C*O). Data consistent with literature.

5-8-2. Tosylation

Ethyl 3,6-diphenyl-2-(tosyloxy)isonicotinate, **253**



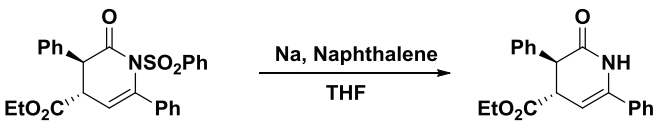
A stirred solution of pyridone **252** (31.9 mg, 0.1 mmol, 1 eq.) in anhydrous THF (1 mL) at −78 ℃ under an argon atmosphere was treated with NaH (60% wt, 6.0 mg, 0.15 mmol, 1.5

eq.) followed by a solution of tosyl chloride (28.6 mg, 0.15 mmol, 1.5 eq.) in anhydrous THF (0.5 mL). After 1 h, the reaction mixture was allowed to warm to rt, then heated to 60 ℃ for 3 h. The reaction was poured into ice water (10 mL), neutralised with K_2CO_3, and extracted with $CHCl_3$ (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by flash chromatography (Et_2O–pet. ether, 3 : 7) to give pyridine **253** (44.6 mg, 0.094 mmol, 94%) as a white solid.

mp. 122-124 ˚C; **ν_{max}** (film, cm-1): 2924, 1732, 1597, 1539, 1375, 1327, 1247, 1192, 1178, 1168, 1155, 1024, 968; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 0.94 (3H, t, *J* 7.1, -CH_2CH_3), 2.47 (3H, s, -C*H*$_3$), 4.07 (2H, q, *J* 7.1, -C*H*$_2$$CH_3$), 7.29 (2H, d, *J* 8.1, NSO_2ArC(3)*H*), 7.31-7.35 (2H, m, Ar*H*), 7.37-7.49 (6H, m, Ar*H*), 7.75-7.85 (4H, m, NSO_2ArC(2)*H* and Ar*H*), 7.99 (1H, s, C(5)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 13.6 (-CH_2*C*H_3), 21.9 (-*C*H_3), 62.0 (-*C*H_2CH_3), 118.1 (*C*(5)), 126.3, 127.1 (Ar*C*), 128.3 (Ar*C*), 128.4 (Ar*C*), 128.7 (Ar*C*), 128.7 (Ar*C*), 128.9 (Ar*C*), 129.6 (Ar*C*), 129.6 (NSO_2Ar*C*(3)), 130.1 (Ar*C*), 133.3 (Ar*C*), 135.1 (NSO_2ArC(1)), 136.6 (Ar*C*), 144.4 (Ar*C*), 144.9 (Ar*C*), 155.0 (Ar*C*), 155.3 (Ar*C*), 166.5 (C(4)*C*O); **HRMS** (ESI^+): $C_{27}H_{24}NO_5S$ ($[M+H]^+$), found 474.1364, requires 474.1370 (−1.2 ppm).

5-8-3. Desulfonylation

(3*S*,4*S*)-Ethyl 2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate**, 259**



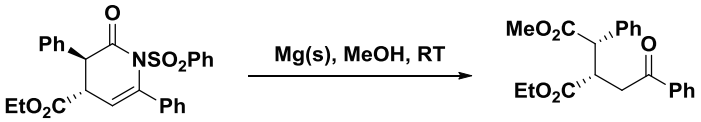
A solution of dihydropyridinone **212** (92.3 mg, 0.2 mmol, 1 eq.) in anhydrous THF (2 mL) at −78 ℃ under an argon atmosphere was treated dropwise with a pre-formed solution of sodium (18.4 mg, 0.8 mmol, 4 eq.) and naphthalene (102.5 mg, 0.8 mmol, 4 eq.) in anhydrous THF (2 mL) that had been stirred for 1.5 h at rt. The reaction was monitored by TLC and when complete (1 h), quenched with brine (5 mL) and extracted with EtOAc (3 × 5 mL). The

combined organics were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to obtain the crude product (>99 : 1 dr). Purification by flash chromatography (Et_2O–pet. ether, 1 : 1) to give **259** (29.5 mg, 0.092 mmol, 46%, >99 : 1 dr) as a white solid.

mp. 100-102 °C; $[\alpha]_D^{20}$ +136.5 (*c* 0.26, CH_2Cl_2); Chiral HPLC (Chiralpak OD-H, 30:70 IPA : hexane, flow rate 0.5 mL min^{-1}, 270 nm, 30 °C) t_R (3*S*, 4*S*): 36.4 min, t_R (3*R*, 4*R*): 29.2 min, 99% ee; ν_{max} (ATR): 3246, 2964, 1728, 1670, 1651, 1456, 1265, 1155.; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.18 (3H, *J* 7.1, -CH_2CH_3), 3.76 (1H, dd, *J* 7.5, 4.8, C(4)*H*), 4.13 (2H, q, *J* 7.1, -CH_2CH_3), 4.19 (1H, d, *J* 7.5, C(3)*H*), 5.43 (1H, dd, *J* 4.8, 1.5, C(5)*H*), 7.29-7.35 (5H, m, C(3)Ar*H*), 7.40-7.43 (2H, m, C(6)ArC(3)*H*), 7.45-7.47 (2H, m, C(6)ArC*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.2 (-CH_2CH_3), 46.7 (*C*(4)), 48.5 (*C*(3)), 61.5 (-CH_2CH_3)), 99.3 (*C*(5)), 125.3 (C(6)Ar*C*(2)), 127.8 (C(3)Ar*C*)), 128.4 (Ar*C*)), 128.9 (Ar*C*), 129.2 (Ar*C*), 129.6 (Ar*C*), 134.5 (C(6)Ar*C*(1)), 137.3 (C(3)Ar*C*(1)), 138.2 (*C*(6)), 170.8 (*C*(2)), 171.9 (C(4)*C*O); **HRMS (ESI+)**: $C_{20}H_{20}NO_3$ ($[M+H]^+$), found 322.1438, requires 322.1443 (+1.6 ppm).

5-8-4. Desulfonylation and Ring Opening

N-((3*S*,4*S*)-5-Hydroxy-3-(hydroxymethyl)-1,4-diphenylpent-1-en-1-yl)benzenesulfonamide**, 260**

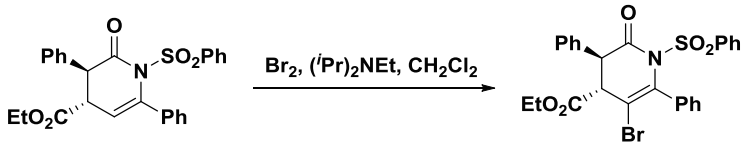


A solution of dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous THF (1 mL) at 0 ℃ under an argon atmosphere was treated dropwise with 2.0 M $LiAlH_4$ in THF (0.1 mL, 0.2 mmol, 2 eq.). The reaction was stirred at 0 °C for 1 h and quenched with 0.1 M HCl (5 mL). The reaction mixture was extracted with Et_2O (3 × 5 mL), the combined organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (Et_2O–pet. ether, 1 : 19) to give **260** (27.6 mg, 0.065 mmol, 65%, >99 : 1 dr) as a white solid.

mp. 80-82 °C; $[\alpha]_D^{20}$ +79.7 (*c* 0.47 in CH_2Cl_2); Chiral HPLC (Chiralpak IA, 30:70 IPA:hexane, flow rate 0.5 mL min^{-1}, 254 nm) t_R (3*S*, 4*S*): 13.6 min, t_R (3*R*, 4*R*): 16.7 min, 97% ee; ν_{max} (ATR) 2916, 1718, 1681, 1448, 1398, 1336, 1271, 1251, 1153, 1002; **^{1}H NMR** (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(13)H_3), 3.17 (1H, dd, *J* 17.3, 3.3, C(4)*H*), 3.58 (1H, dd, *J* 17.3, 10.3, C(4')*H*), 3.67- 3.77 (4H, m, C(3)*H* & C(6)H_3), 3.85 (2H, m, C(12)H_2), 3.92 (1H, d, *J* 9.5, C(2)*H*), 7.26- 7.34 (4H, m, Ar*H*), 7.45 (2H, dd, *J* 8.3, 7.2, Ar*H*), 7.52-7.59 (1H, m, Ar*H*), 7.90-7.97 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 13.8 (*C*(13)), 38.4 (*C*(4) & (*C*(14')), 44.8 (*C*(3)), 52.5 (*C*(6)), 53.5 (*C*(2)), 60.8 (*C*(12)), 128.2 (*Ar*), 128.7 (*Ar*), 133.4 (*Ar*), 135.8 (4ry), 136.5 (4ry), 172.6 (4ry), 173.2 (4ry), 197.7 (4ry); **HRMS (ESI+)**: $C_{21}H_{23}O_5$ ($[M+H]^+$), found 355.1542, requires 355.1540 (+0.6 ppm).

5-8-5. Bromination

(3*S*,4*S*)-Ethyl-5-bromo-2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **261**



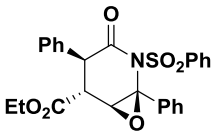
Following the procedure outlined by Harrity *et al*.,[180] a stirred solution of dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous CH_2Cl_2 (10 mL) at −78 ℃ under an argon atmosphere was treated dropwise with bromine (12.8 μL, 0.25 mmol, 2.5 eq.) dropwise. (^{i}Pr)$_2$NEt (19.0 μL, 0.11 mmol, 1.1 eq.) was added and the reaction mixture allowed to warm to rt. The reaction was monitored by TLC and complete in 2 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), the layers separated and the aqueous extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (Et_2O–pet. ether, 1 : 4) to give **261** (46.3 mg, 0.086 mmol, 86%,

>99 : 1 dr) as a white solid.

mp: 130-132 °C; $[\alpha]_D^{22}$ −26.7 (*c* 0.61, CH_2Cl_2); Chiral HPLC Chiralpak IA (30% IPA: hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R (3*S*, 4*S*): 10.9 min, t_R (3*R*, 4*R*): 15.3 min, 97% ee. ν_{max} (ATR): 2924, 1750, 1732, 1446, 1371, 1181, 1066, 885; δ_H (500 MHz $CDCl_3$) 1.36 (3H, t, *J* 7.1, -CH_2CH_3), 4.00 (1H, d, *J* 3.4, C(4)*H*), 4.33 (2H, ddq, *J* 47.0, 10.8, 7.1, -CH_2CH_3), 4.54 (1H, d, *J* 3.4, C(3)*H*), 7.19 (2H, d, *J* 7.5, C(3)ArC(6)*H*), 7.23-7.39 (10H, m, Ar*H*), 7.55 (1H, t, *J* 7.4, NSO_2ArC(4)*H*), 7.59 (2H, t, *J* 7.4, NSO_2ArC(2)*H*); δ_C (126 MHz, $CDCl_3$) 14.2 (-CH_2CH_3), 53.8 (*C*(3)), 54.4 (*C*(4)), 62.8 (-CH_2CH_3), 110.2 (*C*(5)), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 129.0 (Ar*C*), 129.1 (NSO_2Ar*C*(2)), 129.3 (Ar*C*), 129.8 (C(3)Ar*C*(2)), 133.9 (NSO_2Ar*C*(4)), 134.2 (C(6)Ar*C*(1)), 134.9 (C(3)Ar*C*(1)), 137.1 (*C*(6)), 139.0 (NSO_2Ar*C*(1)), 168.9 (C(4)*C*O), 170.4 (*C*(2)); **HRMS (ESI+)**: $C_{26}H_{23}NO_5S^{79}Br$ ($[M+H]^+$), found 540.0469, requires 540.0475 (— 1.1 ppm)).

5-8-6. Epoxidation

(1*S*,4*S*,5*R*,6*S*)-Ethyl-3-oxo-1,4-diphenyl-2-(phenylsulfonyl)-7-oxa-2-azabicyclo[4.1.0]heptane-5-carboxylate, **266**



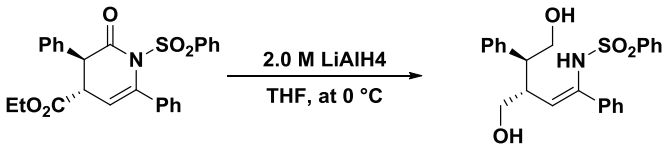
A solution of dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq.) in CH_2Cl_2 (1 mL) at 0 ℃ was treated with *m*CPBA (70% wt, 37.0 mg, 0.15 mmol, 1.5 eq.). The reaction was allowed to warm to rt and stirred for 24 h, before being quenched with sat. $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over $MgSO_4$, filtered, and the solvent removed in vacuo to obtain the crude product (>99 : 1 dr). Purification by flash chromatography (Et_2O–pet. ether, 1 : 4) gave **266** (34.2 mg, 0.072 mmol, 72%, >99 : 1 dr) as a white solid.

mp. 116-118 °C; $[\alpha]_D^{20}$ −29.8 (*c* 0.50, CH_2Cl_2); ν_{max} (ATR):2976, 2360, 2322, 1726, 1448,

1361, 1273, 1174; **^{1}H NMR** (500MHz, CD_2Cl_2) δ_H 0.84 (3H, *J* 7.1, -CH_2CH_3), 3.13 (1H, dd, *J* 13.1, 3.7, C(4)*H*), 3.79 (1H, d, *J* 3.79, C(5)*H*), 3.85 (2H, q, *J* 7.1, -CH_2CH_3), 4.02 (1H, d, *J* 13.1, C(3)*H*), 6.87 (2H, dd, *J* 7.3, 2.0, C(3)ArC(3)*H*), 7.24-7.28 (3H, m, C(3)Ar*H* and C(6)Ar*H*), 7.42-7.55 (7H, m, Ar*H*), 7.63-7.55 (1H, m, NSO_2ArC(4)*H*), 7.85-7.90 (2H, m, NSO_2ArC(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 13.9, 49.9, 51.1, 62.24, 64.6, 70.0, 125.9, 128.8, 129.0, 129.2, 129.4, 129.6, 129.9, 134.2, 134.8, 136.5, 138.7, 169.9, 170.8; **HRMS (ESI+)**: $C_{26}H_{23}NO_6SNa$ [M + Na]+ found 500.1127, requires 500.1138 (−2.3 ppm).

5-8-7. Reduction

N-((3*S*,4*S*)-5-Hydroxy-3-(hydroxymethyl)-1,4-diphenylpent-1-en-1-yl)benzenesulfonamide, **267**

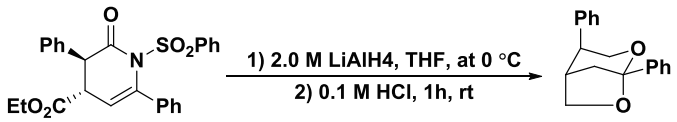


A solution of dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq.) in anhydrous THF (1 mL) at 0 ℃ under an argon atmosphere was treated dropwise with 2.0 M $LiAlH_4$ in THF (0.1 mL, 0.2 mmol, 2 eq.). The reaction was stirred at 0 °C for 1 h and quenched with 0.1 M HCl (5 mL). The reaction mixture was extracted with Et_2O (3 × 5 mL), the combined organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (Et_2O–pet. ether, 1 : 19) to give **267** (27.6 mg, 0.065 mmol, 65%, >99 : 1 dr) as a white solid.

mp. 74-76 °C; $[\alpha]_D^{20}$ −1.1 (*c* 0.45, CH_2Cl_2); Chiral HPLC (Chiralpak AD-H, 30:70 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 9.2 min, t_R (3*R*, 4*R*): 11.1 min, 97% ee; ν_{max} (ATR): 2920, 2358, 2320, 1446, 1328, 1165, 1112, 1091, 1049, 1026; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.65 (1H, ddd, *J* 11.7, 4.9, 3.1, C(4)*H*), 1.67-1.81 (1H, m, C(3)*H*), 3.18 (2H, d, *J* 5.2, C(3)CH_2), 3.60 (1H, dd, *J* 11.5, 4.7, C(5)H_2), 3.65-3.73 (1H, m, C(5)H_2), 5.59

(1H, dd, *J* 9.6, C(2)*H*), 7.09-7.19 (2H, m, C(4)ArC(3)*H*), 7.20-7.42 (6H, m, C(1)ArC*H* and C(4)ArC*H*), 7.41-7.50 (4H, m, C(1)ArC*H* and NSO_2ArC(3)*H*), 7.50-7.59 (1H, m, NSO_2ArC(4)*H*), 7.75 (2H, dd, *J* 8.4, 1.3, NSO_2ArC(2)*H*), 8.11 (1H, br s, -N*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 41.5 (*C*(3)), 48.6 (*C*(4)), 65.0 (C(3)*C*H_2), 65.8 (C(5)*C*H_2), 125.6, 126.5, 127.4, 127.4, 127.5, 128.2, 128.3, 128.6, 129.0, 129.1, 129.3, 132.8, 137.5, 138.2, 140.3, 140.6; **HRMS (ESI+)**: $C_{24}H_{25}NO_4SNa$ $[M+Na]^+$ found 446.1389, requires 446.5162 ($-$ 1.7 ppm).

(1*R*,4*S*,5*S*)-1,4-diphenyl-2,7-dioxabicyclo[3.2.1]octane, **268**



To a solution of the corresponding racemic dihydropyridinone **212** (46.2 mg, 0.1 mmol, 1 eq) in dry THF, was dropwise 2.0 M $LiAlH_4$ in THF (2 eq) at 0 °C, under N_2. The reaction mixture was left stirring in the same temperature and monitored by TLC and complete in 1 h. Excess 0.1 м HCl was then added into the reaction mixture then stirred for further 2 h, then extracted with CH_2Cl_2. The combined organic layer then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography to afford product **268** as white solid (9.8 mg, 0.037 mmol, 37 %, >99:1 dr).

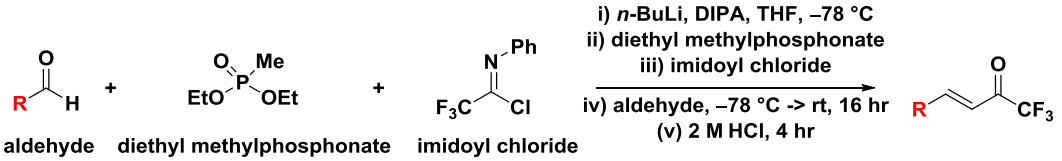
mp. 74-76 °C; Chiral HPLC (Chiralpak OD-H, 10:90 IPA : hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C) t_R (3*S*, 4*S*): 18.9 min, t_R (3*R*, 4*R*): 21.4 min, 57% ee; $\boldsymbol{\nu_{max}}$ (ATR): 2953, 1887, 1490, 1448, 1330, 1170, 1112, 1039, 1010, 950; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 1.72 (1H, dd, *J* 11.7, 5.0, C(8)H_2), 2.28 (1H, d, *J* 11.7, C(8)H_2), 2.78 (1H, q, *J* 4.0, C(5)*H*), 2.99 (1H, t, *J* 4.4, C(4)*H*), 4.21-4.35 (2H, m, C(3)H_2 and C(6)H_2), 4.35- 4.50 4.26 (2H, m, C(3)H_2 and C(6)H_2), 7.23-7.42 (6H, m, ArC*H*), 7.44-7.54 (2H, m, ArC*H*), 7.55-7.63 (2H, m, ArC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 38.1 (*C*(8)), 42.2 (*C*(5)), 43.1 (*C*(4)), 64.4 (*C*(3)), 74.1 (*C*(6)), 106.6 (*C*(1)), 125.6 (Ar*C*), 128.1 (Ar*C*), 128.3 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 140.9

(C(1)*C*(1)), 143.3 (C(4)Ar*C*(1)); **HRMS (ESI+)**: $C_{18}H_{19}O_2$ $[M+H]^+$ found 267.1381, requires 267.1380 (+0.5 ppm).

Data for Trifluoromethyl enones

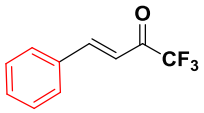
The synthesis of (E)-4-(4-Bromophenyl)-1,1,1-trifluorobut-3-en-2-one, (E)-1,1,1-trifluoro-4-(4-nitrophenyl)but-3-en-2-one and (E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one have been reported previously.[181]

General procedure E: preparation of trifluoromethyl enones



Following the procedure outlined by Zhang *et al*.,[108] to a solution of diisopropylamine (2 eq.) in THF was added *n*BuLi (2.5 M in hexanes, 2 eq.) at −78 ℃ and the solution was allowed to stir for 20 minutes. Diethyl methylphosphonate (1 eq) was added at −78 ℃ followed by a further 30 minutes of stirring. (*Z*)-2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (1 eq.) was then added slowly followed by stirring at −78 ℃ for 1 h. The required aldehyde (1 eq.) was then added dropwise at −78 ℃. The reaction mixture was then warmed slowly to rt and then stirred for 16 h. 2M HCl (4 eq.) was added and the reaction mixture was stirred for further 4 h before being extracted with Et_2O three times. The combined organic extracts were washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product which was purified by flash chromatography on silica gel as indicated.

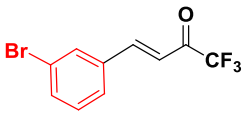
(*E*)-1,1,1,-trifluoro-4-phenylbut-3-en-2-one, **323**[181]



Following general procedure E, diisopropylamine (8.16 mL, 60 mmol) and *n*BuLi (2.5 M in hexanes, 24 mL, 60 mmol) in THF (150 mL), diethyl methylphosphonate (4.44 mL, 30 mmol), imidoyl chloride (6.23 mL, 30 mmol) and benzaldehyde (3.06 mL, 30 mmol) followed by 2 M HCl (60 mL, 120 mmol), gave enone **323** (5.80 g, 97%) as light yellow oil after purification (CH_2Cl_2 : petrol, 5 : 95).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.02 (1H, dq, *J* 16.0, 0.9, C(3)*H*), 7.43-7.48 (2H, m, Ar*H*), 7.48-7.53 (1H, m, Ar*H*), 7.67-7.62 (2H, m, Ar*H*), 7.98 (1H, d, *J* 16.0, C(4)*H*).; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −77.6. Data consistent with literature.[181]

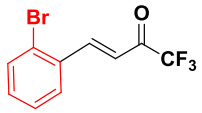
(*E*)-4-(3-bromophenyl)-1,1,1-trifluorobut-3-en-2-one, **324**[181]



Following general procedure E, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and *m*-bromobenzaldehyde (0.29 mL, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **324** (438 mg, 63%) as an orange solid after purification (CH_2Cl_2 : petrol, 3:97).

mp. < 30 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 7.00 (1H, dq, *J* 16.0, 0.7, C(3)*H*), 7.34 (2H, t, *J* 7.9, Ar*H*), 7.52-7.65 (2H, m, Ar*H*), 7.79 (1H, d, *J* 1.9, Ar*H*), 7.88 (1H, d, *J* 16.0, C(4)*H*). Data consistent with literature.[181]

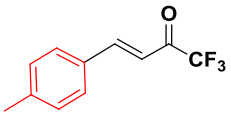
(*E*)-4-(2-bromophenyl)-1,1,1-trifluorobut-3-en-2-one, **325**[181]



Following general procedure E, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and *o*-bromobenzaldehyde (0.29 mL, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **325** (540 mg, 77%) as solid after purification (CH_2Cl_2 : petrol, 5:95).

mp. < 30 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 6.96 (1H, dq, *J* 16.0, 0.9, C(3)*H*), 7.33 (1H, td, *J* 7.7, 1.8, Ar*H*), 7.39 (1H, tdd, *J* 7.8, 1.4, 0.6, Ar*H*), 7.64-7.70 (1H, m, Ar*H*), 7.70-7.76 (1H, m, Ar*H*), 8.37 (1H, dq, *J* 16.0, 0.6, C(4)*H*). Data consistent with literature.[181]

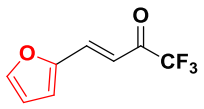
(*E*)- 1,1,1-trifluoro-4-(p-tolyl)but-3-en-2-one, **326**[181]



Following general procedure E, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and *p*-tolualdehyde (0.3 mL, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **326** (373 mg, 70%) as yellow solid after purification (CH_2Cl_2 : petrol 5:95).

mp 29-30 ℃ {Lit.[181] 30-32 ℃}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s, *Me*), 6.98 (1H, dq, *J* 15.9, 1.1, C(3)*H*), 7.21-7.29 (3H, m, Ar*H*), 7.57-7.50 (2H, m, Ar*H*), 7.95 (1H, d, *J* 15.9, C(4)*H*). Data consistent with literature.[181]

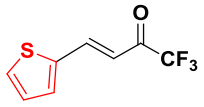
(*E*)- 1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one, **327**[181]



Following general procedure E, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and furfural (0.21 mL, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **327** (113.2 mg, 24%) as light yellow oil after purification (CH_2Cl_2 : petrol 10 : 90).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 6.58 (1H, dd, *J* 3.5, 1.8, Ar*H*), 6.85-6.93 (2H, m, C(3)*H* and Ar*H*), 7.58-7.64 (1H, m, Ar*H*), 7.69 (1H, d, *J* 15.5, C(4)*H*).; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −77.7. Data consistent with literature.[181]

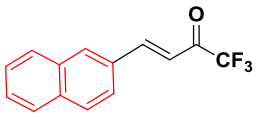
(*E*)- 1,1,1-trifluoro-4-(thophen-2-yl)but-3-en-2-one, **S6**[181]



Following general procedure A, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and 2-thiophenecarboxaldehyde (0.24 mL, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **S6** (386 mg, 75%) as light yellow solid after purification (CH_2Cl_2 : petrol 10 : 90).

mp 37-38 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 6.79 (1H, d, *J* 15.9, C(3)*H*), 7.15 (2H, dd, *J* 5.0, 3.7, Ar*H*), 7.45-7.50 (1H, m, Ar*H*), 7.58 (1H, d, *J* 5.1, 1.0, Ar*H*) , 8.07 (1H, d, *J* 15.5, C(4)*H*). Data consistent with literature.[181]

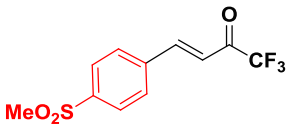
(*E*)- 1,1,1-trifluoro-4-(naphthalen -2-yl)but-3-en-2-one, **328**[181]



Following general procedure E, diisopropylamine (0.70 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and 2-naphthaldehyde (0.39 g, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **328** (448 mg, 72%) as light yellow solid after purification (CH_2Cl_2 : petrol 5:95).

mp 62-64 ℃ {Lit.[1] 65-67 ℃}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 7.13 (1H, dq, *J* 15.9, 1.1, C(3)*H*), 7.52-7.63 (2H, m, Ar*H*), 7.75 (1H, dd, *J* 8.6, 1.8, Ar*H*), 7.83-7.95 (3H, m, Ar*H*) , 8.08 (1H, s, Ar*H*), 8.14 (1H, d, *J* 15.9, C(4)*H*). Data consistent with literature.[181]

(*E*)- 1,1,1-trifluoro-4-(4-(methylsulfonyl)phenyl)but-3-en-2-one, **367**



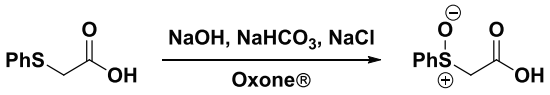
Following general procedure A, diisopropylamine (0.7 mL, 5.0 mmol) and *n*BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imidoyl chloride (0.52 g, 2.5 mmol) and 4-(methylsulfonyl)benzaldehyde (0.46 g, 2.5 mmol) followed by 2 M HCl (5.0 mL, 20 mmol), gave enone **367** (481 mg, 69%) as light yellow solid after purification (CH_2Cl_2).

mp. 102-104 ℃; **ν_{max}** (ATR): 2993, 1722, 1692, 1612, 1588, 1401, 1294, 1203, 1139, 1122, 1089, 1053, 950, 831; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.09 (3H, s, *Me*), 7.11 (1H, dq, *J* 16.1, 0.9, C(3)*H*), 7.78-7.88 (2H, m, C(4)ArC(2')*H*), 7.96 (1H, d, *J* 16.1, C(4)*H*), 8.00-8.08 (2H, m, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 44.4 (*Me*), 116.2 (q, $^1J_{CF}$ 290.5, C(2)*C*F), 120.5, 128.3, 129.8, 138.2, 143.2, 147.2, 179.7 (q, $^2J_{CF}$ 36.2, *C*(1)); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −78.2; HRMS (ESI^-) $C_{11}H_8O_3F_3S$ ($[M-H]^-$), found 277.0152, requires

277.0152 (+0.1 ppm)).

5-10. Data for (phenylthio)acetic Acid Analogues

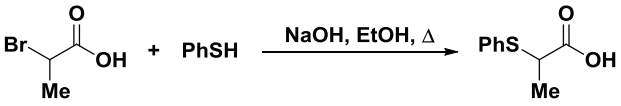
2-(Phenylsulfinyl)acetic acid, **321**



Following the procedure outlined by Webb *et al.*,[105] to a solution of sodium hydroxide (1.54 g, 51.3 mmol, 1.7 eq) and (phenythio)acetic acid (5.08 g, 30.2 mmol, 1 eq) in deionised water (30 mL) was stirred at rt for 10 minutes followed by the addition of sodium bicarbonate (20.0 g) and acetone (25 mL), and the solution cooled down to 0 ℃. A solution of Oxone® (12.13 g in 50 mL of 4 x 10^{-4} M aq. EDTA) was added dropwise over 10 minutes, keeping the internal temperature below 5 ℃. The suspension was stirred for 5 minutes then quenched immediately with a solution of sodium bisulfite (7.5 g in 15 mL water). EtOAc (200 mL) was added and the reaction mixture was acidified with 6 M HCl (45 mL). The layers were separated, and the aqueous layer treated with NaCl (37.5 g) and extracted with EtOAc (200 mL). The combined organic layers were washed with deionised water (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product **321** as a white solid which was dried *in vacuo* overnight (4.73 g, 85%).

mp. 112-114 ℃ {Lit.[4] 112-113 ℃}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.80 (1H, d, *J* 14.6, S(O)C*H*^{A}H^B), 3.88 (1H, d, *J* 14.6, S(O)CH^A*H*^{B}), 7.54-7.57 (3H, m, Ar*H*), 7.69-7.73 (2H, m, Ar*H*), 10.17 (1H, bs, CO_2*H*). Data consistent with literature.[182]

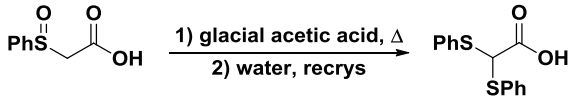
2-(Phenylsulfanyl)propanoic acid, **320**



Following the procedure outlined by Gualtieri *et al.*,[106] to a solution of NaOH (0.80 g, 20 mmol, 2 eq) in absolute EtOH (30 mL) was added thiophenol (1.10 mL, 10 mmol, 1 eq) and 2-bromopropionic acid (0.90 mL, 10 mmol, 1 eq), and the reaction refluxed overnight. The solvent was removed *in vacuo*, the residue dissolved in water (10 mL), acidified with 6 M HCl and extracted with Et_2O (3 x 20 mL). The combined organic layers were extracted with sat. aq. Na_2CO_3 (3 x 20 mL). The combined aqueous layers were acidified with 6 M HCl, extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound **320** as a yellow oil (2.09 g, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.51 (3H, d, *J* 7.2, *Me*), 3.78 (1H, q, *J* 7.2, C(2)*H*), 7.27-7.35 (3H, m, Ar*H*), 7.45-7.52 (2H, m, Ar*H*), 10.39 (1H, s, O*H*). Data consistent with literature.[183]

2,2-Bis(phenylsulfanyl)acetic acid, **322**



Following the procedure of Kenney *et al.*,[107] 2-(phenylsulfinyl)acetic acid **321** (4.65 g, 25.2 mmol, 2.0 eq) was refluxed overnight in glacial acetic acid (100 mL). The acetic acid was removed *in vacuo*, and the residue washed with water (3 x 20 mL). The resulting solid was recrystallised from AcOH : H_2O (19 : 1), filtered and the solid dried *in vacuo* to leave acid **322** (2.20 g, 63%) as a white solid.

mp. 100-101 °C {Lit.[107] 101-103 °C}; **ν_{max}** (ATR): 3059, 2798, 2671, 2563, 1697, 1468, 1439, 1416, 1298, 1163, 1152, 1069, 1024, 908; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.82 (1H, s, $(PhS)_2CH$), 7.31-7.38 (6H, m, Ar*H*), 7.49-7.52 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (125 MHz,

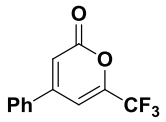
$CDCl_3$) δ_C: 58.2, 129.1, 129.4, 132.3, 133.7, 173.6; **HRMS** (ESI^+) $C_{14}H_{12}O_2S_2Na$ ($[M+Na]^+$) found 299.0166, requires 299.0171 (−1.6 ppm).

Data for 2-Pyrones

General Procedure F-*2-pyrone synthesis*

To a flame dried vial under N_2 was added (phenylthio)acetic acid (2 eq), (^{i}Pr)$_2$NEt (3 eq) and anhydrous MeCN (2.5 mL / 1.0 mmol acid) and cooled to 0 ℃. Pivaloyl chloride (2 eq) was then added, and the reaction stirred for 30 minutes. DHPB **214** (indicated mol %) was added followed by the addition of α,β-unsaturated trifluoromethyl ketone (1 eq), additional (^{i}Pr)$_2$NEt (2.5 eq) and anhydrous MeCN (2.5 mL / 1.0 mmol acid). The reaction mixture was stirred at rt for 24 h unless otherwise stated, then quenched with 0.1 M HCl, extracted with CH_2Cl_2 (x 3) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product which was purified by flash chromatography on silica gel as indicated.

4-Phenyl-6-(trifluoromethyl)-2*H*-pyran-2-one, **285**[104]



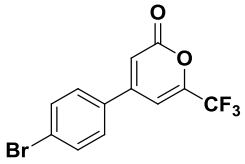
Following general procedure F, (phenylthio)acetic acid (2.02 g, 12.0 mmol), (^{i}Pr)$_2$NEt (3.10 mL, 18.0 mmol) and pivaloyl chloride (2.20 mL, 18.0 mmol) in MeCN (30.0 mL), followed by DHPB (228 mg, 1.2 mmol, 20 mol %), **323** (1.20 g, 6.0 mmol), (^{i}Pr)$_2$NEt (2.60 mL, 15.0 mmol) and MeCN (30.0 mL), gave the title compound **285** as an orange solid (1.30 g, 90%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 56-57 ℃ {Lit.[104] 60 ℃}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 6.59-6.69 (1H, m, C(3)*H*), 6.916.94-7.02 (1H, m, C(5)*H*), 7.38-7.70 (5H, m, Ar*H*). Data consistent with literature.[104]

The reaction was repeated using **323** (40.0 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol,

1 mol %) under the above conditions, giving **323** (36.8 mg, 77%). Spectral data of **11** identical to the above.

4-(4-Bromophenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **337**

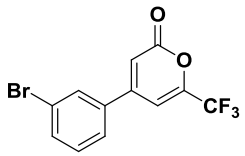


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), (*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut- 3-en-2-one (55.8 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL) gave the title compound **337** as an orange solid (60.5 mg, 95%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 114-116℃; **ν_{max}** (ATR): 3118, 1739, 1688, 1587, 1490, 1348, 1139, 1097, 827; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 6.64 (1H, d, *J* 1.6, C(3)*H*), 6.91 (1H, d, *J* 1.6, C(5)*H*), 7.47 (2H, dt, *J* 8.7, 2.4, C(4)ArC(2')*H*), 7.67 (2H, dt, *J* 8.7, 2.4, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ_C: 104.5 (q, $^{3}J_{CF}$ 3.8, *C*(5)), 114.0 (*C*(3)), 118.9 (q, $^{1}J_{CF}$ 273.0, C(4)*C*F_3), 126.4 (C(4)Ar*C*(1')), 128.2 (C(4)Ar*C*(3')), 132.9 (C(4)Ar*C*(2')), 133.1 (4ry, *C*(4)), 148.9 (q, $^{2}J_{CF}$ 39.4, *C*(6)), 152.2 (4ry, C(4)Ar*C*(4')), 159.1 (4ry, *C*(2)); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −71.21 ; **HRMS** (ESI+) $C_{12}H_7O_2{}^{79}BrF_3$ $[M+H]^+$ found 318.9578, requires 318.9576 (+0.6 ppm).

The reaction was repeated using (*E*)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one (55.8 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **337** (46.9 mg, 73%). Spectral data of **15** identical to the above.

4-(3-Bromophenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **338**

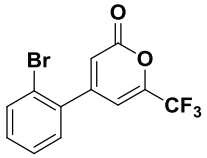


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **324** (55.8 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), gave the title compound as an orange solid **338** (60.5 mg, 95%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 90).

mp. 65-66 ℃; **ν_{max}** (ATR): 2924, 1741, 1664, 1556, 1342, 1197, 1145, 1095, 1028, 850; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 6.64 (1H, d, *J* 1.6, C(3)*H*), 6.91 (1H, d, *J* 1.6, C(5)*H*), 7.41 (1H, t, *J* 7.9, C(4)ArC(5')*H*), 7.53 (1H, ddd, *J* 7.9, 1.9, 1.0, C(4)ArC(4')*H*), 7.67 (1H, ddt, *J* 8.0, 1.8, 0.8, C(4)ArC(6')*H*), 7.72 (1H, t, *J* 1.8, C(4)ArC(2')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 104.5 (q, $^{3}J_{CF}$ 3.8, *C*(5)), 114.7 (*C*(3)), 118.0 (q, $^{1}J_{CF}$ 272.9, C(4)*C*F$_3$), 123.8 (C(4)Ar*C*(1')), 125.4 (C(4)Ar*C*(4')), 129.8 (C(4)Ar*C*(2')), 131.1 (C(4)Ar*C*(5')), 134.5 (C(4)Ar*C*(6')), 136.3 (*C*(4)), 148.9 (q, $^{2}J_{CF}$ 38.4, *C*(6)), 151.9 (C(4)Ar*C*(3')), 159.0 (*C*(2)); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −71.2; **HRMS** (ESI$^+$) $C_{12}H_7O_2{}^{79}BrF_3$ $[M+H]^+$ found 318.9582, requires 318.9576 (+1.9 ppm).

The reaction was repeated using **324** (55.8 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **338** (46.9 mg, 73%). Spectral data of **338** identical to the above.

4-(2-Bromophenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **339**

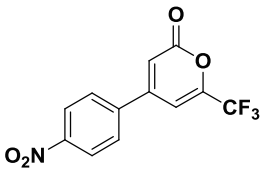


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **325** (55.8 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), gave the title compound **339** as a yellow solid (52.2 mg, 82%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 68-69 °C; **ν_{max}** (ATR): 2926, 1747, 1666, 1568, 1343, 1276, 1195, 1145, 1095, 827, 758; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 6.50 (1H, s, C(3)*H*), 6.83 (1H, d, *J* 1.6, C(5)*H*), 7.31 (1H, dd, *J* 7.6, 1.7, C(4)ArC(6')*H*), 7.36 (1H, td, *J* 7.8, 1.8, C(4)ArC(4')*H*), 7.45 (1H, td, *J* 7.5, 1.2, C(4)ArC(5')*H*), 7.71 (1H, dd, *J* 8.0, 1.2, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 107.4 (q, $^{3}J_{CF}$ 3.9, *C*(5)), 118.1 (q, $^{1}J_{CF}$ 273.7, C(4)*C*F_3), 119.2 (*C*(3)), 121.0, 125.4, 129.8, 131.1, 134.5, 136.5 (*C*(4)), 147.8 (q, $^{2}J_{CF}$ 39.5, *C*(6)), 154.5 (C(4)Ar*C*(2')), 158.9 (*C*(2)); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −71.1; **HRMS** (ESI^+) $C_{12}H_7O_2{}^{79}BrF_3$ $[M+H]^+$ found 318.9576, requires 318.9576 (+0.0 ppm).

The reaction was repeated using **325** (55.8 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **339** (39.9 mg, 63%). Spectral data of **339** identical to the above.

4-(4-Nitrophenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **340**[104]

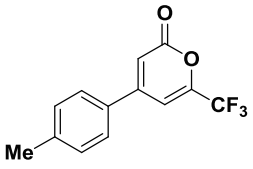


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), (*E*)-4-(4-nitrophenyl)-1,1,1-trifluorobut-3-en-2-one (49.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL) gave the title compound **340** as an orange solid (48.7 mg, 85%) after purification by flash chromatography on silica gel (Et_2O : petrol, 10 : 90).

mp. 170-172 °C {Lit.[104] 178-180 °C}; $\boldsymbol{\nu_{max}}$ (ATR): 3115, 1745, 1521, 1350, 1227, 1139, 1097, 846; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 6.73 (1H, d, *J* 1.0, C(3)*H*), 6.94 (1H, d, *J* 0.9, C(5)*H*), 7.74-7.81 (2H, m, C(4)ArC(2')*H*), 8.36-8.43 (2H, m, C(4)ArC(3)*H*); **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ_C: 104.2 (q, $^{3}J_{CF}$ *J* 3.6, *C*(5)), 116.2 (*C*(3)), 117.9 (q, $^{1}J_{CF}$ 269.1, C(4)*C*F$_3$), 124.8, 128.0, 140.3, 149.4 (q, $^{2}J_{CF}$ 39.8, *C*(6)), 151.2, 158.4; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ_F: −71.72; **HRMS** (ESI$^+$) $C_{12}H_7O_4F_3$ $[M+H]^+$ found 286.0326, requires 286.0322 (+1.5 ppm).

The reaction was repeated using (*E*)-4-(4-nitrophenyl)-1,1,1-trifluorobut-3-en-2-one (49.0 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **340** (36.0 mg, 71%). Spectral data of **340** identical to the above.

4-(4-Methylphenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **341**[104]



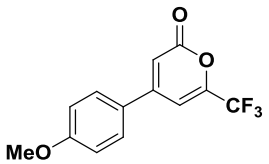
Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104

μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **326** (42.8 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL) gave the title compound **341** as an orange solid (44.7 mg, 88%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 108-110 ℃ {Lit.[104] 114-115 ℃}; **ν_{max}** (ATR): 3101, 1724, 1664, 1558, 1355, 1207, 1138, 1101, 808; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 2.43 (1H, s, *-Me*), 6.64 (1H, d, *J* 0.9, C(3)*H*), 6.96 (1H, d, *J* 0.9, C(5)*H*), 7.32 (2H, d, *J* 8.0, C(4)ArC(3')*H*), 7.50 (2H, d, *J* 8.3, C(4)ArC(2')*H*); **^{13}C{^{1}H} NMR** (75 MHz, $CDCl_3$) δ_C: 21.5 (Me), 104.8 (q, $^{3}J_{CF}$ 3.7, *C*(5)), 113.0 (*C*(3)), 118.23 (q, $^{1}J_{CF}$ 272.9, C(4)*C*F_3), 126.7 (C(4)ArC(2')), 130.3 (C(4)ArC(3')), 131.3 (4ry, C(4)ArC(1')), 142.4 (4ry,*C*(4)), 148.52 (q, $^{2}J_{CF}$ 39.0, *C*(6)), 153.2 (4ry, C(4)Ar*C*(4')), 159.6 (4ry, *C*(2)); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ_F: −71.70; **HRMS** (ESI+) $C_{13}H_{10}O_2F_3$ $[M+H]^+$ found 255.0629, requires 255.0627 (+0.6 ppm).

The reaction was repeated using **326** (42.8 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol) under the above conditions, giving **341** (36.0 mg, 71%). Spectral data of **16** are identical to the above.

4-(4-Methoxyphenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **342**

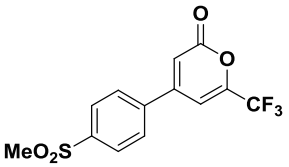


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB **1** (7.6 mg, 0.04 mmol, 20 mol %), (*E*)-4-(4-methoxyphenyl)-1,1,1-trifluorobut-3-en-2-one (46.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), with stirring for 72 h, gave the title compound **342** as a orange solid (32.9 mg, 61%) after

purification by flash chromatography on silica gel (Et_2O : petrol, 10 : 90).

mp. 84-86 °C; **ν_{max}** (ATR): 2926, 1735, 1664, 1604, 1577, 1556, 1516, 1429, 1352, 1307, 1274, 1247, 1197, 1184, 1145, 1095, 1031, 829; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.88 (3H, s, O*Me*), 6.60 (1H, dt, *J* 1.6, 0.7, C(3)*H*), 6.96 (1H,dt, *J* 1.6, 0.7, C(5)*H*), 6.98-7.06 (2H, m, C(4)ArC(3')*H*), 7.54-7.61 (2H, m, C(4)ArC(2')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 55.6 (O*Me*), 104.5 (q, $^3J_{CF}$ 3.6, *C*(5)), 111.7 (*C*(3)), 115.1 (Ar*C*), 118.3 (q, $^1J_{CF}$ 272.9, C(4)*C*F_3), 126.2 (Ar*C*), 128.4 (Ar*C*), 148.4 (q, $^2J_{CF}$ 39.1, *C*(6)), 159.8, 162.6; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −71.2; **HRMS** (ESI^+) $C_{13}H_{10}O_3F_3$ $[M+H]^+$ requires 271.0579, found 271.0577 (+0.9 ppm).

4-(4-Methanesulfonylphenyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **343**

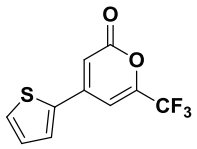


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **367** (55.7 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL) gave the title compound **343** as a white solid (60.2 mg, 95%) after purification by flash chromatography on silica gel (Et_2O : CH_2Cl_2, 2 : 98).

mp. 201-202 °C; **ν_{max}** (ATR): 2916, 1749, 1668, 1558, 1394, 1294, 1149, 1091, 950, 829; **^{1}H NMR** (500 MHz, CD_3CN) δ_H: 3.11 (3H, s, *Me*), 6.85 (1H, s, C(3)*H*), 7.23 (1H, s, C(5)*H*), 7.95 (2H, d, *J*8.4, C(4)ArC(2')*H*), 8.06 (2H, d, *J*8.4, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (126 MHz, CD_3CN) δ_C: 44.3 (*Me*), 106.3 (q, $^3J_{CF}$ 3.6, *C*(5)), 116.1 (*C*(3)), 119.3 (q, $^1J_{CF}$ 271.6, C(4)*C*F_3), 128.9 (Ar*C*), 140.0 (Ar*C*), 143.9 (Ar*C*), 148.4 (q, $^2J_{CF}$ 38.8, *C*(6)), 152.4, 159.8; **^{19}F{^{1}H} NMR** (376 MHz, CD_3CN) δ_F: −72.0; HRMS (ESI^+): $C_{13}H_{10}O_4F_3S$ $[M+H]^+$ found 319.0246, requires 319.0246 (−0.1 ppm).

The reaction was repeated using **367** (55.7 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **343** (36.4 mg, 57%). Spectral data of **343** identical to the above.

4-(Thiophen-2-yl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **344**[104]

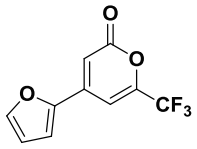


Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **S6** (41.2 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), gave the title compound **344** as a red solid (41.0 mg, 83%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 136-137 °C {Lit.[104] 141-143 °C}; $\boldsymbol{\nu_{max}}$ (ATR): 2922, 1741, 1688, 1564, 1352, 1192, 1136, 839; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 6.59 (1H, s, C(3)*H*), 6.93 (1H, s, C(5)*H*), 7.21 (1H, dd, *J* 5.0, 3.8, C(4)ArC(4')*H*), 7.57 (1H, dd, *J* 3.8, 1.0, C(4)ArC(3')*H*), 7.61(1H, dd, *J* 1.1, 5.1, C(4)ArC(5')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 103.8 (q, $^{3}J_{CF}$ 3.6, *C*(5)), 110.2 (*C*(3)), 118.0 (q, $^{1}J_{CF}$ 273.0, C(4)*C*F$_3$), 129.2 (C(4)Ar*C*(5')), 129.2 (C(4)Ar*C*(4')), 131.3 (C(4)Ar*C*(3')), 137.4 (*C*(4)), 146.1 (C(4)Ar*C*(1')), 148.5 (q, $^{2}J_{CF}$ 39.3, *C*(6)), 159.5 (*C*(2)); **^{19}F NMR** (471 MHz, $CDCl_3$) δ_F: −71.35; **HRMS** (ESI$^+$) $C_{10}H_6O_2F_3S$ $[M+H]^+$ found 247.0035, requires 247.0035 (+0.0 ppm).

The reaction was repeated using **S6** (41.2 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **344** (22.0 mg, 45%). Spectral data of **21** identical to the above.

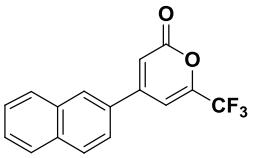
4-(Furan-2-yl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **345**



Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **327** (38.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), gave the title compound **345** as an orange solid (31.3 mg, 68%) after purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 123-124 °C; **ν_{max}** (ATR): 2922, 1718, 1670, 1593, 1359, 1286, 1197, 1095, 862; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H: 6.62 (1H, dd, *J* 3.6, 1.8, 1H, C(4)ArC(4')*H*), 6.64-65 (1H, m, C(3)*H*), 6.89 (1H, dd, *J* 1.6, 0.8, C(5)*H*), 7.01 (1H, d, *J* 3.6, C(4)ArC(5')*H*) 7.66 (1H, d, *J* 1.7, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 102.08 (q, $^{3}J_{CF}$ 3.6, *C*(5)), 108.2 (*C*(3)), 113.3 (C(4)Ar*C*(4')), 114.5 (C(4)Ar*C*(5')), 118.0 (q, $^{1}J_{CF}$ 272.9, CF_3), 141.1 (C(4)Ar*C*(1')), 146.9 (C(4)Ar*C*(3')), 148.1(*C*(4)), 148.8 (q, $^{2}J_{CF}$ 39.3, *C*(6)), 159.5 (*C*(2)); **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ_F: −71.96; **HRMS** (ESI^+): $C_{10}H_6O_3F_3$ $[M+H]^+$ found 231.0263, requires 231.0264 (−0.2 ppm).

4-(Naphthalen-2-yl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **346**[104]



Following general procedure F, (phenylthio)acetic acid (67.3 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), followed by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **328** (50.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol) and MeCN (1.0 mL), gave the title compound **346** as an orange solid (58.7 mg, 99%) after

purification by flash chromatography on silica gel (Et_2O : petrol, 5 : 95).

mp. 138-139 ℃ {Lit.[8] 147-148 ℃}; ν_{max} (ATR): 2922, 1743, 1766, 1624, 1558, 1351, 1272, 1199, 1132, 850; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 6.77 (1H, s, C(3)*H*), 7.11 (1H, s, C(5)*H*), 7.57-7.63 (2H, m, Ar*H*), 7.65 (1H, dd, *J* 8.6, 1.8, Ar*H*), 7.88-7.96 (3H, m, Ar*H*), 7.97 (1H, d, *J* 8.6, Ar*H*), 8.09 (1H, d, *J* 1.8, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 104.8 (q, $^3J_{CF}$ 3.4, *C*(5)), 113.9 (*C*(3)), 118.2 (q, $^1J_{CF}$ 273.0, C(4)*C*F_3), 123.0 (Ar*C*), 127.3 (Ar*C*), 127.5 (Ar*C*), 127.9 (Ar*C*), 128.3 (Ar*C*), 128.9 (Ar*C*), 131.3 (4ry, Ar*C*), 133.3 (4ry, Ar*C*), 134.5 (4ry, Ar*C*), 148.5 (q, $^2J_{CF}$ 39.2, *C*(6)), 159.5 (4ry, *C*(2)); **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −71.12; **HRMS** (ESI^+) $C_{16}H_{10}O_2F_3$ $[M+H]^+$ found 291.0630, requires 291.0627 (+0.9 ppm).

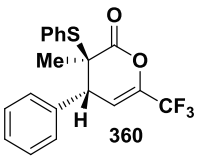
The reaction was repeated using **328** (50.0 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol, 1 mol %) under the above conditions, giving **346** (51.9 mg, 89%). Spectral data of **3463** identical to the above.

5-12. Data for α-substituted pyrones

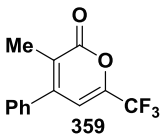
General procedure G: *α-substituted pyrone synthesis*

To a flame dried vial under N_2 was added (phenylthio)acetic acid (2 eq), (^{i}Pr)$_2$NEt (3 eq) and anhydrous MeCN (2.5 mL / 1.0 mmol acid) and cooled to 0 ℃. Pivaloyl chloride (3 eq) was then added, and the reaction stirred for 30 minutes. DHPB **1** (indicated mol%) was added followed by the addition of α,β-unsaturated trifluoromethyl ketone (1 eq) and additional (^{i}Pr)$_2$NEt (2.5 eq) and anhydrous MeCN (2.5 mL / 1.0 mmol acid). The vial was sealed and the reaction mixture was stirred and heated to 95 ℃ for 24 h, then cooled and quenched with 0.1 M HCl (10 mL), extracted with CH_2Cl_2 (x 3) and dried over $MgSO_4$. The solvent was removed *in vacuo* to obtain the crude product which was purified by flash chromatography on silica gel as indicated.

3-Methyl-4-phenyl-3-(phenylsulfanyl)-6-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-2-one, **360** and 3-methyl-4-phenyl-6-(trifluoromethyl)-2*H*-pyran-2-one, **359**



360



359

Following general procedure G, **320** (72.9 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104.0 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL), following by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **323** (40.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87.0 μL, 0.5 mmol) and MeCN (1.0 mL), gave **360** as a white solid (21.9 mg, 30%) after purification by flash chromatography on silica gel (Et_2O : petrol 3 : 97).

mp. 127-128℃; **ν_{max}** (ATR): 2927, 1774, 1703, 1454, 1438, 1361, 1290, 1192, 1139, 1085, 956; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.10 (3H, s, *Me*), 3.73 (1H, dd, *J* 6.3, 1.6, C(4)*H*), 6.16 (1H, dd, *J* 6.5, C(5)*H*), 7.05-7.11 (2H, m, Ar*H*), 7.30-7.39 (5H, m, Ar*H*), 7.45 (1H, t, *J* 67.4, Ar*H*), 7.48-7.52 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 21.4 (*Me*), 48.8 (*C*(4)), 55.3, 109.2 (q, $^{3}J_{CF}$ 3.3, *C*(5)), 118.6 (q, $^{1}J_{CF}$ 271.2, C(4)*C*F_3), 125.7, 128.2, 128.6, 128.8, 129.4, 129.6, 130.7, 135.7, 137.5, 139.9 (q, $^{2}J_{CF}$ 38.3, *C*(6)), 165.1; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −72.5; **HRMS** (ESI$^+$) $C_{19}H_{15}O_2F_3SNa$ $[M+Na]^+$ found 387.0634, requires 387.0636 (−0.3 ppm).

Purification also gave **359** as a white solid (26.3 mg, 52%); **mp.** 62-63 ℃; **ν_{max}** (ATR): 2926, 1732, 1363, 1263, 1197, 1145, 1087, 1043; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.15 (3H, s, *Me*), 6.66 (1H, s, C(5)*H*),7.29-7.35 (2H, m, Ar*H*), 7.44-7.51 (3H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.8 (*Me*), 108.1 (q, $^{3}J_{CF}$ 3.5, *C*(5)), 118.3 (q, $^{1}J_{CF}$ 272.2, C(4)*C*F_3), 125.7, 128.0, 129.0, 129.7, 136.3, 144.88 (q, $^{2}J_{CF}$ 39.4, *C*(6)), 149.5, 161.3; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −71.4; **HRMS** (ESI$^+$) $C_{13}H_{10}O_2F_3$ $[M+H]^+$ found 255.0628, requires 255.0627 (+0.2 ppm).

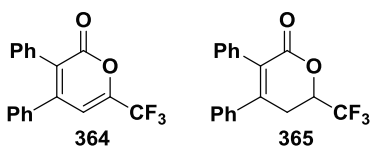
Formation of **359** from the Oxidation of **360**[9]

A solution of **360** (14.1 mg, 0.039 mmol, 1 eq) and Na_2CO_3(160.0 mg, 1.510 mmol, 39 eq) in CH_2Cl_2 (2 mL) at 0 ℃ was treated with a solution of *m*-CPBA (70%, 28.6 mg, 0.116 mmol, 3 eq) in CH_2Cl_2 (2 mL), allowed to warm to rt and stirred for 30 minutes. The mixture was filtered though a plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* and the crude product purified by flash chromatography on silica gel (Et_2O : petrol, 5 : 95), to give **359** as a white solid (9.0 mg, 91%). Spectral data of **359** identical to the above.

One-Pot Procedure for the formation of **359** from **323** and **320**

Following general procedure C, **320** (72.9 mg, 0.4 mmol, 2 eq), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol, 3 eq) in MeCN (1.0 mL), pivaloylchloride (74 μL, 0.6 mmol, 2 eq), followed by DHPB **1** (7.6 mg, 0.04 mmol, 20 mol %), **323** (40.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87.0 μL, 0.5 mmol, 2.5 eq) and MeCN (1.0 mL). After work-up and extraction, the crude product was re-dissolved in CH_2Cl_2 (5 mL) then treated with *m*-CPBA (70% pure, 148 mg, 0.6 mmol, 3 eq) in CH_2Cl_2 (2 mL) at 0 ℃, and warmed to rt for 30 minutes. The mixture was filtered though a plug of silica gel (Et_2O eluent). The solvent was removed *in vacuo* was purified by flash chromatography on silica gel (Et_2O : petrol, 5 : 95), to give **359** as a white solid (32.4 mg, 64%). Spectral data of **359** identical to the above.

3,4-Diphenyl-6-(trifluoromethyl)-2*H*-pyran-2-one, **364** and 3-methyl-4-phenyl-6- (trifluoro methyl)-5,6-dihydro-2*H*-pyran-2-one, **365**



364 365

Following general procedure G, α-(phenylthio)phenylacetic acid (97.7 mg, 0.4 mmol), (^{i}Pr)$_2$NEt (104.0 μL, 0.6 mmol) and pivaloyl chloride (74 μL, 0.6 mmol) in MeCN (1.0 mL),

following by DHPB (7.6 mg, 0.04 mmol, 20 mol %), **323** (40.0 mg, 0.2 mmol), (^{i}Pr)$_2$NEt (87.0 μL, 0.5 mmol) and in MeCN (1.0 mL), gave pyrone **364** as a white solid (29.4 mg, 46%), after flash chromatography on silica gel (Et_2O : petrol 2 : 98).

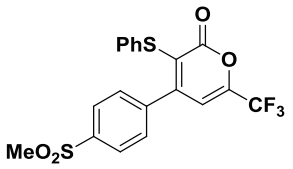
mp. 94-96℃; ν_{max} (ATR): 2926, 1739, 1365, 1271, 1199, 1145, 1105, 1053, 985; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 6.84 (1H, s, C(5)*H*), 7.08-7.13 (2H, m, Ar*H*), 7.14-7.20 (2H, m, Ar*H*), 7.23-7.33 (6H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 108.6 (q, $^{3}J_{CF}$ 3.5, *C*(5)), 118.2 (q, $^{1}J_{CF}$ 272.6, C(4)*C*F_3), 128.3, 128.6, 128.7, 129.5, 130.6, 132.6, 136.2, 146.4 (q, $^{2}J_{CF}$ 39.4, *C*(6)), 150.1, 160.1; **^{19}F{^{1}H} NMR** (470 MHz, $CDCl_3$) δ_F: −71.0; **HRMS** (ESI$^+$) $C_{18}H_{12}O_2F_3$ ($[M+H]^+$) found 317.0782, requires 317.0784 (−0.6 ppm).

Dihydropyranone **365** was also isolated from the above reaction as a white solid (21.3 mg, 33%).

mp. 102-104 ℃; **ν_{max}** (ATR): 2924, 1730, 1444, 1363, 1282, 1188, 1143, 948; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.02 1H, dd, *J* 17.7, 4.2, C(5)*H*^{A}H^{B}), 3.25 (1H, dd, *J* 17.7, 11.5, C(5)H^{A}*H*^{B}), 5.02 (1H, sept, *J* 5.8, C(6)*H*, 7.00-7.14 (4H, m, Ar*H*), 7.17-7.29 (6H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 29.1 (*C*(5)), 73.1 (q, $^{2}J_{CF}$ 33.9, *C*(6)), 122.8 (q, $^{1}J_{CF}$ 280.2, C(6)*C*F_3), 128.1, 128.2, 128.3, 128.5, 128.9, 129.3, 133.8, 137.4, 149.4, 162.5; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −7.26; **HRMS** (ESI$^+$) $C_{18}H_{13}O_2F_3Na$ $[M+Na]^+$ found 341.0757, requires 341.0760 (−0.8 ppm).

5-13. COX-2 inhibitor Synthesis

4-(4-Methanesulfonylphenyl)-3-(phenylsulfanyl)-6-(trifluoromethyl)-2*H*-pyran-2-one, **366**



Following general procedure F, **322** (110.5 mg, 0.4 mmol, 2 eq), (^{i}Pr)$_2$NEt (104 μL, 0.6 mmol, 3 eq) and pivaloylchloride (74 μL, 0.6 mmol, 2 eq) in MeCN (1.0 mL), following by DHPB (7.6 mg, 0.04 mmol, 0.2 eq), **367** (55.7 mg, 0.2 mmol, 1 eq), (^{i}Pr)$_2$NEt (87 μL, 0.5 mmol, 2.5 eq) and MeCN (1.0 mL), with stirring for 2 h, gave the title compound **366** as yellow solid (39.6 mg, 46%) after flash chromatography on silica gel (CH_2Cl_2).

mp. 151-152 ℃; ν_{max} (ATR): 2927, 1741, 1683, 1506, 1313, 1197, 1149, 954; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.08 (3H, s, *Me*), 6.68 (1H, s, C(5)*H*), 7.13-7.24 (5H, m, Ar*H*), 7.56 (2H, d, *J* 8.5, C(4)ArC(2')*H*), 7.99 (2H, d, *J* 8.5, C(4)ArC(3')*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C: 44.5 (*Me*), 107.4 (q, $^{3}J_{CF}$ 3.5, *C*(5)), 118.0 (q, $^{1}J_{CF}$ 273.1, C(4)*C*F$_3$), 126.7, 127.9, 128.1, 129.2, 129.4, 132.4, 141.3, 141.8 147.0 (q, $^{2}J_{CF}$ 39.9, *C*(6)), 152.7, 157.4; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −71.4; **HRMS** (ESI$^+$) $C_{19}H_{13}O_4F_3S_2Na$ $[M+Na]^+$ found 449.0098, requires 449.0100 (−0.3 ppm).

Pyrone **14** was also isolated from this reaction (29.5 mg, 46%). Spectral data of **14** identical to the above.

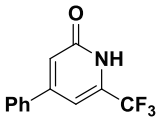
The reaction was repeated using **367** (55.7 mg, 0.2 mmol) and DHPB (0.38 mg, 0.002 mmol) under the above conditions, giving **366** (26.3 mg, 31%). Spectral data of **366** are identical to the above.

Pyrone **343** was also isolated from this reaction (29.6 mg, 47%). Spectral data of **343** identical to the above.

5-14. Data for derivatisation of 2-pyrone

5-14-1. Pyridone Synthesis

4-Phenyl-6-(trifluoromethyl)-1,2-dihydropyridin-2-one, **384**[104]

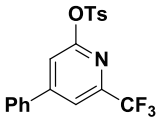


Following the conditions of Usachev *et al.*,[104] a solution of **285** (120 mg, 0.50 mmol, 1 eq) and NH_4OAc (77.1 mg, 1.0 mmol, 2 eq) in 80% aq. DMF (5 mL) was stirred and heated to 170 ℃ for 2 h. The reaction mixture was poured into water (25 mL), and the white precipitate filtered and washed with cold petrol to obtain the title compound **384** as a white solid (87.9 mg, 74%).

mp. 198-200 ℃ {Lit.[8] 213-214 ℃}; **^{1}H NMR** (300 MHz, DMSO-d_6) δ_H: 7.21 (1H, d, *J* 1.3, C(3)*H*), 7.46-7.58 (3H, m, Ar*H*), 7.62 (1H, d, *J* 1.3, C(5)*H*), 7.78-7.89 (2H, m, Ar*H*), 11.81 (1H, br s, N*H*). Data consistent with literature.[104]

5-14-2. Tosylation

4-Phenyl-6-(trifluoromethyl)pyridin-2-yl 4-methylbenzene-1-sulfonate, **385**[10]



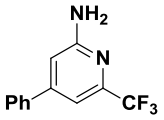
Following the conditions of Fujita *et al.*,[114] a solution of tosyl chloride (14.3 mg, 0.075 mmol, 1.5 eq) in THF (0.25 mL) was added to a stirred suspension of **384** (12.0 mg, 0.050 mmol, 1 eq) and NaH (60% in mineral oil, 3.0 mg, 0.075 mmol, 1.5 eq) in THF (0.5 mL) at −78 ℃. The reaction mixture was stirred at −78 ℃ for 1 h then heated to 60 ℃ for further 5 h. The mixture was poured into ice water (5 mL), neutralised with K_2CO_3, and then extracted with $CHCl_3$ (3 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product which was purified by flash chromatography on silica gel (Et_2O : petrol, 10 : 90) to give the title compound **385** as a yellow solid (20.6 mg,

99%).

mp. 128-130 °C {Lit.[149] 130-132 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 2.47 (3H, s, *Me*), 7.37 (2H, d, *J* 8.2, Ar*H*), 7.48 (1H, d, *J* 1.3, Ar*H*), 7.51-7.53 (3H, m, Ar*H*), 7.61-7.63 (2H, m, Ar*H*), 7.76 (1H, d, *J* 1.3, Ar*H*), 7.99 (2H, d, *J*8.2, Ar*H*). Data consistent with literature.[149]

5-14-3. 2-Amino Pyridine Synthesis

4-Phenyl-6-(trifluoromethyl)pyridin-2-amine, **386**

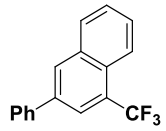


The conditions of Ram *et al.* were modified for this procedure.[112] A solution of **285** (48.0 mg, 0.2 mmol, 1 eq), cyanamide (42.0 mg, 1.0 mmol, 5 eq) and anhydrous KOH powder (56.1 mg, 1.0 mmol, 5 eq) in anhydrous DMF (2.0 mL) was stirred at rt for 72 h. The reaction mixture was poured into ice water then acidified to pH 4 with 0.1 M HCl. The mixture was extracted with CH_2Cl_2 (5 mL x 3), the combined organic layers washed with water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain the crude product which was purified by flash chromatography on silica gel (Et_2O : petrol, 30 : 70) to give the title compound **386** as a white solid (25.8 mg, 54%).

mp. 110-112 °C; **ν_{max}** (ATR): 3321, 3201, 1637, 1558, 1558, 1282, 1205, 1122, 767; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 4.78 (2H, s, NH_2), 6.83 (1H, s, C(3)*H*), 7.25 (1H, d, *J* 1.3, C(5)*H*), 7.41-7.53 (3H, m, Ar*H*), 7.55-7.62 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 109.3, 121.9 (q, $^1J_{CF}$ 274.2, C(6)*C*F_3), 127.0, 129.2, 129.5, 137.7, 147.1 (q, $^2J_{CF}$ 33.6, *C*(6), 151.7, 159.2; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −68.5; **HRMS** (ESI^+) $C_{12}H_{10}N_2F_3$ $[M+H]^+$ found 255.0792, requires 239.0791 (+0.6 ppm).

5-14-4. Naphthalene Synthesis

3-Phenyl-1-(trifluoromethyl)naphthalene, **375**

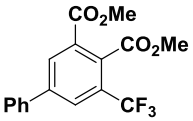


The conditions of Bronner *et al.* were modified for this procedure.[184] A solution of **285** (24.0 mg, 0.10 mmol, 1 eq), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (149 mg, 0.50 mmol, 5 eq) and CsF (76.0 mg, 0.50 mmol, 5 eq) in anhydrous MeCN (1.0 mL) was heated at 100 ℃ for 18 h. The reaction mixture was cooled rt and the solvent removed *in vacuo* to obtain the crude product that was purified by flash chromatography on silica gel (petrol) to give the title compound **375** as a colourless oil (14.8 mg, 54%).

ν_{max} (ATR): 2922, 1521, 1323, 1267, 1128, 1118, 979, 893; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 7.40-7.47 (1H, m, Ar*H*), 7.49-7.56 (2H, m, Ar*H*), 7.58-7.68 (1H, m, Ar*H*), 7.69-7.76 (1H, m, Ar*H*), 7.98 (1H, dd, *J* 7.0, 2.5, Ar*H*), 8.15 (1H, dd, *J* 1.9, 0.9, Ar*H*), 8.19-8.22 (2H, m, Ar*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 124.3 (q, $^{3}J_{CF}$ 2.0, *C*(6)), 124.7 (q, $^{3}J_{CF}$ 6.0, *C*(2)), 124.8 (q, $^{1}J_{CF}$ 274.6, C(1)*C*F_3), 126.7 (q, $^{2}J_{CF}$ 30.0, *C*(1)), 127.1, 127.4, 127.7, 128.1, 128.2, 129.1, 129.2, 130.3; **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F: −60.2; **HRMS** (ESI^+) $C_{17}H_{12}F_3$ $[M+H]^+$ found 273.0887, requires 273.0886 (+0.5 ppm).

5-14-5. Diels-Alder Reaction

1,2-dimethyl 5-phenyl-3-(trifluoromethyl)benzene-1,2-dicarboxylate, **374**

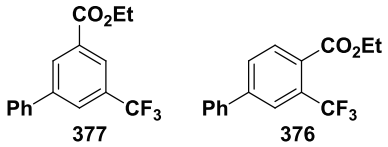


The conditions of Ziegler *et al.* were modified for this procedure.[185] A stirred solution of **285** (48.0 mg, 0.2 mmol, 1 eq) and dimethylacetylene dicarboxylate (0.13 mL, 1.0 mmol, 5 eq) in xylene (0.2 mL) in a sealed tube was heated to 200 ℃ for 72 h. The reaction mixture was cooled to rt and the solvent removed *in vacuo* to obtain the crude product which was purified

by flash chromatography on silica gel (Et_2O : petrol, 10 : 90) to give **374** as a white solid (64.3 mg, 95%).

mp. 82-84 °C; **ν_{max}** (ART): 2954, 1743, 1734, 1456, 1435, 1355, 1280, 1231, 1138, 1062; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.95 (3H, s, OMe), 3.99 (3H, s, OMe), 7.46 (1H, t, *J* 7.5, C(5)ArC(4')*H*), 7.51 (2H, t, *J* 7.5, C(5)ArC(3')*H*), 7.62 (2H, t, *J* 7.5, C(5)ArC(4')*H*), 8.07 (1H, d, *J* 1.5, C(6)*H*), 8.41 (1H, d, *J* 1.5, C(4)*H*). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 53.1 (*Me*), 53.3 (*Me*), 123.2 (q, $^1J_{CF}$ 274.5, C(3)*C*F_3), 127.3 (Ar*C*), 128.7 (q, $^3J_{CF}$ 4.6, *C*(4)), 129.1 (q, $^2J_{CF}$ 32.3, *C*(3)), 129.2 (Ar*C*), 129.4 (Ar*C*), 130.0 (Ar*C*), 132.0 (Ar*C*), 132.1 (q, $^3J_{CF}$ 1.8, *C*(2)), 137.9 (Ar*C*), 143.1 (Ar*C*), 165.1, 167.3; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −59.8; **HRMS** (ESI^+) $C_{17}H_{14}O_4F_3$ $[M+H]^+$ found 339.0838, requires 339.0839 (−0.2 ppm).

Ethyl 3-phenyl-5-(trifluoromethyl)benzoate, **377** and Ethyl 4-phenyl-2- (trifluoromethyl) benzoate, **376**



The conditions of Ziegler *et al.* were modified for this procedure.[14] A solution of **285** (24.0 mg, 0.1 mmol, 1 eq) and ethyl propiolate (51.0 μL, 0.5 mmol, 5 eq) in xylene (0.2 mL) in a sealed tube was refluxed for 72 h. The reaction mixture was cooled to rt and the solvent removed *in vacuo* to obtain the crude product, which was purified by flash chromatography on silica gel (Et_2O : petrol, 2 : 98) to give the ester **377** as a colourless oil (17.1 mg, 58%).

ν_{max} (ATR): 2927, 1724, 1440, 1373, 1355, 1263, 1244, 1170, 1128, 1068, 1020, 900; **^{1}H NMR** (500MHz, $CDCl_3$) δ_H: 1.45 (3H, t, *J* 7.1, *Me*), 4.45 (2H, q, *J* 7.1, CH_2), 7.43 (1H, t, *J* 7.3, Ar*H*), 7.50 (2H, t, *J* 7.5, Ar*H*), 7.60-7.68 (2H, m, Ar*H*), 8.01 (1H, s, C(4)*H*), 8.28 (1H, s, C(6)*H*), 8.45 (1H, s, C(2)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.1 (*Me*), 61.8 (*C*H_2), 123.9 (q, $^1J_{CF}$ 272.7, C(5)*C*F_3), 125.2 (q, $^3J_{CF}$ 3.8, *C*(6)), 127.3 (Ar*C*), 128.0 (q, $^3J_{CF}$ 3.6, *C*(4)),

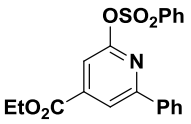
128.6, 129.2, 131.5, 131.7 (q, $^{2}J_{CF}$ 32.8, *C*(5)), 132.0, 138.8 (Ar*C*), 146.6 (Ar*C*), 165.4; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −62.6; **HRMS** (ESI^+) $C_{16}H_{14}O_2F_3$ $[M+H]^+$ found 295.0942, requires 295.0940 (+0.5 ppm).

Ester **376** was also isolated from the above reaction as a colourless oil (6.8 mg, 23%).

ν_{max} (ATR): 2927, 1724, 1614, 1452, 1367, 1323, 1294, 1257, 1170, 1136, 1047, 902; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.41 (3H, t, *J* 7.2, *Me*), 4.42 (2H, q, *J* 7.2, C*H*$_2$), 7.47-7.53 (1H, m, Ar*H*), 7.57-7.65 (2H, m, Ar*H*), 7.81 (1H, dd, *J* 8.0, 1.6, C(5)*H*), 7.89 (1H, d *J* 8.0, C(6)*H*), 7.95 (1H, d *J* 1.3, C(3)*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C: 14.1 (*Me*), 62.9 (*C*H$_2$), 123.5 (q, $^{1}J_{CF}$ 273.6, C(2)*C*F$_3$), 125.6 (q, $^{3}J_{CF}$ 5.4, *C*(3)), 127.4 (Ar*C*), 128.9 (Ar*C*), 129.5 (q, $^{2}J_{CF}$ 32.4, *C*(2)), 130.0 (q, $^{3}J_{CF}$ 1.3, *C*(1)), 131.1 (Ar*C*), 138.8 (Ar*C*), 144.4 (Ar*C*), 166.9; **^{19}F{^{1}H} NMR** (471 MHz, $CDCl_3$) δ_F: −59.3; **HRMS** (ESI^+) $C_{16}H_{14}O_2F_3$ $[M+H]^+$ found 295.0943, requires 295.0940 (+0.9 ppm).

5-15. Data for Tri-Substituted Pyridine

Ethyl 2-phenyl-6-((phenylsulfonyl)oxy)isonicotinate,**400**



A flask containing a stirrer bar was charged with CH_2Cl_2 (to give 0.4 M acid), (phenylthio)acetic acid (33.6 mg, 0.2 mmol, 2 eq.), (^{i}Pr)$_2$NEt (35 μL, 0.2, 1 eq.) and cooled to 0 °C. Pivaloyl chloride (25 μL, 0.2, 1 eq.) was added and the reaction stirred for 30 minutes. (−)-Tetramisole·HCl (7.6 mg, 0.04 mmol, 20 mol%) was added followed by the ketimine xx (68.7 mg, 0.2 mmol, 1 eq.) and additional (^{i}Pr)$_2$NEt (35 μL, 0.2, 1 eq.) in CH_2Cl_2 (to give 0.4 M of ketimine). The reaction was allowed to warm to rt and stirred until complete by TLC. The reaction was quenched with 0.1 M HCl (~ 20 mL/mmol acid), the layers separated and

the aqueous layer extracted with CH_2Cl_2 (2 × eq. vol.). The combined organics were dried over $MgSO_4$, the solvent removed *in vacuo* and the residue purified by flash chromatography giving the title compound **400** as white solid (31.7 mg, 0.08 mmol, 41%);

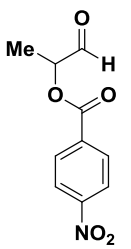
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.43 (3H, t, *J* 7.1, CH_2CH_3), 4.45 (2H, q, *J* 7.1, CH_2CH_3), 7.36-7.45 (3H, m, Ar*H*), 7.54-7.61 (3H, m, Ar*H*), 7.68-7.72 (1H, m, Ar*H*), 7.73-7.76 (2H, m, Ar*H*), 8.21 (1H, d, *J* 1.0, C(5)); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 14.3 (CH_2CH_3), 62.4 (CH_2CH_3), 113.56, 118.3, 127.1, 128.9, 129.2, 130.2, 134.2, 136.8, 137.5, 143.1, 157.3, 157.7, 164.1

5-16. Data for α-Aroyloxyaldehydes

General procedure H: *Preparation of α-Aroyloxyaldehydes*

On the basis of a literature procedure,[168] *tert*-butyl hydroperoxide (5−6 M in decane) was added to a solution of the appropriate aldehyde (1.5 equiv), *p*-nitrobenzoic acid (1 equiv), tetrabutylammonium iodide (20 mol %), and piperidine (10 mol %) in ethyl acetate (to make 0.2 M solution of acid). The resulting solution was heated at 50 ℃ for 5 h before being cooled to room temperature and quenched with $Na_2S_2O_3$ and $NaHCO_3$. The phases were separated, the aqueous phase was extracted with ethyl acetate (×2), and the combined organics were washed with brine before being dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography.

1-oxopropan-2-yl 4-nitrobenzoate, **476**

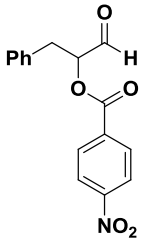


Following general procedure H, propionaldehyde (2.71 mL, 37.5 mmol), *p*-nitrobenzoic acid

(4.18 g, 25 mmol), tetrabutylammonium iodide (1.85 g, 5.00 mmol) and piperidine (0.25 mL, 2.50 mmol) in EtOAc (125 mL), and *tert*-butyl hydroperoxide (5.00 mL, 27.5 mmol) resulted the crude mixture, which purified by column chromatography on silica (70:30 petrol:EtOAc) the recrystallistion (Et_2O) to give the title compound **476** as a white crystal (1.65 g, 30%).

mp. 84-85 {Lit.[168]78−80 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 1.59 (3H, d, *J* 7.2, CH_3), 5.39 (1H, q, *J* 7.2, CH3C*H*), 8.27 (2H, d, *J* 8.9, ArC(2)H_2), 8.33 (2H, d, *J* 8.9, ArC(3)H_2), 9.60 (1H, s, C*H*O). Data consistent with literature.[168]

1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate, **S7**

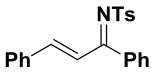


Following general procedure H, 3-phenylpropionaldehyde (4.93 mL, 37.5 mmol), *p*-nitrobenzoic acid (4.18 g, 25 mmol), tetrabutylammonium iodide (1.85 g, 5.00 mmol) and piperidine (0.25 mL, 2.50 mmol) in EtOAc (125 mL), and *tert*-butyl hydroperoxide (5.00 mL, 27.5 mmol) resulted the crude mixture, which purified by column chromatography on silica (70:30 petrol:EtOAc) the recrystallistion (Et_2O) to give the title compound **S7** as a pale yellow powder (1.15 g, 15%).

mp. 91-92 {Lit.[168] 85−86 °C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H: 3.22 (1H, dd, *J* 8.4, 14.6, ArCH$_a$$H_b$), 3.35 (1H, dd, *J* 4.8, 14.5, ArCH_aH$_b$), 5.52 (1H, dd, *J* 4.9, 8.4, C*H*CHO), 7.28 (2H, d, Ar*H*), 7.30-7.38 (2H, m, Ar*H*), 8.19 (2H, d, *J* 8.6, Ar*H*), 8.30 (2H, d, *J* 8.6, Ar*H*), 9.68 (1H, s, C*H*O). Data consistent with literature.[168]

5-17. Data for aryl ketimines

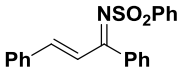
N-((1*Z*,2*E*)-1,3-diphenylallylidene)-4-methylbenzenesulfonamide, **464**



Following general procedure C (see page 156), the reaction of (*E*)-chalcone (4.16 g, 20 mmol), *p*-toluenesulfonamide (3.42 g, 20 mmol), NEt_3 (5.6 mL, 40 mmol) and $TiCl_4$ (2.2 mL, 20 mmol) in CH_2Cl_2 (40 mL) gave the title compound **464** after trituration (Et_2O) (6.54 g, 18.1 mmol, 90%) as yellow solid.

mp. 146-148 °C {Lit.[68] 116-120°C }; $\boldsymbol{\nu_{max}}$ (ATR): 3120, 1610, 1545, 1495, 1304, 1157, 1094; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 2.45 (3H, s, -*Me*), 7.10 (1H, d, *J* 16.0, C(3)*H*), 7.34 (2H, d, *J* 8.0, Ar*H*), 7.39-7.53 (5H, m, Ar*H*), 7.53-7.72 (5H, m, Ar*H*), 7.89-8.02 (2H, m, Ar*H*), 8.12 (1H, s, Ar*H*); Data consistent with literature.[68]

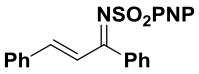
N-((1*Z*,2*E*)-1,3-diphenylallylidene)benzenesulfonamide, **465**



Following general procedure C (see page 156), the reaction of (*E*)-chalcone (4.16 g, 20 mmol), benzeenesulfonamide (3.14 g, 20 mmol), NEt_3 (5.6 mL, 40 mmol) and $TiCl_4$ (2.2 mL, 20 mmol) in CH_2Cl_2 (40 mL) gave the title compound **465** after trituration (Et_2O) (5.46 g, 15.7 mmol, 79%) as white solid.

mp. 123-125 °C; $\boldsymbol{\nu_{max}}$ (ATR): 3062, 1612, 1527, 1442, 1296, 1149, 1080; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.09 (1H, d, *J* 16.2, C(3)*H*), 7.38-7.49 (5H, m, Ar*H*), 7.48-7.75 (8H, m, Ar*H*), 8.05-8.06 (3H, m, Ar*H*); **HRMS** (ESI^+): $C_{21}H_{17}NO_2S$ ($[M+H]^+$), found 348.1055, requires 348.1053 (+0.6 ppm); Data consistent with literature. [186]

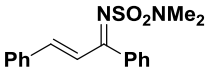
N-((1*Z*,2*E*)-1,3-diphenylallylidene)-4-nitrobenzenesulfonamide, **466**



Following general procedure C (see page 156), the reaction of (*E*)-chalcone (2.08 g, 10 mmol), p-nitrobenzenesulfonamide (2.02 g, 10 mmol), NEt_3 (2.8 mL, 20 mmol) and $TiCl_4$ (1.1 mL, 10 mmol) in CH_2Cl_2 (20 mL) gave the title compound **466** after trituration (Et_2O) (3.06 g, 7.9 mmol, 79%) as yellow solid.

mp. 154-156 °C; $\boldsymbol{\nu_{max}}$ (ATR): 1614, 1517, 1440, 1298, 1145, 1082; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.17 (1H, d, *J* 15.9, C(3)*H*), 7.38-7.54 (5H, m, Ar*H*), 7.54-7.75 (5H, m, Ar*H*), 8.00 (1H, s, Ar*H*), 8.23 (2H, d, *J* 8.0, Ar*H*), 8.37 (2H, d, *J* 8.6, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 124.2, 128.6 128.7, 129.1, 129.3, 130.4, 131.7, 132.6, 134.4, 136.7, 147.3, 150.1, 150.6, 179.2; **HRMS** (ESI^+): $C_{21}H_{16}N_2O_4SNa$ ($[M+Na]^+$), found 415.0720, requires 415.0723 (−0.7 ppm).

N-((1*Z*,2*E*)-1,3-diphenylallylidene)-*N*-(*N*,*N*dimethylamino)sulfonamide, **467**



Following general procedure C (see page 156), the reaction of (*E*)-chalcone (417 mg, 2.0 mmol), *N*,*N*-dimethylsulfamide (250 mg, 2.0 mmol), NEt_3 (558 μL, 4.0 mmol) and $TiCl_4$ (220 μL, 2.0 mmol) in CH_2Cl_2 (25 mL) gave the title compound **467** after flash column chramgraphy (Et_2O: petrol, 1:4) (0.19 g, 0.6 mmol, 30%) as yellow solid.

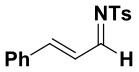
mp. 56-58 °C {Lit.[187] 58-10 °C }; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.94 (6H, s, N*Me*$_2$), 7.06 (1H, d, *J* 16.2, C(3)*H*), 7.40-7.41 (3H, m, Ar*H*), 7.44-7.52 (2H, m, Ar*H*), 7.53-7.62 (3H, m, Ar*H*), 7.68-7.74 (2H, m, Ar*H*), 7.88 (1H, d, *J* 16.2, C(2)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 39.0, 122.8, 128.6, 128.8, 129.1, 130.2, 131.1, 134.8, 137.7, 148.2, 178.5; Data consistent with literature.[187]

5-18. Data for aldimines

General procedure I: *Preparation of aldimines*

A Dean-Stark containing a stirrer bar was charged with the requisite sulfonamide (1 eq.), *trans*-cinnamaldehyde (1 eq.) and toluene (ca. 0.1 M). The resulting solution was heated at reflux overnight. The solid product precipitated with Et_2O and the suspension filtered. The solid was dried *in vacuo* to leave the pure aldimine.

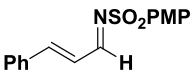
4-methyl-*N*-((1*E*,2*E*)-3-phenylallylidene)benzenesulfonamide, **469**



Following general procedure I, the reaction of tosylamide (0.66 g, 5.0 mmol), *trans*-cinnamaldehyde (0.68 g, 5.0 mmol) in CH_2Cl_2 (5 mL), gave the title compound **469** as a white solid (1.26 g, 4.4 mmol, 88%).

mp. 115-116 ℃; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 2.44 (3H, s, $SO_2ArC(4)CH_3$), 6.99 (1H, dd, *J* 9.5, 15.8, C(2)*H*),7.31-7.37 (2H, m, Ar*H*), 7.41-7.46 (2H, m, Ar*H*), 7.49 (1H, dd, *J* 15.8, C(3)),7.55 (2H, d, *J* 1.9, 7.7, Ar*H*), 7.86 (2H, d, *J* 8.3, Ar*H*), 8.78 (1H, d, *J* 9.4, NC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 12.8 (*C*H_3), 124.9, 128.1, 128.8, 129.3, 130, 131.8, 134.3, 135.5, 144.7, 154.0, 171.0 (*C*(1)); Data consistent with literature.

4-methoxy-N-((1E,2E)-3-phenylallylidene)benzenesulfonamide, **470**



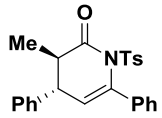
Following general procedure I, the reaction of 4-methoxylsulfonamide (0.94 g, 5.0 mmol), *trans*-cinnamaldehyde (0.68 g, 5.0 mmol) in CH_2Cl_2 (5 mL), gave the title compound **470** as a solid crystal (1.25 g, 4.1 mmol, 83%).

mp. 121-122 ℃{Lit.[188] 125-190 ˚C}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 3.88 (3H, s, OCH_3), 6.94-7.04 (2H, m, Ar*H* and C(2)*H*), 7.42-7.43 (2H, m, Ar*H*)7.48 (1H, d, *J* 6.9, C(3)*H*), 7.55

(2H, d, *J* 7.7, Ar*H*), 7.90 (2H, d, *J* 8.9, Ar*H*), 8.76 (1H, d, *J* 9.4, NC*H*); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 55.8 (O*C*H_3), 114.6, 124.9, 128.7 129.3, 129.9, 130.3, 131.7, 134.3, 153.7, 170.5 (*C*(1)); Data consistent with literature.[188]

5-19. Data for dihydropyridinones

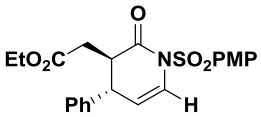
(3*R*,4*S*)-3-methyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one, **478**



Following the procedure outlined by Smith *et al.*,[168] The appropriate α-aroyloxyaldehyde **476** (134.0 mg, 0.6 mmol, 1.5 equiv), ketimine **467** (144.6 mg, 0.4 mol, 1.0 equiv), and NHC precatalyst **477** (14.7 mg, 10 mol %) were dissolved in anhydrous THF (8 ml) in a sealed vial containing 4 Å molecular sieves. Et_3N (84 μl, 60.7 mg, 1.5 equiv) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted with EtOAc and washed successively with 1 M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product that was purified by flash silica column chromatography (Et_2O: Petrol, 5:95), gave the title compound **478** as a white solid (145.5 mg, 0.35 mmol, 87%, 74:26 dr).

mp. 148-150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer (selected)* δ_H 0.94 (3H, d, *J* 6.9, -C*H*$_3$), 2.45 (3H, s, SO_2ArCH_3), 2.66 (1H, dq, *J* 6.9, 12.1, C(3)*H*), 3.45 (1H, dd, *J* 3.7, 12.0, C(4)*H*), 5.91 (1H, *J* 3.7, C(5)*H*); *minor diastereomer (selected)* δ_H 1.03 (3H, d, *J* 7.1, -C*H*$_3$), 2.45 (3H, s, SO_2ArCH_3), 2.86-2.98 (1H, m, C(3)*H*), 3.89 (1H, t, *J* 5.8, C(4)*H*), 5.99 (1H, *J* 5.7, C(5)*H*); *both diastereoisomers* δ_H 7.18 (2H, m, Ar*H*), 7.23-7.43 (11H, m, Ar*H*), 7.83 (2H, m, Ar*H*); **HRMS** (ESI^+): $C_{25}H_{23}NO_3SNa$ ($[M+Na]^+$), found 440.1282, requires 440.5122 (−2.0 ppm). Data consistent with literature.[189]

Ethyl-2-((3R,4S)-1-((4-methoxyphenyl)sulfonyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridin-3-yl)acetate, **481**



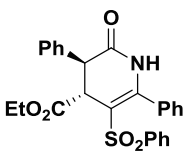
Following the procedure outlined by Bode *et al.*,[65] The ethyl trans-4-oxo-2-butenoate (66 μl, 0.55 mmol, 1.1 equiv), ketimine **470** (150.7 mg, 0.5 mol, 1.0 equiv), and NHC precatalyst **480** (16.6 mg, 10 mol %) were dissolved in toluene/THF (10:1 V/V, 10 ml) in a sealed vial containing 4 Å molecular sieves. *i*-Pr_2NEt (8.6 μl, 0.05 mmol, 10 mol%) was added and the reaction mixture was stirred at rt until complete by TLC analysis. The mixture was diluted with EtOAc and washed successively with 1 M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give the crude product that was purified by flash silica column chromatography (Et_2O: Petrol, 5:95), gave the title compound **481** as a white solid (49.9 mg, 0.13 mmol, 25%, 85:15 dr).

5-20. Data for C-sulfonyl Dihydropyridinones

General procedure J: preparation of *C*-sulfonyl dihydropyridinone

A solution of dihydropyridinone (1 eq.) in CH_2Cl_2 (0.1 M) in RBF, which was thoroughly cleaned in a KOH bath and washed with water before used, under UV light at 365 nm at rt for 16 hours. The solvent removed in vacuo on a rotary evaporator and the crude mixture was purified by flash silica column chromatography in the solvent system stated.

(3*S*,4*S*)-Ethyl-2-oxo-3,6-diphenyl-5-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **482**

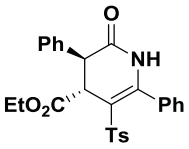


Following general procedure **J**, the reaction of dihydropyridinone **212** (185.0 mg, 0.4 mmol)

in degased CH_2Cl_2 (4.0 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **482** as a white solid (174.6 mg, 0.34 mmol, 95%).

mp. 144-145 ˚C; ν_{max} (ATR): 3267, 2962, 2926, 1730, 1627, 1446, 1261, 1143, 1089, 1022, 802 ; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.38 (3H, t, *J* 7.1, -CH_2CH_3), 4.28-4.39(3H, m, C(3)*H* and -CH_2CH_3), 4.52 (1H, d, *J* 1.0, C(4)*H*), 6.82 (2H, d, *J* 7.7, Ar*H*), 6.99-7.03 (3H, m, Ar*H*), 7.14 (1H, br s, N*H*), 7.27-7.34 (6H, m, Ar*H*), 7.37-7.41 (4H, m, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.3 (-CH_2CH_3), 47.3 (*C*(3)), 48.0 (*C*(4)), 62.5 (-CH_2CH_3), 114.8 (*C*(5)), 127.1 (Ar*C*), 127.6 (Ar*C*), 128.3 (Ar*C*), 128.8 (Ar*C*), 129.4 (Ar*C*), 130.7 (Ar*C*), 131.9 (C(3)Ar*C*(1)), 132.5 (Ar*C*), 135.6 (NSO_2Ar*C*(1)), 141.1 (C(6)Ar*C*(1)), 147.1 (*C*(6)), 168.4 (*C*(2)), 170.5 (C(4)*C*O); **HRMS** (ESI^+): $C_{26}H_{24}NO_5S$ ($[M+H]^+$, found 462.1372 requires 472.1370 (+ 0.5 ppm).

(3*S*,4*S*)-Ethyl 2-oxo-3,6-diphenyl-5-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **484**

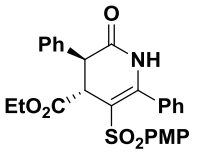


Following general procedure **J**, the reaction of dihydropyridinone **241** (47.6 mg, 0.1 mmol) in degaseded CH_2Cl_2 (1.0 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **484** as a white solid (41.9 mg, 0.088 mmol, 88%).

mp. 169-170 ˚C; ν_{max} (film, cm-1): 3240, 2924, 1726, 1691, 1631, 1452, 1348, 1145, 1087, 1014, 813; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 1.38 (3H, t, *J* 7.1, -CH_2CH_3), 2.30 (3H, s, -CH_3), 4.23-4.40 (3H, m, C(3)*H* and -CH_2CH_3), 4.47 (1H, d, *J* 1.5, C(4)*H*), 6.76 (2H, d, *J* 8.2 SO_2Ar(3)*H*), 6.83 (2H, d, *J* 8.2 SO_2Ar(2)*H*), 7.17 (2H, m, Ar*H*), 7.26-7.34 (5H, m, Ar*H*), 7.36 (3H, m, Ar*H*), 7.41 (1H, t, *J* 7.5, Ar*H*)); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.3 (-CH_2CH_3), 21.6 (SO_2Ar(4)CH_3), 47.3 (*C*(3)), 49.2 (*C*(4)), 62.4 (-CH_2CH_3), 115.6 (*C*(5)), 127.1 (Ar*C*),

127.7 (Ar*C*), 128.5 (Ar*C*), 128.9 (Ar*C*), 129.4 (Ar*C*), 130.6 (Ar*C*); **HRMS** (ESI^+): $C_{27}H_{26}NO_5S$ ($[M+H]^+$, found 476.1524, requires 476.1526 (− 0.5 ppm).

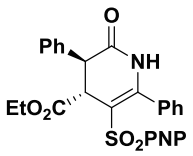
(3*S*,4*S*)-Ethyl-5-((4-methoxyphenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **485**



Following general procedure **J**, the reaction of dihydropyridinone **245** (77.6 mg, 0.158 mmol) in degased CH_2Cl_2 (1.6 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 5 : 95) gave the title compound **485** as a white solid (70.8 mg, 0.44 mmol, 91%).

mp. 196-198 ˚C; ν_{max} (film, cm-1): 3232, 2978, 1722, 1703, 1633, 1593, 1496, 1454, 1267, 1141, 1091, 1016; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.37 (3H, t, *J* 7.1, -CH_2CH_3), 3.76 (3H, s, -OCH_3), 4.24-4.38 (3H, m, C(3)*H* and -CH_2CH_3), 4.46 (1H, d, *J* 1.7, C(4)*H*), 6.48 (2H, d, *J* 9.0, NSO_2ArC(3)*H*), 6.79 (2H, d, *J* 8.9, NSO_2ArC(2)*H*), 7.14-7.18 (3H, m, Ar*H*), 7.28-7.42 (8H, m, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.2 (-CH_2CH_3), 47.3 (*C*(4)), 48.1 (*C*(3)), 55.7 (-OCH_3), 62.4 (-CH_2CH_3), 113.5 (NSO_2Ar*C*(3)), 115.2 (*C*(5)), 127.1 (Ar*C*), 128.1 (Ar*C*), 128.5 (Ar*C*), 129.1 (Ar*C*), 129.3 (Ar*C*), 129.7 (Ar*C*), 130.6 (Ar*C*), 132.1 (C(6)Ar*C*(1)), 132.7 (NSO_2Ar*C*(1)), 135.7 (C(3)Ar*C*(1)), 146.7 (*C*(6)), 162.8 (NSO_2Ar*C*(4)), 168.6 (*C*(2)), 170.6 (C(4)*C*O); **HRMS** (ESI^+): $C_{27}H_{26}NO_6S$ ($[M+H]^+$, found 492.1472, requires 492.1475 (− 0.7 ppm).

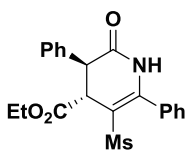
(3*S*,4*S*)-Ethyl-5-((4-nitrophenyl)sulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **486**



Following general procedure **J**, the reaction of dihydropyridinone **246** (50.7 mg, 0.1 mmol) in degased CH_2Cl_2 (1.0 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **486** as a white solid (43.1 mg, 0.085 mmol, 85%).

mp. 220-221 ˚C; ν_{max} (film, cm-1): 3255, 2981, 1728, 1624, 15.27, 1448, 1348, 1303, 1145, 1089, 854; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.40 (3H, t, *J* 7.1, -CH_2CH_3), 4.28-4.43 (3H, m, C(3)*H* and -CH_2CH_3), 4.52 (1H, d, *J* 1.8, C(4)*H*), 6.87 (2H, d, *J* 9.0, NSO_2ArC(2)*H*), 7.13 (2H, m, N*H* and Ar*H*), 7.28-7.31 (4H, m, Ar*H*), 7.37-7.42 (3H, m, Ar*H*), .37-7.42 (3H, m, Ar*H*), 7.46 (1H, *J* 7.6, 1.2, Ar*H*), 7.78 (2H, d, *J* 9.0, NSO_2ArC(3)*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.2 (-CH_2CH_3), 47.3 (*C*(4)), 47.6 (*C*(3)), 62.6 (-CH_2CH_3), 113.7 (*C*(5)), 123.1 (NSO_2Ar*C*(3)), 126.9 (Ar*C*), 128.3 (C(6)Ar*C*(1)), 128.6 (NSO_2Ar*C*(2)), 128.7 (Ar*C*), 129.4 (Ar*C*), 131.1 (Ar*C*), 135.3 (C(3)Ar*C*(1)), 146.6 (NSO_2Ar*C*(1)), 148.3 (*C*(6)), 149.5 (NSO_2Ar*C*(4)), 168.2 (*C*(2)), 170.1 (C(4)*C*O); **HRMS** (ESI^+): $C_{27}H_{26}NO_5S$ ($[M+NH_4]^+$, found 524.1481, requires 524.1486 (− 0.9 ppm).

(3*S*,4*S*)-Ethyl-5-(methylsulfonyl)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **487**

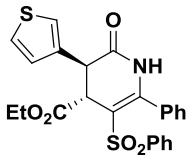


Following general procedure **J**, the reaction of dihydropyridinone **244** (62.7 mg, 0.157 mmol)

in degased CH_2Cl_2 (1.6 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **487** as a white solid (42.3 mg, 0.11 mmol, 67%) and recovered starting material **244** dihydropyridinone (16.4 mg, 0.041 mmol, 26%).

mp. 86-87 ˚C; **ν_{max}** (film, cm-1): 3250, 2926, 1726, 1701, 1629, 1448, 1300, 1132, 954; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.1, -CH_2CH_3), 2.5 (3H, s, -CH_2), 4.24-4.38 (2H, m, -CH_2CH_3), 4.38 (1H, d, *J* 1.5, C(3)*H*), 4.46 (1H, d, *J* 1.9, C(4)*H*), 7.28-7.55 (10H, m, Ar*H*),; **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 14.3 (-CH_2CH_3), 44.0 (-CH_3), 46.4 (*C*(4)), 47.7 (*C*(3)), 62.5 (-CH_2CH_3), 113.8 (*C*(5)), 127.0 (Ar*C*), 128.4 (Ar*C*), 128.8 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 131.1 (Ar*C*), 132.0 (C(6)Ar*C*(1)), 135.2 (C(3)Ar*C*(1)), 147.6 (*C*(6)), 169.0 (*C*(2)), 170.6 (C(4)*C*O); **HRMS** (ESI^+): $C_{27}H_{26}NO_5S$ ($[M+H]^+$, found 400.1218, requires 400.1213 (+ 1.2 ppm).

Ethyl-2-oxo-6-phenyl-5-(phenylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate, 488

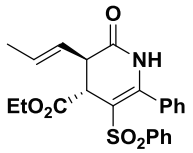


Following general procedure **J**, the reaction of dihydropyridinone **236** (68.7 mg, 0.147 mmol) in degased CH_2Cl_2 (1.5 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **488** as a white solid (54.2 mg, 0.115 mmol, 79%).

mp. 152-153 ˚C; **ν_{max}** (film, cm-1): 3265, 2980, 2360, 1730, 1701, 1627, 1446, 1301, 1145, 1089, 756; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.35 (3H, t, *J* 7.1, -CH_2CH_3), 4.14-4.39(3H, m, C(3)*H* and -CH_2CH_3), 4.58 (1H, d, *J* 1.7, C(4)*H*), 6.98-7.04 (2H, m, Ar*H*), 7.05-7.17 (6H, m, Ar*H* and N*H*), 7.19-7.28 (2H, m, Ar*H*), 7.28-7.42 (3H, m, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz,

$CDCl_3$) δ_C 14.3 (-CH_2CH_3), 44.5 (*C*(3)), 46.0 (*C*(4)), 62.4 (-*C*H_2CH_3), 114.7 (*C*(5)), 122.3 (C(3)Ar*C*), 126.9 (Ar*C*), 127.1 (Ar*C*), 127.6 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 128.9 (Ar*C*), 130.5 (Ar*C*), 131.9 (C(3)Ar*C*(1)), 132.6 (Ar*C*), 135.2 (NSO_2Ar*C*(1)), 141.1 (C(6)Ar*C*(1)), 147.0 (*C*(6)), 168.2 (*C*(2)), 170.3 (C(4)*C*O); **HRMS** (ESI^+): $C_{24}H_{22}NO_5S_2$ ($[M+H]^+$), found 468.0931, requires 468.0934 (− 0.6 ppm).

Ethyl-(*E*)-2-oxo-6-phenyl-5-(phenylsulfonyl)-3-(prop-1-en-1-yl)-1,2,3,4-tetrahydropyridine-4-carboxylate, **489**

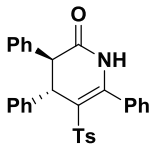


Following general procedure **J**, the reaction of dihydropyridinone **237** (60.0 mg, 0.141 mmol) in degased CH_2Cl_2 (1.5 mL) for 18 h gave the crude mixture (92:8 dr). Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 97) gave the title compound **489** as a white solid (48.0 mg, 0.113 mmol, 80%, 96:4 dr).

mp. 155-156 ˚C; ν_{max} (film, cm-1): 3265, 2978, 1728, 1701, 1629, 1446, 1303, 1226, 1178, 1145, 1091, 1031, 964; **^{1}H NMR** (400 MHz, $CDCl_3$) *major diastereomer* δ_H 1.23 (3H, t, *J* 7.1, -CH_2CH_3), 1.61 (3H, t, *J* 7.1, -C(3)CHCHCH_3), 3.49-3.58 (1H, m, C(3)*H*), 4.03 (1H, d, *J* 1.8, C(4)*H*), 4.07-4.24 (1H, m, -CH_2CH_3), 5.26 (1H, ddq, *J* 15.3, 6.3, 1.6, -C(3)C*H*CHCH_3), 5.72 (1H, dqd, *J* 14.5, 6.5, 1.5, -C(3)CHC*H*CH_3), 6.80 (1H, s, N*H*), 7.11 (2H, *J* 7.3, Ar*H*), 7.17-7.29 (4H, m, Ar*H*), 7.30-7.42 (4H, m, Ar*H*); *minor diastereomer (selected)* δ_H 1.18 (3H, t, *J* 7.1, -CH_2CH_3), 1.73 (3H, ddd, *J* 17.4, 6.7, 1.4, -C(3)CHCHCH_3), 3.45 (1H, t, *J* 7.0, C(3)*H*), 3.95 (1H, d, *J* 1.9, C(4)*H*), 5.52 (1H, ddq, *J* 15.3, 7.7, 1.5, -C(3)C*H*CHCH_3); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer* δ_C 14.0 (-CH_2CH_3), 21.2 (-CH_3), 45.2 (*C*(4)), 53.7 (*C*(3)), 61.7 (-*C*H_2CH_3), 116.0 (*C*(5)), 126.2 (C(6)Ar*C*), 128.5 (C(6)Ar*C*), 128.7 (C(3)Ar*C*(2)), 128.9 (NSO_2Ar*C*(3)), 129.5 (NSO_2Ar*C*(2)), 129.5 (C(3)Ar*C*(3)), 132.3 (C(3)Ar*C*(1)), 134.1

($NSO_2ArC(4)$), 136.7 (C(6)Ar*C*(1)), 137.9 (C(3)Ar*C*(4)), 139.2 ($NSO_2ArC(1)$), 141.3 (*C*(6)), 170.9 (C(4)*C*O), 172.1 (*C*(2)); **HRMS** (ESI^+): $C_{23}H_{24}NO_5S$ ($[M+H]^+$), found 426.1370, requires 426.1370 (+ 0.1 ppm).

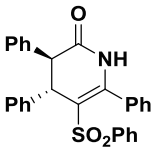
3,4,6-triphenyl-5-tosyl-3,4-dihydropyridin-2(1H)-one, **490**



Following general procedure **J**, the reaction of dihydropyridinone **474** (48.0 mg, 0.1 mmol) in degaseded CH_2Cl_2 (1.0 mL) for 18 h gave the crude mixture. Recrystalisation (Et_2O) gave the title compound **490** as a white solid (42.4 mg, 0.088 mmol, 88%).

mp. 232-234 ˚C {Lit.[68] 238-240˚C }; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 2.29 (3H, s, -C*H*$_3$), 4.10(1H, s, C(3)*H*), 4.82 (1H, s, C(4)*H*), 6.63 (2H, d, *J* 8.3, SNO_2ArC(3)*H*), 6.77 (2H, d, *J* 8.0, SNO_2ArC(2)*H*), 7.10 (1H, d, *J* 9.4, Ar*H*), 7.24-7.51 (14H, m, Ar*H* and N*H*). Data consistent with literature.[68]

3,4,6-triphenyl-5-(phenylsulfonyl)-3,4-dihydropyridin-2(1H)-one, **491**

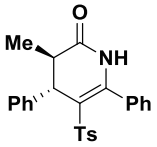


Following general procedure **J**, the reaction of dihydropyridinone **475** (46.7 mg, 0.1 mmol) in degased CH_2Cl_2 (1.0 mL) for 18 h gave the crude mixture. Recrystallisation gave the title compound **491** as a white solid (40.2 mg, 0.087 mmol, 87%).

mp. 249-250 ˚C; **ν_{max}** (film, cm-1): 3209, 2897, 1695, 1672, 1494, 1315, 1145, 1089, 800; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.11 (1H, s, C(3)*H*), 4.87 (1H, s, C(4)*H*), 6.72 (2H, d, *J* 7.4, Ar*H*), 6.97 (2H, d, *J* 7.9, Ar*H*), 7.20-7.48 (16H, m, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 47.3 (*C*(4)), 53.9 (*C*(3)), 119.2 (*C*(5)), 127.1 (Ar*C*), 127.3 (Ar*C*), 127.5 (Ar*C*), 127.9

(Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 129.4 (Ar*C*), 129.5 (Ar*C*), 130.5 (Ar*C*), 132.3 (NSO_2Ar*C*(1)), 132.4 (Ar*C*), 137.2 (C(3)Ar*C*(1)), 139.7 (C(4)Ar*C*(1)), 141.3 (C(6)Ar*C*(1)), 146.2 (*C*(6)), 168.9 (*C*(2)); **HRMS** (ESI^+): $C_{29}H_{24}NO_3S$ ($[M+H]^+$, found 466.1468, requires 466.1471 (-0.7 ppm).

Ethyl 3-methyl-2-oxo-6-phenyl-5-tosyl-1,2,3,4-tetrahydropyridine-4-carboxylate, **492**



Following general procedure **J**, the reaction of dihydropyridinone **478** (47.6 mg, 0.114 mmol, 74:26 dr) in degaseded CH_2Cl_2 (1.2 mL) for 18 h gave the crude mixture. Purification by flash chromatography (Et_2O : CH_2Cl_2, 3 : 95) gave the title compound **492** as a white solid (31.6 mg, 0.076 mmol, 66%, 69:31 dr).

mp. 182-184 ˚C; $\boldsymbol{\nu_{max}}$ (film, cm-1): 3244, 2972, 1697, 1629, 1597, 1456, 1288, 1145, 1089, 813; **^{1}H NMR** (500Hz, $CDCl_3$) *major diastereomer (selected)* δ_H 1.39 (3H, d, *J* 7.3, -C*H*$_3$), 2.31 (3H, s, SO_2ArC*H*$_3$), 2.83 (1H, q, *J* 7.4, C(3)*H*), 4.24 (1H, d, *J* 1.0, C(4)*H*), 6.96 (2H, d, *J* 8.1, NSO_2ArC(3)*H*), 7.03 (2H, d, *J* 8.3, NSO_2ArC(2)*H*); *minor diastereomer (selected)* δ_H 1.06 (3H, d, *J* 6.9, -C*H*$_3$), 2.27 (3H, s, SO_2ArC*H*$_3$), 3.22 (1H, q, *J* 6.8, C(3)*H*), 4.43 (1H, d, *J* 7.4, C(4)*H*), 6.75 (2H, d, *J* 8.3, NSO_2ArC(3)*H*), 6.84 (2H, d, *J* 8.0, NSO_2ArC(2)*H*); *both diastereoisomers* δ_H 7.21 (1H, dd, *J* 2.9, 6.6, Ar*H*), 7.24-7.32 (7H, m, Ar*H*), 7.34 (1H, t, *J* 7.6, Ar*H*), 7.38 (1H, t, *J* 7.7, Ar*H*), 7.43 (1H, d, *J* 7.5, Ar*H*), 7.47 (1H, t, *J* 7.5, Ar*H*); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) *major diastereomer (selected)* δ_C 17.9 (-*C*H_3), 21.6 (SO_2Ar(4)*C*H_3), 43.8 (*C*(3)), 46.8 (*C*(4)), 118.4 (*C*(5)), 127.7 (NSO_2Ar*C*(2)), 129.0 (NSO_2Ar*C*(3)), 132.7 (C(6)Ar *C*(1), 138.6 (SO_2Ar *C*(1)), 140.1 (C(4)Ar*C*(1)), 143.5 (SO_2Ar *C*(4)), 145.7 (*C*(6)), 172.2 (*C*=O); *minor diastereomer (selected)* δ_C 12.3 (-*C*H_3), 21.4 (SO_2Ar(4)*C*H_3), 40.5 (*C*(3)), 45.2 (*C*(4)), 118.1(*C*(5)),127.6 (NSO_2Ar*C*(3)), 128.7 (NSO_2Ar*C*(2)); *both diastereoisomers* δ_C

127.1 (Ar*C*), 127.5 (Ar*C*), 127.5 (Ar*C*), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.5 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.0 (Ar*C*), 129.0 (Ar*C*), 129.2 (Ar*C*), 130.2 (Ar*C*), 130.4 (Ar*C*); **HRMS** (ESI^+): $C_{25}H_{24}NO_3S$ ($[M+H]^+$, found 418.1470, requires 418.1471 (-0.3 ppm).

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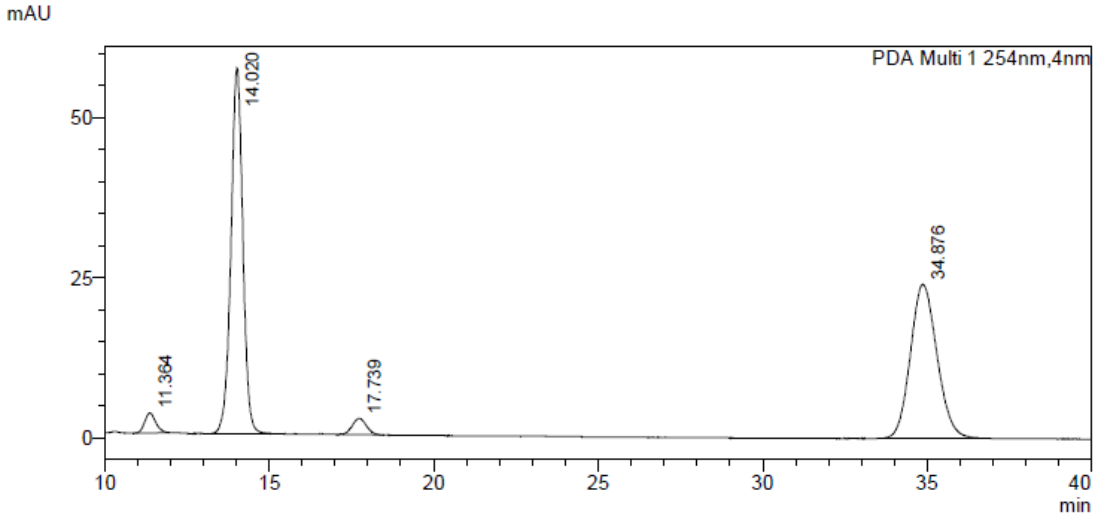
Appendix I. Selected HPLC Trace

(3S,4S)-Ethyl-2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, 212

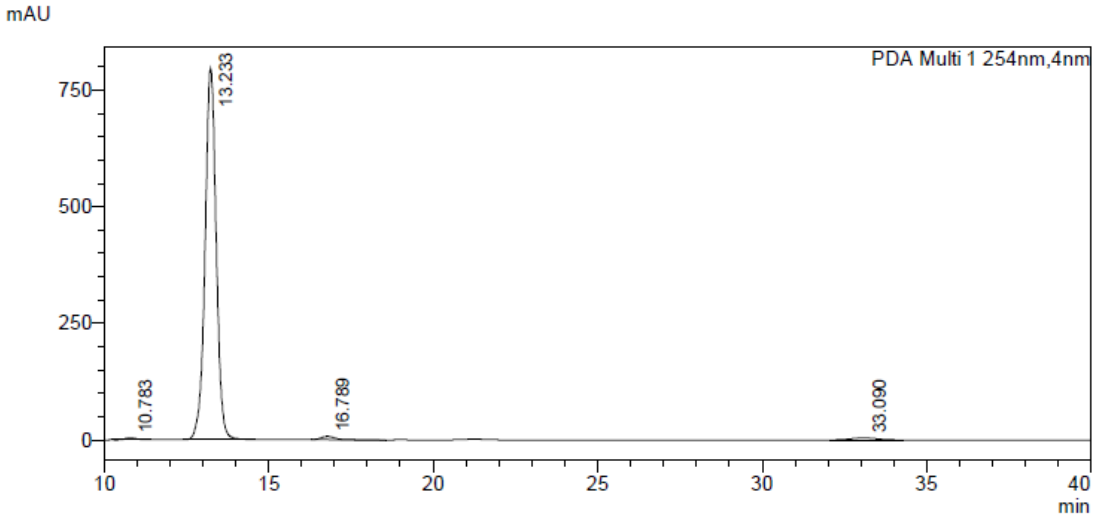
Chiral HPLC, (Chiralpak IA, 20:80 IPA: hexane, flow rate 0.5 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 13.2 min, t_R (3*R*, 4*R*): 33.1 min, 98% ee



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	11.364	2.465
2	14.020	49.000
3	17.739	2.612
4	34.876	45.924
Total		100.000



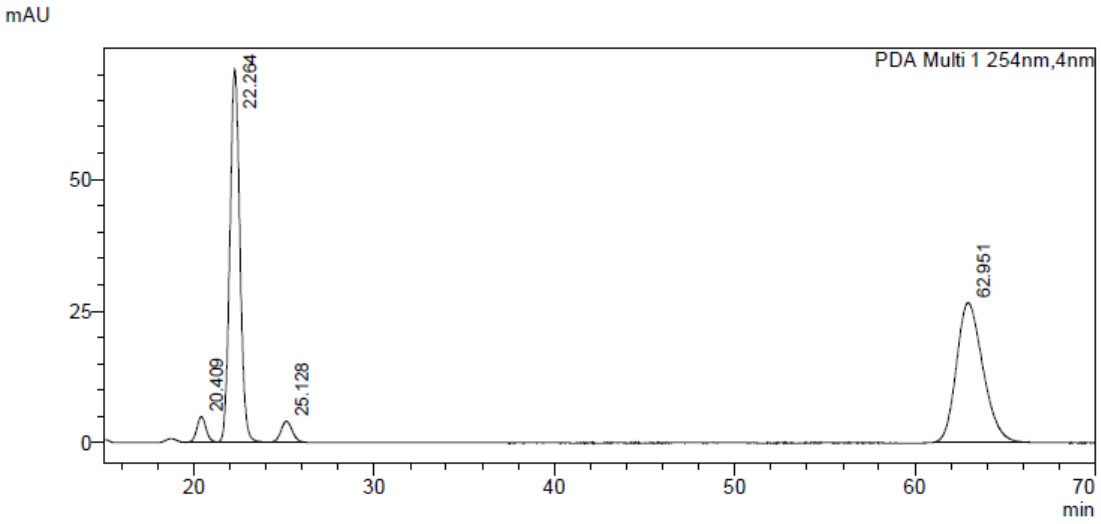
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	10.783	0.477
2	13.233	97.338
3	16.789	1.032
4	33.090	1.153
Total		100.000

(3S,4S)-Ethyl-2-oxo-6-phenyl-1-(phenylsulfonyl)-3-(m-tolyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, 225

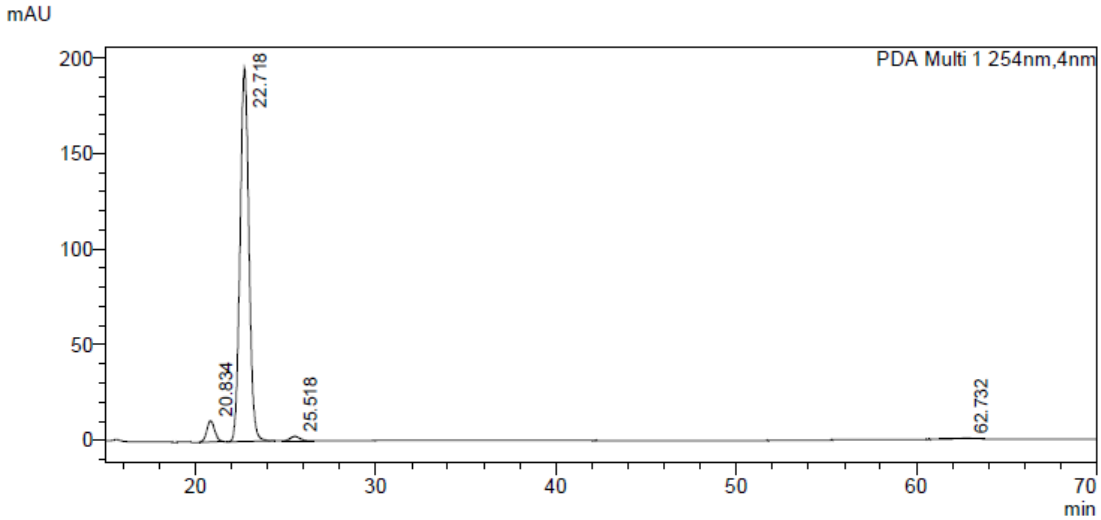
Chiral HPLC Chiralpak IA (10% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 22.7 min, t_R (3*R*, 4*R*): 62.7 min, 99% ee.



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	20.409	2.953
2	22.264	47.373
3	25.128	2.951
4	62.951	46.723
Total		100.000



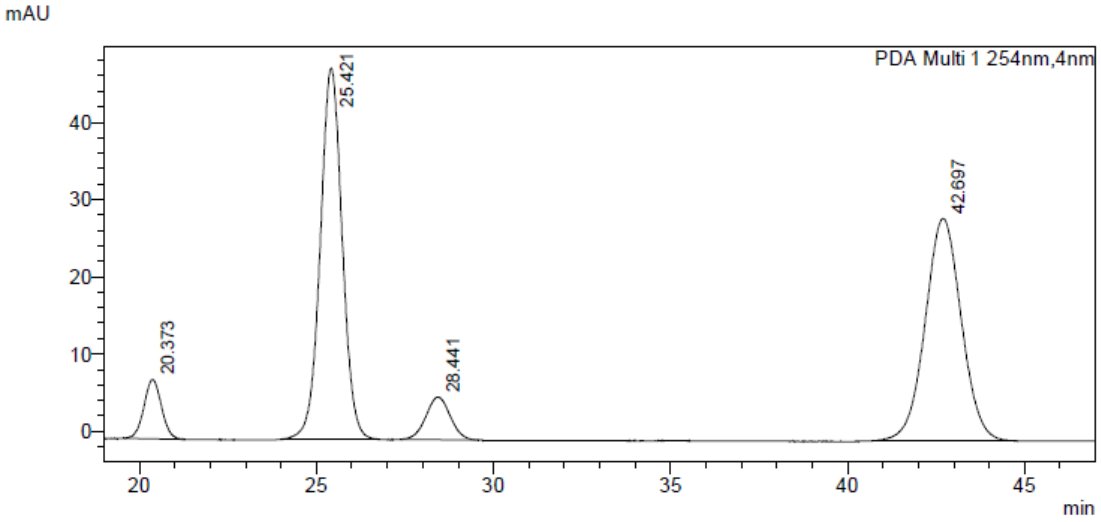
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	20.834	4.710
2	22.718	93.599
3	25.518	1.219
4	62.732	0.472
Total		100.000

(3S,4S)-Ethyl-3-(4-methoxyphenyl)-2-oxo-6-phenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, 230

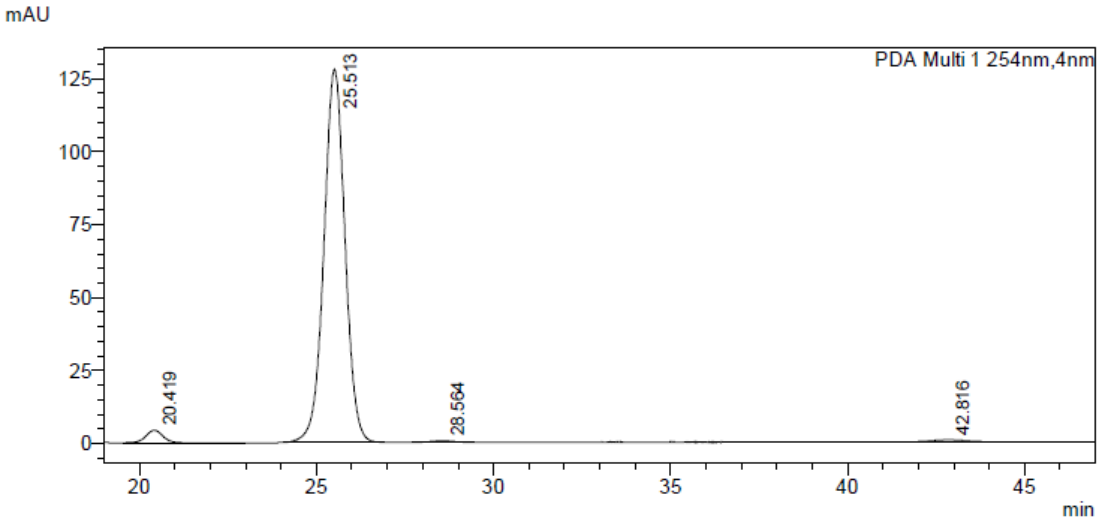
Chiral HPLC, (Chiralpak AD-H, 20:80 IPA: Chexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*S*, 4*S*): 25.5 min, t_R (3*R*, 4*R*): 42.8 min, 98% ee



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	20.373	5.681
2	25.421	44.641
3	28.441	5.705
4	42.697	43.972
Total		100.000



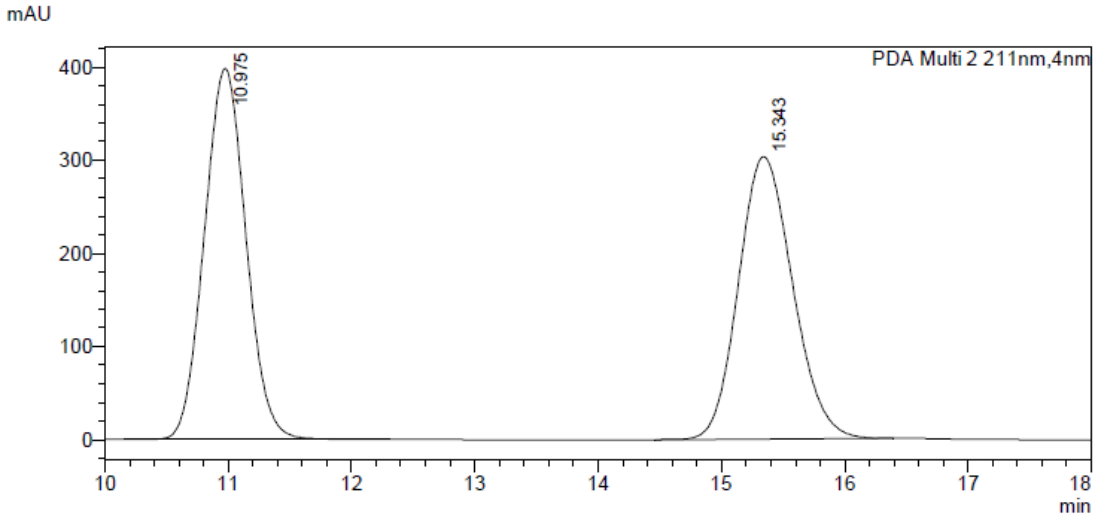
<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	20.419	2.537
2	25.513	96.157
3	28.564	0.439
4	42.816	0.868
Total		100.000

(3S,4S)-Ethyl-5-bromo-2-oxo-3,6-diphenyl-1-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine -4-carboxylate, 261

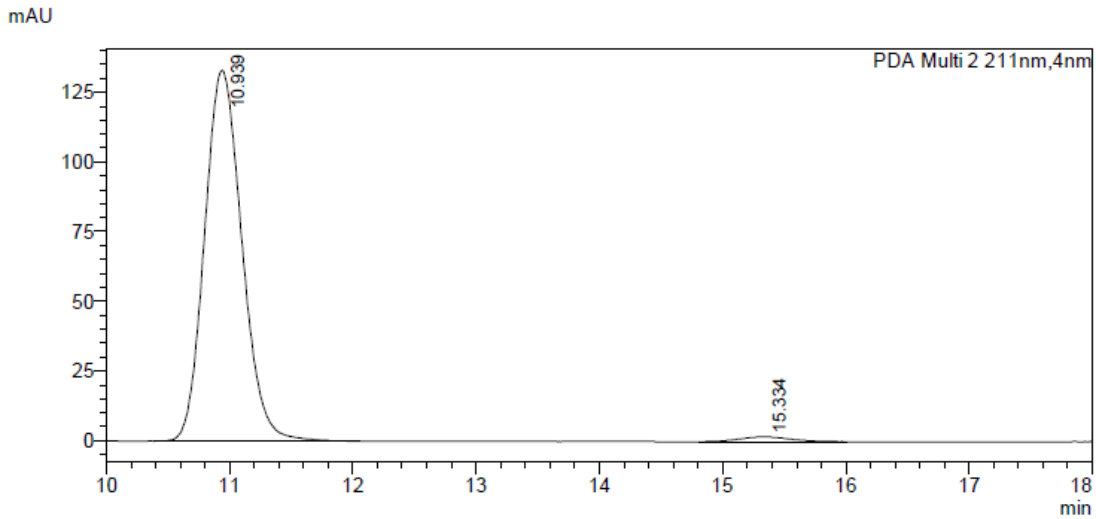
Chiral HPLC Chiralpak IA (30% IPA:hexane, flow rate 1.0 mL min^{-1}, 254 nm) t_R (3*S*, 4*S*): 10.9 min, t_R (3*R*, 4*R*): 15.3 min, 97% ee.



<Peak Table>

PDA Ch2 211nm

Peak#	Ret. Time	Area%
1	10.975	50.261
2	15.343	49.739
Total		100.000



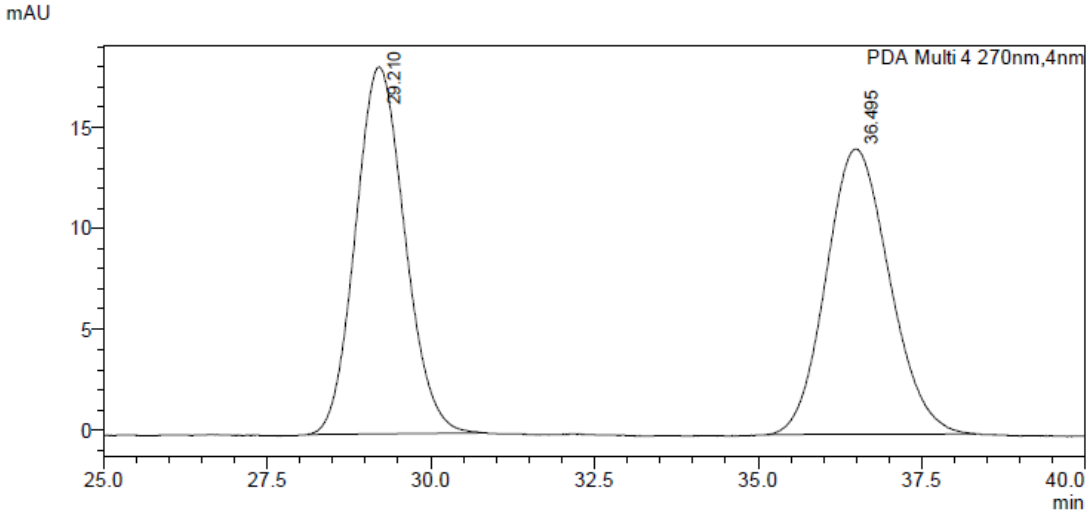
<Peak Table>

PDA Ch2 211nm

Peak#	Ret. Time	Area%
1	10.939	98.307
2	15.334	1.693
Total		100.000

Ethyl (3S,4S)-2-oxo-3,6-diphenyl-1,2,3,4-tetrahydropyridine-4-carboxylate, 259

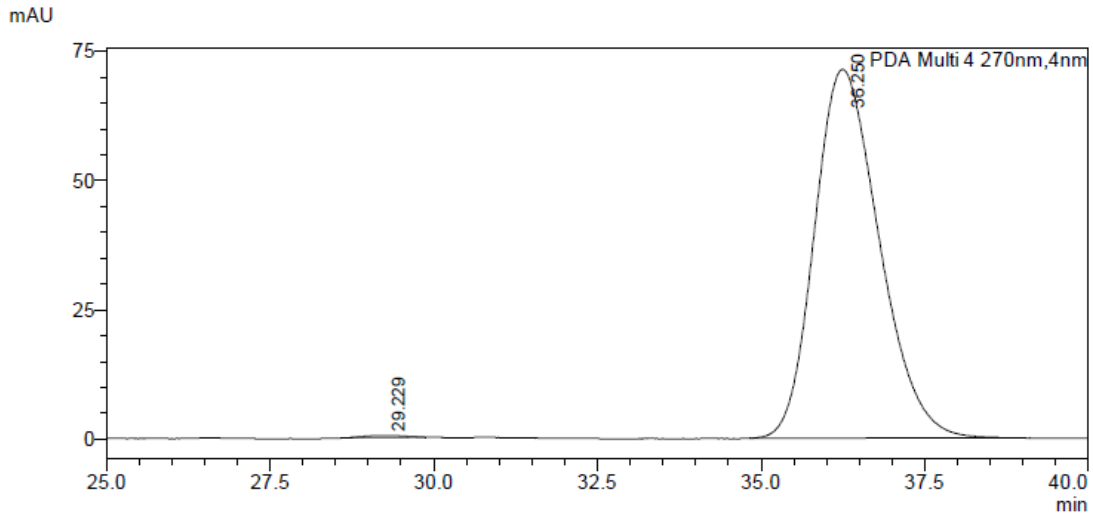
Chiral HPLC (Chiralpak OD-H, 30:70 IPA : hexane, flow rate 0.5 mL min^{-1}, 270 nm, 30 °C) t_R (3*S*, 4*S*): 36.4 min, t_R (3*R*, 4*R*): 29.2 min, 99% ee;



<Peak Table>

PDA Ch4 270nm

Peak#	Ret. Time	Area%
1	29.210	50.038
2	36.495	49.962
Total		100.000



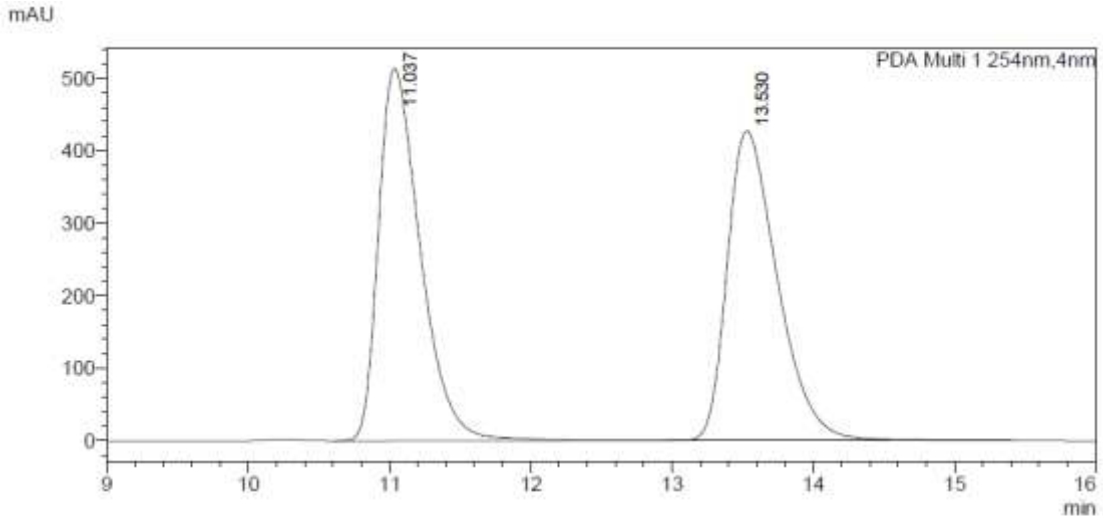
<Peak Table>

PDA Ch4 270nm

Peak#	Ret. Time	Area%
1	29.229	0.365
2	36.250	99.635
Total		100.000

(3S,4S)-Ethyl-2-oxo-3,6-diphenyl-5-(phenylsulfonyl)-1,2,3,4-tetrahydropyridine-4-carboxylate, 482

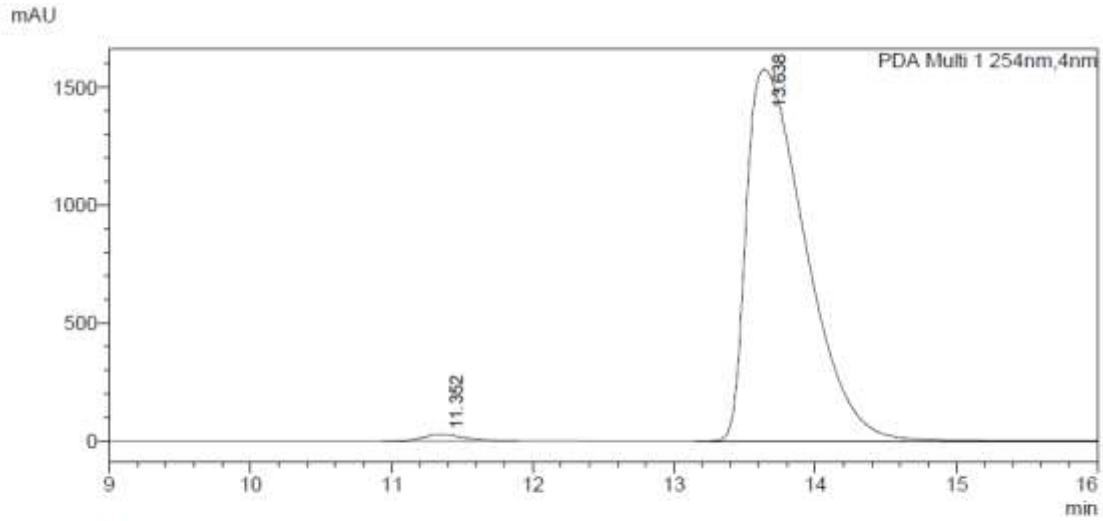
Chiral HPLC, (Chiralpak IA, 30:70 IPA: hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 ˚C) t_R (3*R*, 4*R*): 11.4 min, t_R (3*S*, 4*S*): 13.6 min, 98% ee



<Peak Table>

PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	11.037	49.994
2	13.530	50.006
Total		100.000

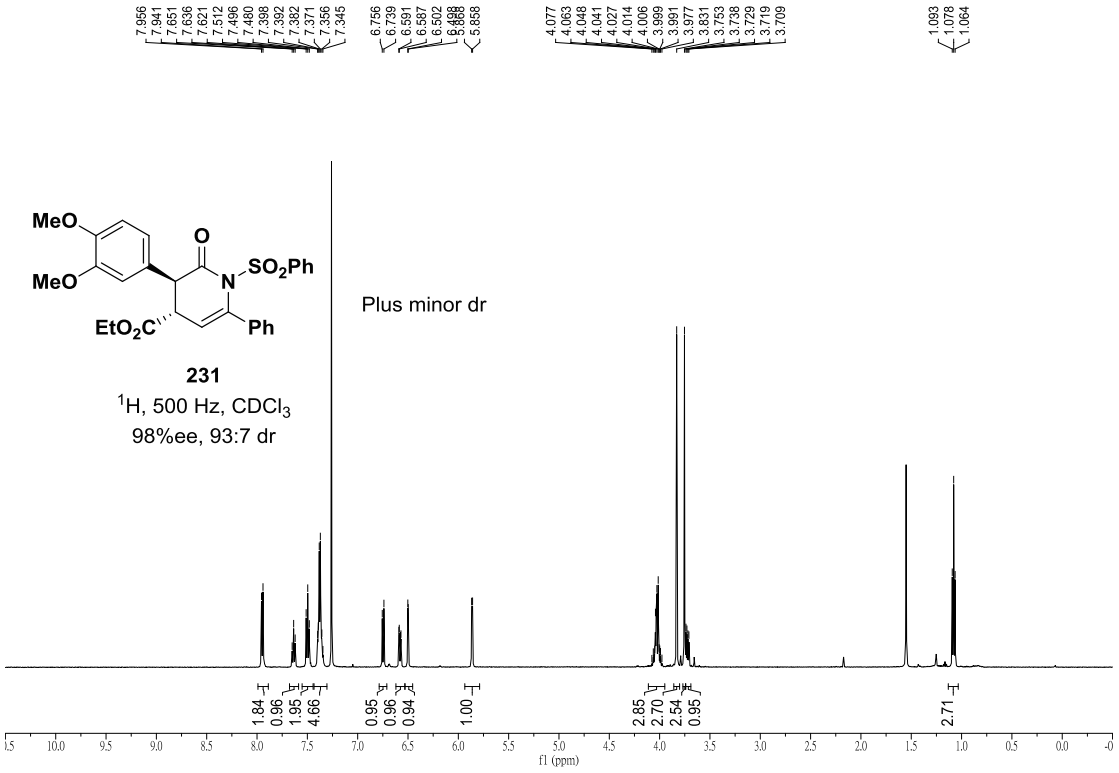


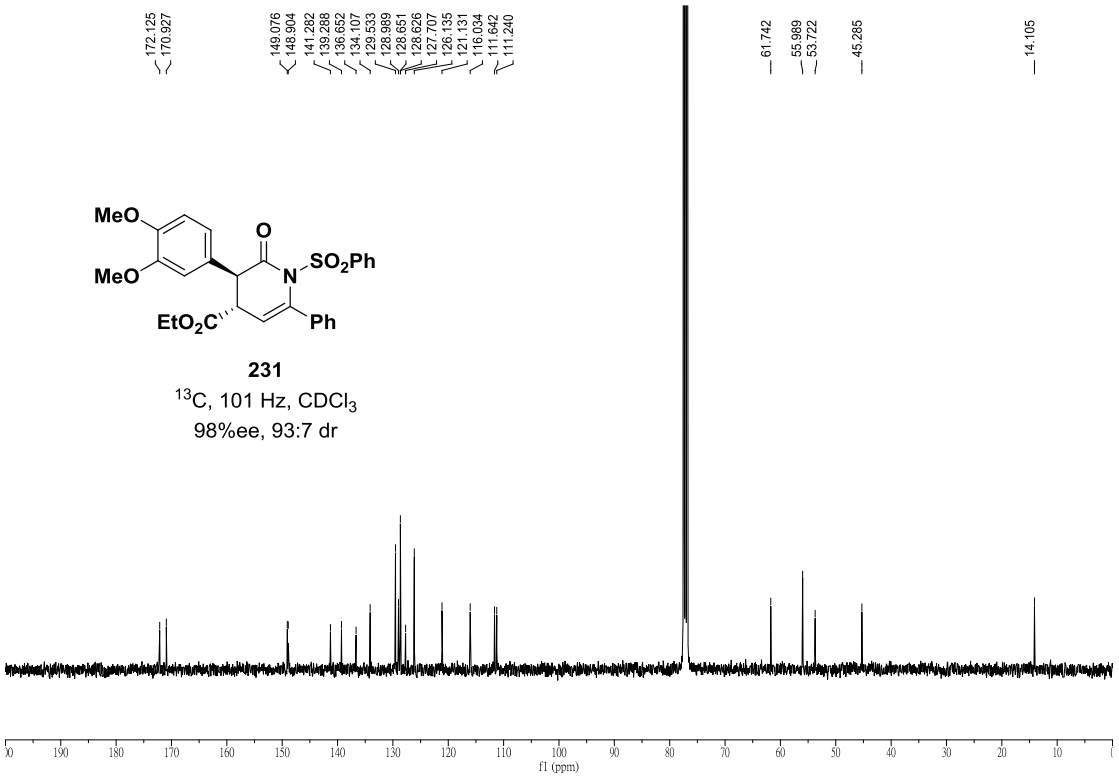
<Peak Table>

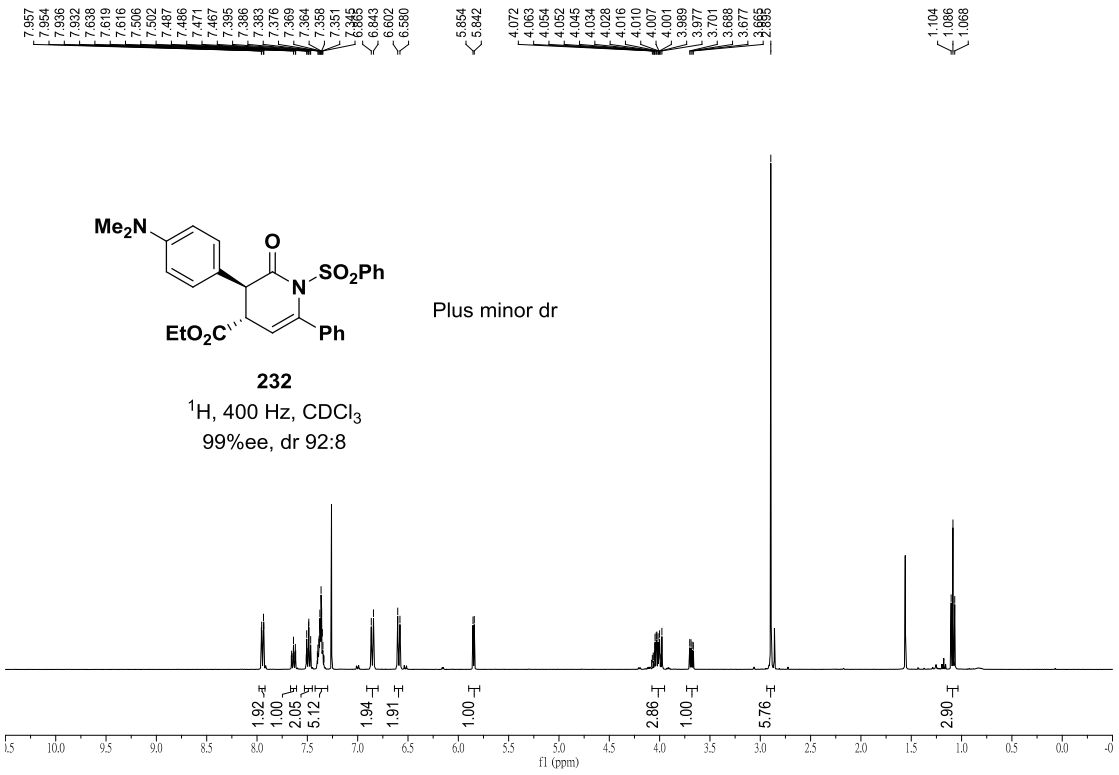
PDA Ch1 254nm

Peak#	Ret. Time	Area%
1	11.352	1.202
2	13.638	98.798
Total		100.000

Appendix II. Selected NMR Spectra





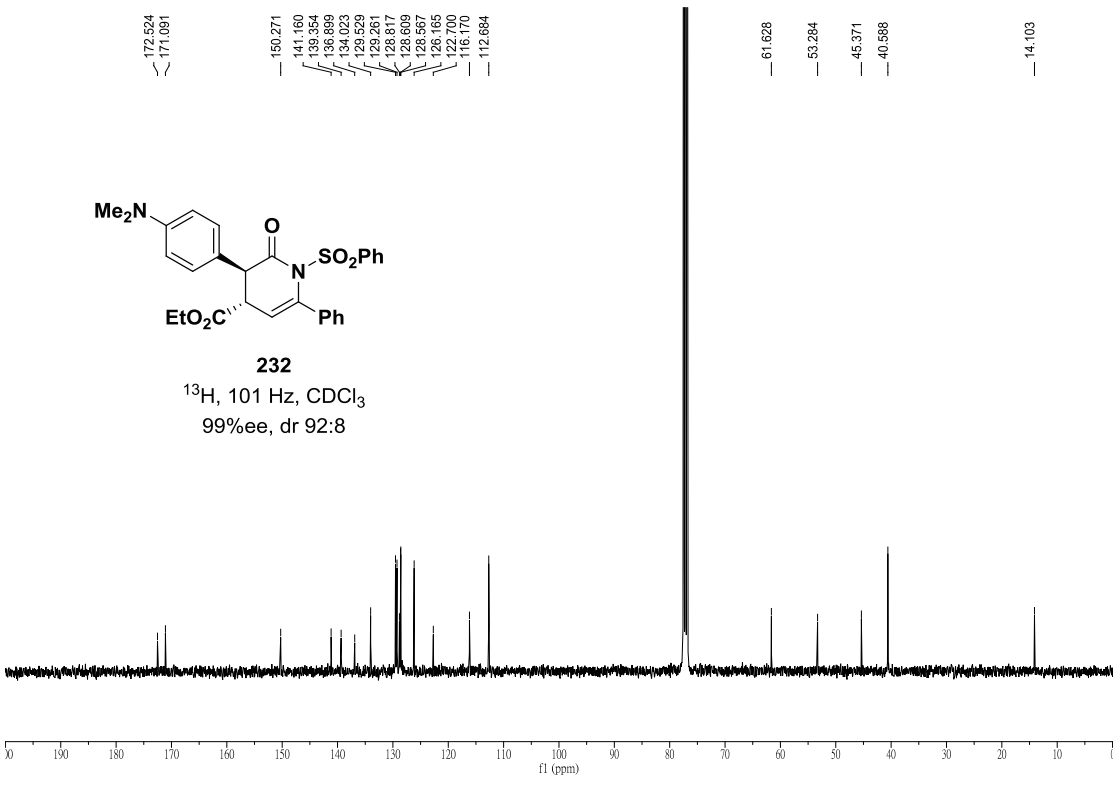


Plus minor dr

232

^{1}H, 400 Hz, $CDCl_3$

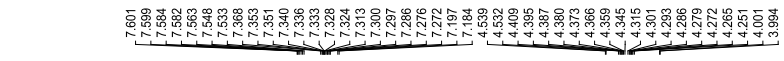
99%ee, dr 92:8

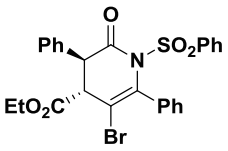


232

^{13}H, 101 Hz, $CDCl_3$

99%ee, dr 92:8

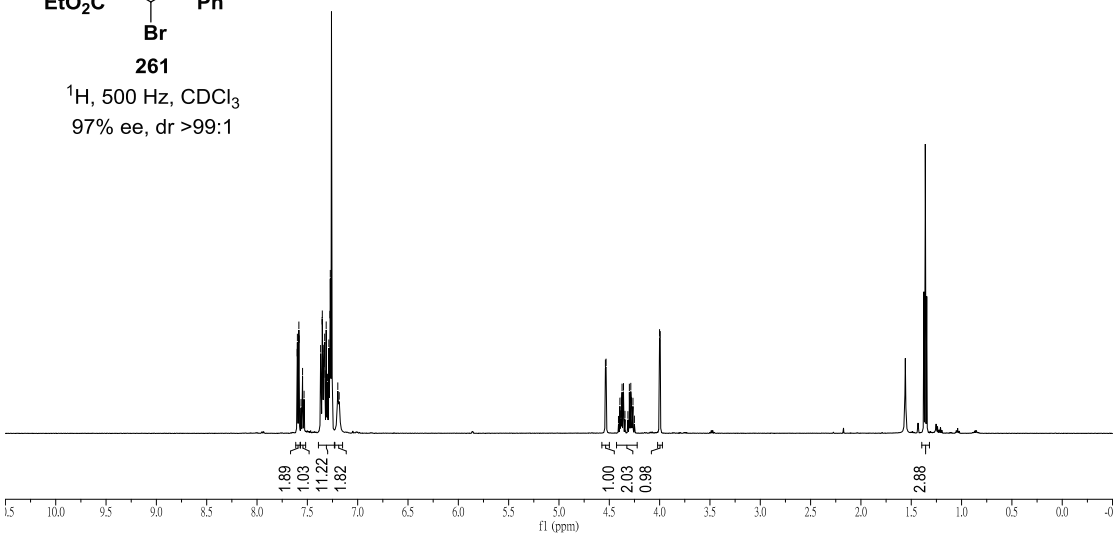


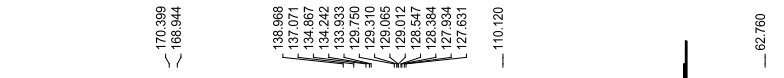


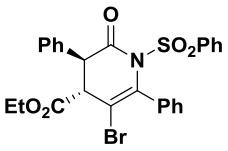
261

^{1}H, 500 Hz, $CDCl_3$

97% ee, dr >99:1



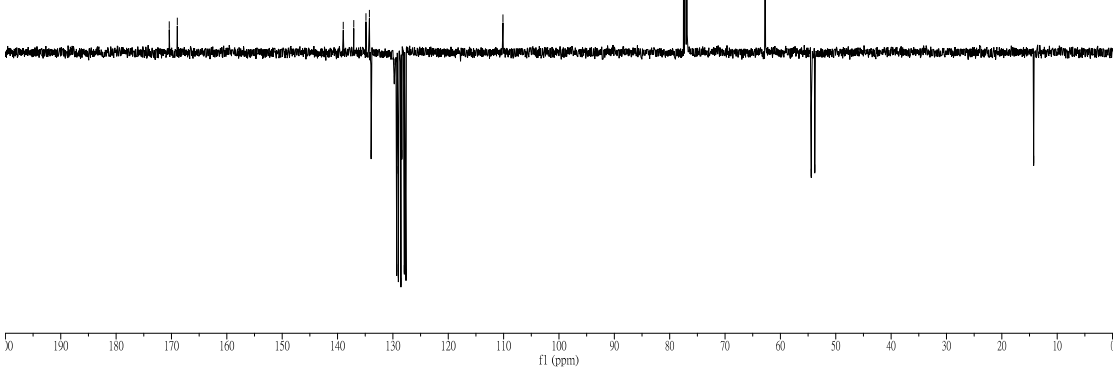


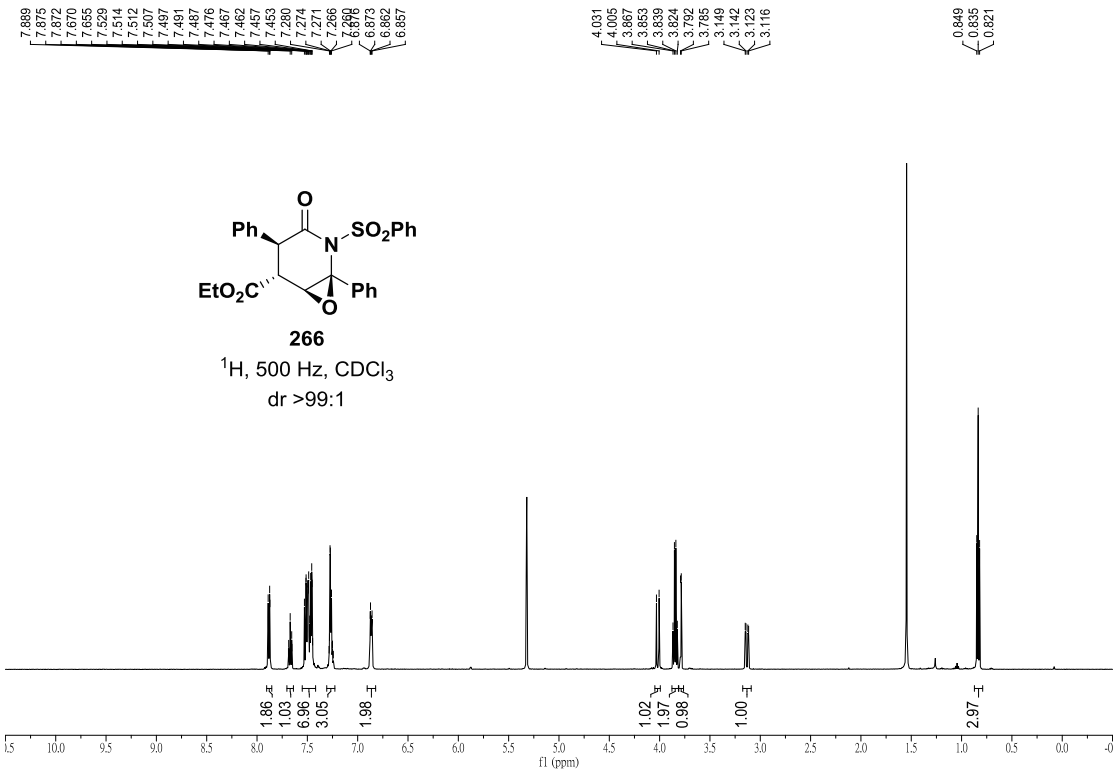


261

^{13}C, 126 Hz, $CDCl_3$

97% ee, dr >99:1

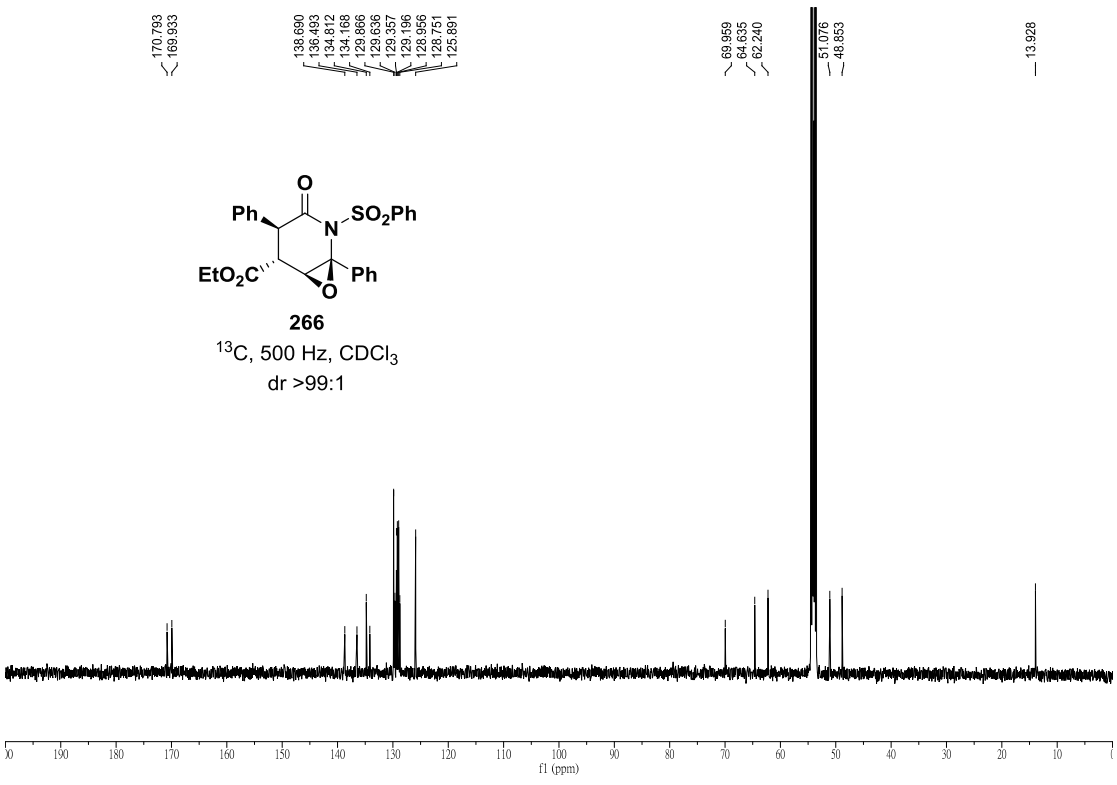




266

^{1}H, 500 Hz, $CDCl_3$

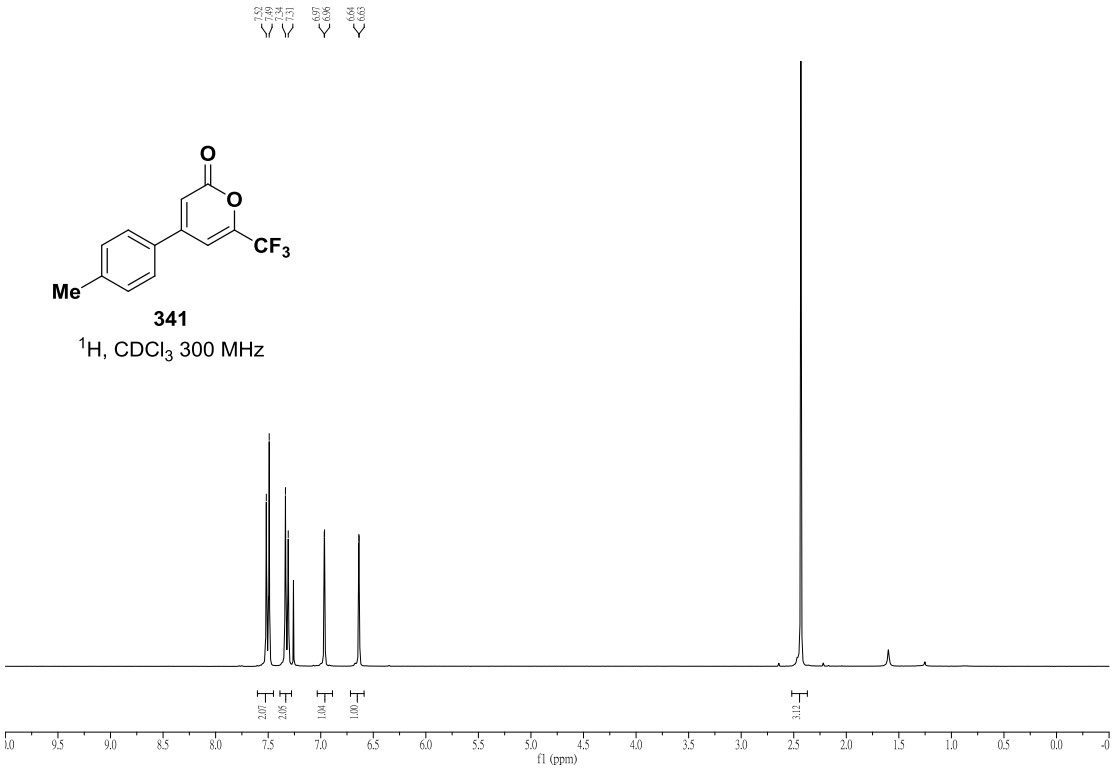
dr >99:1



266

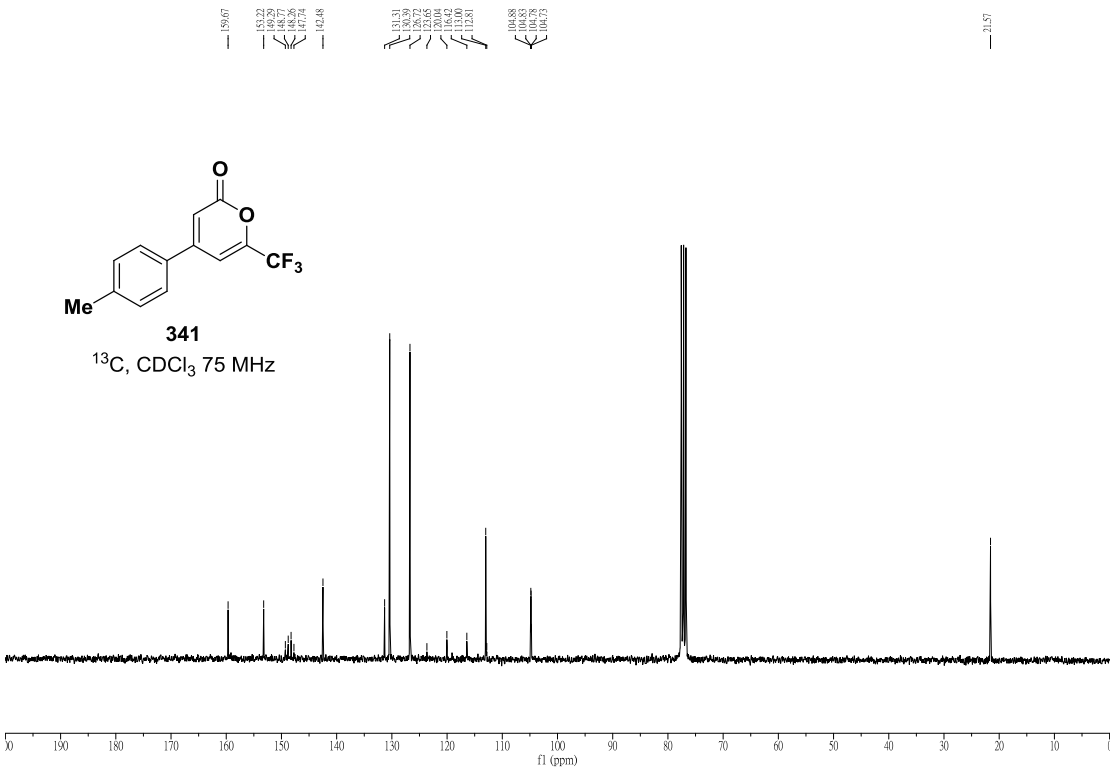
^{13}C, 500 Hz, $CDCl_3$

dr >99:1



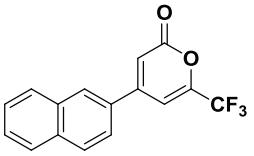
341

^{1}H, $CDCl_3$ 300 MHz



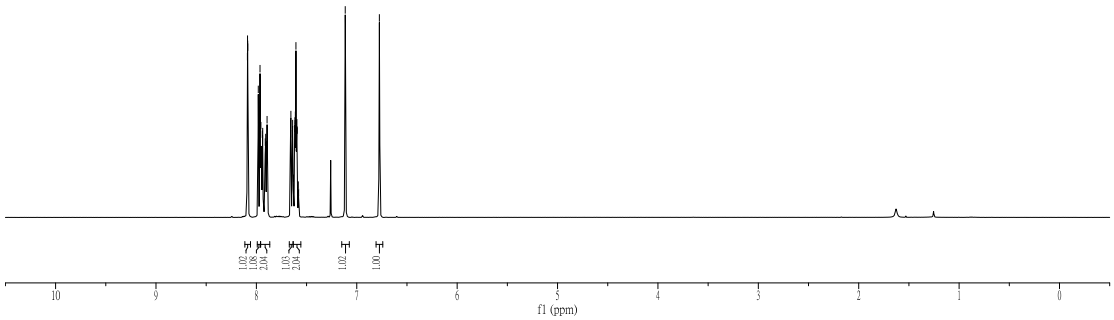
341

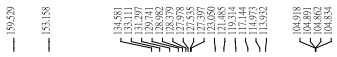
^{13}C, $CDCl_3$ 75 MHz

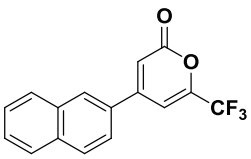


346

^{1}H, $CDCl_3$ 500 MHz

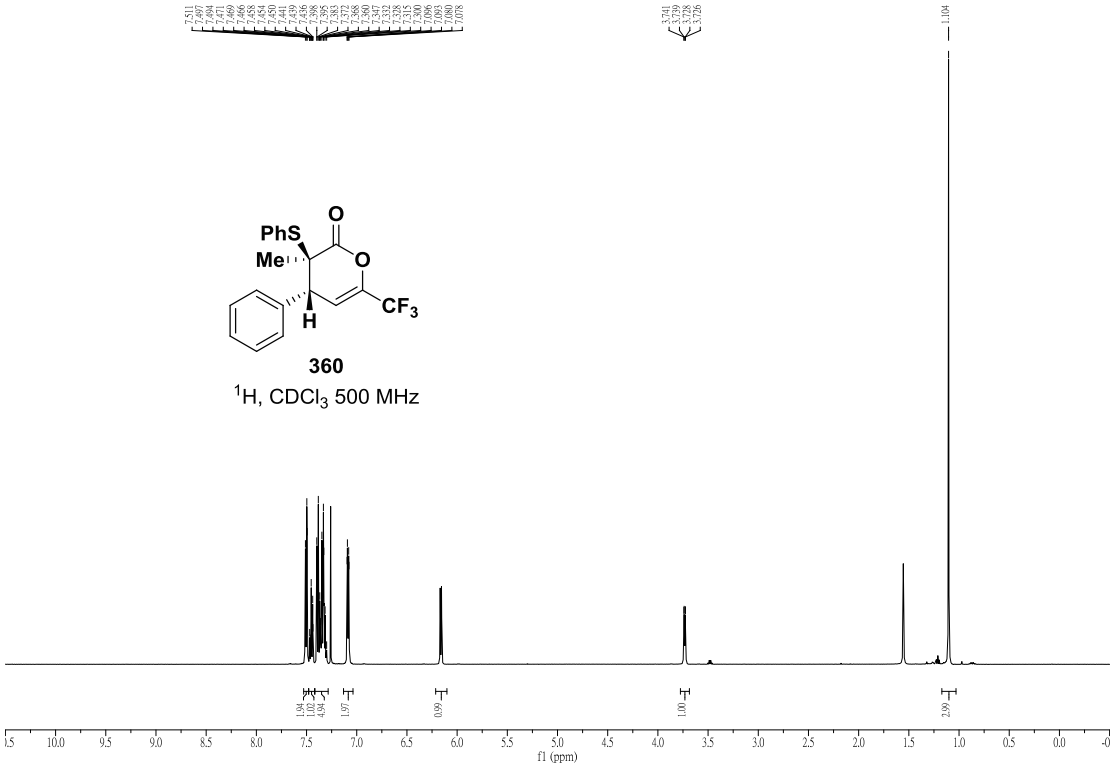






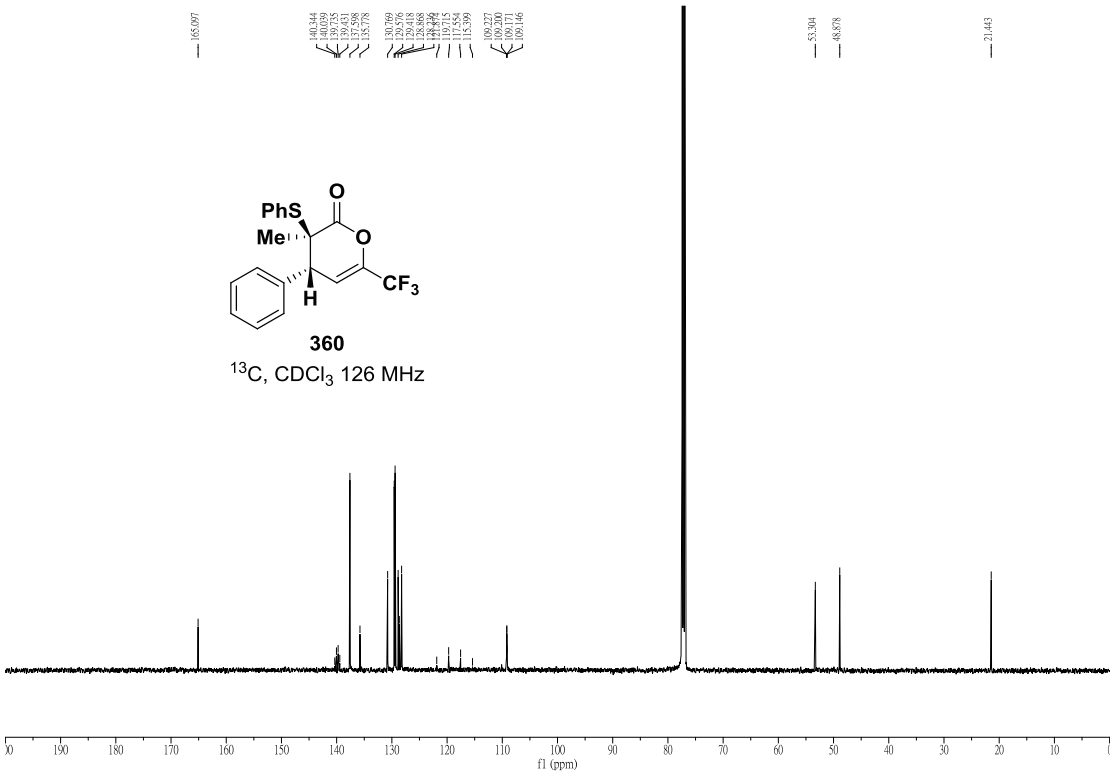
346

^{13}C, $CDCl_3$ 126 MHz



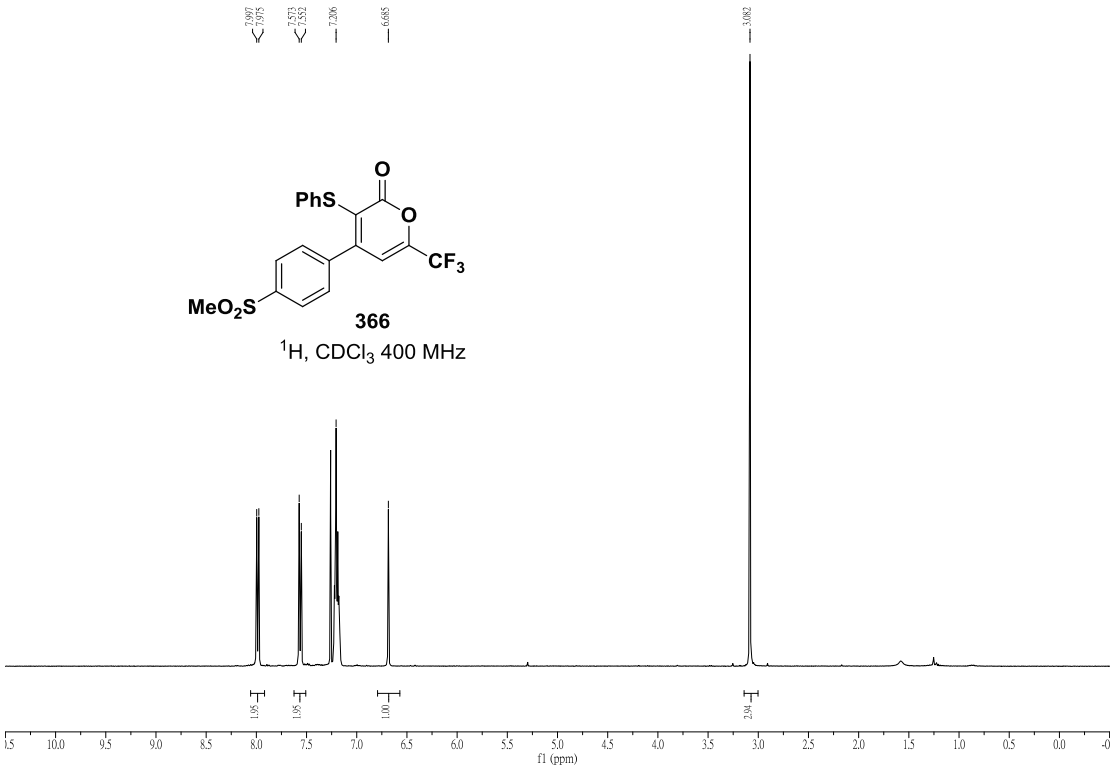
360

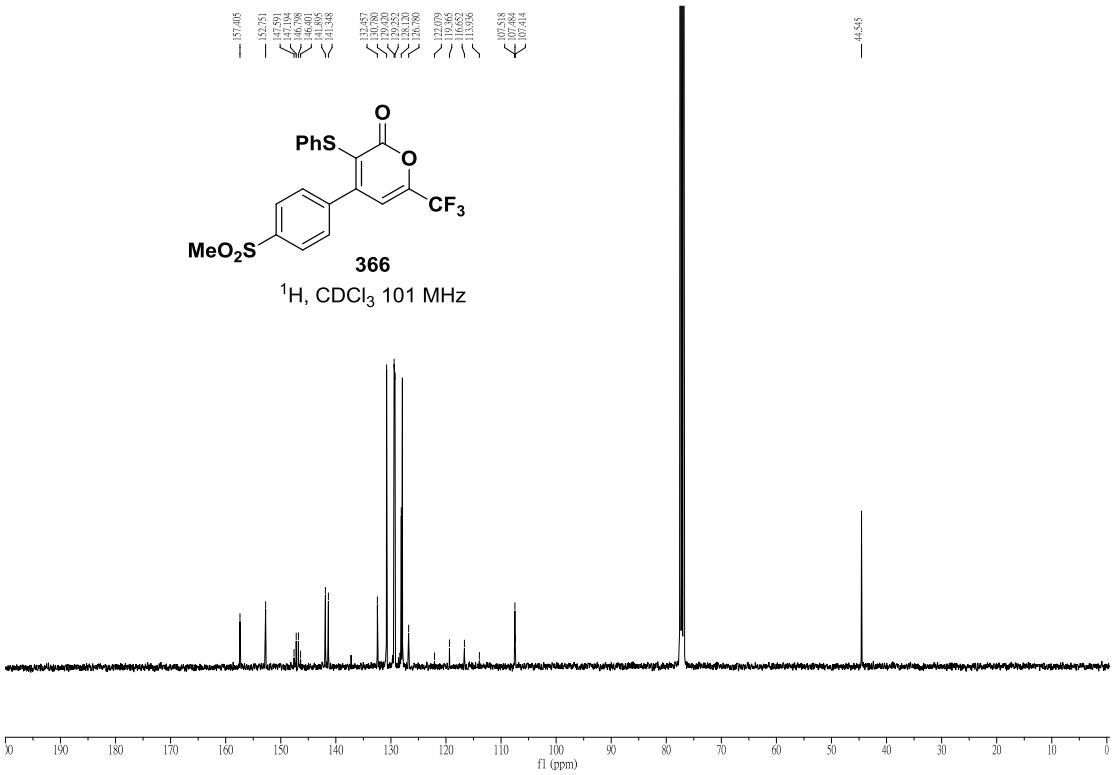
^{1}H, $CDCl_3$ 500 MHz

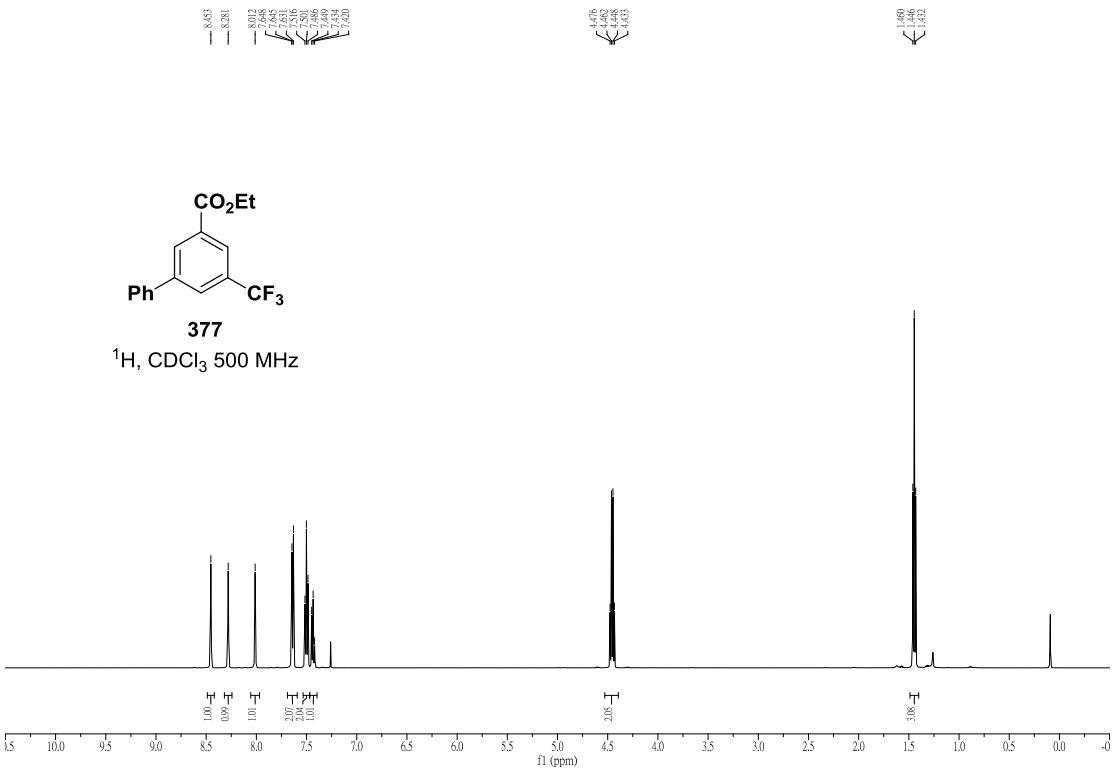


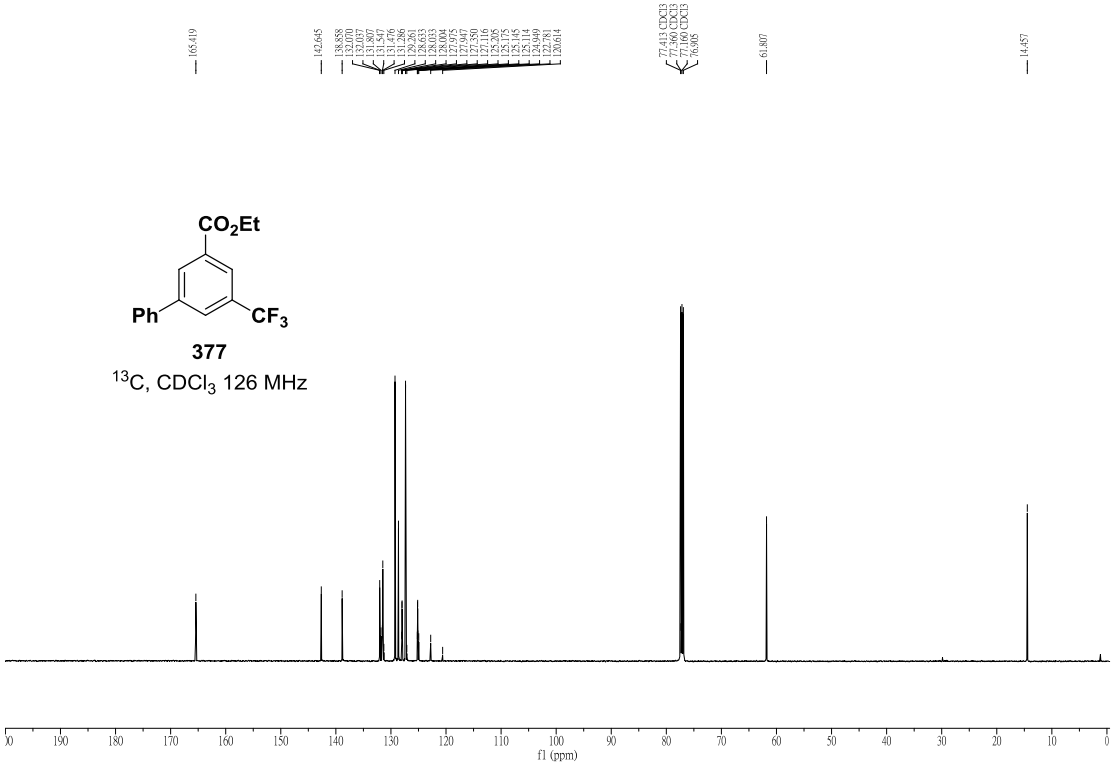
360

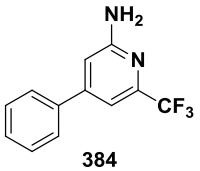
^{13}C, $CDCl_3$ 126 MHz


7.997
7.975
7.573
7.552
7.206
6.685
3.082
PhS
O
O
CF3
MeO2S
366
1H, CDCl3 400 MHz
1.95
1.95
1.00
2.94
f1 (ppm)


157.405
152.751
147.591
147.104
146.708
146.401
141.495
141.348
132.457
130.780
129.420
129.252
128.720
126.769
122.079
119.385
116.652
113.936
107.518
107.484
107.414
44.545
PhS
O
O
CF3
MeO2S
366
1H, CDCl3 101 MHz
f1 (ppm)

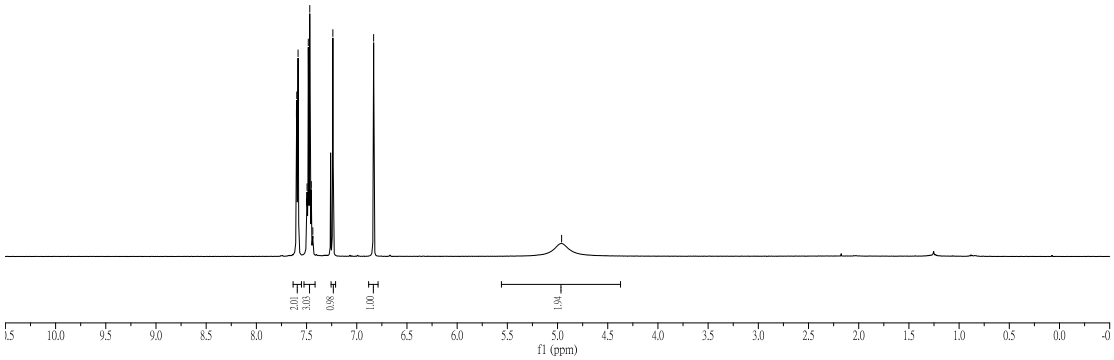

8.453
8.281
8.012
7.698
7.645
7.631
7.516
7.501
7.486
7.449
7.434
7.420
1.476
1.462
1.448
1.433
1.460
1.446
1.432
CO2Et
Ph
CF3
377
1H, CDCl3 500 MHz
1.00
0.99
1.01
2.07
2.04
1.01
2.05
3.08
f1 (ppm)

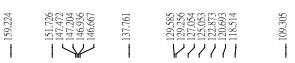

165.419
142.645
138.858
133.070
132.037
131.807
131.547
131.476
131.286
129.261
128.633
128.015
128.004
127.975
127.947
127.358
127.116
125.305
125.175
125.145
125.114
123.949
122.781
120.014
77.413 CDCl3
77.199 CDCl3
76.985 CDCl3
63.807
14.457
CO2Et
Ph
CF3
377
13C, CDCl3 126 MHz
f1 (ppm)

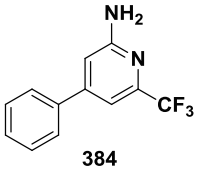


384

^{1}H, $CDCl_3$ 500 MHz

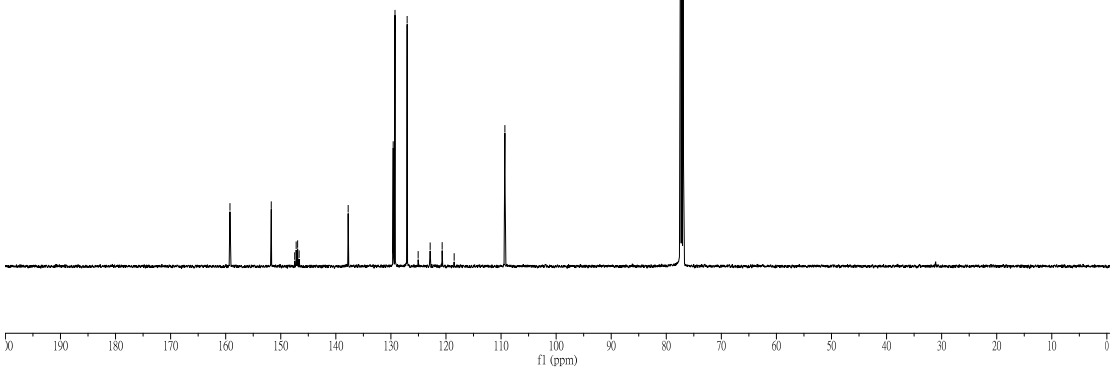


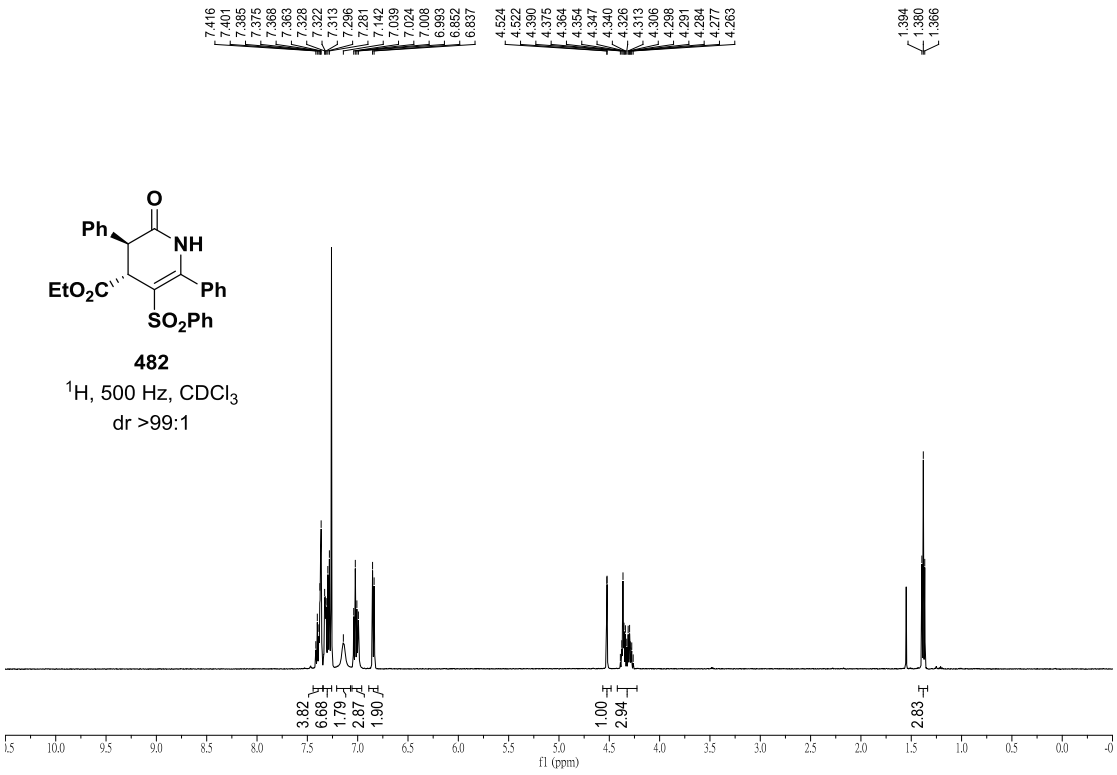


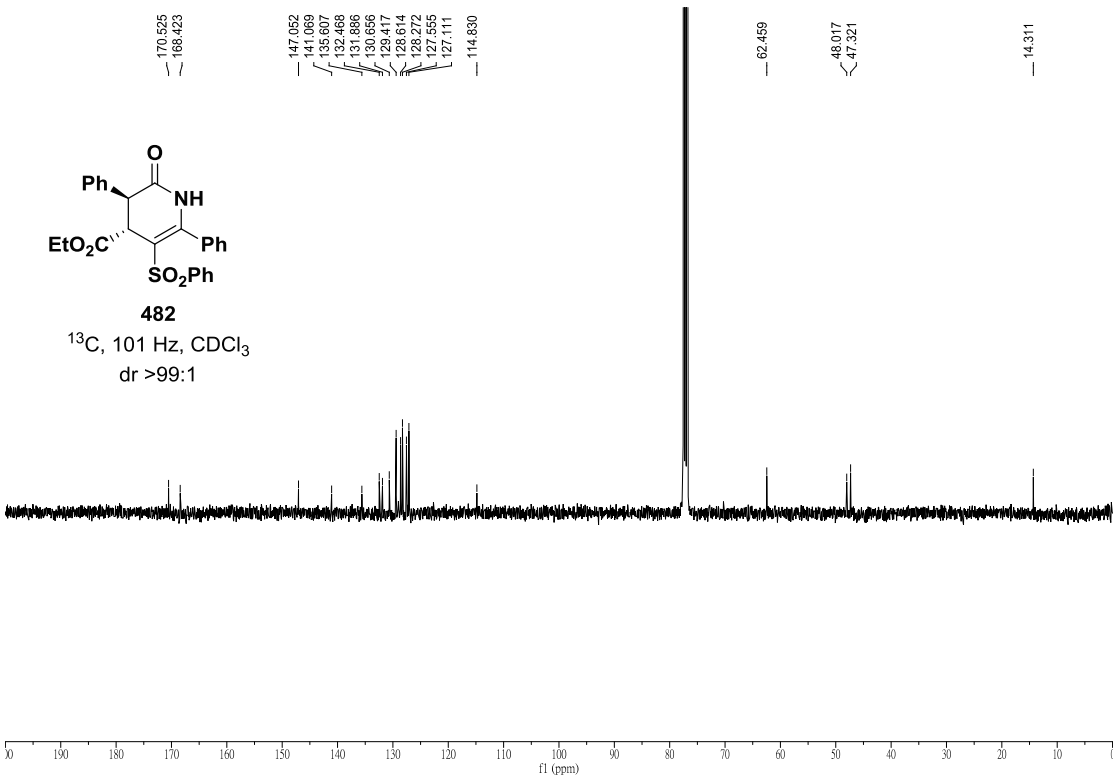


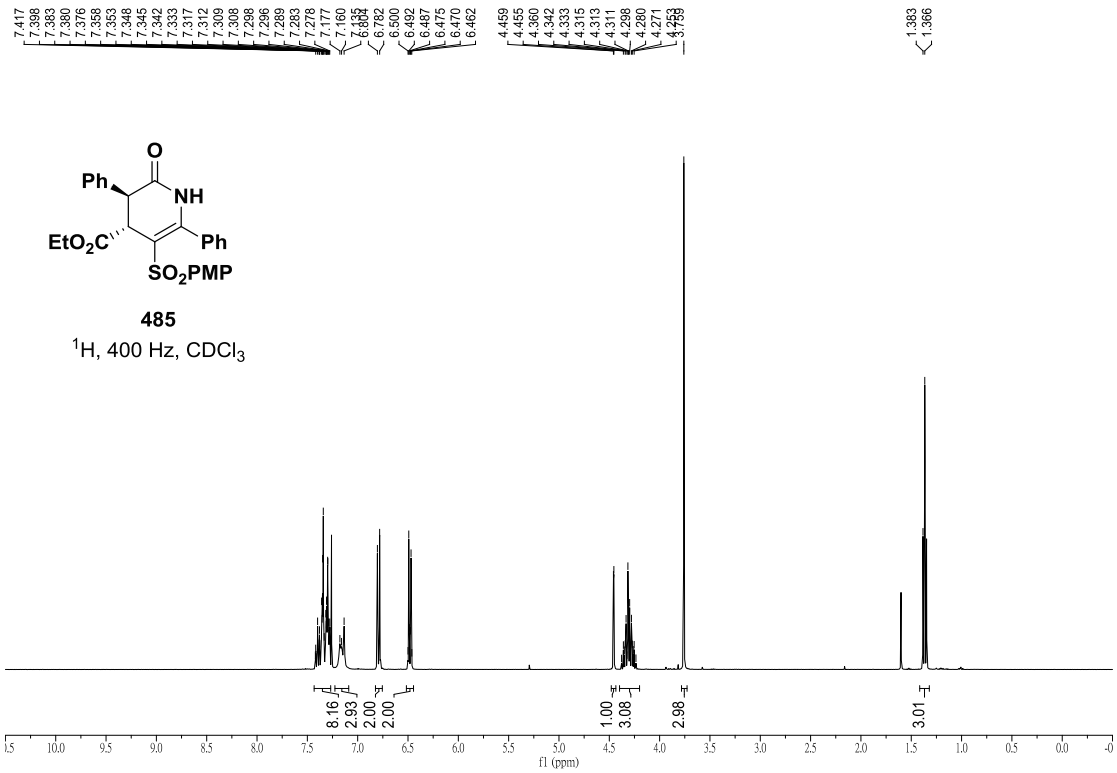
384

^{13}C, $CDCl_3$ 126 MHz



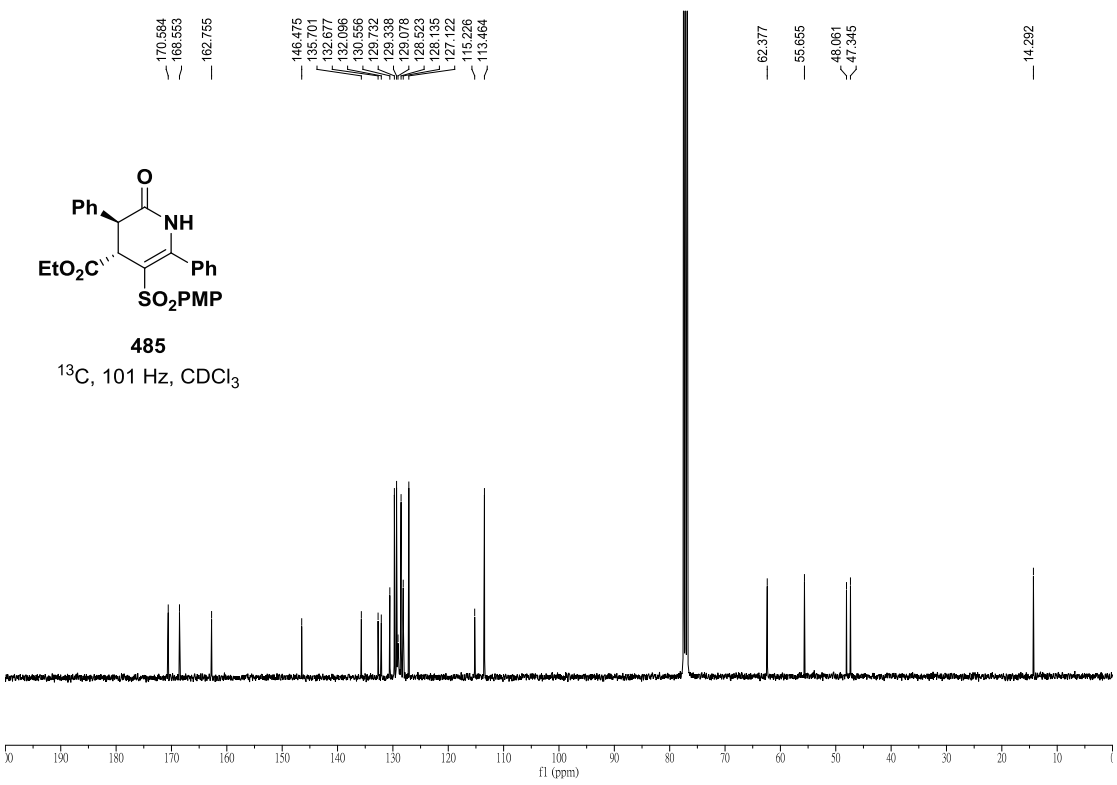

7.416
7.401
7.385
7.375
7.368
7.363
7.328
7.322
7.313
7.296
7.281
7.142
7.039
7.024
7.008
6.993
6.852
6.837
4.524
4.522
4.390
4.375
4.364
4.354
4.347
4.340
4.326
4.313
4.306
4.298
4.291
4.284
4.277
4.263
1.394
1.380
1.366
O
Ph
NH
EtO2C
Ph
SO2Ph
482
1H, 500 Hz, CDCl3
dr >99:1
3.82
6.68
1.79
2.87
1.90
1.00
2.94
2.83
f1 (ppm)


170.525
168.423
147.052
141.069
135.607
132.468
131.886
130.656
129.417
128.614
128.272
127.555
127.111
114.830
62.459
48.017
47.321
14.311
O
Ph
NH
EtO2C
Ph
SO2Ph
482
13C, 101 Hz, CDCl3
dr >99:1
f1 (ppm)



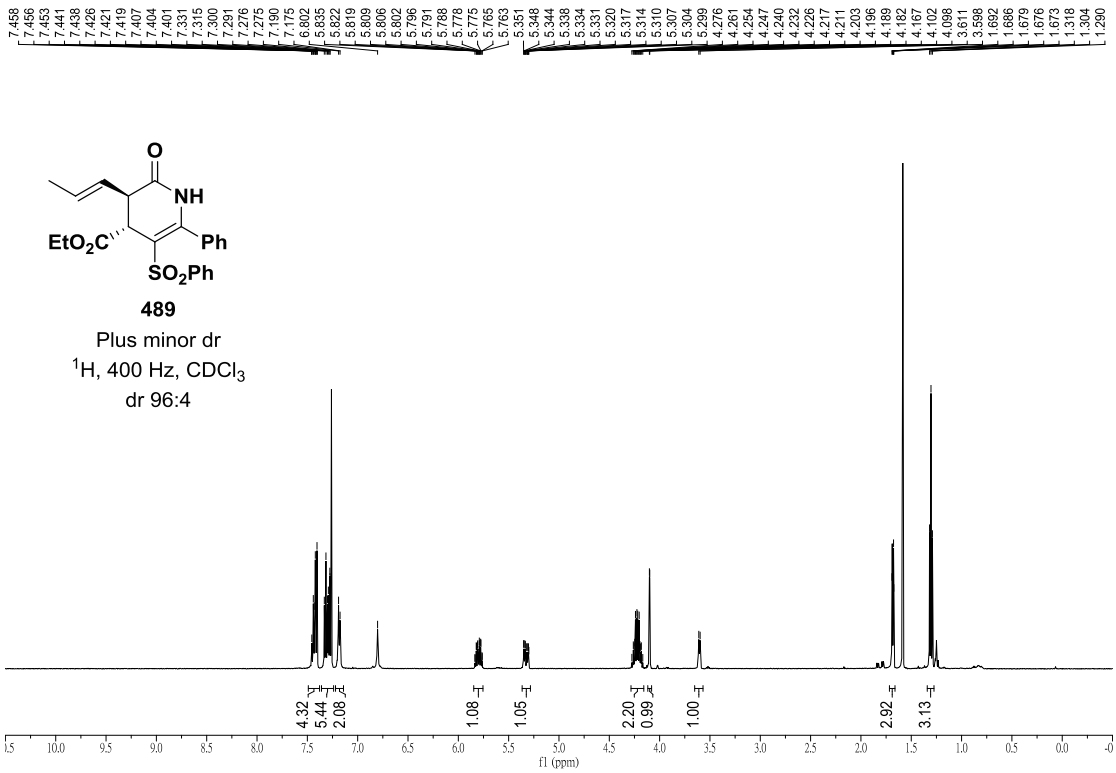
485

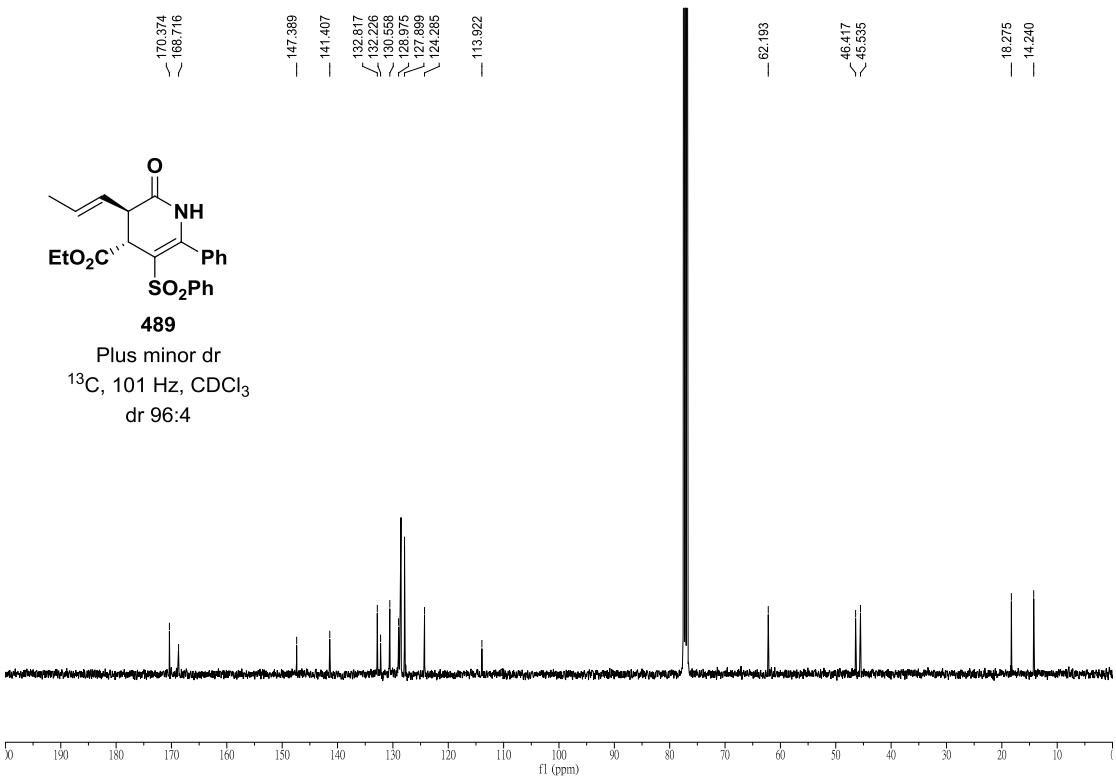
^{1}H, 400 Hz, $CDCl_3$



485

^{13}C, 101 Hz, $CDCl_3$


O
NH
EtO2C
Ph
SO2Ph
489
Plus minor dr
1H, 400 Hz, CDCl3
dr 96:4
4.32
5.44
2.08
1.08
1.05
2.20
0.99
1.00
2.92
3.13
f1 (ppm)


O
NH
EtO2C
Ph
SO2Ph
489
Plus minor dr
13C, 101 Hz, CDCl3
dr 96:4
f1 (ppm)