Exploring the Tertiary Amine-Mediated Reactivity of Allenoates: Efficient Access to 3-Alkenyl-2-oxindoles, Pyridopyrimidines and Spiropyran Frameworks

by

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Under the supervision of
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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled, **"Exploring the Tertiary Amine-Mediated Reactivity of Allenoates: Efficient Access to 3-Alkenyl-2-oxindoles, Pyridopyrimidines and Spiropyran Frameworks"**, submitted by ***Ms. Athira C. S.***, to the Academy of Scientific and Innovative Research (AcSIR) in fulfilment of the requirements for the award of the Degree of ***Doctor of Philosophy in Science***, embodies original research work carried out by the student. We further certify that this work has not been submitted to any other University or Institution in part or in full for the award of any degree or diploma. Research materials obtained from other sources and used in this research work have been duly acknowledged in the thesis. Images, illustrations, figures, tables, etc., used in the thesis from other sources, have also been duly cited and acknowledged.

22/04/25
Athira C. S.

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Dr. Sasidhar B. S.

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Athira C. S.

CONTENTS

LIST OF ABBREVIATIONS

NHC	*N*-heterocyclic carbene
Ac	Acetyl
Å	Angstrom
rt	Room temperature
h	Hour
THF	Tetrahydrofuran
Ts	Tosyl
DABCO	1,4-Diazabicyclo[2.2. 2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
S_NAr	Nucleophilic aromatic substitution
PBu_3	Tributylphosphine
DMAP	4-(Dimethylamino)pyridine
EWG	Electron withdrawing group
PPh_3	Triphenylphosphine
PMB	*para*-Methoxybenzyl
DIPEA	(*N*,*N*-diisopropylethylamine)
DFT	Density Functional Theory
BoC	*tert*-Butyloxycarbonyl
Ar	Argon
Bn	Benzyl
dr	Diastereomeric ratio
t-Bu	Tertiary butyl
FTIR	Fourier Transform Infrared Spectroscopy
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
TBD	1,5,7-Triazabicyclo[4.4. 0]dec-5-ene
QIKs	Quinone Imine Ketals
KSMs	Key starting materials
FDA	Food and Drug Administration
AIBN	Azobisisobutyronitrile
NMP	*N*-Methyl-2-Pyrrolidone

MW	Microwave
TLC	Thin Layer Chromatography
R_f	Retention factor
CCDC	Cambridge crystallographic Data Centre
Equiv.	Equivalent
ND	Not detected
NMR	Nuclear Magnetic Resonance
HRMS	High-Resolution Mass Spectrometry
ESI	Electron spray ionization
FT-IR	Fourier transform infrared spectroscopy
mg	Milligram
Hz	Hertz
J	Coupling constant
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
dd	Doublet of doublet
ppm	Parts per million
TMS	Tetramethylsilane
mL	Millilitre
min	Minute
µL	Microlitre
mmol	Millimol
mol%	Mole percentage
mp	Melting point
MS	Molecular sieves
DCE	1,2-Dichloroethane
DCM	Dichloromethane
EDG	Electron withdrawing group

PREFACE

Allenes are valuable organic molecules with distinct physical and chemical properties. In addition to being frequently present in natural products, they also serve as versatile synthons for the access of complex molecular targets, including natural products, functional materials and pharmaceuticals.

Allenoates, as a class of electron-deficient olefins, make intriguing substrates for Lewis base catalysis due to their diverse reactivities. The synthesis of various valuable cycles, particularly the preparation of biologically active natural products and pharmaceuticals, can be achieved most effectively using Lewis base-catalysed annulations of allenoates. Tertiary phosphine, NHC, and tertiary amine catalysts are often the most effective Lewis bases. In recent decades, significant progress has been achieved in the construction of valuable motifs by the transformation of allenoates mediated by tertiary amines.

Owing to these aspects, our work is focused on the tertiary amine-mediated reaction of allenoates for constructing diverse functionalized carbocycle and heterocycle frameworks. Therefore, herein we discuss the diverse synthetic strategies which utilizes tertiary amine-promoted reactions of allenoate with easily accessible substrates, environmentally friendly, metal-free, and mild reaction conditions for the synthesis of valuable scaffolds. The results of these studies are embodied in the thesis entitled "Exploring the Tertiary Amine-Mediated Reactivity of Allenoates: Efficient Access to 3-Alkenyl-2-oxindoles, Pyridopyrimidines and Spiropyran Frameworks".

The thesis is divided into four chapters. **Chapter 1** describes a comprehensive and updated summary of tertiary amine Lewis base-mediated annulation reactions of allenoates for the synthesis of valuable carbocycles and heterocycles, emphasizing their diverse reactivity, chemoselectivity and detailed reaction mechanisms.

In **Chapter 2**, we reported the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) mediated tandem reaction of easily accessible isatins and allenoates to functionalized 3-alkenyl-2-oxindoles is disclosed. The reaction allows the synthesis of a wide range of 3-alkenyl-2-oxindoles in good yields with excellent functional group tolerance under mild reaction conditions. The current strategy will provide a novel path for the sustainable synthesis of functionalized 3-alkenyl-2-oxindole derivatives. Furthermore, it is the first protocol to utilize allenoate reactivity to build structurally varied 3-alkenyl-2-oxindole motifs. We have also demonstrated the significance of 3-alkenyl-2-oxindoles as key starting materials

(KSMs) *via* their synthetic utility in producing oxindole-appended pyrazole, oxazole, and coumarin hybrids of medicinal relevance.

The tandem cyclization of easily accessible allenoates and cyclic amidines for the synthesis of functionalized tricyclic pyridopyrimidines is reported in **Chapter 3**. The annulation featured a broad substrate scope with good functional group tolerance under very mild conditions. The pyridopyrimidines were obtained in a very short reaction time, at room temperature, under neat conditions, which offers an alternative way to the sustainable synthesis of functionalized pyridopyrimidines.

A simple one-pot synthesis of spirooxindoles incorporating a 2-amino pyran-3-carbonitrile unit *via* readily available isatin, malononitrile, allenoate, and alkyl amine is described in **Chapter 4**. The metal/organocatalyst-free, Et_3N-catalyzed tandem reaction is proposed to proceed through cascade spiro-cyclization of *in situ* generated Knoevenagel/aza-Michael adducts and imine hydrolysis. This strategy is highly efficient, which allows mild synthesis of spiro[4H-pyran-oxindole] with wide substrate scope and good functional group compatibility. Additionally, we have showcased the late-stage transformations of the developed spiro[4H-pyran-oxindole] motif for the synthesis of some complex molecules.

We have developed novel and operationally simple protocols for the stereo-selective synthesis functionalized 3-alkenyl-2-oxindoles, tricyclic pyridopyrimidine and spiro[4H-pyran-oxindole]. We have mostly used readily accessible substrates isatins and allenoates. The other substrates, such as malononitrile and amines, are also readily available precursors. All the reactions were carried out under mild and environmentally friendly conditions without the usage of metal catalysts. We have synthesized a library of functionalized 3-alkenyl-2-oxindoles, tricyclic pyridopyrimidine and spiro[4H-pyran-oxindole] to demonstrate the versatility of the developed protocols. The synthesized library of compounds can serve as the source of "Hit" molecules for medicinal chemistry and drug discovery endeavours.

Chapter 1

Tertiary Amine-Mediated Reactions of Allenoates for the Synthesis of Carbocycles and Heterocycles

1.1. Abstract

Lewis base-mediated cycloaddition of allenoates has been one of the most effective synthetic strategies for the construction of numerous valuable cycles, particularly in the construction of biologically active natural products and pharmaceuticals. Tertiary phosphine, NHC, and tertiary amine catalysts are often the most effective Lewis bases; of these, tertiary amine Lewis bases have demonstrated efficacy as catalysts for a variety of synthetic transformations. Significant advancements in the synthesis of useful motifs have been made in recent decades through the cycloaddition of allenoates mediated by tertiary amines. This chapter provides a comprehensive and updated summary of tertiary amine Lewis base-mediated annulation reactions of allenoates for the synthesis of valuable carbocycles and heterocycles, emphasizing their diverse reactivity, chemo selectivity and detailed reaction mechanisms.

1.2. Introduction

Allene's units are valuable organic molecules with distinct physical and chemical properties.[1] In addition to being frequently present in natural products, they also serve as versatile synthons for accessing complex molecular targets, including functional materials and pharmaceuticals (**Figure 1.1**).[2] For a long time, allenes were merely regarded as curiosities -thought to be difficult to prepare and work with, and lacking synthetic utility. Reportedly, the synthesis of glutinic acid, the first allene by Burton and Pechmann in 1887, was carried out to prove the non-existence of this family of compounds.[3] However, due to the limited analytical tools available at that time, distinguishing allenes from the corresponding alkynes was nearly impossible. With the advent of IR and Raman spectroscopy, scientists were finally able to identify the unique C–C stretching vibration of allenes (1950 cm^{-1}), confirming that Burton and Pechmann had indeed synthesized an allene. To date, approximately 150 natural products containing allenic structures have been identified. The Scifinder database yields over 18,000 results for the keyword search of

"allene", demonstrating the significance of allenes beyond mere chemical curiosities. Furthermore, in recent years, many attempts have been made to enhance the biological and pharmacological properties of existing pharmacologically active compounds by simply incorporating an allenic moiety into their molecular frameworks.

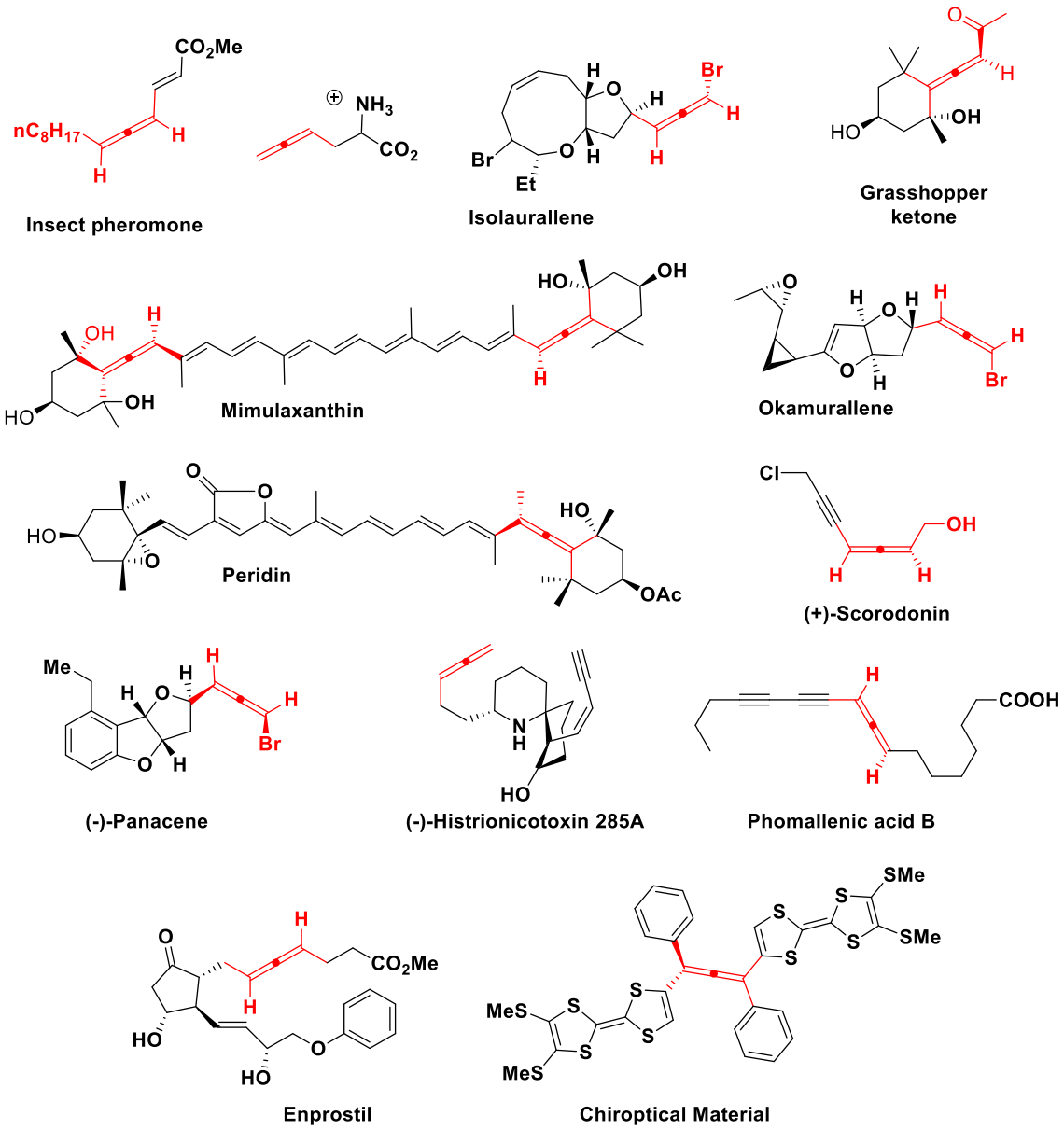


Figure 1.1. Selected natural products, pharmaceuticals and functional materials containing allenic skeleton

1.3. Chemistry of allenoates

Allenoates, as a class of electron-deficient olefins, serve as intriguing substrates for Lewis base catalysis due to their diverse reactivity. The synthesis of various valuable cyclic structures, particularly biologically active natural products and pharmaceuticals, can be

most effectively achieved through Lewis base-catalyzed annulations of allenoates. As illustrated in **Figure 1.2**, the nucleophilic addition of a Lewis base to the electrophilic *β*-carbon of an allenic ester generates a zwitterionic intermediate. This intermediate can be represented in several ways, with the anion localized at the *α*-carbon, *γ*-carbon, or delocalized, serving as a C1, C2, or C3 synthon. These resonance types are associated with the varied reactivity of allenoates. Zwitterionic intermediates can take part in several different reactions, such as cycloadditions, general base-mediated reactions, and processes that are mechanistically connected to the Morita–Baylis–Hillman and Rauhut–Currier reactions. Tertiary phosphine, NHC, and tertiary amine catalysts are often the most effective Lewis bases.[4] In recent decades, significant progress has been achieved in the construction of valuable motifs by the transformation of allenoates mediated by tertiary amines. In this chapter, we discuss recent progress in tertiary amine-promoted reactions of allenoates for the synthesis of carbocycles and heterocycles.

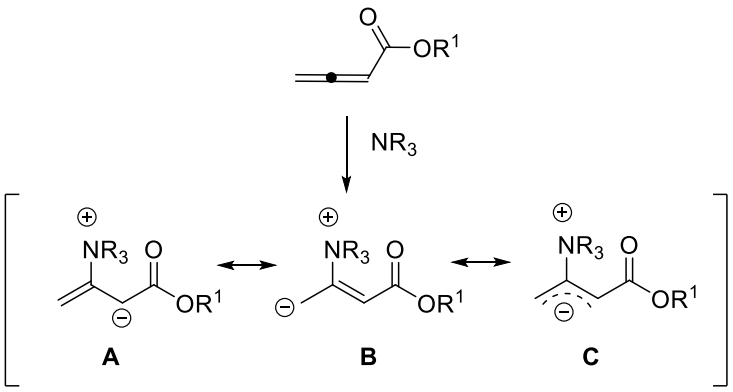
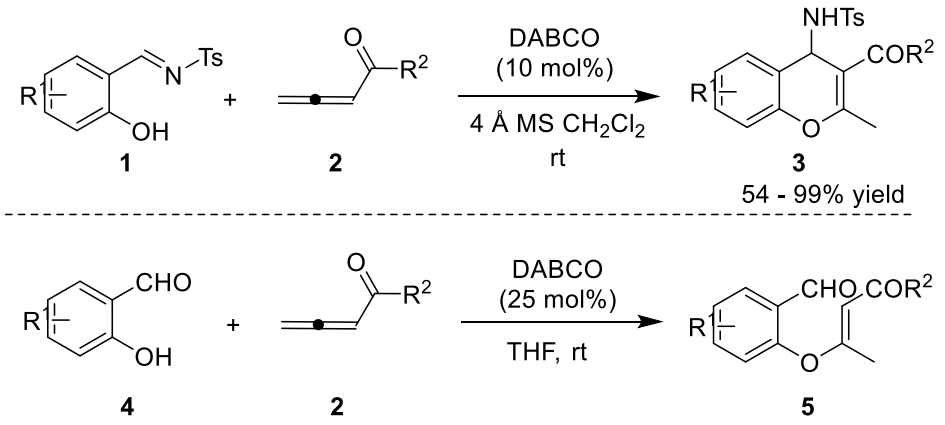


Figure 1.2. Reactivity of allenoates in the presence of Lewis base

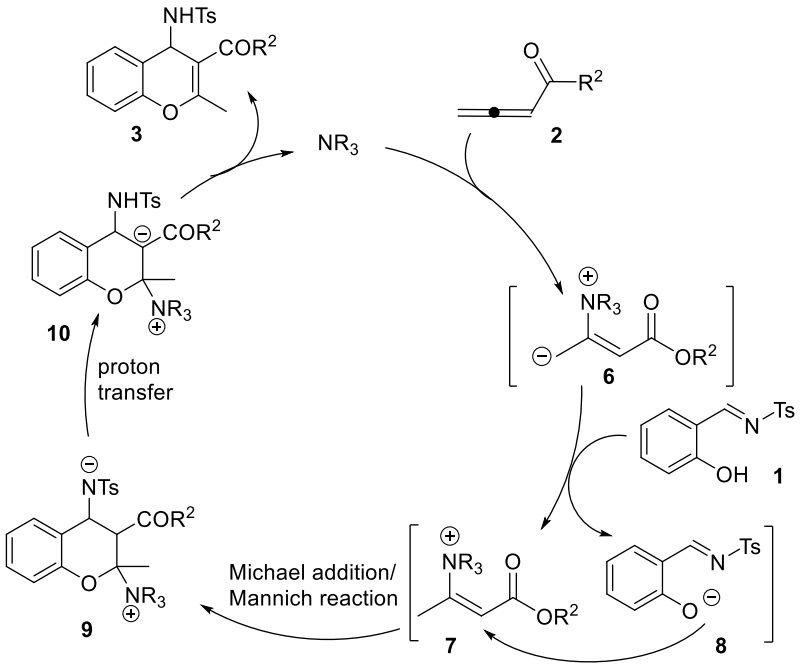
1.3.1. Tertiary amine-catalyzed synthesis of six-membered carbocycles/heterocycles

The [4+2] cycloaddition of allenoates catalyzed by DABCO was originally reported in 2005. In the literature, Shi and co-workers generated highly functionalized chromene derivatives **3** in good to excellent yields by cyclizing various salicyl *N*-tosylimines with ethyl 2,3-butadienoate/penta-3,4-dien-2-one using DABCO. Remarkably, allenoates were employed in the [4+2] cycloaddition as a unique C2 synthon. Instead of using salicyl *N*-tosylimines **1** as the substrate, the authors used salicylaldehyde **4**, and instead of chromenes, the corresponding phenolic Michael addition product **5** was formed (**Scheme 1.1**).[5]



Scheme 1.1. DABCO-catalyzed [4+2] cycloaddition of salicyl *N*-tosylimine

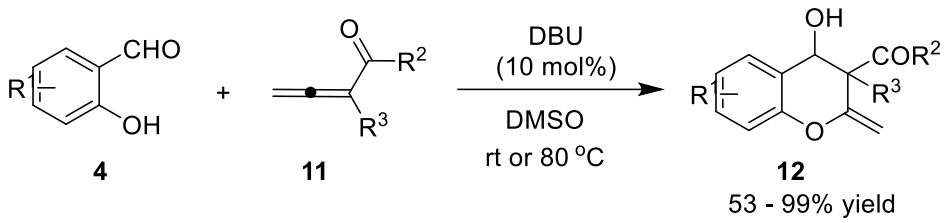
The authors proposed a plausible reaction mechanism as shown in **Scheme 1.2**. Firstly, the nucleophilic attack of DABCO on β carbon of the allenoate generated a zwitterionic intermediate **6**, which deprotonated the phenol group in imine **1** to give intermediates **7** and **8**. Next, a tandem Michael addition/ Mannich reaction, followed by proton transfer and elimination, produced chromene **3** and regenerated DABCO.



Scheme 1.2. A plausible mechanism for DABCO-catalyzed [4+2] cycloaddition of salicyl *N*-tosylimines

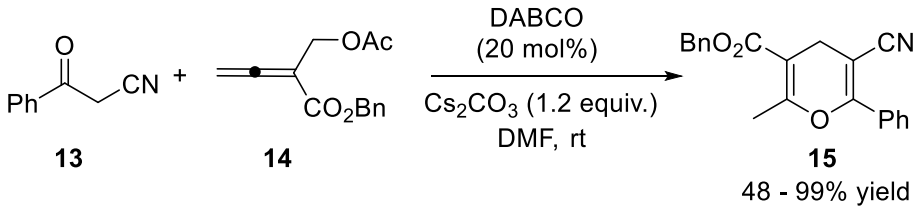
In 2005, Shi group presented a DBU-catalyzed reaction of salicylic aldehydes with 3-methylpenta-3,4-dien-2-one/ 3-benzylpenta-3,4-dien-2-one/ ethyl 2-methylbuta-2,3-dienoate. The [4+2] cycloaddition reaction proceeded smoothly, providing the

corresponding functionalized 2*H*-1-chromenes in good to excellent yields with a preference for anti-addition over syn-addition (**Scheme 1.3**).[6]



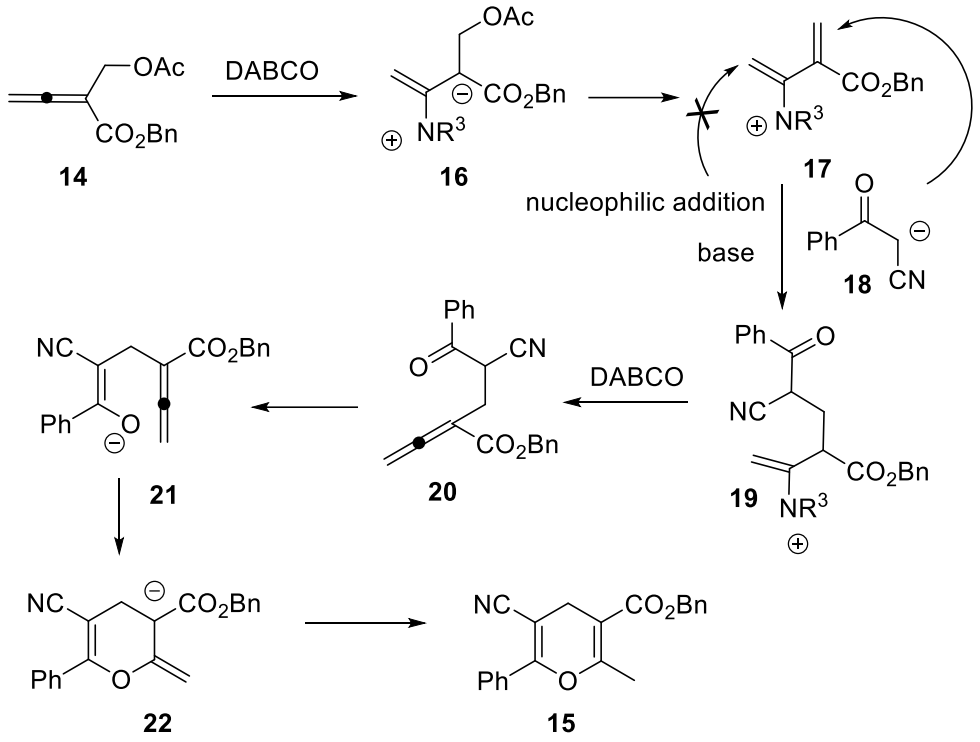
Scheme 1.3. DBU-catalyzed [4+2] cycloadditions of salicylaldehydes

In 2010, Tong and co-workers employed *β*-acetoxy allenoates as reactive substrates for the DABCO-catalyzed [3+3] cycloaddition with 3-oxo-3-phenylpropanenitrile, producing the corresponding 4-substituted 4*H*-pyrans **15** in moderate to excellent yields (**Scheme 1.4**).[7]



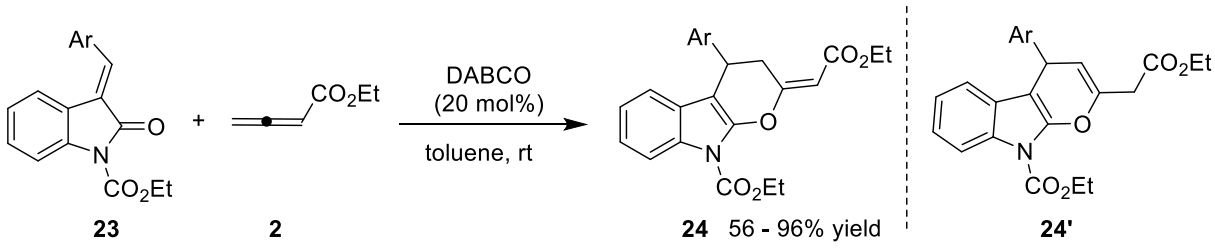
Scheme 1.4. DABCO-catalyzed [3+3] cycloaddition with 3-oxo-3-phenylpropanenitrile

The plausible mechanism is shown in **Scheme 1.5**. The attack of DABCO on the *β*-carbon of the allenoate initiated the addition–elimination process to give intermediate **17**. According to previous reports, the Michael-type addition of **14** to the *γ*-position of intermediate **17** was considered unlikely due to the ammonium ion's poorer ability to stabilize the ylide. Intermediate **19** was produced through a Michael-type addition of **93** to the *β*-position of **17** in the presence of a base. Subsequently, 1,2- elimination of DABCO yielded intermediate **20**, which was then followed by 6-endo-trig type oxo-Michael addition to generate intermediate **22**. Finally, continuous isomerization and protonation could yield compound **15**.



Scheme 1.5. A Plausible mechanism for [3+3] cycloaddition with 3-oxo-3-phenylpropanenitrile

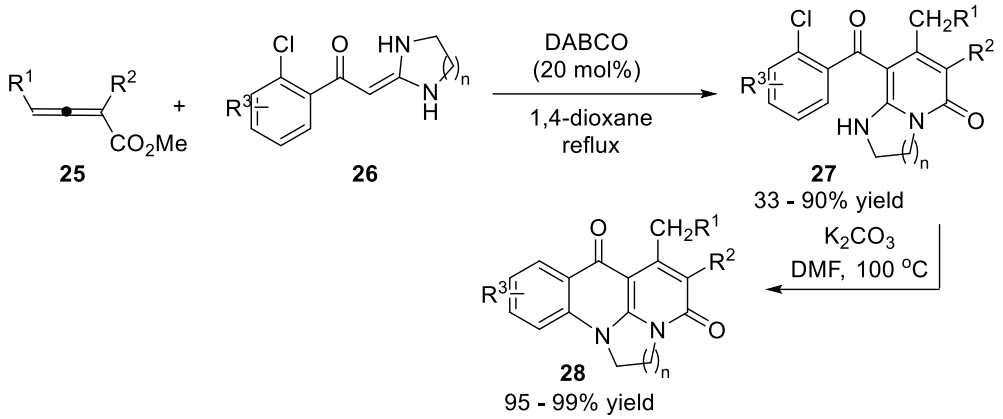
In 2011, Ye and Wang reported a regio/ diastereoselective synthesis of functionalized dihydropyran-fused indoles by a novel DABCO-catalyzed [4+2] cycloadditions of allenoates with arylidenoxindoles. In this report, the β- and γ-sites of allenoates participated in chemical bond formation. Unexpectedly, when strong electron-withdrawing groups (3-NO_2, 2-NO_2) were introduced, the double bond migrated isomers **24'** was also produced along with normal products **24** (**Scheme 1.6**).[8]



Scheme 1.6. DABCO-catalyzed [4+2] cycloaddition with arylidenoxindoles

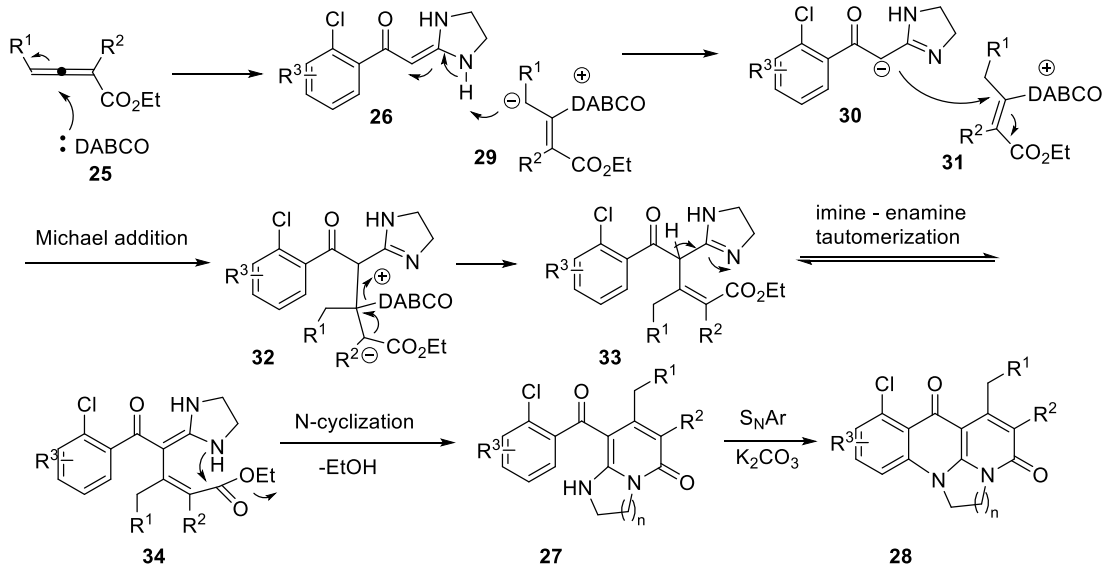
In 2011, Li and Wen developed a DABCO-catalyzed [3+3] cycloaddition between 2-(2-chloroaroyl)methyleneimidazolidines and allenoates. This opens an efficient and flexible way to the synthesis of imidazo(pyrido)[1,2-a]pyridine **27** and imidazo(pyrido)[3,2,1-ij][1,8]naphthyridine **28** derivatives in moderate to good yields. According to the

experimental results, nine reactive sites were involved in this domino process. All reactants are effectively used in the chemical transformation to create one C-C bond, two C-N bonds, and two new rings (**Scheme 1.7**).[9]



Scheme 1.7. DABCO-catalyzed [3+3] cycloaddition with 2-(2-chloroaroyl) methyleneimidazolidines

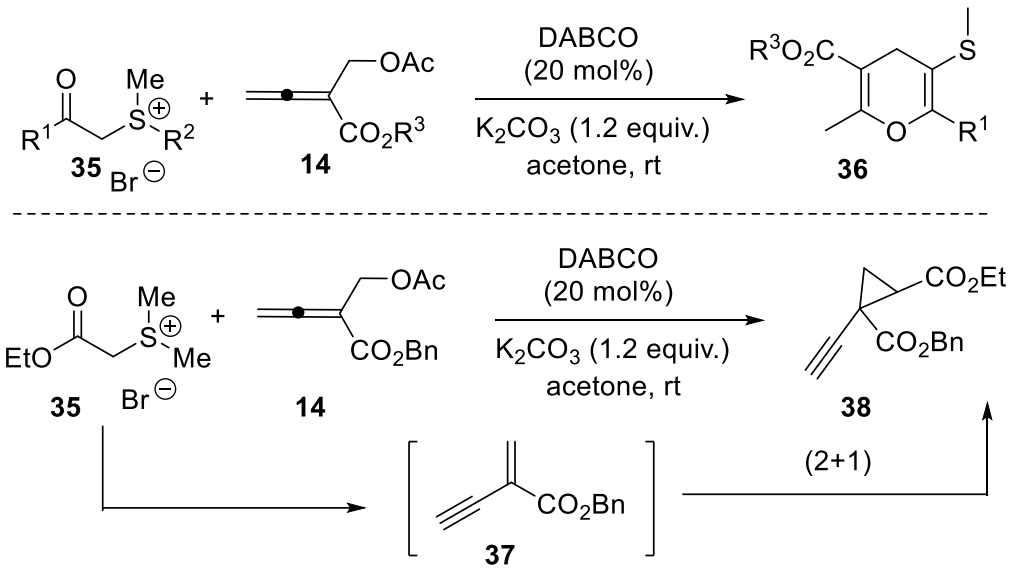
Based on the experimental findings, a plausible mechanism is proposed as shown in **Scheme 1.8**. At first, DABCO produces the zwitterionic intermediate **29** by reacting with the allenic esters **25**, which subsequently removes a proton from **26** to produce **30**. The following Michael addition of **30** to **31** results in the formation of another zwitterionic intermediate, **32**. Intermediate **33** is formed by the elimination of DABCO from **32**.



Scheme 1.8. A Plausible mechanism for DABCO-catalyzed [3+3] cycloaddition of 2-(2-chloroaroyl) methyleneimidazolidines

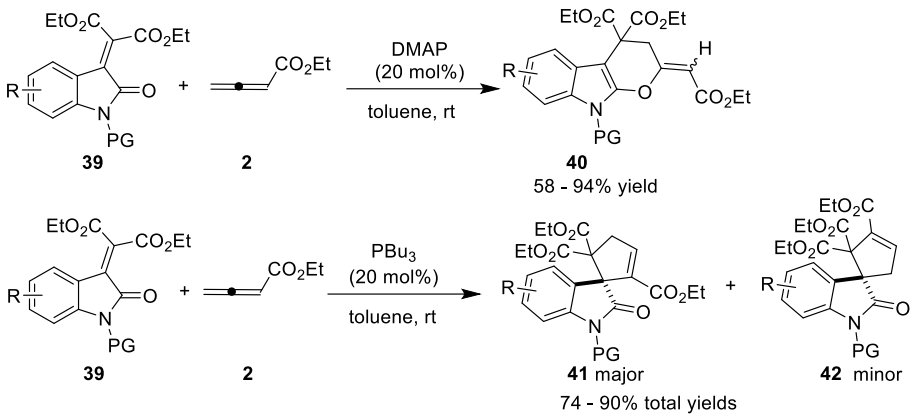
Further imine enamine tautomerization and intramolecular cyclization generates dihydroimidazo[1,2-a] pyridine(1H)-ones **27**. Ultimately, an intramolecular S_NAr of the *o*-chloro of the aryl group leads to the removal of HCl and the generation of imidazo[3,2,1ij][1,8]naphthyridine derivatives **28**.

In 2012, Tong and co-workers reported a [3+3] annulation between *β*-acetoxy allenoates and sulfur ylides. The DABCO-catalyzed reaction in the presence of potassium carbonate in acetone generates S-containing 4*H*-pyran **36** in good yields. Further study showed that the behaviour of ester-stabilized sulphur ylides differed significantly from that of ketone-stabilized ylides. The reaction between **35** and **14** under the identical circumstances delivered cyclopropane derivative **38** in 24% yield. In 2009, Lee and colleagues discovered that compound **37** readily forms from allenoate **14** in the presence of DABCO and a base. As a result, **38** might be created *via* normal cyclopropanation between **37** and the corresponding ylide derived from **35** (**Scheme 1.9**).[10]



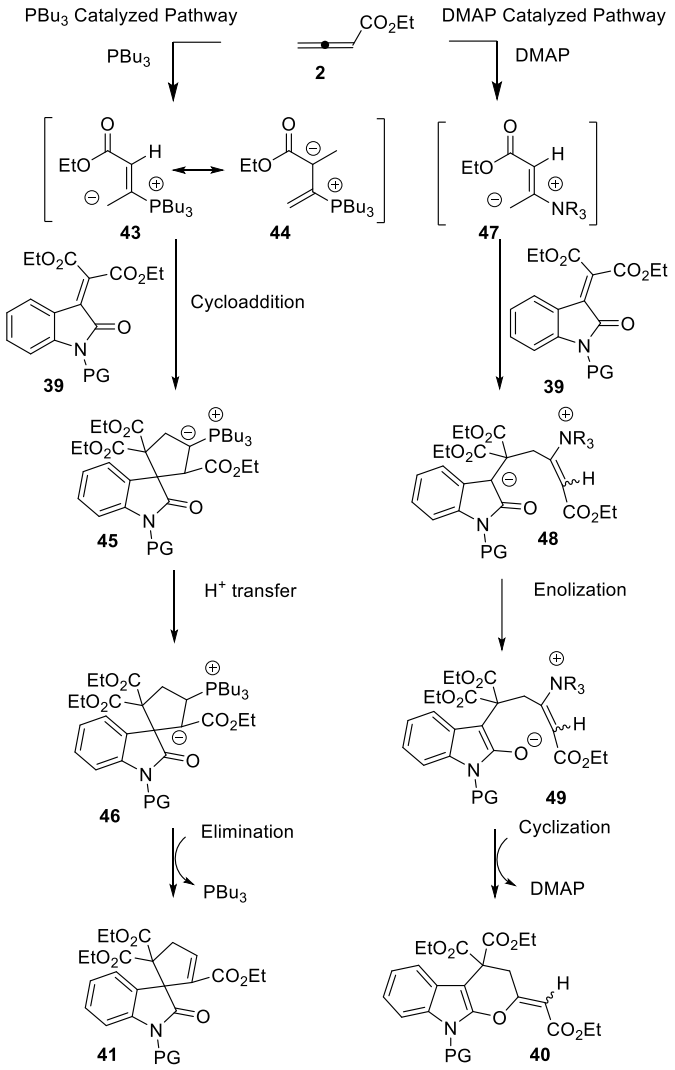
Scheme 1.9. DABCO-catalyzed [3+3] annulation of allenoates and sulfur ylides

In 2012, an interesting DMAP catalyzed highly geometric selective [4+2] cycloaddition and Bu_3P catalyzed regioselective [3+2] cycloaddition of isatin derived *α,β*-unsaturated diesters with *α*-allenic ester have been disclosed by Shi group, which give the corresponding cyclic products in good to excellent yields under mild conditions (**Scheme 1.10**).[11]



Scheme 1.10. PBu_3 and DMAP-catalyzed cyclization of allenoates with oxindoles

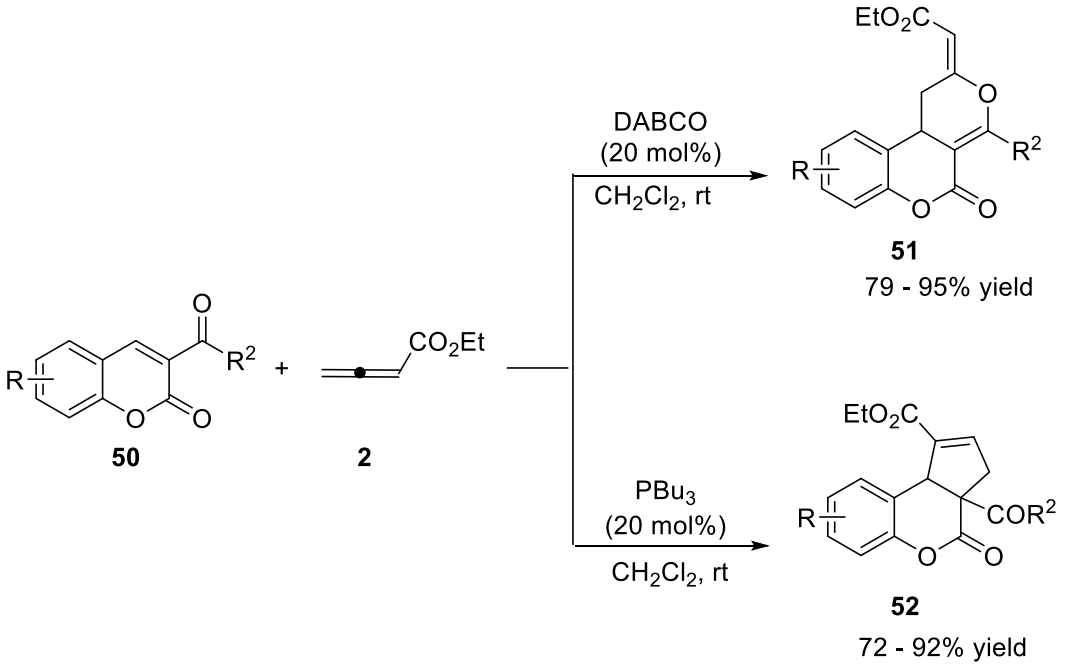
The plausible reaction mechanism suggested is shown in **Scheme 1.11**. In the PBu_3-catalyzed reaction, the nucleophilic addition of catalyst to the allenic ester **2** give a zwitter-



Scheme 1.11. Mechanism for PBu_3 and DMAP-catalyzed cyclization with oxindoles

-ionic intermediate **43**, which serves as a dipole for the subsequent [3+2] cycloaddition with **39** to generate intermediate **45**. The facile 1,2-proton transfer affords intermediate **46**, and then, the product **41** is formed after elimination of the catalyst. This mechanism, has the advantage of the ability of phosphorus to stabilize the ylide structure **45**. On the other hand, the DMAP-catalyzed route is not assisted by the same stabilisation. The zwitterionic intermediate **47** reacts with **39** to give intermediate **48**, which then follows enolization to yield intermediate **49**. The DMAP catalyst is regenerated and cyclic adduct **40** is produced through subsequent cyclization.

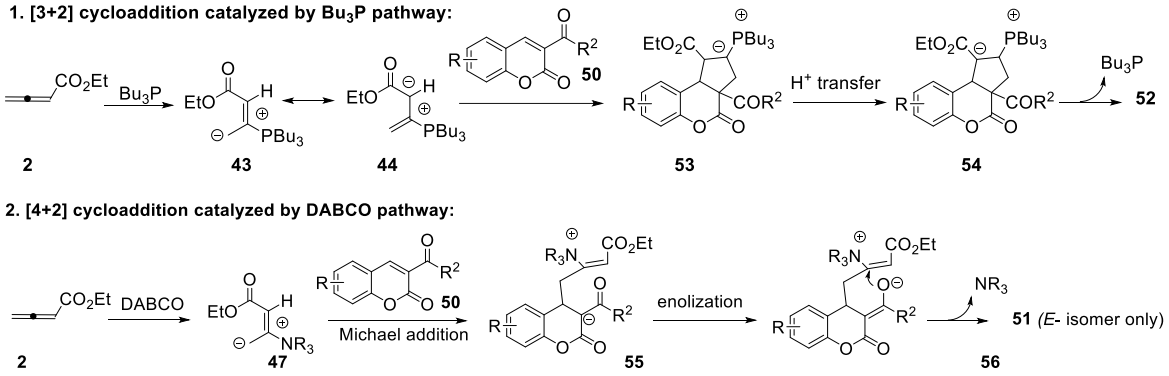
In 2012, Shi and co-workers developed DABCO-catalyzed [4+2] and Bu_3P-catalyzed [3+2] cycloadditions between 3-acyl-2H-chromen-ones and ethyl 2,3-butadienoate for the synthesis of dihydropyran-fused and cyclopenten-fused chromen-2-ones with high regio- and stereo-selectivities, respectively (**Scheme 1.12**).[12]



Scheme 1.12. DABCO and Bu_3P catalyzed cycloadditions of 3-acyl-2*H*-chromen-ones

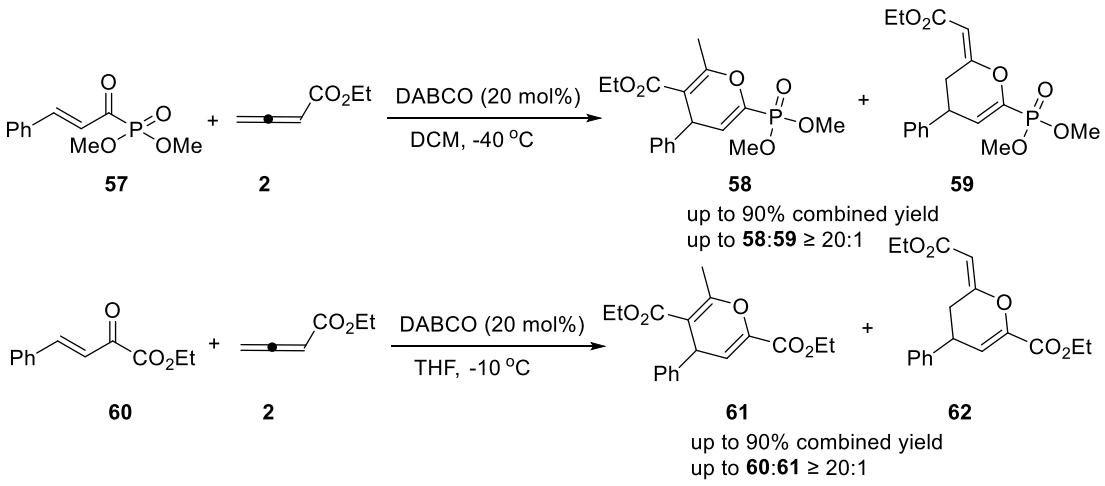
The plausible mechanism is depicted in **Scheme 1.13**. The reactions proceed through different cycloaddition modes in the presence of Bu_3P and DABCO. In the case of the PBu_3-catalyzed reaction, Bu_3P attacks the *β*-carbon of 2,3-butadienoate **2** to give intermediate **43**, as *β*-carbanion of **44** can be stabilised by both the ester group and the phosphonium salt. Consequently, compound **44** serves as a 1,3 dipole for the [3+2] cycloaddition with activated olefins **50**, which is followed by 1,2-proton transfer and Bu_3P elimination, resulting in the [3+2] cycloadduct **52**. While considering the [4+2]

cycloaddition pathway which is catalyzed by DABCO, reaction with 2,3-butadienoate **2** generates zwitterionic **47**, in which the γ-position carbanion attacks the β-carbon of enones **50** leading to the *Z*-configuration of **55** and thereby avoiding steric interaction between the ester group and the 3-position acyl group. The intermediate **55** is then converted to the enolate **56**, in which the oxygen anion of enolate **56** undergoes molecular nucleophilic substitution with the β-carbon of the α, β-unsaturated ester moiety. Finally, the release of DABCO generated the product **51**.



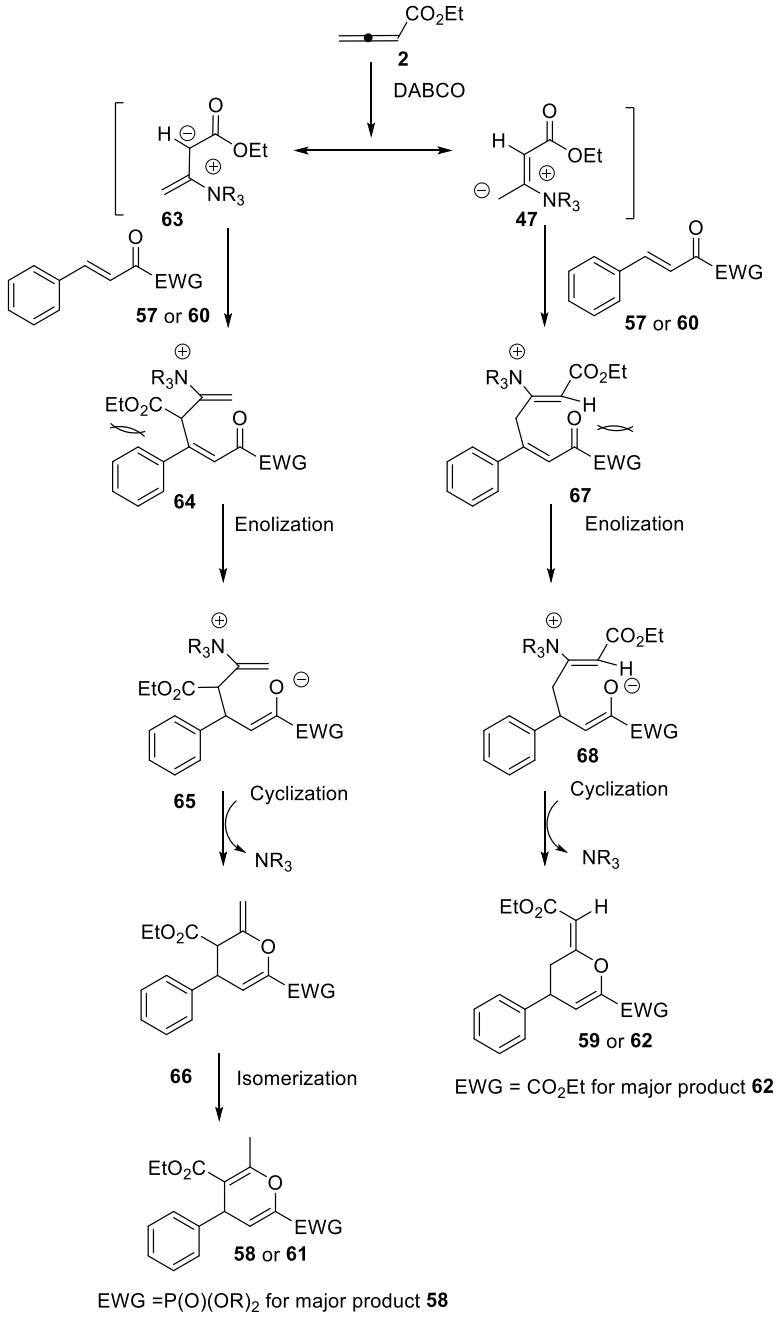
Scheme 1.13. A plausible mechanism for DABCO and Bu_3P catalyzed cycloadditions of 3-acyl-2*H*-chromen-ones

In 2012, Pei et al. reported a DABCO catalyzed [4+2] cycloaddition of β, γ-unsaturated α-ketophosphonates or β,γ-unsaturated α-ketoesters with allenoates. The products-functionalized tetrahydropyrans and dihydropyrans were obtained in good to excellent yields with moderate regioselectivity (**Scheme 1.14**).[13]



Scheme 1.14. DABCO catalyzed [4+2] cycloaddition of β, γ-unsaturated α-ketophosphonates or β,γ-unsaturated α-ketoesters

The zwitterionic intermediate **63** is produced when DABCO is added to allenoate **2**. This intermediate coexists with its resonance form **47**. The reaction of zwitterion intermediate **63** with **57** or **60** resulted in **64**, which is then enolized to intermediate **65**. The DABCO

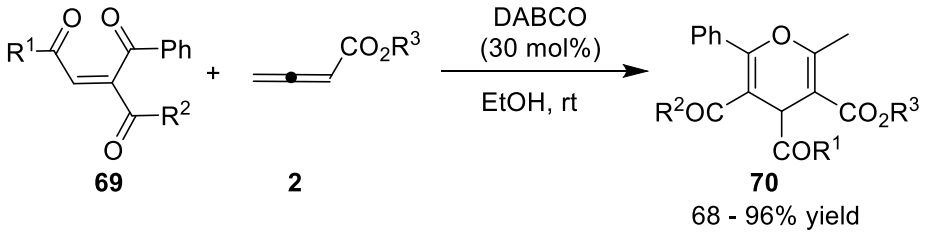


Scheme 1.15. Plausible mechanism for the cycloaddition of *β*,*γ*-unsaturated *α*-ketophosphonates or *β*,*γ*-unsaturated *α*-ketoesters

catalyst is removed and cyclic product **66** is produced through subsequent cyclization. Finally, **66** undergoes isomerization to produce the more stable adducts **58** or **61**.

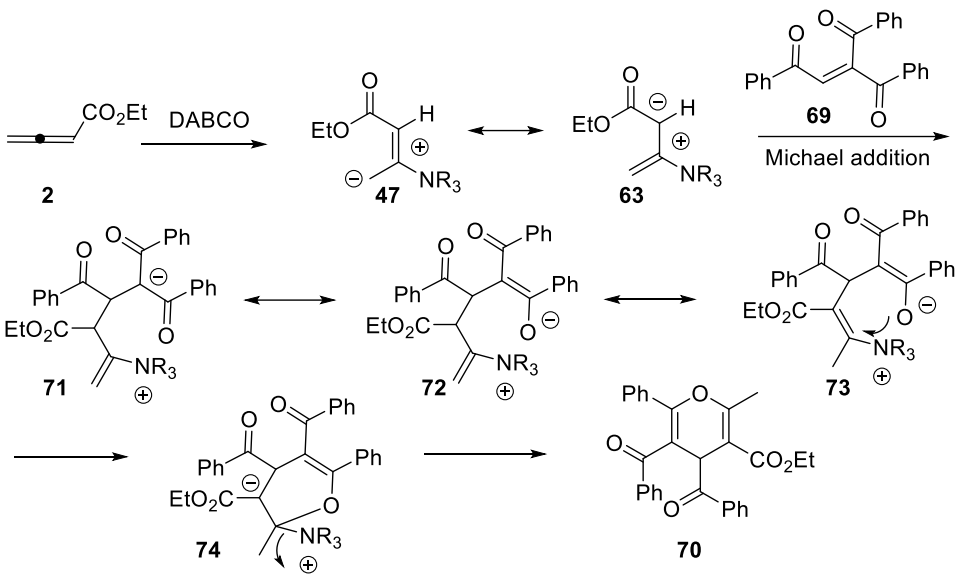
Meanwhile, the zwitterionic intermediate **47** reacts with **57** or **60** to generate intermediate **67**, which then undergoes enolization to form intermediate **68**. Subsequent cyclization furnished cyclic product **59** or **62** and regenerated the catalyst. The major products in the reaction might be mainly due to the steric interaction between intermediates **64** and **67**. When EWG=$PO(OiPr)_2$, which is sterically bulkier than the aromatic ring, the steric repulsion between CO_2Et and EWG is greater than that between CO_2Et and the aromatic ring. Hence, intermediate **64** is more stable than intermediate **67**, resulting in **58** as the major product. When EWG=CO_2Et, which is sterically smaller than an aromatic ring, the steric repulsion between CO_2Et and EWG is less than that of CO_2Et and an aromatic ring. Consequently, intermediate **67** is more stable than intermediate **64**, giving **62** as the major product (**Scheme 1.15**).

Later in 2013, the authors utilized 2,3-butadienoates as a reactive substrate, to accomplish an efficient regioselective [4+2] cycloaddition with 3-acyl(or alkoxycarbonyl)-1,4-enediones catalyzed by DABCO. Based on the findings, α and β sites of allenoates participated in the chemical bond formation to generate functionalized pyrans in moderate to excellent yields (**Scheme 1.16**).[14]



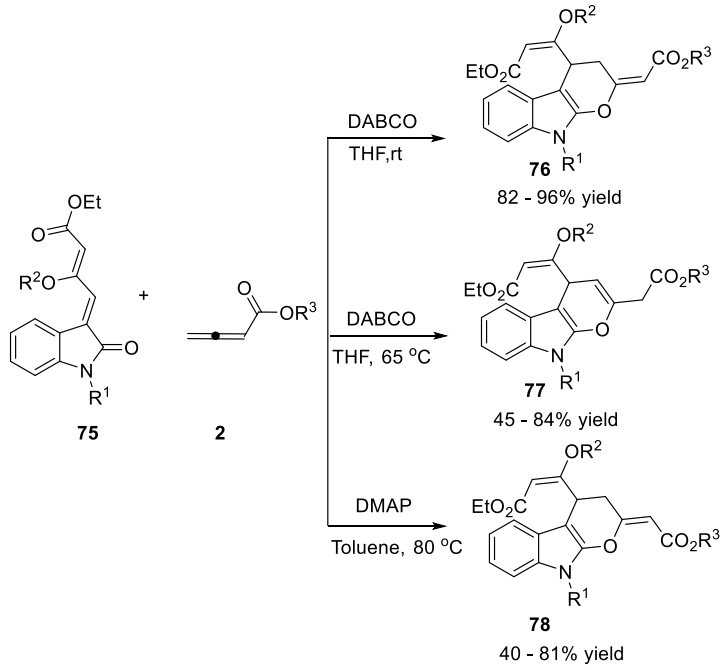
Scheme 1.16. DABCO catalyzed [4+2] cycloaddition of 3-acyl(or alkoxycarbonyl)-1,4-enedione

First, DABCO attacks the β-carbon of ethyl 2,3-butadienoate **2**, leading to the formation of intermediate **47**. The intermediate **47** can then isomerize into a more stable intermediate **63**, as both the ester group and ammonium salt ion can stabilize the β-carbanion of **63**. Following the 1,4-addition of compound **63** to 1,4-enedione **69**, intermediate **71** is produced. This is followed by the enolization and 1,3-proton transfer, resulting in intermediate **73**. Finally, an intramolecular nucleophilic attack followed by the release of DABCO leads to the formation of the formal [4+2] cycloadduct **70**. (**Scheme 1.17**).



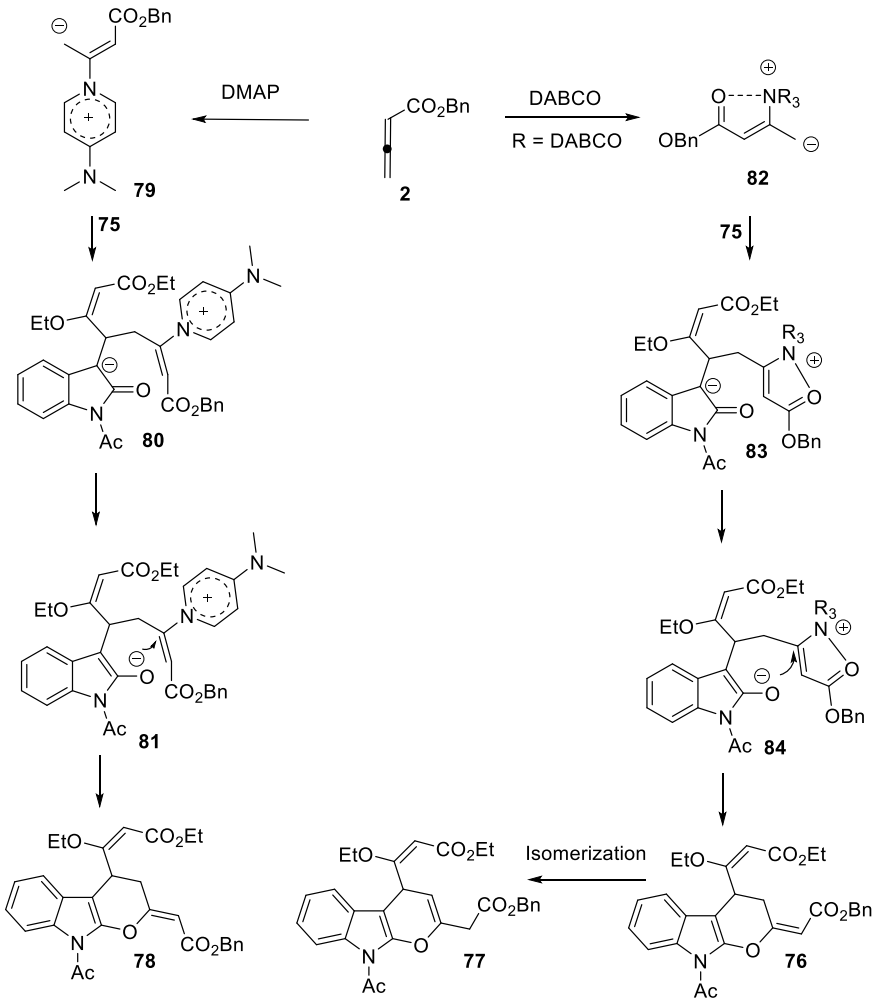
Scheme 1.17. A Plausible mechanism for cycloaddition of 3-acyl(or alkoxycarbonyl)-1,4-enedione

In 2015, the Meng group described a tunable domino [4+2] reaction of methyleneindolonones with allenoates to give pyran and dihydropyran rings. Using DABCO as the catalyst and THF as a solvent, the authors were able to tune toward dihydropyrano[2,3-b]indol with *E* exocyclic double bond and pyrano[2,3-b]indol at room temperature and 65 ^{o}C respectively. In contrast, when DMAP was used as a catalyst, the domino reaction afforded dipyrnao[2,3-b]indol with *Z* exocyclic double bond at 80 ^{o}C (**Scheme 1.18**).[15]



Scheme 1.18. DABCO catalyzed [4+2] cycloaddition of methyleneindolonones

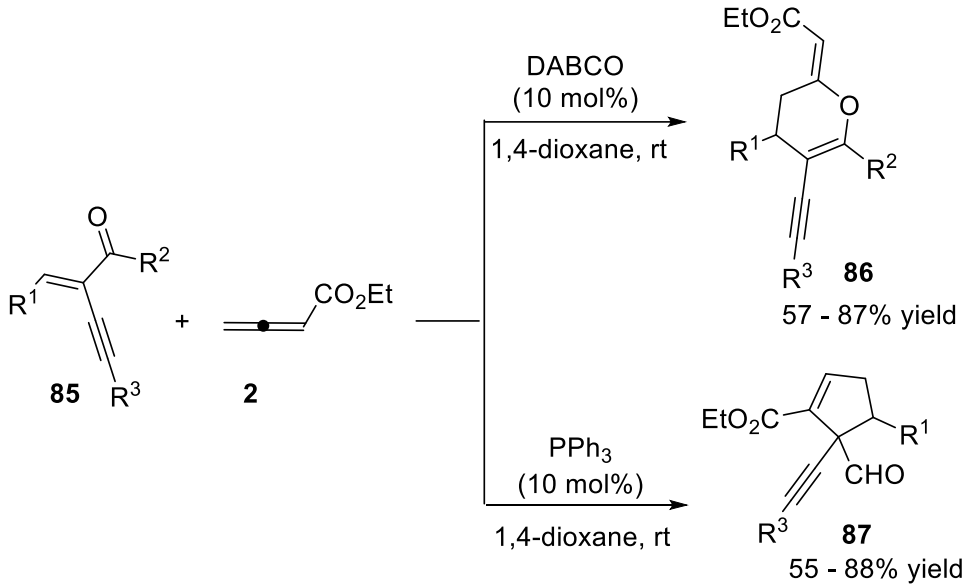
The addition of DABCO or DMAP to allenoate **2** generates zwitterionic intermediate **79** or **82**. The zwitterionic intermediate **79** or **82** combines with **75** to produce intermediate **80** or **83** which then undergoes enolization and cyclization. Consequently, the desired product **78** or **76** is formed with the release of DABCO or DMAP catalysts. Ultimately, at 65 ^{0}C in THF, **76** isomerizes to generate product **77**. The strong electrostatic interaction between the oxygen atom of ester and ammonium in the DABCO-catalyzed domino reaction helps it exclusively adopt the *E* form. On the other hand, in the DMAP-catalyzed domino reaction, the steric barrier between the ester group in **79** and the pyridyl ring may become the dominant component, leading mostly to the *Z* product (**Scheme 1.19**).



Scheme 1.19. A plausible mechanism for the DABCO catalyzed [4+2] cycloaddition of methyleneindolonones

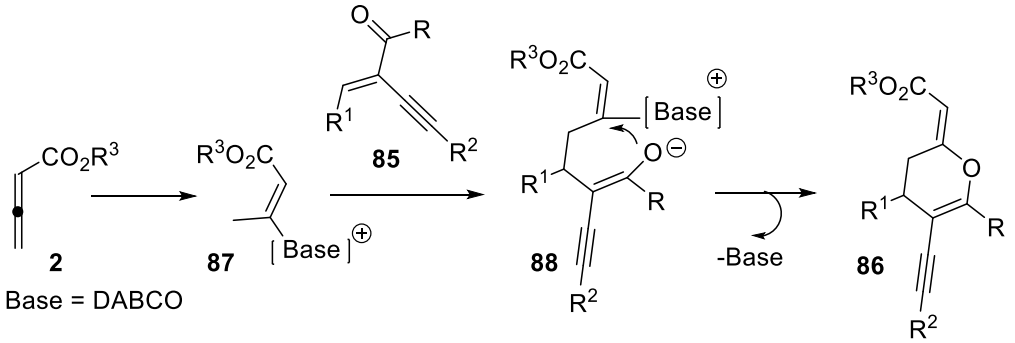
In 2015, Swamy and co-workers reported the divergent reactivity of DABCO and PPh_3-catalyzed cycloaddition reaction of allenoates with enynals for the synthesis of

functionalized dihydropyran derivatives and 1,1-alkyne (aldehyde)-substituted cyclopentenes respectively. When DABCO was used as the catalyst, [4+2] cycloaddition occurred, affording dihydropyran derivatives in good to excellent yields. However, [3+2] cycloaddition adducts were formed in the presence of a PPh_3 catalyst (**Scheme 1.20**).[16]



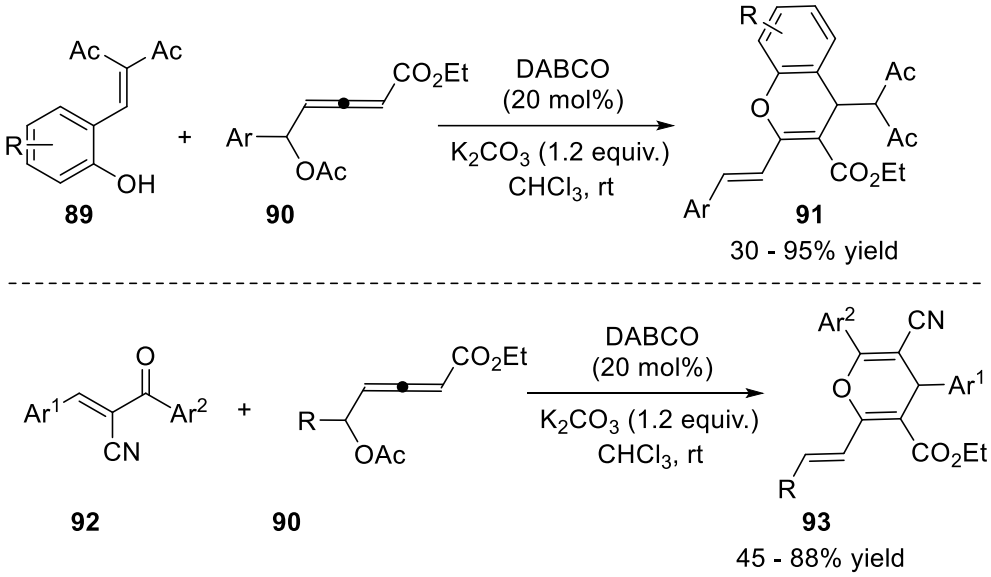
Scheme 1.20. Divergent reactivity of amine and phosphine-catalyzed cycloaddition with enynals

The authors proposed a plausible pathway for the synthesis of functionalized dihydropyrans. As shown in **Scheme 1.21**, the zwitterionic intermediate **87** is generated upon the addition of the Lewis base onto allenoate **2**. In the presence of DABCO, enynal/enynone **85** then interacts with intermediate **87** resulting in the intermediate **88**, which undergoes intramolecular attack of oxygen nucleophile at the *β*-position of the allenoate and concomitant elimination of the DABCO affording the final product **86**.



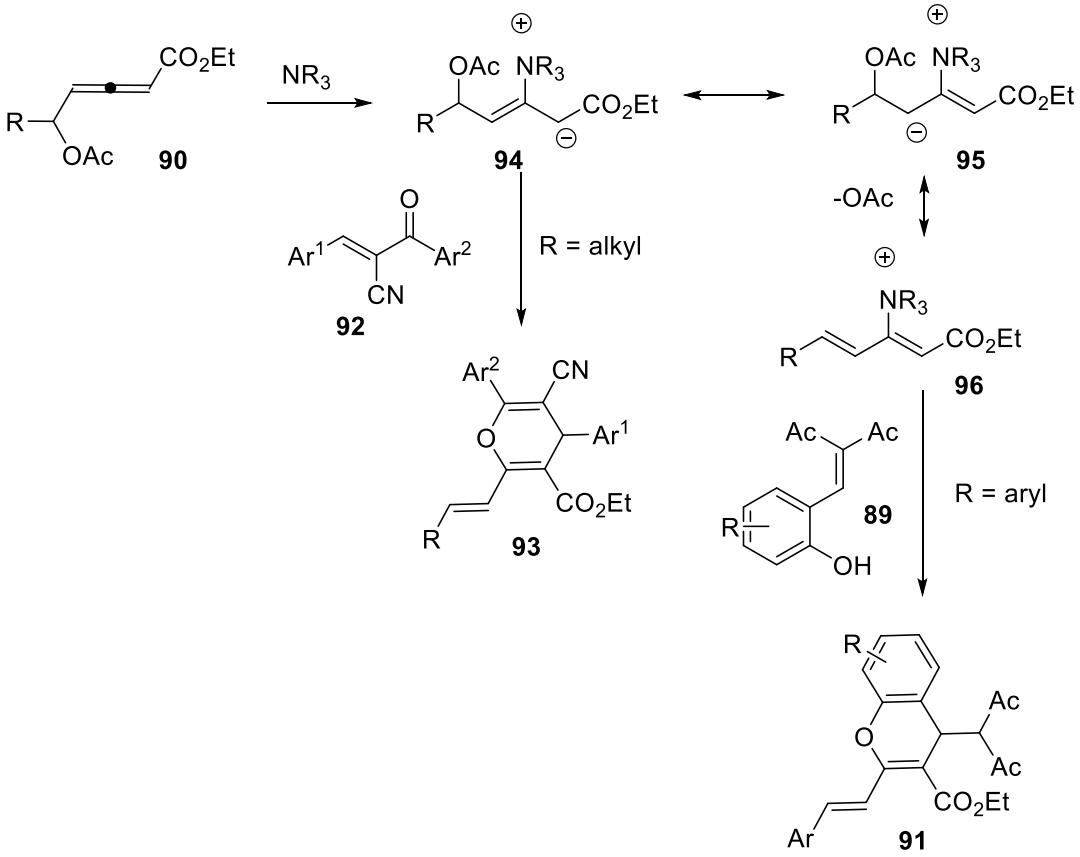
Scheme 1.21. A Plausible mechanism for DABCO-catalyzed [2 + 4] cycloaddition of with enynals

In 2015, Tong and co-workers reported DABCO-catalyzed divergent [4+2] annulations of *δ*-acetoxy allenoates. It was found that the chemical behaviour of **90** under the DABCO catalyst depended on the substrate. Allenoate **90** with an aromatic group at *δ*C and salicylaldehyde derivative **89** reacted preferentially to give 4H-chromenes **91**. Conversely, allenoates **90** with an alkyl group at *δ*C readily underwent [4 + 2] annulations with oxo diene **92** to afford 4H-pyrans **93** (**Scheme 1.22**).[17]



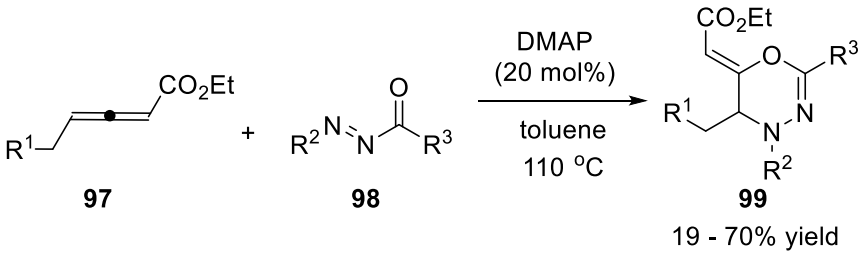
Scheme 1.22. DABCO-catalyzed divergent [4+2] annulations with salicylaldehydes or oxo dienes

The authors provided a plausible mechanistic explanation (**Scheme 1.23**), stating that the steric hindrance could potentially decrease the reactivity of zwitterionic intermediate **95** in the case of *δ*-aryl allenoates under tertiary amine catalysis. Thus, intermediate **95** might undergo 1,2-elimination of the acetoxy group, resulting in intermediate **96**. In the case of *δ*-methyl-substituted allenoates, the formation of intermediate **95** might be unfavorable due to the interaction of allenoates with DABCO, as there is no conjugation effect imposed by the aryl substituent. In this scenario, zwitterionic intermediate **94** would be prominent, providing a distinct [4+2] annulation with a suitable electrophile under tertiary amine catalysis.



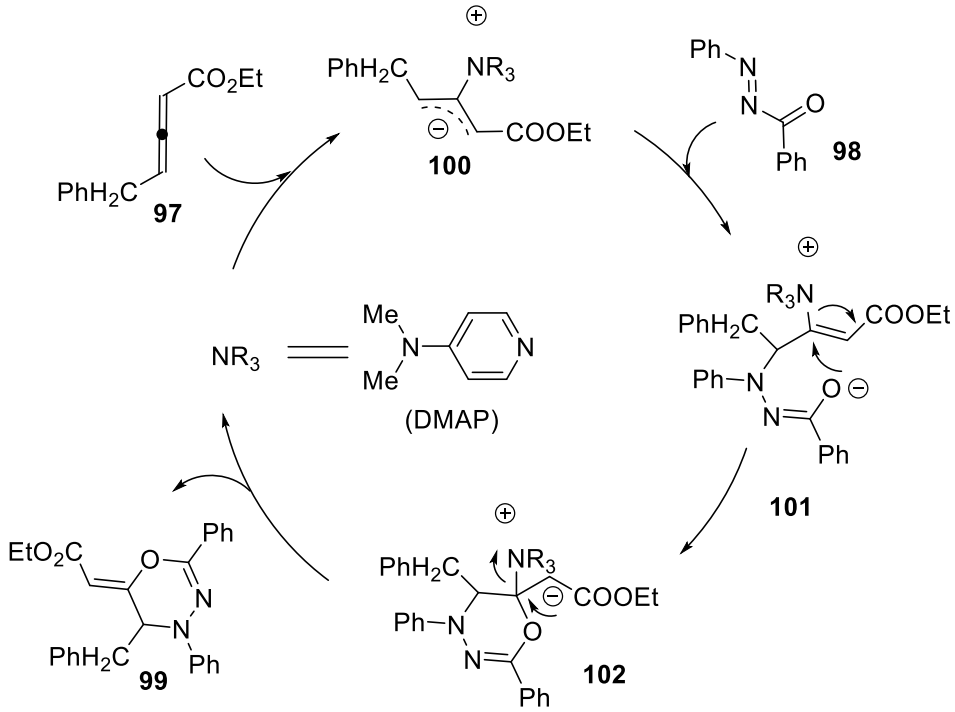
Scheme 1.23. A plausible mechanism for DABCO-catalyzed divergent [4+2] annulations with salicylaldehydes or oxo dienes

In 2015, Meng and Wang reported an efficient DMAP-catalyzed [4+2] cycloaddition of *N*-acyldiazenes and ethyl allenoates with the benzyl group at the *γ*-position. In the process, three heteroatoms were inserted into a six-membered ring to produce 1,3,4-oxadiazine derivatives. According to the study, the reactivity was mostly determined by the nucleophilicity of the catalysts, while other amines (such as DABCO, Et_3N, and DBU) and phosphines (like PPh_3, PBu_3) shut down the cycloaddition reaction (**Scheme 1.24**).[18]



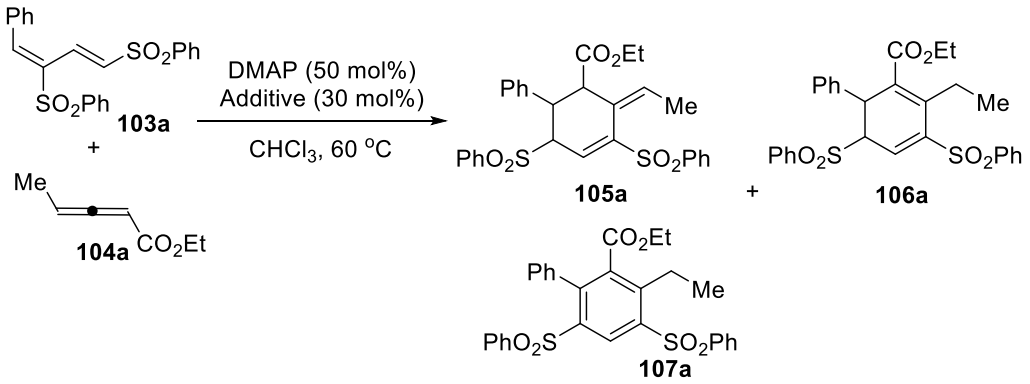
Scheme 1.24. DMAP-catalyzed [2+4] cycloaddition with *N*-acyldiazenes

A plausible mechanism was proposed for this [4+2] cyclization, as shown in **Scheme 1.25**. The activation of allenic ester **97** by DMAP generated a zwitterionic intermediate **100**. Subsequent *γ*-nucleophilic attack of the electrophile **98** resulted in the formation of intermediate **101**, which then undergoes intramolecular Michael addition to produce intermediate **102**. Finally, the catalyst DMAP was eliminated, and the C=C double bond was regenerated, to furnish the product **99**.

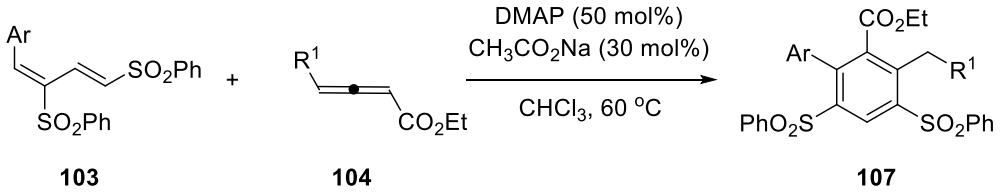


Scheme 1.25. A plausible mechanism for DMAP-catalyzed [4+2] cycloaddition with *N*-acyldiazenes

In 2016, Huang and co-workers reported a strategy for the synthesis of polysubstituted benzenes through DMAP-catalyzed [4+2] benzannulation from readily prepared 1,3-bis(sulfonyl)butadienes and *γ*-substituted allenoates. The experimental results indicated that when DMAP was used as the catalyst, multisubstituted cyclohexene **105a** and cyclohexadiene derivative **106a** were generated in moderate yields. Some additives, including organic bases (e.g., NEt_3, DIPEA), inorganic bases (e.g., CH_3CO_2Na, NaOH, Cs_2CO_3), and Bronsted acid (PhCOOH), could tune the selectivity of the reaction to give polysubstituted arene **107a** (**Scheme 1.26**).[19]

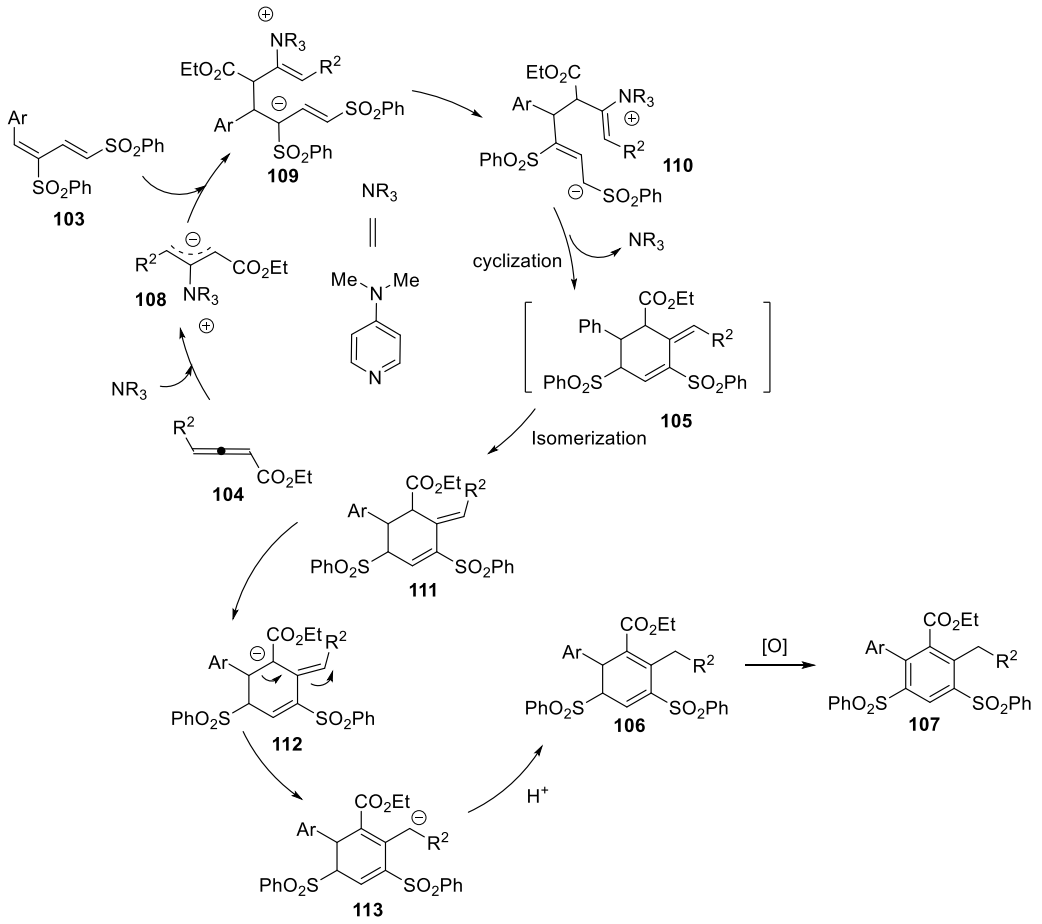


Entry	Additive (mol%)	Time (h)	Yield (%)		
			105a	**106a**	**107a**
1	no additive	24	52	18	-
2	Cs_2CO_3 (50)	54	-	-	48
3	NaOH (50)	48	-	-	38
4	$PhCO_2Na$ (50)	48	-	-	59
5	Et_3N (50)	34	-	-	59
6	DIPEA (50)	24	-	-	60
7	CH_3CO_2Na (50)	24	-	-	61
8	CH_3CO_2Na (30)	24	-	-	62
9	$PhCO_2H$ (30)	23	-	-	42



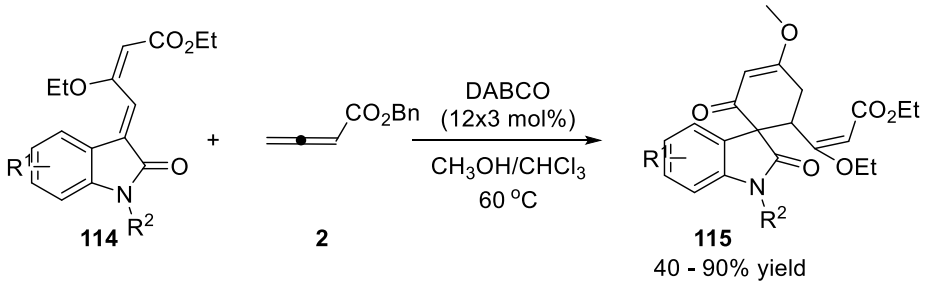
Scheme 1.26. DMAP-catalyzed [4+2] benzannulation with 1,3-bis(sulfonyl)butadienes

Based on the literature precedent, a plausible mechanism is proposed in **Scheme 1.27**. The first step involves the activation of allenoate by DMAP to form the zwitterionic intermediate **108**. The zwitterion intermediate adds to the dienic sulfone **103** to afford intermediate **109**. The intermediate **110** was then generated from **109** by the proton transfer process, and subsequent intramolecular cyclization followed by elimination of the DMAP catalyst produced intermediate **105**. Product **111** was obtained simultaneously from intermediate **105** by carbon-carbon double bond isomerization. In the basic conditions, the active proton of **111** was removed to generate intermediate **112**. Later on, the proton transfer and subsequent protonation resulted in the formation of intermediate **106**. Finally, the product **106** underwent an oxidative aromatization process to afford the corresponding product **107**.



Scheme 1.27. A Plausible mechanism for DMAP-catalyzed [4+2] benzannulation with 1,3-bis(sulfonyl)butadienes

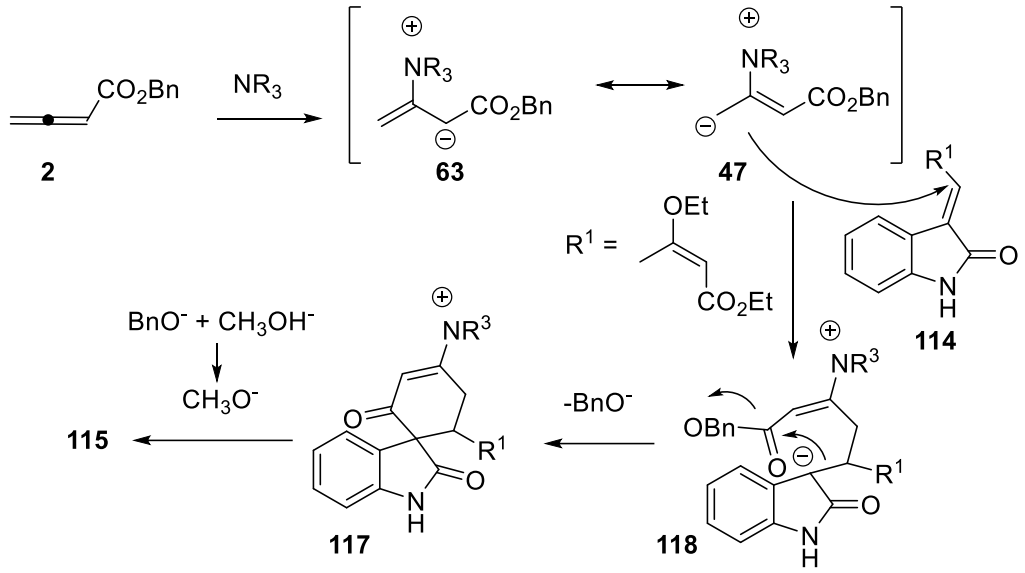
A novel DABCO-catalyzed [4+2] cycloaddition between methyleneoxindoles and allenoate which enables the direct synthesis of spirooxindoles was reported by Meng and co-workers in 2016. This is the first example of a non-substituted allenoate to act as a four-carbon synthon in a tertiary amine-catalyzed reaction (**Scheme 1.28**).[20]



Scheme 1.28. DABCO-catalyzed [4+2] cycloadditions with methyleneoxindoles

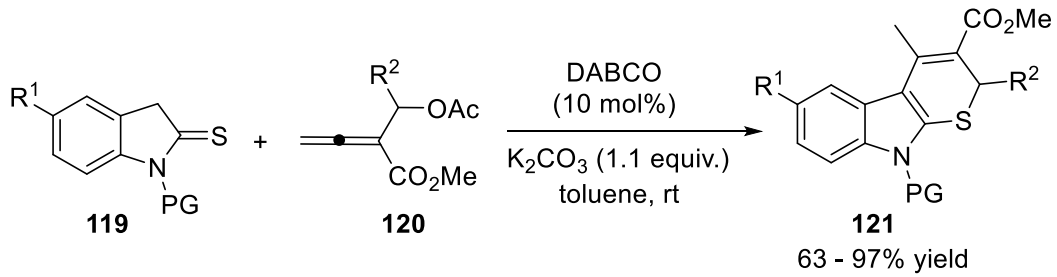
A plausible mechanism for this domino process has been proposed by the authors. First, the nucleophilic attack of DABCO at the *β* carbon of the allenoate generates intermediates

63 and **47**. Subsequently, Michael addition/intramolecular cyclization gave intermediate **117**. Finally, the nucleophilic reagent (CH_3O^-) attack on **117**, followed by the DABCO elimination resulted in the desired product **115** (**Scheme 1.29**).



Scheme 1.29. A plausible mechanism for DABCO-catalyzed [4+2] cycloadditions with methyleneoxindoles

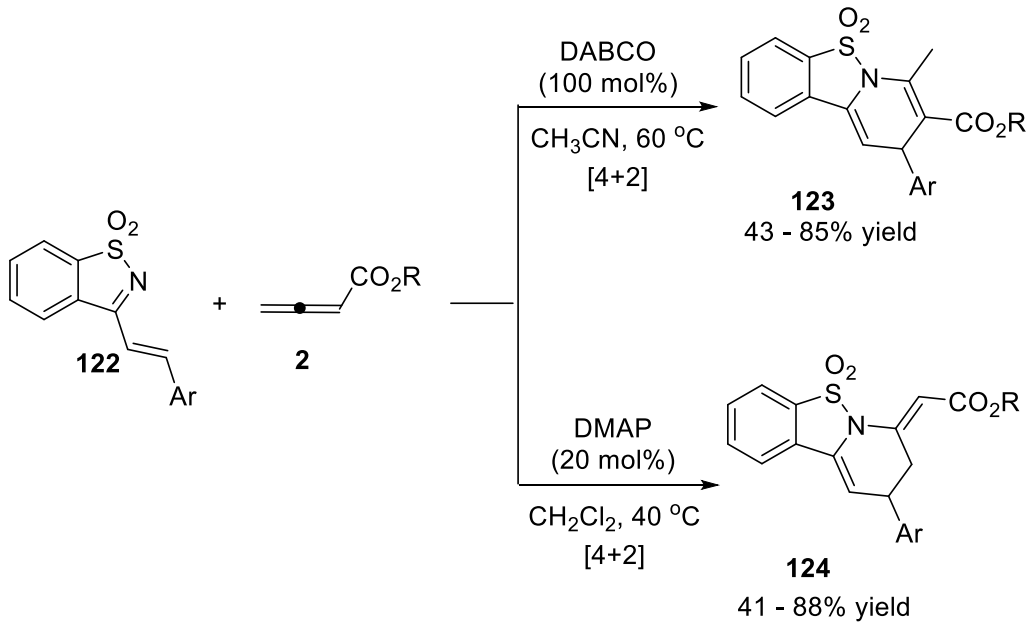
In 2017, the authors successfully performed formal [3+3] annulations of *β*-acetoxy allenoates under DBU catalysis, furnishing functionalized thiopyrano[2,3-*b*]indoles **121** in good to excellent yields. According to the mechanistic investigation, the indoline-2-thiones function as a 1S,3C-bisnucleophile, providing an opportunity to create a stereogenic center at the C2-position of dihydrothiopyrano-indole (**Scheme 1.30**).[21]



Scheme 1.30. DABCO-catalyzed annulations with indoline-2-thiones

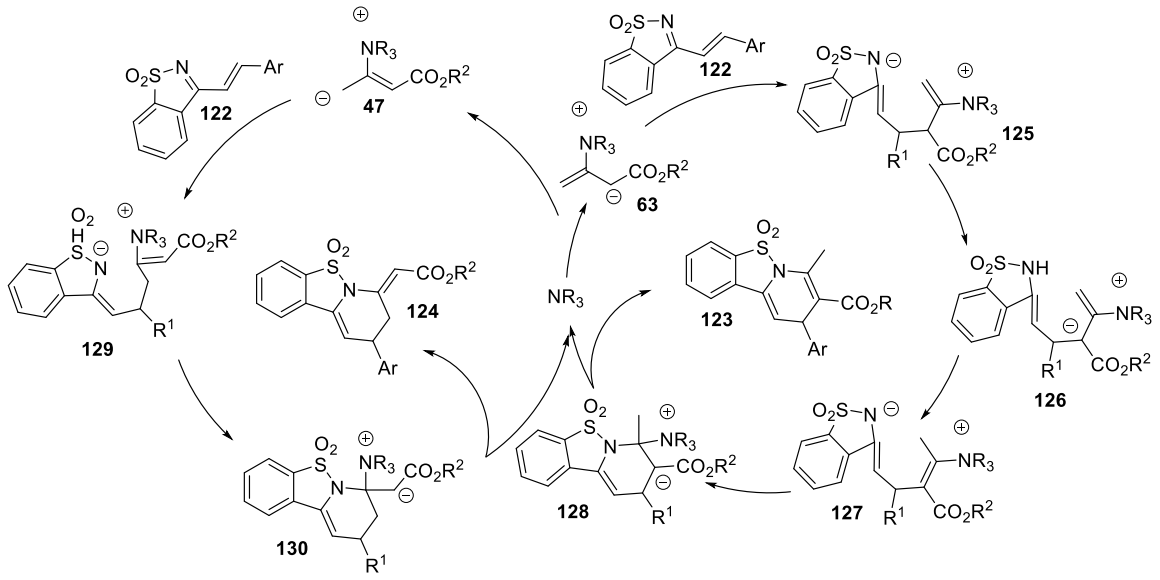
Later in 2017, a regiodivergent DMAP and DABCO promoted [4+2] cyclization strategy of *α,β*-unsaturated ketimines with 2,3-butadienoates, was described by Huang and co-workers to access a series of hydropyridine derivatives in moderate to good yields. The study showed that when DABCO was used as a catalyst, the allenoate was added from the

α position, resulting in partially unsaturated 6-5-6 sulfone-containing ring structures. Meanwhile, a moderate to high yield of the γ addition [4+2] product with an exo-ring double bond was produced by a DMAP-catalyzed reaction (**Scheme 1.31**).[22]



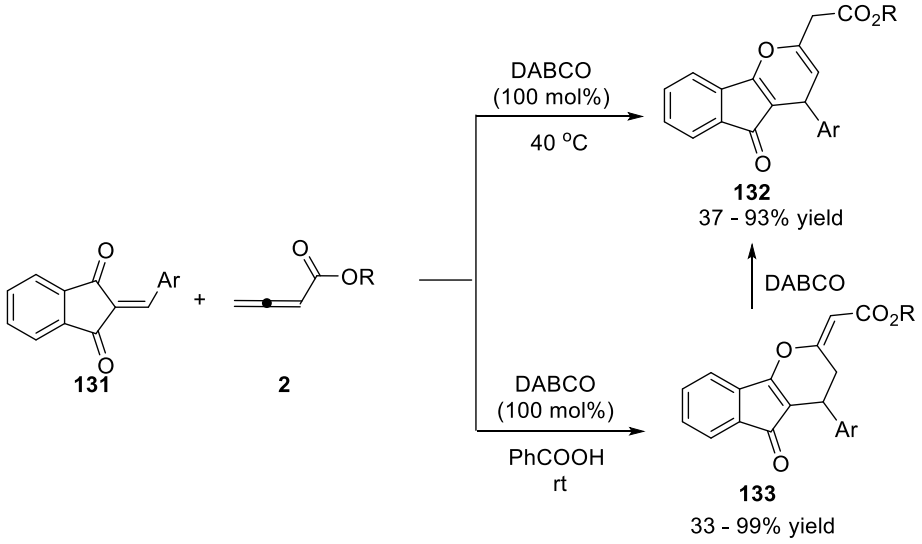
Scheme 1.31. Lewis base mediated [4 + 2] cyclization with α, β-unsaturated ketimines

Based on experiment results and previous reports, a rational reaction pathway for this [4+2] cyclization is illustrated in **Scheme 1.32**. Initially, the nucleophilic attack of Lewis base catalyst (DMAP and DABCO) on the allenic ester generated zwitterionic intermediate **47** and **63**, in which the γ-position or α-position carbanion undergoes conjugate nucleophilic addition to the α,β-unsaturated cyclic ketimines generating intermediate **129** and **125**. The subsequent proton shifts and Michael addition resulted in cycloaddition products **130** and **128**. Finally, the release of DMAP and DABCO afforded the product **124** and **123**.



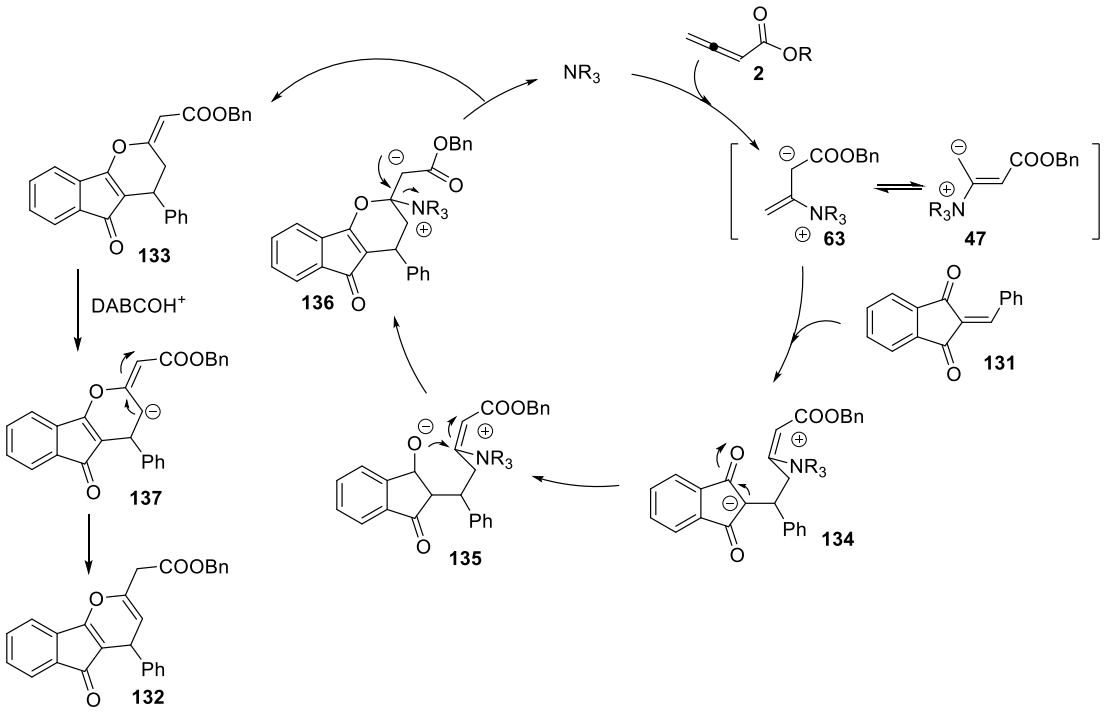
Scheme 1.32. Mechanism for cyclization of allenoate and *α,β*-unsaturated ketimines

In 2018, Zhen and co-workers reported a DABCO-promoted [4+2] cycloaddition reaction of allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones. This reaction selectively produced annulated 4H-pyran and annulated 3,4-dihydro-2H-pyran in moderate to good yields. Further study revealed that the Lewis base catalyst (DABCO) was involved in both Lewis base promoted [4+2] cycloaddition and the consequent Bronsted base mediated C=C isomerization. With the presence of a Bronsted acid ($PhCO_2H$), the role of the Bronsted base could be selectively quenched, leading to the major product being the desired annulated 3,4-dihydro-2H-pyran **133** (**Scheme 1.33**).[23]



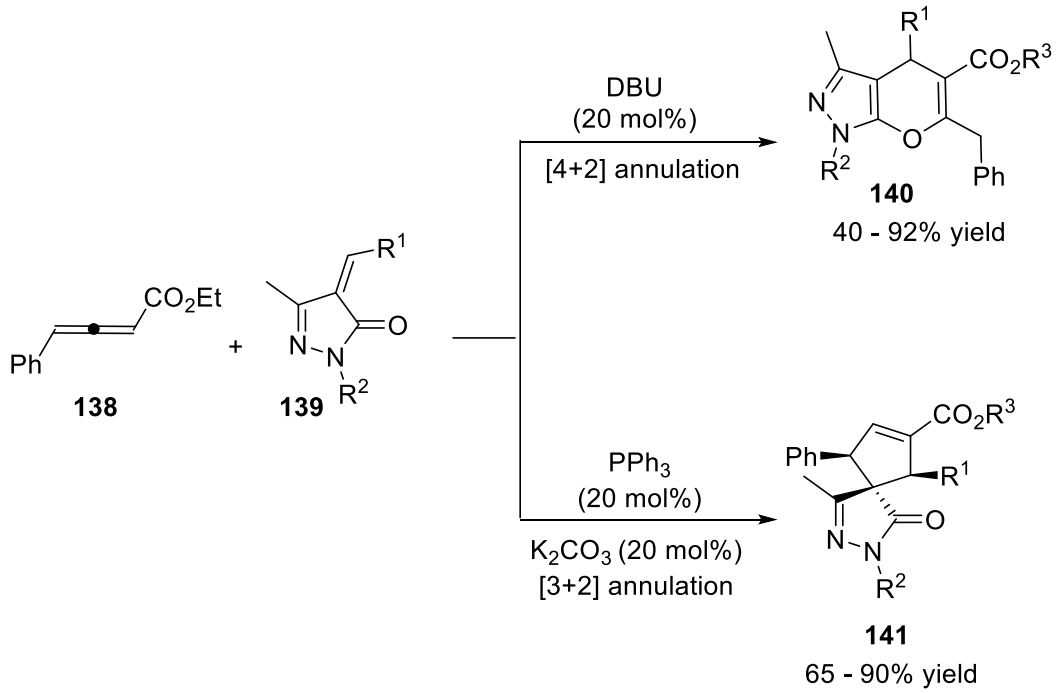
Scheme 1.33. DABCO-promoted [4+2] cycloaddition with 2-arylidene-1*H*-indene-1,3(2*H*)-diones

A plausible mechanism is proposed in **Scheme 1.34**. The reaction seems to proceed *via* the initial nucleophilic addition of DABCO to the allene ester resulting in the formation of a 1,3-dipolar zwitterion intermediate **63**, which then isomerizes to form intermediate **47**. The zwitterionic **47** reacts with **131** to give intermediate **134**, which undergoes enolization to give intermediate **135**. The subsequent cyclization, followed by the elimination of the catalyst, yields **133**. Finally, DABCO as a base captures the proton to generate intermediate **137**, which isomerizes to form product **132**.



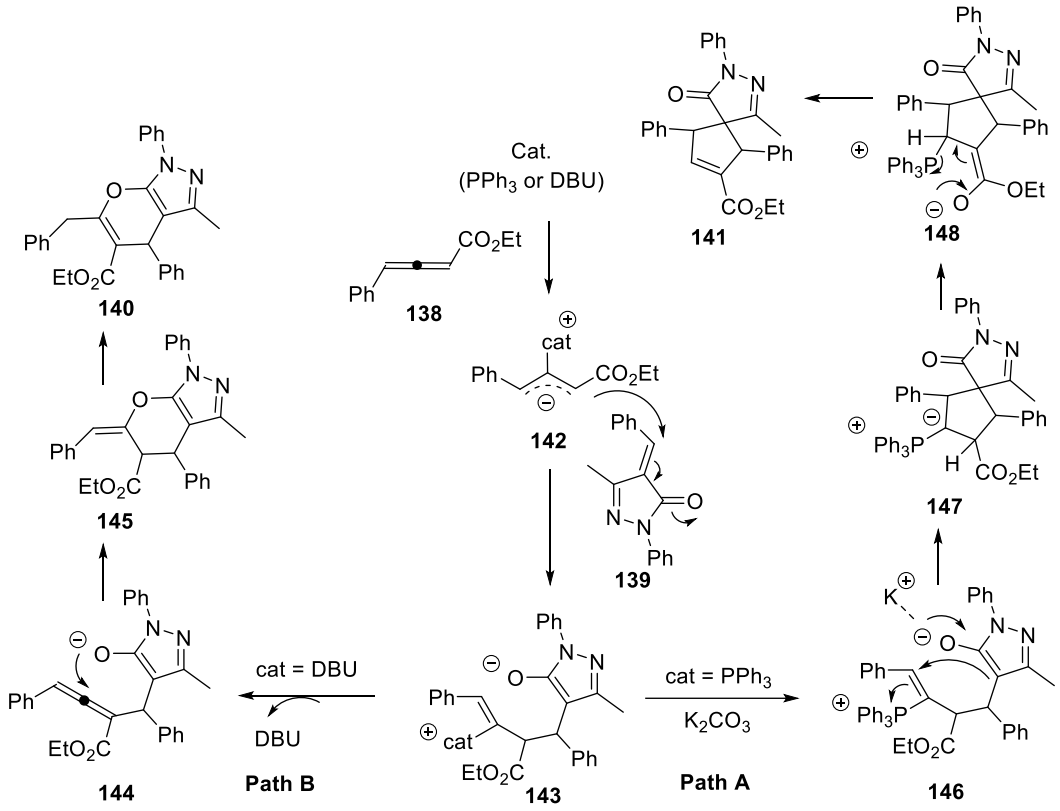
Scheme 1.34. Mechanism of DABCO-promoted [4+2] cycloaddition with 2- arylidene-1*H*-indene-1,3(2*H*)-diones

In 2019 Zhong and co-workers demonstrated an effective Lewis base catalyst-controlled *α*-regioselective divergent annulation reaction of *γ*-substituted allenoates with unsaturated pyrazolones for the preparation of various spirocyclopentene-pyrazolones and pyrano[2,3-c]pyrazoles. The combination of PPh_3 and K_2CO_3 favoured the [3+2] annulation to achieve the spirocyclopentene-pyrazolones in moderate to good yields with excellent diastereoselectivities, whereas [4+2] annulations that generate pyrano[2,3-c]pyrazoles were accomplished by using DBU as catalyst (**Scheme 1.35**).[24]



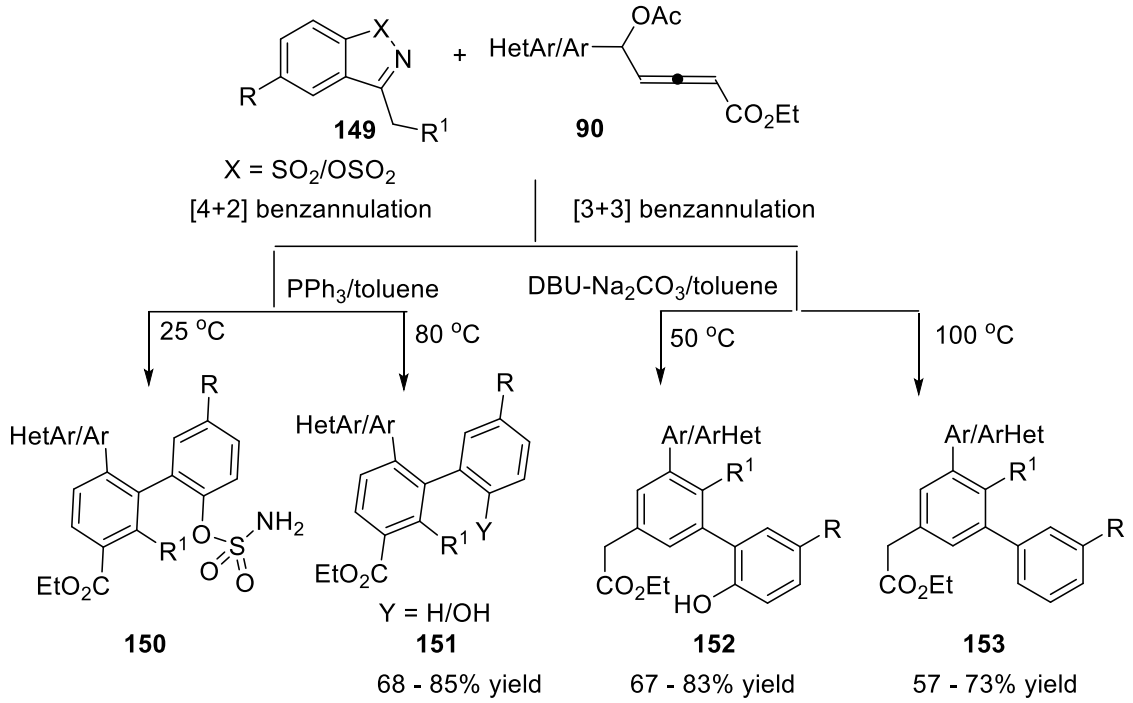
Scheme 1.35. Lewis base mediated annulation of allenoates with unsaturated pyrazolones

A plausible mechanism for the Lewis base-controlled divergent annulation reactions has been outlined in **Scheme 1.36**. Initially, the addition of Lewis base catalysts PPh_3 or DBU to allenoate generates the zwitterionic intermediate **142**, which subsequently undergoes 1,4- addition by α-attacking the unsaturated pyrazolones **139** to give the intermediate **143**. For path A which utilizes the combination of PPh_3 and K_2CO_3 as the base, intermediate **143** was converted to intermediate **147** through intramolecular Michael addition. Ultimately, the [3+2] annulation product **141** was obtained through a proton transfer and removal of PPh_3 moiety. For path B, intermediate **143** eliminates DBU to give allenoate, which subsequently undergoes O- Michael addition to generate intermediate **145**. Finally, the [4+2] annulation product **140** was afforded by 1,3-proton transfer.



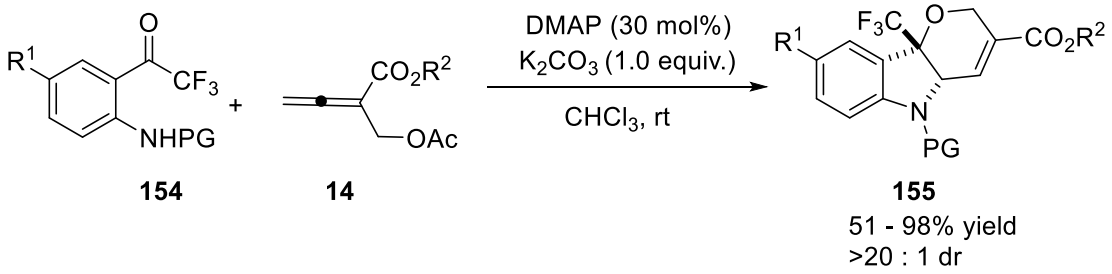
Scheme 1.36. A plausible mechanism for Lewis base mediated annulation with unsaturated pyrazolones

In 2020, Swamy and co-workers established Lewis base-mediated [3+3] or [4+2] benzannulation reactions of *δ*-acetoxy allenoates with cyclic *N*-sulfonyl imines. By simply switching the Lewis bases, the reaction afforded teraryl motifs **150**/**151** or functionalized 2-pyridinyl acetates (*α*-pyridyl acetates) **152**/**153**. The authors observed that different compounds might be synthesised in response to temperature and catalyst variations. Under PPh_3 catalysis, the [4+2] benzannulation generated functionalized teraryls by sequential Mannich coupling/C-N bond cleavage with retention or cleavage of the sulfamoyloxy group depending on the reaction temperature. On the other hand, under DBU as catalyst and Na_2CO_3 as the additive, the [3+3] annulation involving sulfonyl elimination *via* O–S or C–S bond cleavage occurred, affording 2-pyridinyl acetates in good yields (**Scheme 1.37**).[25]



Scheme 1.37. Lewis base-switched [3+3] and [4+2] benzannulation reactions with cyclic *N*-sulfonyl imines

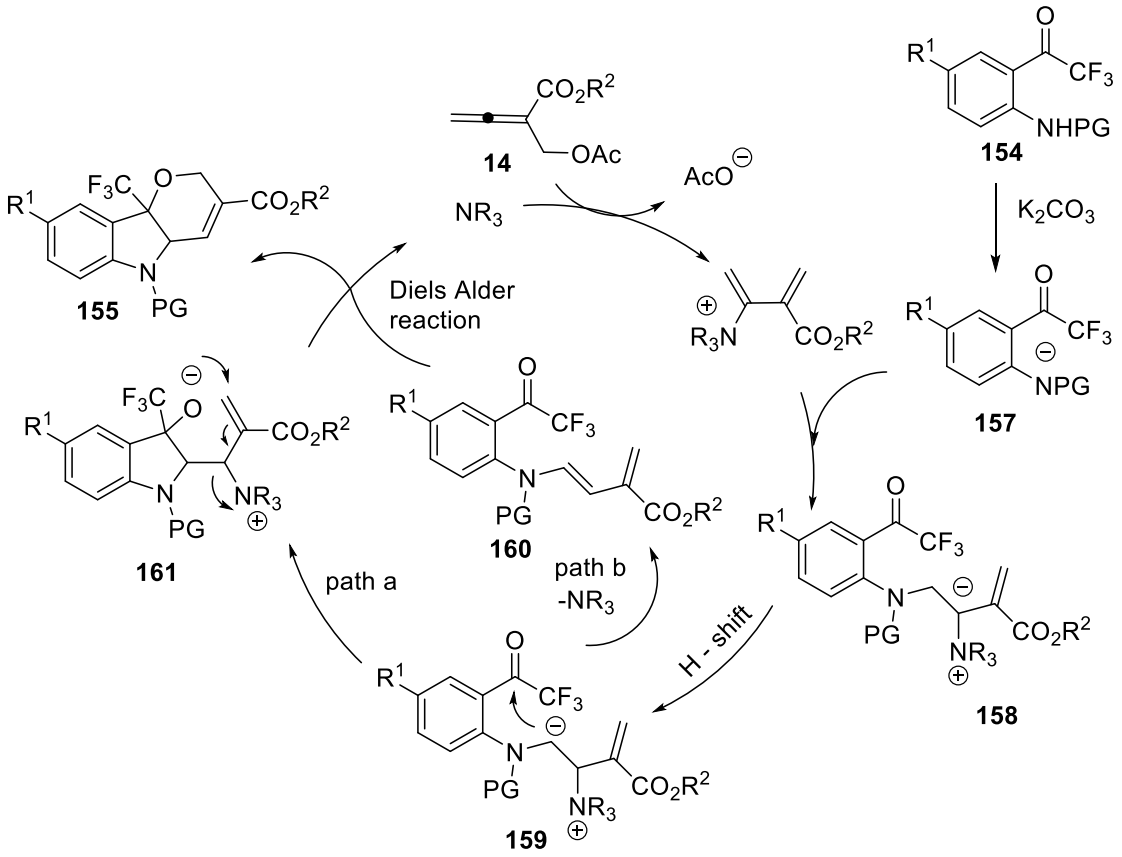
In 2020, Huang and co-workers reported the DMAP-catalyzed [4+1]/[3+3] domino sequential cycloaddition reaction between *o*-aminotrifluoroacetophenone derivatives and *β*-acetoxy allenoates, which afforded a series of CF_3-containing tetrahydropyrano[3,2-*b*]indoles as a single diastereomer in high to excellent yields. The reaction can form one C−N bond, one C−C bond, and one C−O bond sequentially in a single step (**Scheme 1.38**).[26]



Scheme 1.38. DMAP-catalyzed cycloaddition between *o*-aminotrifluoroacetophenones and *β*-acetoxy allenoates

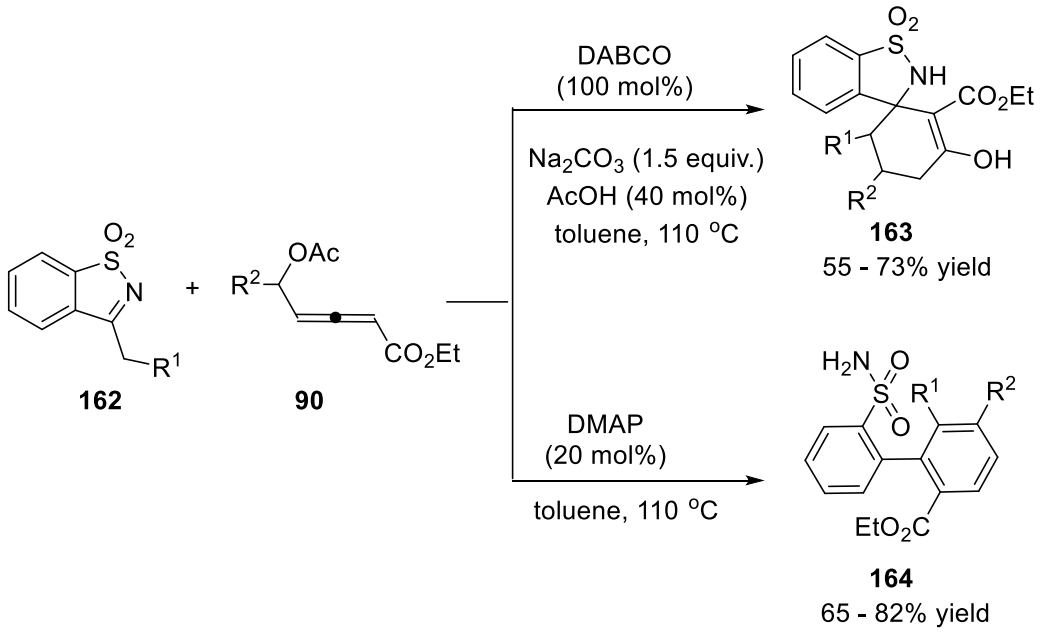
The authors proposed a plausible reaction pathway, as showed in **Scheme 1.39**. The intermediate **156** was formed by 1,2-elimination of acetate after the nucleophilic addition of DMAP to allenoate. The following *γ*-addition of intermediate **157** to intermediate **156**

generated intermediate **158**. Afterwards, tandem proton shift/intramolecular 1,2-addition/intramolecular S_N2-substitution resulted product **155** with the regeneration of catalyst. The authors hypothesised that it may also go through tandem 1,2-elimination by the DMAP/intramolecular Diels-Alder reaction, directly producing product **155**.



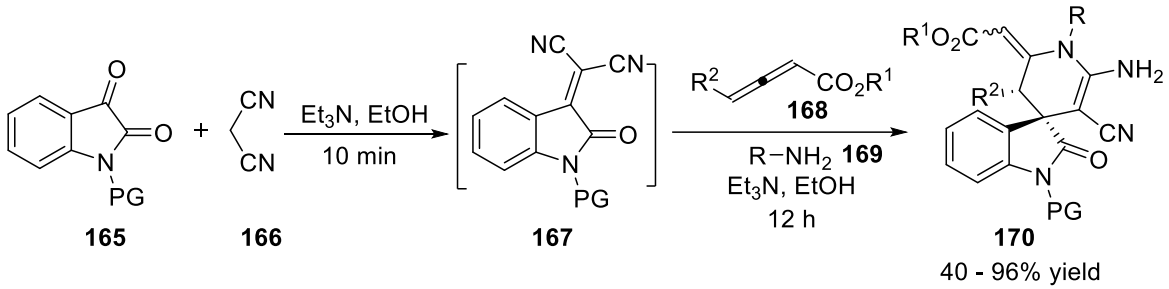
Scheme 1.39. A Plausible reaction pathway of DMAP-catalyzed annulation with *o*-aminotrifluoroacetophenones

In 2021, Swamy and co-workers reported a catalyst-dependent chemo-, regio-, and stereo-selective carboannulation involving *δ*-acetoxy allenoate. The experiment showed that while using DABCO as the catalyst, Na_2CO_3 as the Bronsted base and AcOH as the Bronsted acid, the reaction leads to adduct **163** *via* chemo- and regiospecific [4+2]-carboannulation and a new hydroxyl group is introduced. In contrast, DMAP-catalyzed benzannulation using the same reactants affords unsymmetrical *m*-teraryls **164** *via* Mannich coupling, sequential proton transfers, and C–N bond cleavage. Here, *δ*-acetoxy allenoate serves as a 4C-synthon and the carboannulation is completely base-dependent and mutually exclusive (**Scheme 1.40**).[27]



Scheme 1.40. Tertiary amine mediated [4+2] annulations of *δ*-acetoxy allenoate with cyclic *N*-sulfonyl imines

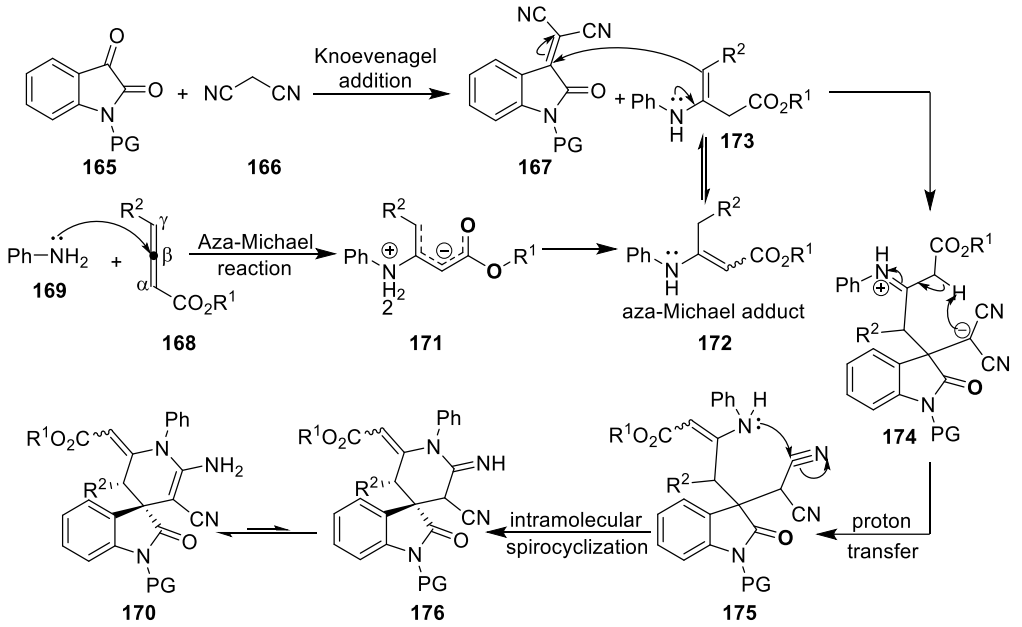
Later in 2022, our group devised a multicomponent synthesis of spiro-dihydropyridine oxindoles from isatin, malononitrile, allenoate, and amines. The Et_3N-assisted reaction proceeds through cascade spiro-cyclization of *in-situ* generated Knoevenagel adduct/aza-Michael adduct (**Scheme 1.41**).[28]



Scheme 1.41. Multicomponent synthesis of spiro-dihydropyridine oxindoles

The plausible mechanistic pathway for spiro-dihydropyridine formation is depicted in **Scheme 1.42**. Initially, the amine **169** undergoes nucleophilic aza-Michael addition at the *β*-position of the allenoate **168** and forms stabilized zwitterionic intermediate **171**. Subsequent protonation at the *γ*-carbon affords *α,β*-unsaturated adduct **172**, which undergoes isomerization to **173**. Next, the nucleophilic attack of aza-Michael adduct **172** at C-3 of an *in-situ* generated Knoevenagel adduct **167** forms an intermediate **174**, which

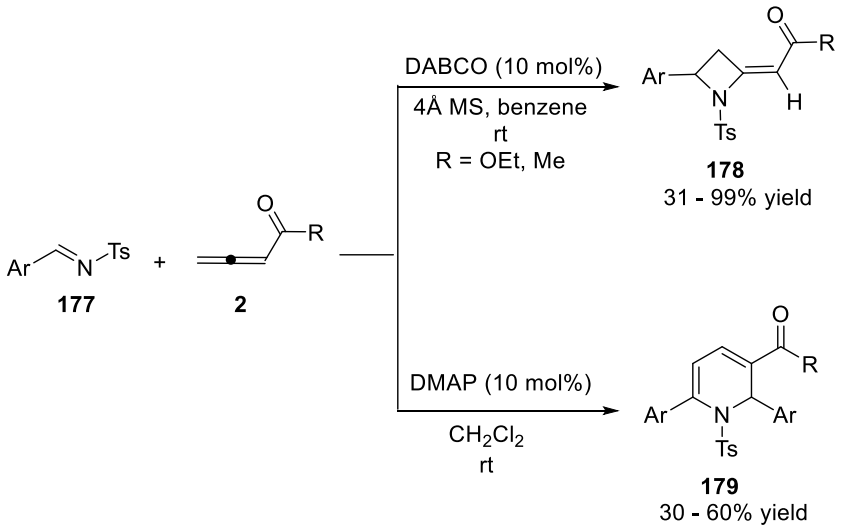
upon proton transfer/ intramolecular spiro-cyclization/ tautomerization delivers the final product **170**.



Scheme 1.42. Proposed mechanism for the synthesis of spiro-dihydropyridine oxindoles

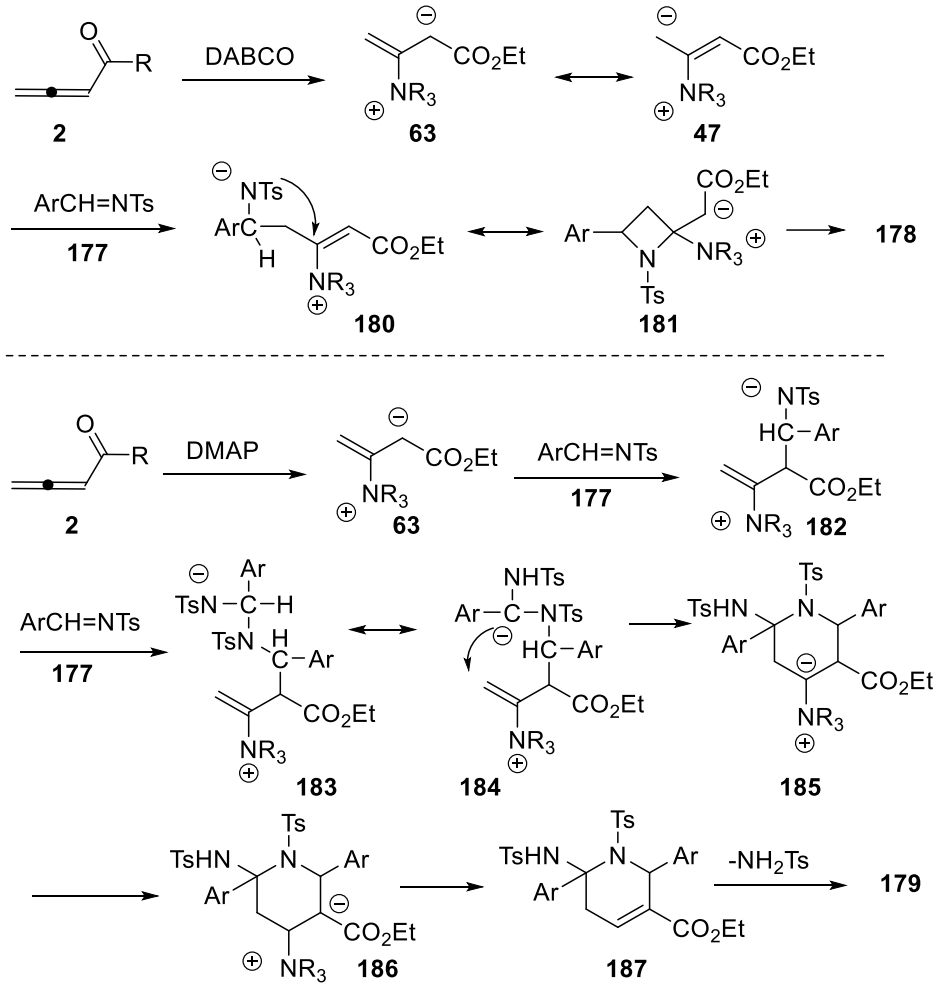
1.3.2. Tertiary amine-catalyzed synthesis of four-membered heterocycles

In 2003, Shi and workers described a tertiary amine-catalyzed cycloaddition of *N*-tosylated imines with ethyl 2,3-butadienoate or penta-3,4-dien-2-one. The authors found that [2+2] cycloaddition adducts were formed in the presence of DABCO. The reaction proceeded smoothly by "abnormal" [3+2+1] cycloaddition when DMAP was employed as a Lewis base catalyst, producing the required products in yields ranging from 30% to 60% (**Scheme 1.43**).[29]



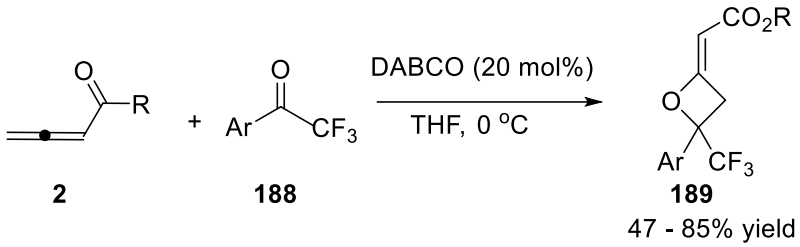
Scheme 1.43. Tertiary amine-catalyzed cycloaddition reaction with *N*-tosylated imines

The authors proposed a plausible mechanism, as shown in **Scheme 1.44**. First, acting as a nucleophilic trigger the Lewis bases DABCO and DMAP attacked the allenoate to generate zwitterionic intermediate **47**, which existed as a resonance-stabilized intermediate **63**. Using DABCO as a Lewis base catalyst, allylic carbanion **47** attacks the *N*-tosylated imine to form intermediate **180**, which then undergoes intramolecular cyclization to generate intermediate **181**. Finally, the removal of DABCO from **181** facilitated the formation of product **178**. In contrast, in the case of DMAP catalysis, the enolate **63** adds to the *N*-tosylated imine to afford the intermediate **182**, which then adds to another molecule of *N*-tosylated imine to give the intermediate **183**. Subsequent proton shift/ intramolecular Michael addition gave intermediate **185**. Finally, a proton shift followed by NHTs elimination afforded product **179**, with the elimination of DMAP.



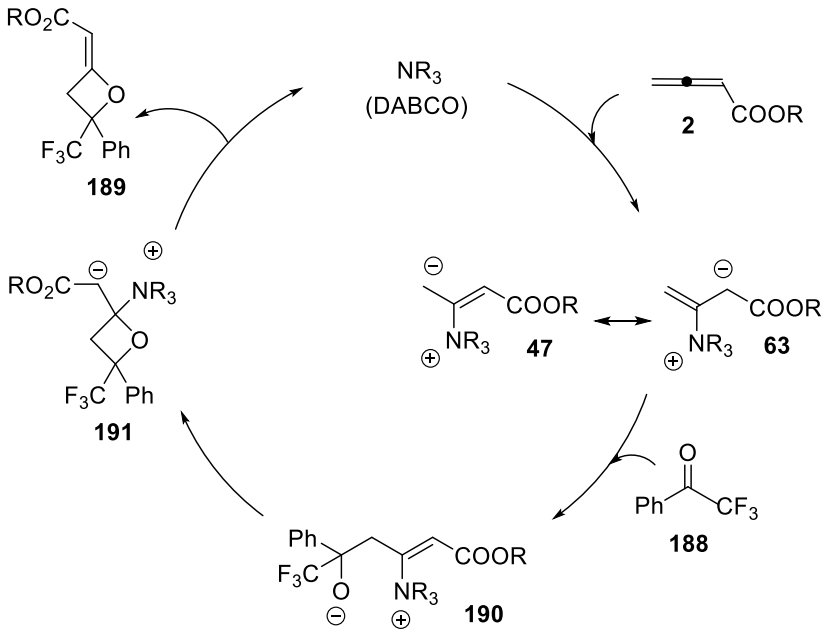
Scheme 1.44. A plausible mechanism for tertiary amine-catalyzed cycloaddition with *N*-tosylated imines

In 2011, the DABCO-catalyzed [2+2] cycloaddition of allenoates and trifluoromethylketones, was reported by Ye and co-workers. The reaction afforded the corresponding 2-alkyleneoxetanes in good yields with good diastereoselectivities (**Scheme 1.45**).[30]



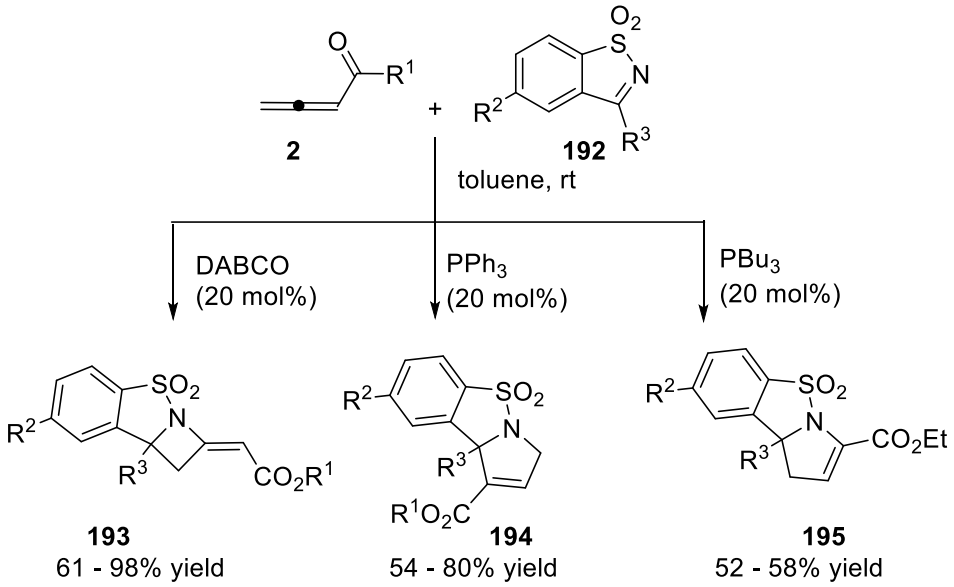
Scheme 1.45. DABCO-catalyzed [2+2] cycloaddition with trifluoromethylketones

The plausible mechanism for this [2+2] cycloaddition is depicted in **Scheme 1.46**. The nucleophilic addition of DABCO to β carbon of allenoate **2** produces the enolate intermediate **63**, which is in resonance with the intermediate **47** (allylic carbanion). The γ-addition of **47** to trifluoromethyl ketone **188** gives the α,β-unsaturated ester **190**. This α,β-unsaturated ester then undergoes an intramolecular Michael addition resulting in the ring-closed zwitterion **191**. The elimination of catalyst from **191** affords the product **189** and regenerates DABCO.



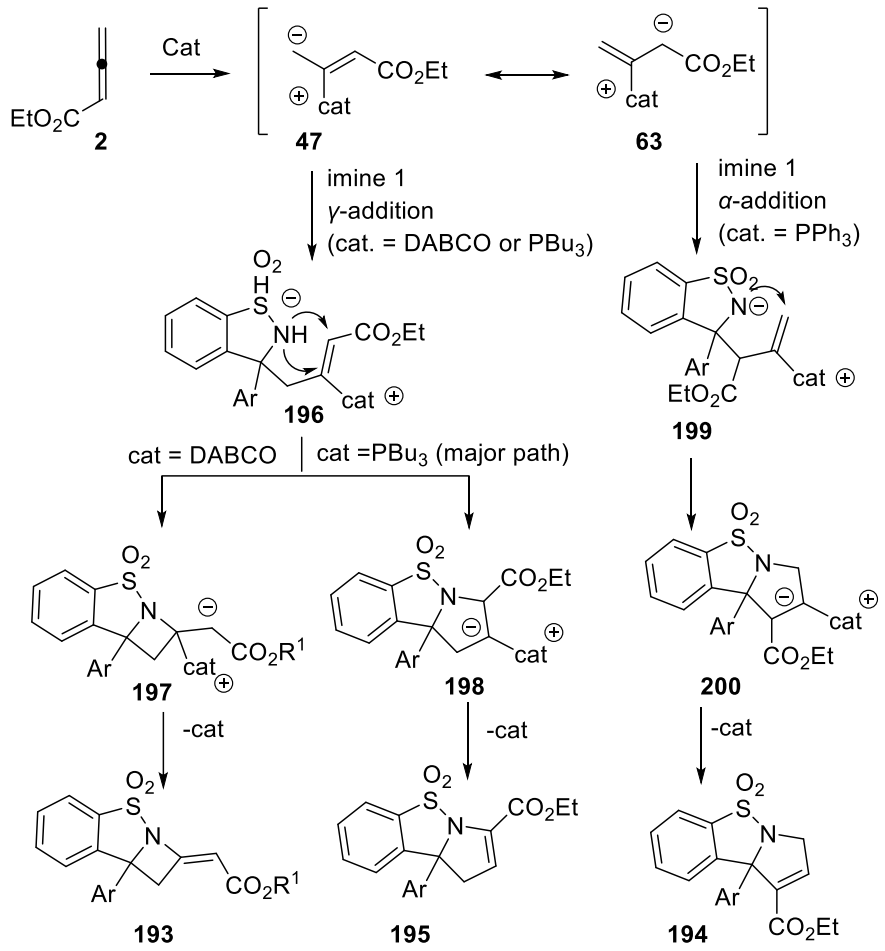
Scheme 1.46. A plausible mechanism for DABCO-catalyzed [2+2] cycloaddition with trifluoromethylketones

In 2012, Ye and co-workers developed a Lewis base catalyzed cycloaddition of cyclic sulphonamides and allenoates. Interestingly, catalyst-controlled [2+2] or α-[3+2] cycloaddition of cyclic sulphonamides with allenoates, gave the corresponding sultam-fused azetidines and dihydropyrroles in good yields with high regioselectivities. The PBu_3 catalyzed reaction gave γ-[3+2] cycloadduct **195** predominately with cycloadducts **193** and **194** (**Scheme 1.47**).[31]



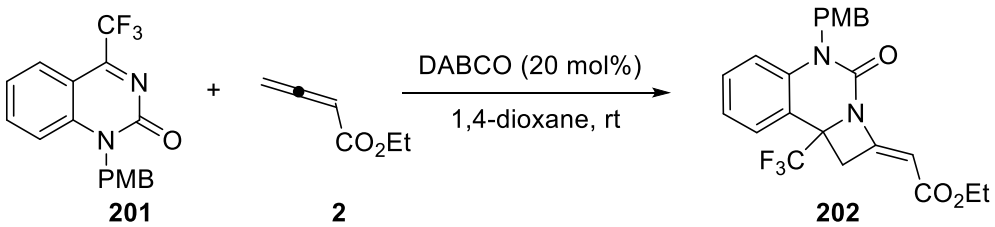
Scheme 1.47. Catalysts-controlled cycloaddition of cyclic sulphonamides with allenoates

The author proposed a reasonable mechanism for the catalyst–controlled cycloadditions as depicted in **Scheme 1.48**. The addition of a Lewis base to allenoate generates the zwitterionic intermediate **47**/**63**, which then reacts with imines *via* γ-or α-addition to form intermediate **196** or **199**. The relatively electron-poor nucleophile PPh_3 will stabilizes the carbonanion **63**, leading to the thermodynamically favoured α-addition, whereas the relative electron-rich nucleophile DABCO or PBu_3 promotes the kinetically favoured γ-addition, which is less sterically hindered. The ring-closure of the intermediate **196**/**199** *via* the addition of the nitrogen anion affords the four or five-cyclic adduct **197**/**198**/**200**. Finally, the elimination of the catalyst furnishes the final product **193**, **194** or **195** and regenerates the catalyst.



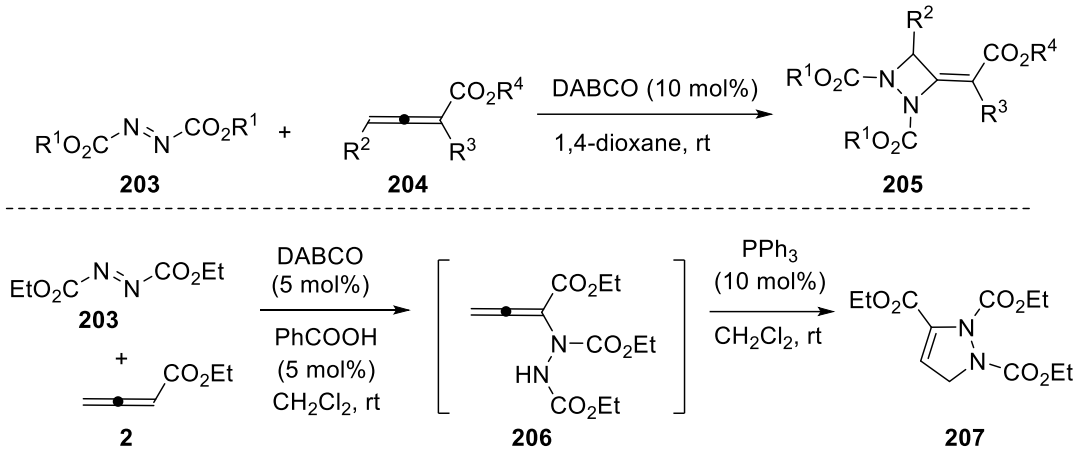
Scheme 1.48. Mechanism for catalysts-controlled cycloaddition with cyclic sulphonamides

In 2014, Yang et al. investigated various organocatalytic reactions between allenic esters and cyclic ketimines. The authors of the work reported a [2+2] cycloaddition of ethyl allenoate with activated cyclic ketimines using DABCO as a catalyst (**Scheme 1.49**). The reaction yielded several azetidine derivatives in good to high yields. It is important to note that the ketimine must be highly activated, and the presence of a trifluoromethyl moiety at the imine position is essential for the reaction to proceed.[32]



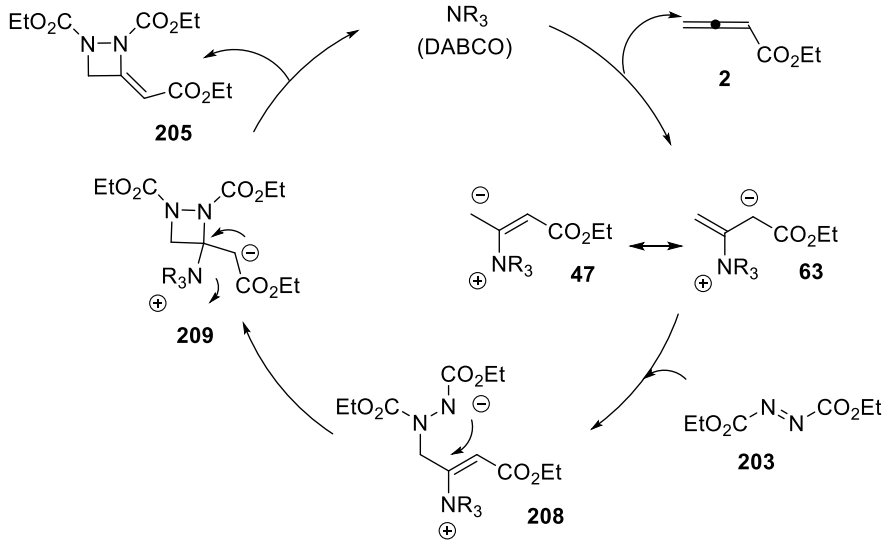
Scheme 1.49. DABCO catalyzed [2+2] cycloaddition with activated cyclic ketimines

In 2015, Xu and co-workers developed the DABCO-catalyzed [2+2] cycloaddition of azidocarboxylates with allenoates, which provides facile access to 3-alkylidene-1,2-diazetidines with excellent *Z*/*E*- and regioselectivity. The authors also employed a DABCO/PPh_3 relay catalytic strategy to achieve the formal [3+2] annulation of allenoates and azodicarboxylates, leading to the formation of pyrazoline (**Scheme 1.50**).[33]



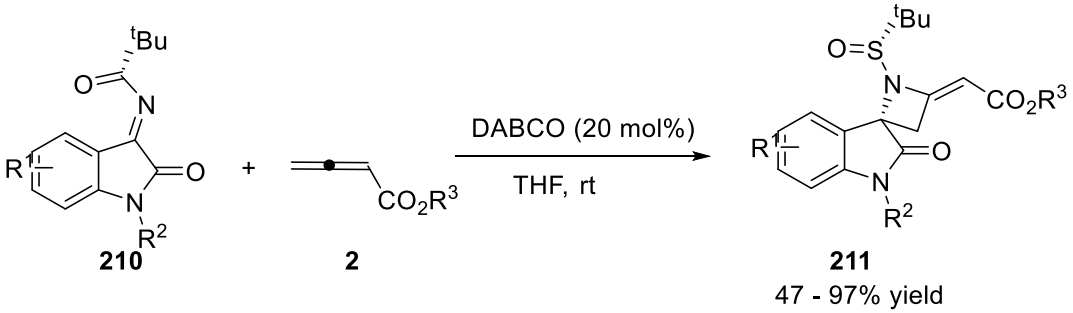
Scheme 1.50. DABCO-catalyzed [2+2] annulation of allenoates with azodicarboxylates

The plausible mechanism for the DABCO-catalyzed [2+2] annulation of allenoates with azodicarboxylates is depicted in **Scheme 1.51**. Initially, the nucleophilic attack of DABCO on the *β*-carbon of allenoate **2** generates the zwitterionic intermediate **63**. The addition of **63** to the azodicarboxylate **203** through its *γ*-carbanion leads to intermediate **208**, which then undergoes a favourable 4-exo-trig cyclization to become intermediate **209**. Finally, 1,2-elimination of the catalyst completes the catalytic cycle and produces the product **205**.



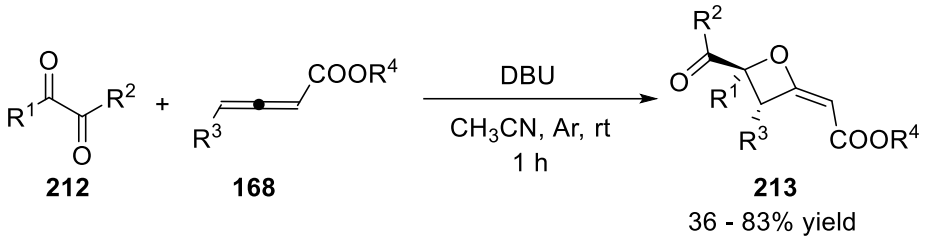
Scheme 1.51. DABCO-catalyzed [2+2] annulation of allenoates with azodicarboxylates

In 2016, Silvani and co-workers used chiral *tert*-butanesulfinyl ketimines as reactive substrates, finishing the DABCO-catalyzed [2+2] cycloaddition of allenoates, which affords enantiopure spirooxindole fused 4-methyleneazetidines. Subsequent investigation revealed that *α*-substituted allenoates were completely unreactive under the reaction conditions. The authors speculated that this outcome could be attributed to the stereoelectronic influence of the methyl group on the allenoate as well as the high steric challenge involved in the formation of the tetrasubstituted double bond joined to the spiroazetidine ring (**Scheme 1.52**).[34]



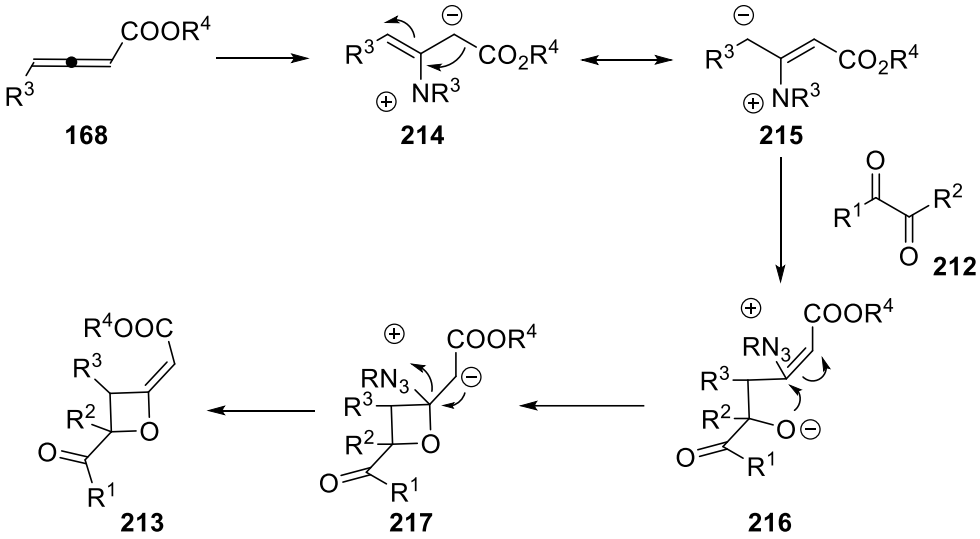
Scheme 1.52. DABCO-catalyzed [2+2] cycloaddition with *tert*-butanesulfinyl ketimines

In 2019 Nair et al. developed a tertiary amine-mediated annulation reaction of 3-alkyl allenoates and diaryl 1,2-diones for the diastereoselective synthesis of highly substituted alkylene-oxetane derivatives (**Scheme 1.53**).[35]



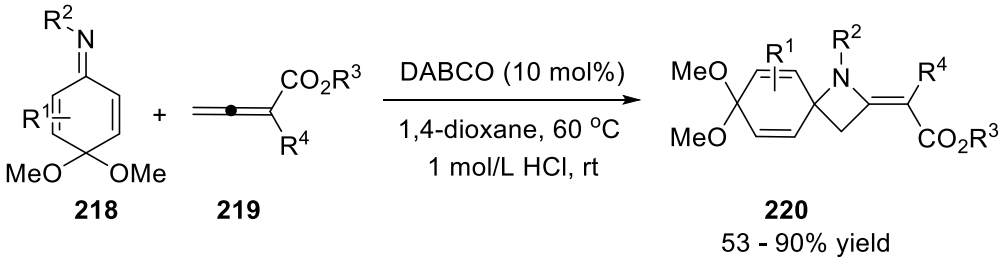
Scheme 1.53. DBU-catalyzed [2+2] cycloaddition of allenoates with diaryl 1,2-dione

A plausible mechanistic pathway for the formation of alkylene-oxetane is depicted in **Scheme 1.54**. The reaction is initiated by the nucleophilic addition of Lewis base to allenoate resulting in the formation of zwitterionic intermediate **215**. The zwitterion intermediate **215** thus formed then adds to the carbonyl carbon of the diaryl 1,2-dione **212** to form the intermediate **216**. Subsequent cyclization of the latter delivers the intermediate **217** which upon removal of the Lewis base resulted in the final product **213**.



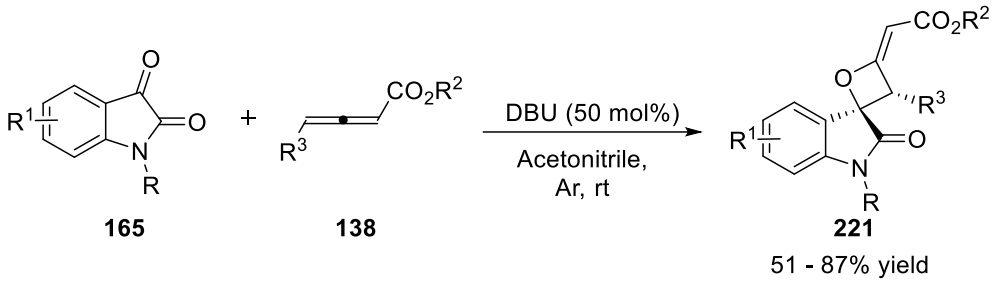
Scheme 1.54. Plausible mechanism for DBU-catalyzed [2+2] cycloaddition with diaryl 1,2-dione

The DABCO-catalyzed [2+2] cycloaddition of quinone imine ketals (QIKs) with allenoates was reported by Huang and Cheng in 2020. The reaction produced an array of azetidine-fused spirohexadienones with high *E*-selectivity and good to excellent yields (**Scheme 1.55**).[36]



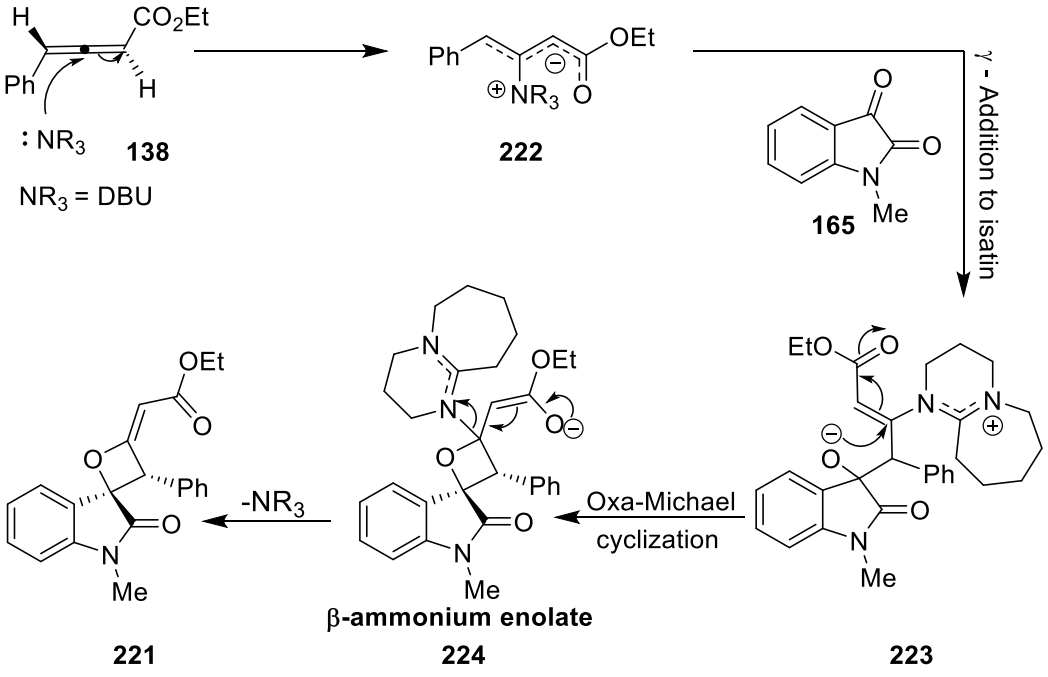
Scheme 1.55. DABCO-catalyzed [2+2] cycloaddition with *tert*butanesulfinyl ketimines or quinone imine ketals

In 2023, our group reported an efficient method for the diastereo-/ regioselective synthesis of functionalized spiro-oxetane. The 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed reaction proceeds *via* the ring annulation of isatins and allenoates, resulting in exclusively *E*-isomer (**Scheme 1.56**).[37]



Scheme 1.56. DBU-catalyzed [2+2] cycloaddition of allenoates with isatin

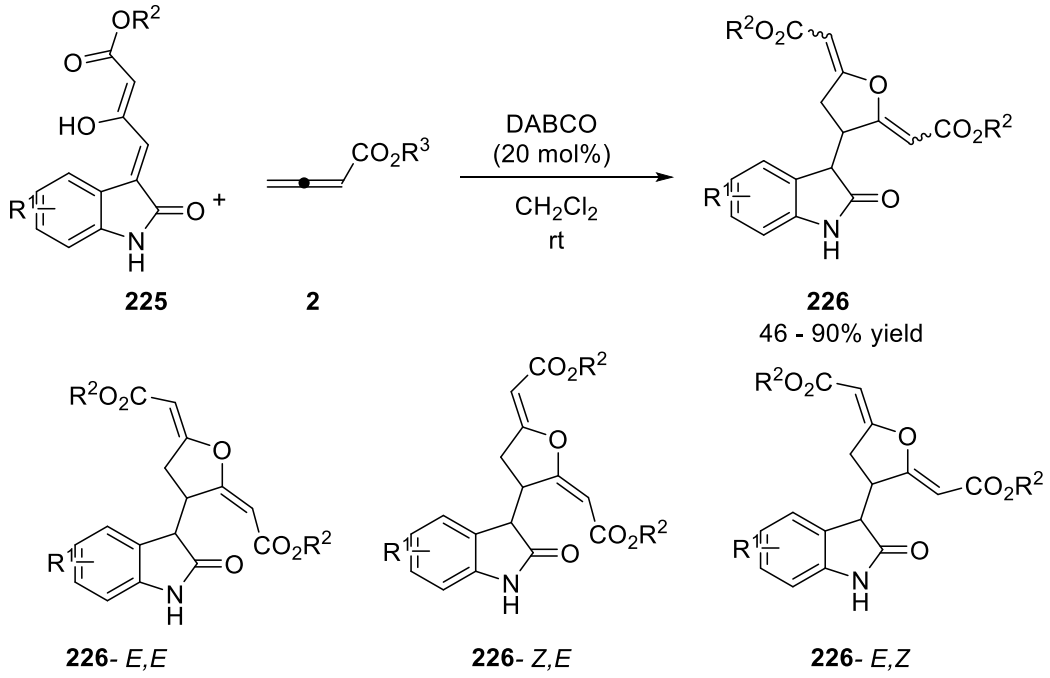
The plausible mechanism for the formation of spiro-oxetane oxindole is depicted in **Scheme 1.57**. Initially, the attack of Lewis base (NR_3) at the *β*-carbon of 3-aryl allenoate generates the zwitterionic intermediate **222**. The zwitterion **222** formed then undergoes *γ*-addition to *N*-protected isatin **165** to form an intermediate **223**. Following oxa-Michael cyclization yielded *β*-ammonium intermediate **224**. Finally, the elimination of the catalyst delivers spiro-oxetane oxindole **221**.



Scheme 1.57. A plausible mechanism for DBU-catalyzed [2+2] cycloaddition of allenoates with isatin

1.3.3. Tertiary amine-catalyzed synthesis of five-membered heterocycles

In 2014, Meng and co-workers reported the DABCO-catalyzed [3+2] cycloaddition involving allenoates and 3-oxo-4-(2-oxoindolin-3-ylidene) for the construction of 2,3,5-substituted tetrahydrofuran derivatives with two exocyclic double bonds and oxindole moieties in a high yield. During the reaction, two carbon atoms and one oxygen atom from 3-oxo-4-(2-oxoindolin-3-ylidene) butanoates are involved. Furthermore, this reaction allows for the isolation of two of the four isomers that were created (**Scheme 1.58**).[38]

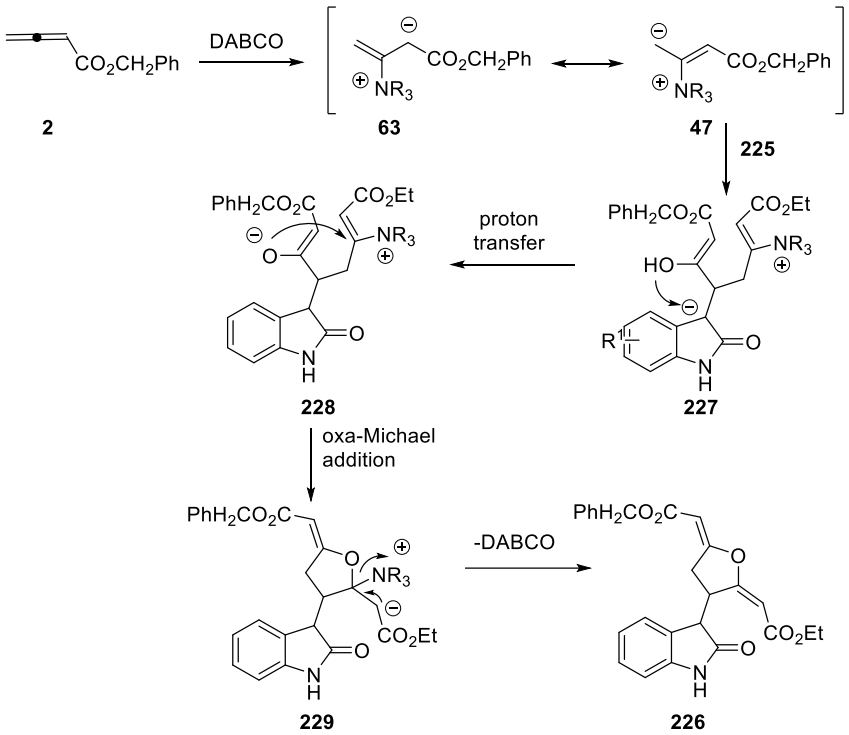


225 **2** **226**

226- *E,E* **226**- *Z,E* **226**- *E,Z*

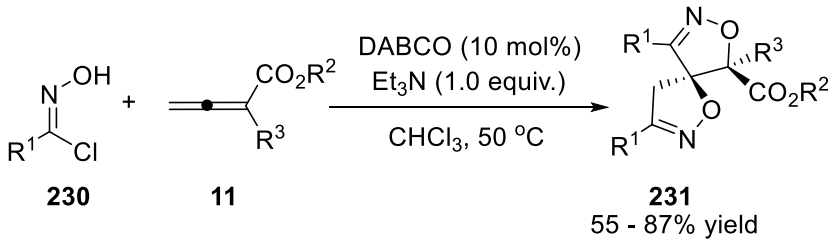
Scheme 1.58. DABCO catalyzed the [3+2] cycloaddition reaction with 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates

The plausible mechanism is shown in **Scheme 1.59**. The DABCO acted as a nucleophilic trigger and attacked the β carbon of allenoates to generate zwitterionic intermediate **47**, which then underwent an umpolung addition to **225** to give the intermediate **227**. Following proton transfer from enol (OH) to carbanion (3 position), and oxa-Michael addition resulted **229**. Finally, the elimination of DABCO to yield the desired product **226**.



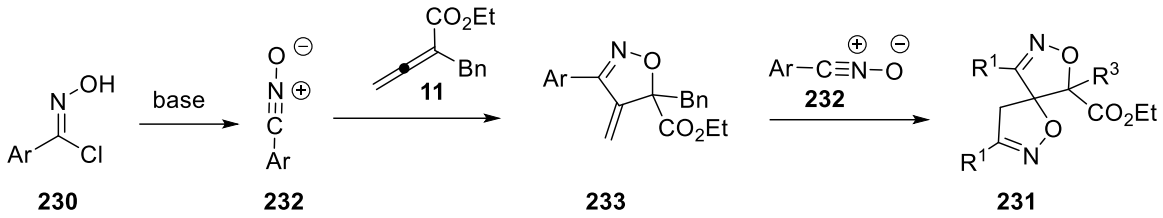
Scheme 1.59. Plausible mechanism for DABCO catalyzed the [3+2] cycloaddition with 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates

In 2018, Li and co-workers developed double [3+2] cycloadditions between nitrile oxides and allenoates, with DABCO acting as a nucleophilic Lewis base catalyst and Et_3N serving as a Bronsted base. The chemical bond formation in the process was facilitated by the α, β, and γ sites of allenoates (**Scheme 1.60**).[39]



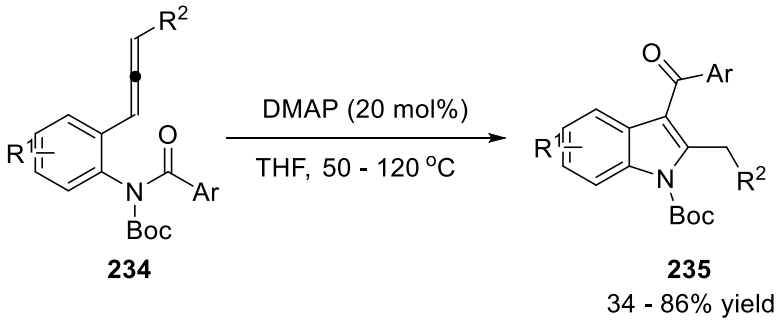
Scheme 1.60. DABCO-catalyzed double [3+2] cycloadditions with nitrile oxides

The suggested mechanism for the [3+2] cycloadditions between nitrile oxides and allenoates is shown in **Scheme 1.61**. In the presence of base, the nitrile oxide **232** was formed *in situ* from the oxime chloride **230**, which then reacted with allenoate between the α- and β-carbon to give the intermediate **233**. Later, the intermediate **233** continued to react with nitrile oxide **232** to afford the final product **231**.



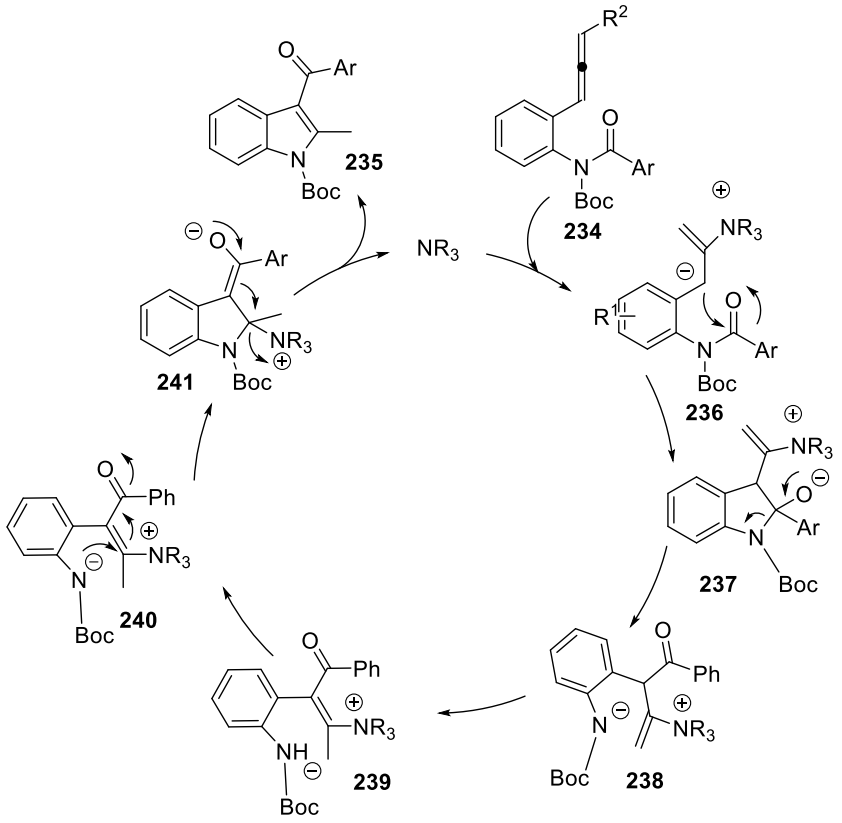
Scheme 1.61. Mechanism for DABCO-catalyzed double [3 + 2] cycloadditions with nitrile oxides

In 2020, Xia and Yu reported the DMAP-catalyzed amino-acylation of aryl allenes for the synthesis of 2-methyl-3-aroylindoles in good yields. In contrast to the conventional amine moieties that are wasted following the cleavage of C(O)-N bonds, both acyl and amine moieties get incorporated into the products by the selective cleavage of amide C-N bonds. The experimental findings indicated that the Boc group was essential for the effective cleavage of C–N bonds, since no cleavage of C–N bonds was observed in the absence of *N*–Boc protection (**Scheme 1.62**).[40]



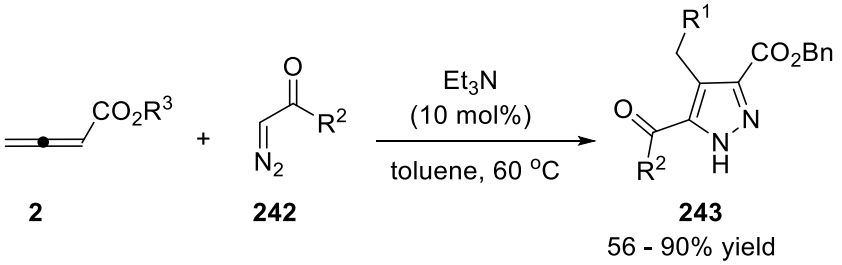
Scheme 1.62. DMAP-catalyzed amino-acylation of arylallenes

Based on the control experiments and DFT calculations, the authors proposed a plausible reaction pathway, as illustrated in **Scheme 1.63**. The nucleophilic addition of DMAP to aryl allene **234** generated the zwitterionic intermediate **236**, which then underwent nucleophilic addition to the carbonyl of amide to form intermediate **237**. Subsequently, successive C-N bond cleavage /[1,4]-/[1,6]-proton transfer /nucleophilic addition of a nitrogen anion to the *β*-position of the *α,β*-unsaturated ketone resulted in the intermediate **241**. Finally, the elimination of DMAP yielded product **235**.



Scheme 1.63. A Plausible reaction pathway of DMAP-catalyzed amino-acylation of aryl allenes

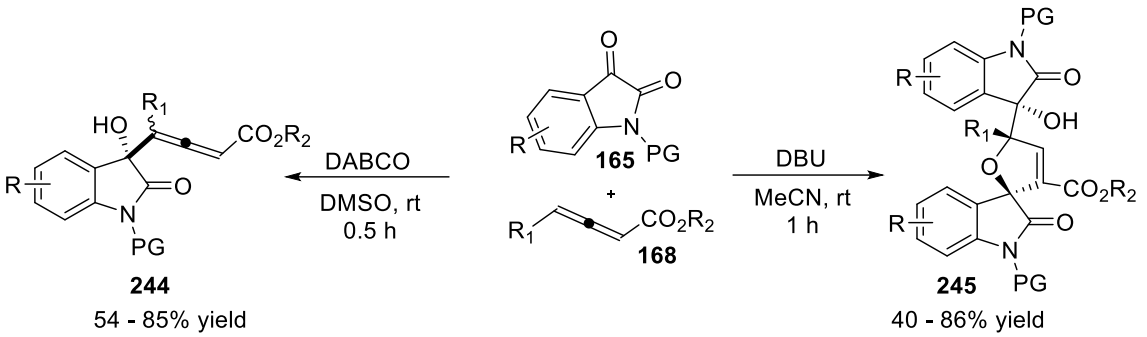
In 2021, Ma and co-workers reported the Et_3N-catalyzed [3+2] cycloaddition reaction of allenoates with acceptor diazo compounds, including diazoesters, diazoketones, and diazoamides. This transformation allows direct and regioselective synthetic routes to a variety of pyrazoles in good to excellent yields (**Scheme 1.64**).[41]



Scheme 1.64. Et_3N-catalyzed [3 + 2] cycloaddition with diazo compounds

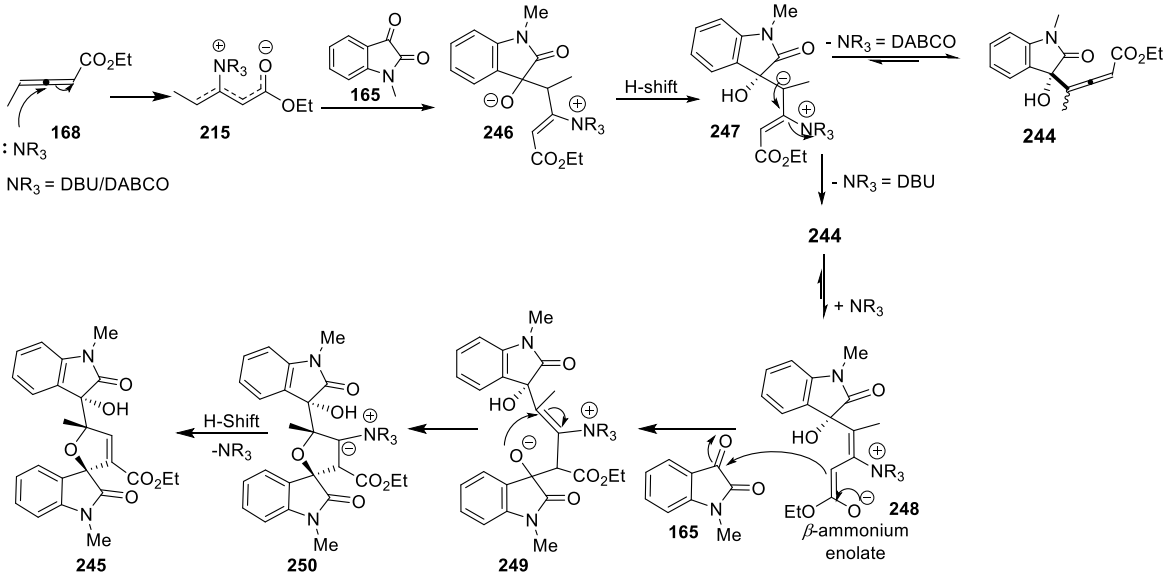
In 2021, our group explored the base-mediated divergent reactivity of isatins and allenoates. We observed that when DBU is used as the base, the Morita-Baylis-Hillman (MBH) reaction followed by the cascade annulation through the stabilized *β*-ammonium enolate intermediate, resulted in the diastereoselective synthesis of spirofuran oxindoles. In

contrast, the use of DABCO led to the formation of γ-functionalized allenoates (**Scheme 1.65**).[42]



Scheme 1.65. DBU/DABCO catalyzed reaction of allenoate with isatin

The plausible mechanism for spirofuran oxindole formation is shown in **Scheme 1.66**. Initially, the nucleophilic addition of DBU to 3-alkyl allenoate **168** occurs, affording a zwitterion intermediate **215**. The zwitterion **215**, thus formed can easily add to the carbonyl carbon of the *N*-protected isatin **165** to form the intermediate **246**. After that, the proton transfer delivers **247**; the elimination of DBU results in an intermediate product **244**, which



Scheme 1.66. Plausible mechanism for DBU/DABCO catalyzed reaction with isatin

eventually, forms stabilized β-ammonium enolate intermediate **248** in the presence of a stoichiometric amount of base. The latter undergoes nucleophilic addition to the second molecule of isatin furnishing **249**, which upon cyclization, leads to **250**. This intermediate, after proton transfer and elimination of DBU, delivers the desired product **245**.

1.4. Summary and outline of the thesis

From the above discussions, it is evident that tertiary amine catalysis has emerged as a prominent and reliable approach for constructing functionalized carbocyclic/heterocyclic structures, which play a crucial role in natural product synthesis and pharmaceutical design. In the presence of tertiary amines, allenoate can serve as versatile C2, C3 and C4 synthons, participating in various cycloaddition reactions to generate valuable building blocks. In that view, the thesis explores the tertiary amine-promoted reactivity of allenoates to access biologically relevant motifs, leveraging readily accessible substrate *viz* isatin, malononitrile and alkyl amine under mild reaction conditions.

In **Chapter 2** we have developed an effective approach to the stereoselective synthesis of functionalized 3-alkenyl-2-oxindoles by the TBD-mediated tandem reaction of isatins and aryl allenoates. We have also demonstrated the synthetic utility of 3-alkenyl-2-oxindoles to convert them into novel oxindole-appended heterocyclic scaffolds. **Chapter 3** describes an unprecedented, 100% atom economic annulation of allenoates with cyclic amidines for the synthesis of functionalized tricyclic pyridopyrimidine scaffolds. **Chapter 4** focuses on a highly efficient multicomponent reaction for the synthesis of functionalized spiro[4H-pyran-oxindole] utilizing readily available isatin, malononitrile, allenoate, and alkyl amine. The Et_3N-mediated reaction involves cascade spiro-cyclization of the *in situ* generated Knoevenagel adduct and aza-Michael adduct. We have synthesized a library of functionalized 3-alkenyl-2-oxindoles, tricyclic pyridopyrimidine and spiro[4H-pyran-oxindole] to demonstrate the versatility of developed protocols. The synthesized library of compounds can serve as the source of "Hit" molecules for medicinal chemistry and drug discovery endeavours.

1.5. References

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Chapter 2

TBD-Mediated Diastereoselective Access to Functionalized 3-Alkenyl-2-oxindoles *via* Tandem Reaction of Isatins and Allenoates

2.1 Abstract

The 1,5,7-Triazabicyclo[4.4.0]dec-5-ene mediated tandem reaction of easily accessible isatins and allenoates to functionalized 3-alkenyl-2-oxindoles are disclosed. The reaction allows synthesising a wide range of 3-alkenyl-2-oxindoles in good yields with excellent functional group tolerance under mild reaction conditions (32 examples, up to 84% yields). The current strategy offers a novel and sustainable approach for the synthesis of functionalized 3-alkenyl-2-oxindole derivatives. We have also demonstrated the significance of the 3-alkenyl-2-oxindoles as key starting materials (KSMs) *via* their synthetic utility in producing oxindole-appended pyrazole, oxazole and coumarin hybrids of medicinal relevance.

2.2 Introduction

3-Alkenyloxindoles are privileged frameworks that are present in a wide spectrum of biologically active candidates of synthetic and natural origin.[1] For instance, the FDA has approved Sunitinib (Sutent), a 3-alkenyl-2-oxindole derivative, as a multi-targeted tyrosine kinase inhibitor for the treatment of advanced renal cell carcinoma and gastrointestinal cancer, becoming the first anticancer drug to be sanctioned for use on two discrete types of cancer cell lines simultaneously. Its mechanism of action involves inhibiting cellular signaling *via* indirectly attacking multiple receptor tyrosine kinases.[2] Soulieotine, extracted from *Souliea vaginata*, is utilized as an anti-inflammatory agent in traditional Chinese medicine.[3] The natural 3-alkenyloxindole derivative Indirubin has shown potent CDK inhibition.[4] Nintedanib is a clinically approved drug for the treatment of adenocarcinoma. Commercially, Nintedanib is marketed under the brand names – 'Ofev' and 'Vargatef'[5] (**Figure 2.1**). Furthermore, the synthesis of natural products[6] including TMC-95[7] and

Maremycins A[8] as well as several spirocyclic oxindoles[9] utilizes 3-alkenyl oxindoles as a versatile precursor.

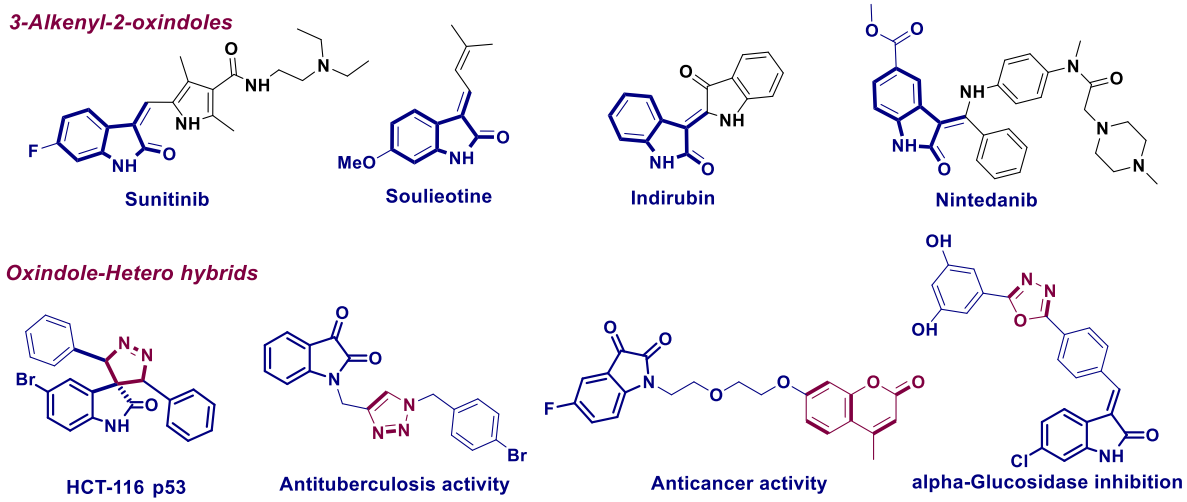


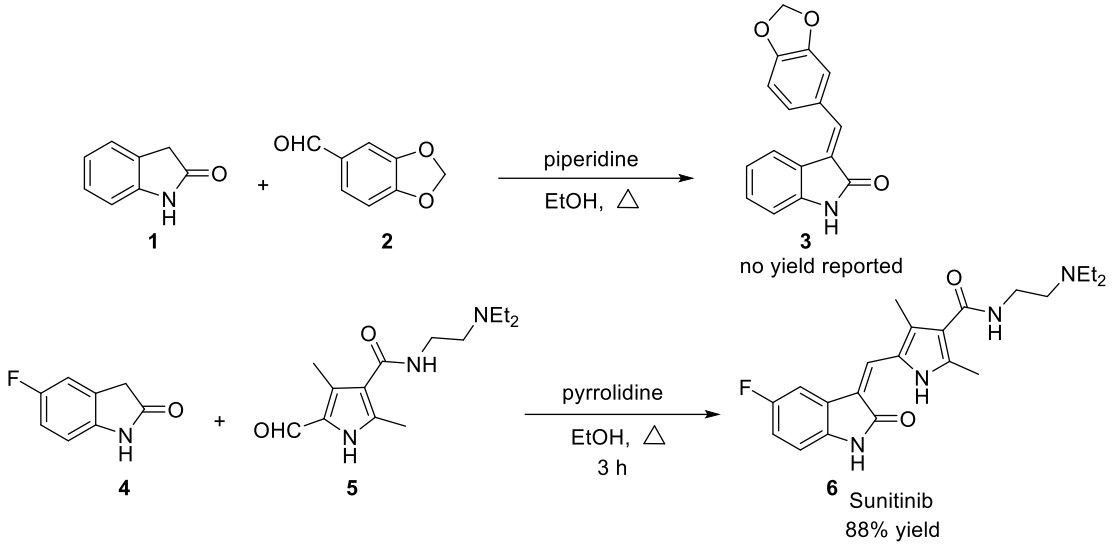
Figure 2.1. Representative biologically active molecules featuring the oxindole core structure

2.2.1 Synthetic approaches towards 3-alkenyl-2-oxindoles

Owing to the diverse medicinal relevance and synthetic pertinence of 3-alkenyl-2-oxindole skeletons, the development of facile and novel routes for their synthesis has drawn considerable interest from chemists. Consequently, quite a few protocols have been developed. The target molecules are typically accessed *via* one of two approaches: (1) condensation reaction between preformed oxindole (e.g. aldol condensations of unsubstituted oxindoles and Wittig-type reactions of isatins); (2) Tandem/telescoped routes utilizing anilines/ *N*-substituted aniline.

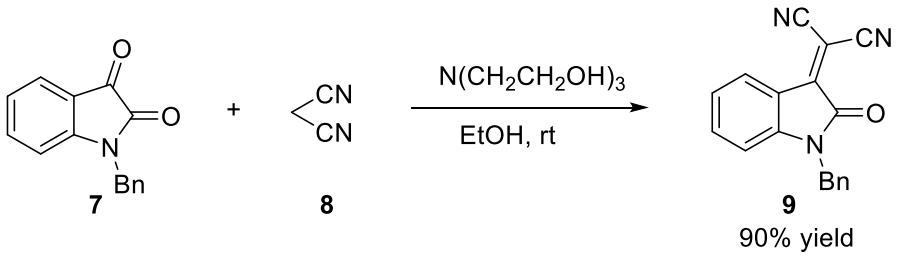
The most often-used procedure involves the condensation of unsubstituted oxindoles with carbonyl compounds. A Beilstein database search yields over 1500 results for this synthetic approach. Wahl and Bayard first reported this process in 1909, preparing (3*E*)-3-(1,3-benzodioxol-5-ylmethylidene)-1,3-dihydro-2H-indol-2-one **3** *via* condensation of oxindole **1** with 1,3-benzodioxole-5-carbaldehyde **2** (**Scheme 2.1**).[10] In this example, only the *E*-isomer was formed, likely due to the steric effect from the aryl group. The simplicity of this aldol approach has contributed to its widespread adoption, enabling the synthesis of numerous 3-alkenyl-oxindole drug candidates. For example, sunitinib (Sutent®, **6**) is synthesized by the condensation reaction of oxindole **4** with pyrrole carbaldehyde **5** (**Scheme 2.1**).[11] Sunitinib (**6**) is obtained solely as the *Z*-isomer, with intramolecular H-bonding likely contributing to the high stereoselectivity.

Despite the stereoselective nature of the two examples shown in **Scheme 2.1**, it should be noted that the aldol approach generally produces 3-alkenyl-oxindoles as *E*/*Z*-mixtures.[12]



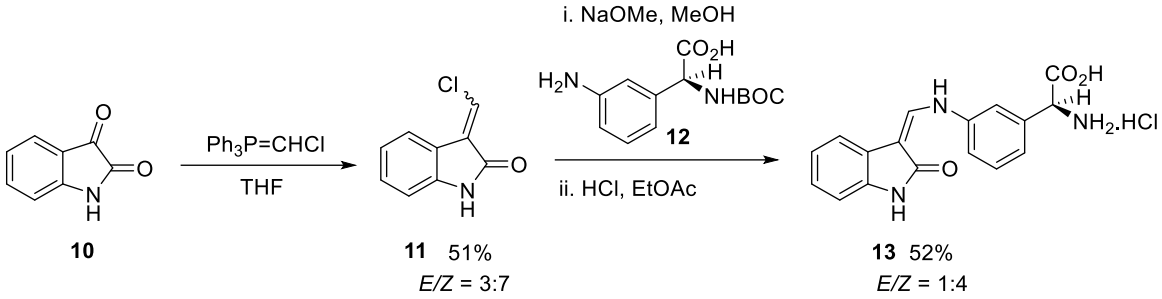
Scheme 2.1. Synthesis of 3-alkenyl-oxindoles *via* aldol condensation

Isatin (1H-indole-2,3-dione) and its derivatives are readily available and undergo enolate-type condensation regioselectively at C-3. The example of the use of such a condensation to prepare 3-alkenyl-oxindoles was reported by Shishkina in 2007 and utilized *N*-benzyl isatin (**7**) and malononitrile (**8**) (**Scheme 2.2**).[13]



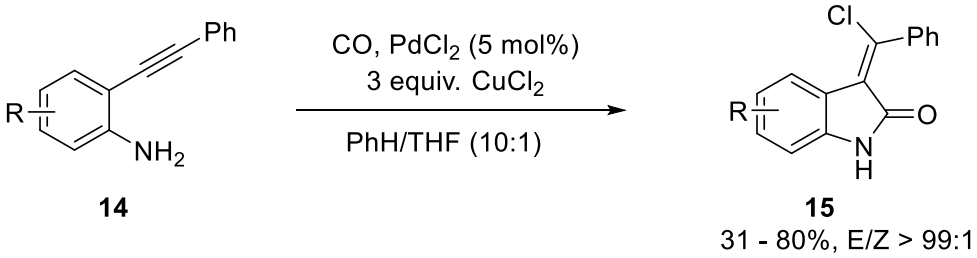
Scheme 2.2. Synthesis of malononitrile adduct *via* condensation of isatin and malononitrile

The Wittig reaction of isatins is also utilized for the synthesis of 3-alkenyl-oxindoles. In 2006 Moreau reported a Wittig route from isatin **10** to the 3-chloro-alkenyl-oxindole **11** and 3-amino-alkenyl-oxindole **13** (**Scheme 2.3**).[14]



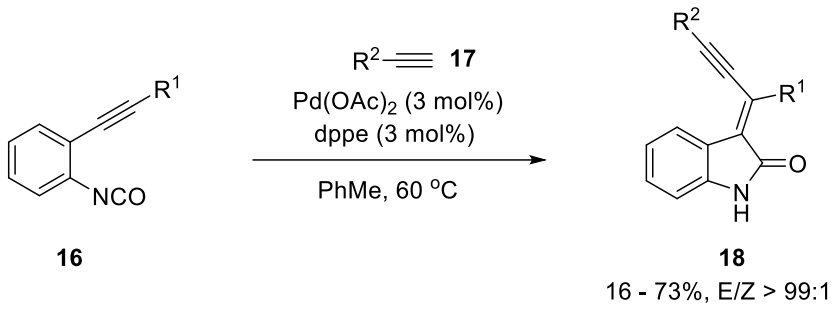
Scheme 2.3. Synthesis of 3-alkenyl-oxindoles *via* Wittig reaction of isatin

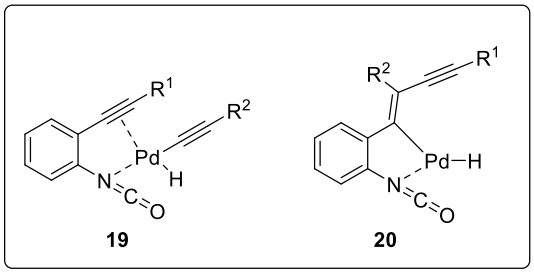
Several groups have utilized the metal-catalyzed carbonylative annulation of alkynyl-arylamines to prepare 3-alkenyl-oxindoles. In 2007, Tang and co-workers developed a stereoselective palladium-catalyzed carbonylative annulation of alkynyl-aryl-amines **14** for the synthesis of vinyl chlorides **15** in 31 – 80% yields (**Scheme 2.4**).[15]



Scheme 2.4. Synthesis of vinyl chlorides *via* carbonylative annulation

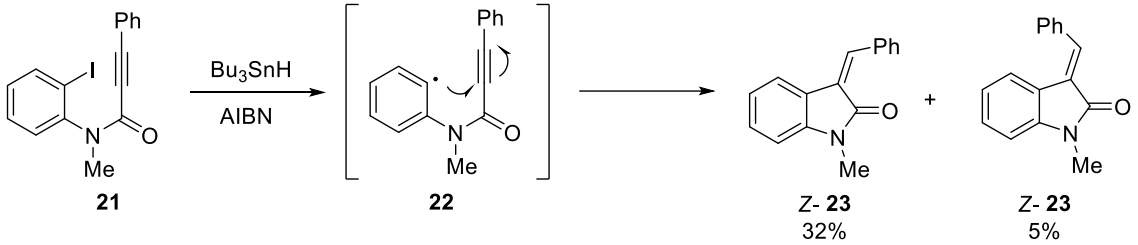
In 2005, Kamijo and co-workers reported a novel strategy for the synthesis of 3-enynyloxindoles **18**, utilizing the palladium-catalyzed cyclisation of acetylenic aryl isocyanates **16** in the presence of terminal alkynes **17**. The proposed mechanism involves an "intramolecular nucleophilic vinyl palladation" *via* intermediates **19** and **20**, with subsequent alkene isomerization occurring after oxindole formation (**Scheme 2.5**).[16]





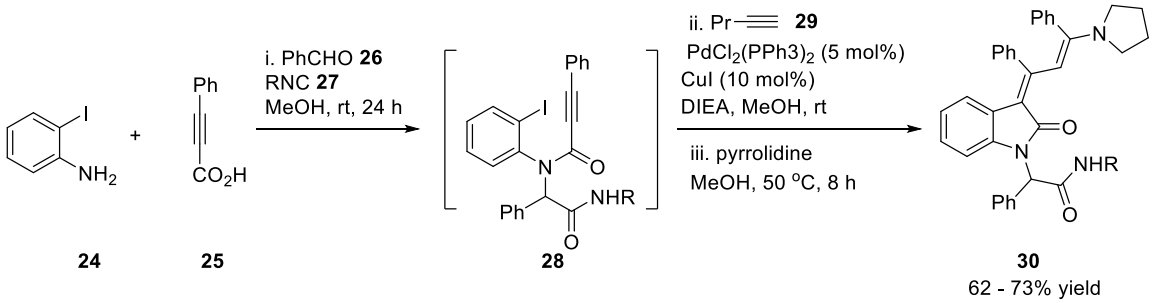
Scheme 2.5. Synthesis of 3-enynyloxindoles utilising acetylenic aryl isocyanates

Halogenated aryl propionamides, such as compound **21,** are commonly employed in the synthesis of 3-alkenyl-oxindoles. A pioneering approach of this type was reported by Bowman, Heaney, and Jordan in 1988, employing a tin hydride-AIBN-initiated radical cyclization (**Scheme 2.6**). However, this method suffered from low yields and produced an *E*/*Z*-mixture of 3-alkenyl-oxindoles.[17]



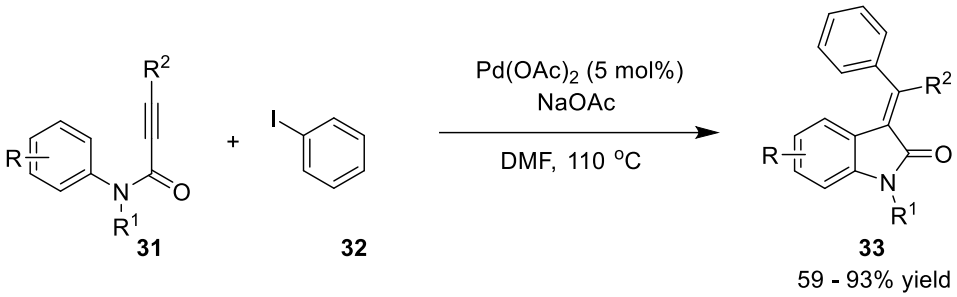
Scheme 2.6. Synthesis of 3-alkenyl-oxindoles *via* radical cyclisation

In 2010 Balalaie and co-workers developed a one-pot, six-component process for the synthesis of 3-arylidene-oxindoles **30**. The approach begins with an initial Ugi four-component reaction, transforming iodoaniline **24** into aryl propionamide **28**. Subsequent *in situ* addition of a palladium catalyst and phenylacetylene **29** facilitated a tandem Heck carbocyclisation/ Sonogashira sequence, followed by Michael-type addition of pyrrolidine to yield complex 3-methylene- oxindole **30** with complete *Z*-selectivity (**Scheme 2.7**).[18]



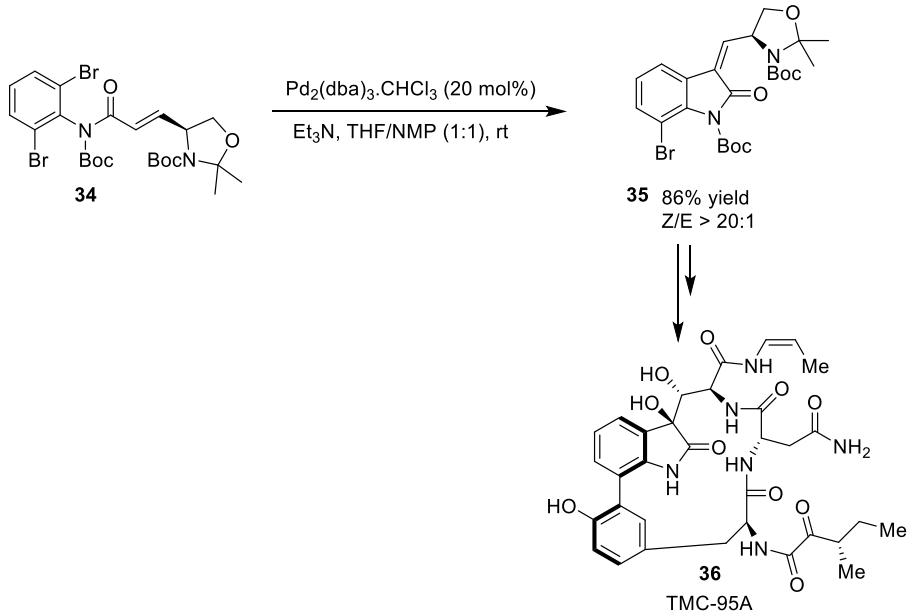
Scheme 2.7. Synthesis of 3-alkenyl-oxindoles *via* arene-alkyne cyclisation

Recent advances in C–H activation has led to the development of aryl propionamide cyclisation methods to be carried out without the requirement for *α*-halogeno-anilide. In 2006, Zhu and co-workers developed an efficient tandem process to convert amides **31** and aryl iodides **32** into unsymmetrically substituted 3-alkenyl-oxindoles **33**. The mechanism involves palladium-catalyzed oxidative addition, regioselective *syn*-carbopalladation, aryl C–H activation, and reductive elimination to form the new C–C bond (**Scheme 2.8**).[19]



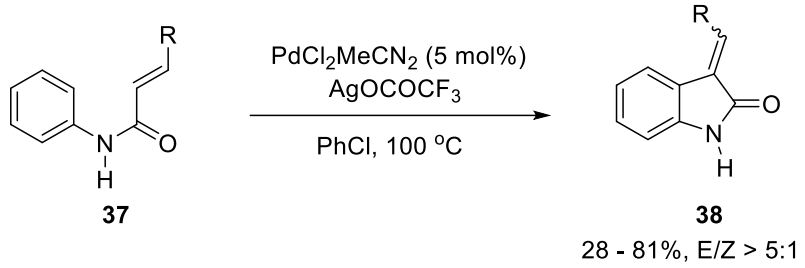
Scheme 2.8. Aryl propionamide cyclisation *via* aryl C–H activation

In 2006, Hirama and co-workers employed an intramolecular Heck reaction to synthesize 3-alkenyl-oxindole **35** as a key intermediate in the total synthesis of TMC-95A (**36**), a potent and selective proteasome inhibitor. As shown in **Scheme 2.9**, the intramolecular Heck reaction of *N*-Boc-protected aniline **34** gave 3-alkenyl-oxindole **35** in 86% yield, with high selectivity for the *Z*-isomer.[20]



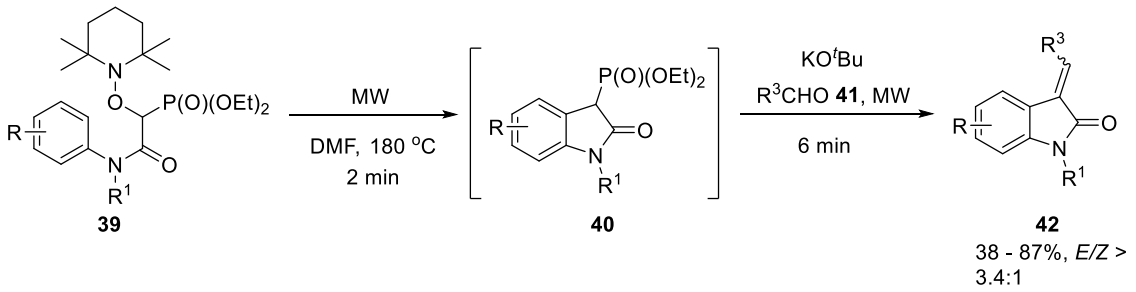
Scheme 2.9. Intramolecular Heck reaction for the synthesis of 3-alkenyl-oxindole

In 2010, Nagasawa and co-workers developed a straightforward method for the synthesis of 3-alkenyl-oxindoles **38**, utilizing palladium-catalyzed aromatic C–H activation/Heck reaction starting from *N*-acryloyl anilines **37** (**Scheme 2.10**).[21]



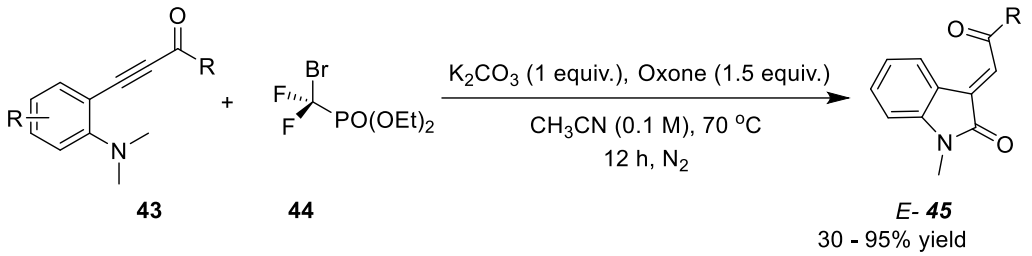
Scheme 2.10. Synthesis of 3-alkenyl-oxindoles by C–H activation/Heck reaction

In 2004, Studer and co-workers devised a novel, one-pot telescoped route to 3-alkenyl-oxindoles **42** involving tandem radical generation then homolytic aromatic substitution and finally Horner–Wadsworth–Emmons olefination (**Scheme 2.11**). Microwave-induced nitroxide cleavage initiated the cyclisation process, while various aryl aldehydes were employed in the subsequent HWE olefination step, which was also accelerated by MW irradiation.[22]



Scheme 2.11. Synthesis of 3-alkenyl-oxindoles *via* HWE strategy

In 2023 Song et al. developed a transition-metal-free [4+1] cyclization method to synthesize 3-alkenyl-2-oxindoles **45**. The approach utilizes *ortho*-amino aryl alkynone **43**; and *in situ* generated difluorocarbene from commercially available halogenated difluoroalkylative reagent **44**, enabling the cleavage of a C−N bond and formation of new C−N bonds and C−C bonds (**Scheme 2.12.**).[23]

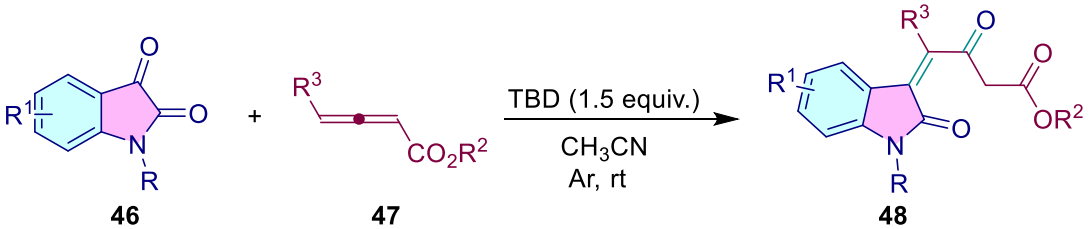


Scheme 2.12. Difluorocarbene-mediated synthesis of 3-alkenyl-2-oxindoles

2.3. Background to the present work

Despite the advancements discussed in section **2.2.1** for the synthesis of 3-alkenyl-2-oxindoles, many of these strategies have numerous shortcomings concerning the usage of extra carbonyl sources, expensive metal catalysts, and reagents and often result in 3-alkenyl-oxindoles as *E*/*Z*-mixtures. Therefore, the development of new, simple, and reliable protocols using readily accessible starting materials to access a wide range of structurally diverse 3-alkenyl-oxindoles is both valuable and highly appealing. Therefore, in continuation to our devoted efforts towards the novel routes,[24] herein, we report a tandem reaction between isatin and allenoates that leads to the diastereoselective synthesis of 3-alkenyl-2-oxindole functionalized with *β*-keto ester.

Very recently our group devised an effective approach for the diastereo-/ regiospecific synthesis of highly substituted spiro-oxetane oxindoles *via* DBU-catalyzed spiro annulation of isatins and aryl-allenoates (**Scheme 2.13**).[25] During the optimization studies of spiro-oxetane, we came across a serendipitous observation. When the DBU loading was increased to 1.5 equiv. from 50 mol%, the TLC revealed a new product with a slight variation in retention factor (R_f) value. This observation prompted us to study the reaction in more detail. The newly formed product was purified and characterized as ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate, **48a** *via* Nuclear Magnetic Resonance (NMR) and High-Resolution Mass (HRM) spectrometry.



Scheme 2.13. TBD-catalyzed synthesis of 3-alkenyl-oxindoles

2.4. Results and discussion

We started the investigation by reacting 1.0 equiv. of *N*-methyl isatin **46a** (0.31 mmol) with 1.0 equiv. of ethyl 4-phenylbuta-2,3-dienoate **47a** in the presence of 1.0 equiv. of DBU in acetonitrile at room temperature under Ar atmosphere for 1 h (**Table 2.1**, entry 1). To our delight, a single isomer of the anticipated product ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (**48a**), was obtained in 32% yield. Here the greater 1,3-allylic strain in the (*E*)-isomer will favour the formation of the (*Z*)-product over (*E*)-product, thus rationalizing the diastereoselectivity.[25,26]

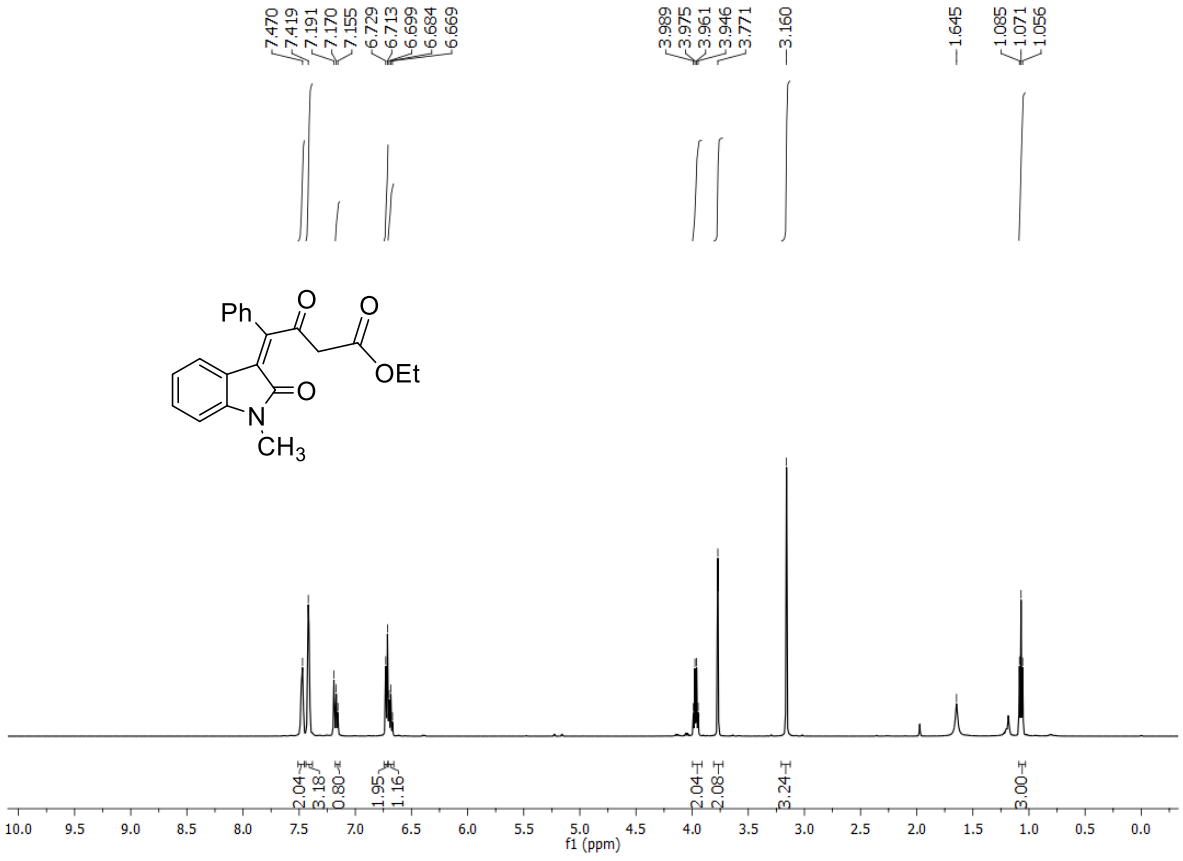


Figure 2.2. ^{1}H NMR (500 MHz, $CDCl_3$) of **48a**

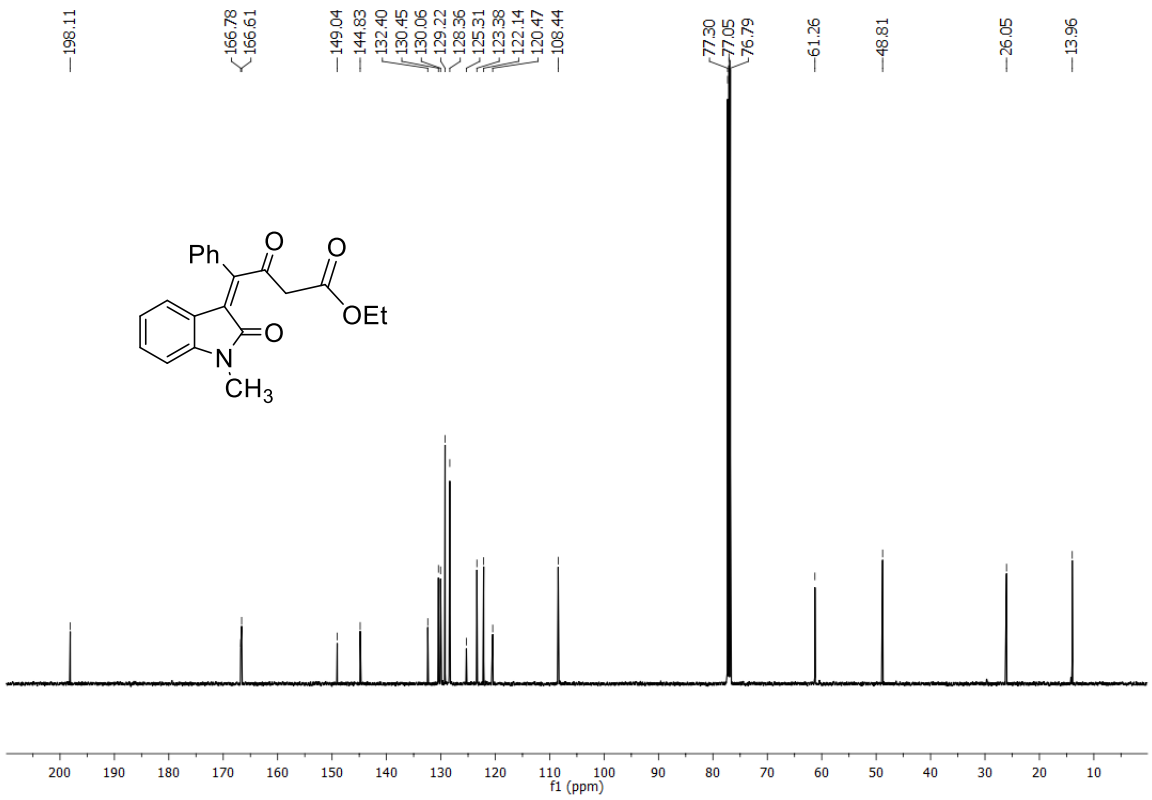


Figure 2.3. $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) of **48a**

The single-crystal X-ray analysis of one of the derivatives methyl (*Z*)-4-(5-chloro-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate, **48ad** provided further confirmation of the relative stereochemistry (**Figure 2.4**).

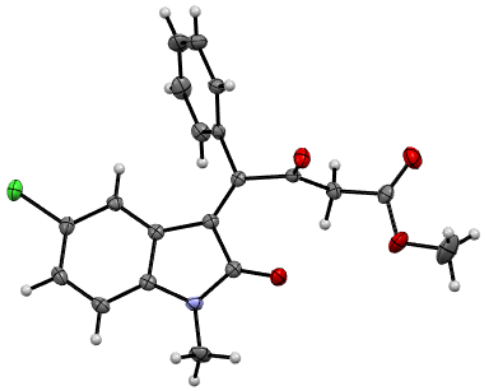
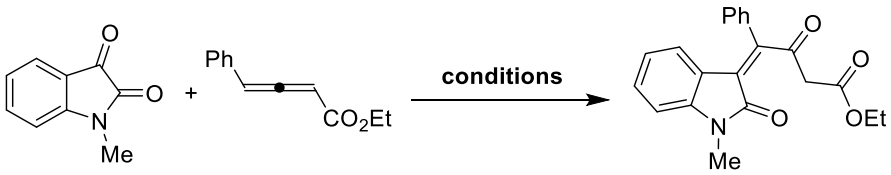


Figure 2.4. Single crystal X-ray structure of **48ad** (**CCDC 2339404**)

The reaction parameters were then tuned to further enhance the yield of the process (**Table 2.1**). Firstly, we screened the stoichiometric amount of the substrates (**Table 2.1**, entries 1

to 3); 1.0 equiv. of *N*-methyl isatin **46a** and 1.5 equiv. of 3-ethyl 4-phenylbuta-2,3-dienoate **47a** furnished 45% yield of **48a** (**Table 2.1**, entry 2). Further increase in the equiv. of allenoate **47a** yielded unsatisfactory outcomes (**Table 2.1**, entry 3). To further enhance the yields, the loading of the base was carefully tested (**Table 2.1**, entries 4 - 6). Interestingly,

Table 2.1. Optimization of the reaction[a]



46a **47a** **48a**

Entry	**47a** (in equiv.)	Base (in equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	1	DBU (1.0)	Acetonitrile	rt	1	32
2	1.5	DBU (1.0)	Acetonitrile	rt	1	45
3	2	DBU (1.0)	Acetonitrile	rt	1	36
4	1.5	DBU (1.2)	Acetonitrile	rt	1	54
5	1.5	DBU (1.5)	Acetonitrile	rt	1	62
6	1.5	DBU (2.0)	Acetonitrile	rt	1	56
7	1.5	DBU (1.5)	Acetonitrile	0 - 5	1	42
8	1.5	DBU (1.5)	Acetonitrile	50	1	18
9	1.5	DBU (1.5)	Acetonitrile	rt	0.5	38
10	1.5	DBU (1.5)	Acetonitrile	rt	2	57
11	1.5	DBU (1.5)	EtOH	rt	1	19
12	1.5	DBU (1.5)	DMF	rt	1	ND
13	1.5	DBU (1.5)	DCM	rt	1	trace
14	1.5	DBU (1.5)	Acetone	rt	1	trace
15	1.5	DBU (1.5)	Toluene	rt	1	ND
16	1.5	TBD (1.5)	Acetonitrile	rt	1	79
17	1.5	TBD (2.0)	Acetonitrile	rt	1	71
18	1.5	DBN (1.5)	Acetonitrile	rt	1	32
19	1.5	DABCO (1.5)	Acetonitrile	rt	1	trace
20	1.5	DMAP (1.5)	Acetonitrile	rt	1	trace
21	1.5	Et_3N (1.5)	Acetonitrile	rt	1	trace
22	1.5	PPh_3 (1.5)	Acetonitrile	rt	1	trace

[a]All the reactions were carried out with **46a** (0.31 mmol, 1.0 equiv.) in solvent (2 mL) under Ar atmosphere, [b]Yield of isolated product. ND: Not detected

an increased yield of 62% was obtained by the loading of 1.5 equiv. of DBU (**Table 2.1**, entry 5). Further assessment of reaction temperature lowered the yields, confirming that the reaction is more favourable at room temperature (**Table 2.1**, entries 7, 8). The screening of

the reaction time between 0.5 h to 2 h didn't give any positive results (**Table 2.1**, entries 9, 10). Then we screened various solvents (**Table 2.1**, entries 11 - 15), and found that acetonitrile was still the most effective one. In addition, we investigated the effect of several bases including TBD, DBN, DABCO, DMAP, Et_3N and PPh_3 (**Table 2.1**, entries 16 - 22), which revealed that the TBD was the optimal candidate for conducting the reaction. Therefore, the optimized reaction condition identified was: 1.0 equiv. of *N*-methyl isatin (**46a**), 1.5 equiv. of allenoate (**47a**) and 1.5 equiv. of TBD in acetonitrile at room temperature under Ar atmosphere for 1 h (**Table 2.1**, entry 16).

After determining the optimal reaction conditions, we systematically examined the generality of the reaction. At the outset, we explored an array of isatins having various *N*-substituents, electron-releasing and electron-withdrawing groups, with aryl allenoate **47a** to generate the corresponding 3-alkenyl-2-oxindole **48** (**Table 2.2**). The substitution effect on isatin skeleton exhibited excellent functional group tolerance. The isatins with electron-donating substituents such as –Me and –OMe was successfully converted to the corresponding products (**48b**, **48c**) with yields of 78 and 84% respectively. However, 5,7-dimethyl substituted isatin provided product **48o** only in the trace. The isatins with halo substituents like -F, -Cl and -Br were also compatible with the reaction system to produce the desired products (**48d** - **48f**, **48m**) in good yields (62 - 79%), indicating that they can be used as a handle for further synthetic transformations. In addition, isatin with electron-withdrawing groups such as $-NO_2$, $-OCF_3$, and $-CF_3$, tolerated well, leading to the expected products (**48g**, **48h**, **48n**) in satisfying yields (54 – 58%). To our delight, the reaction proceeded well on isatins with bulky *N*-substitutions such as ethyl, propyl, benzyl, and propargyl groups, yielding the targeted products (**48i** - **48l**, **48p** - **48s**) in 56 - 77% yields.

Table 2.2. Substrate scope concerning various *N*-substituted isatins

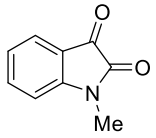
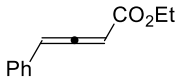
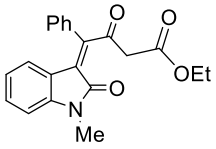
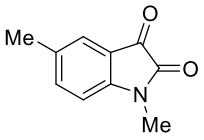
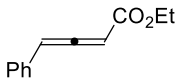
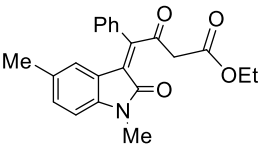
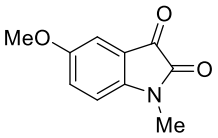
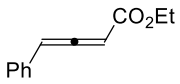
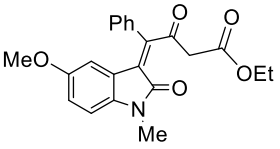
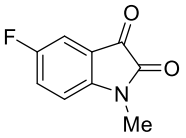
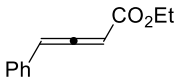
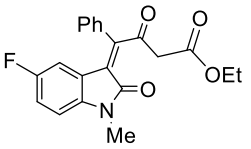
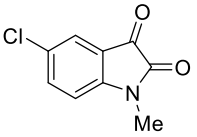
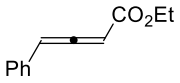
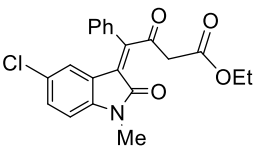
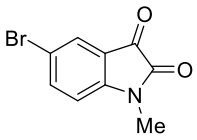
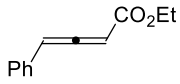
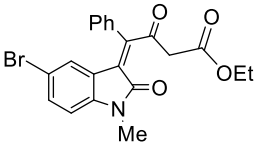
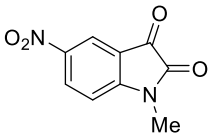
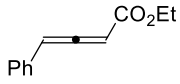
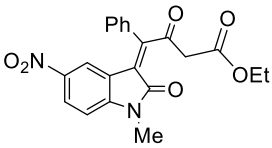
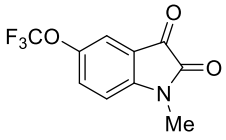
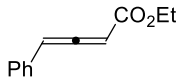
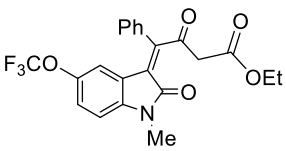
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1	 **46a**	 **47a**	 **48a**	**79**
2	 **46b**	 **47a**	 **48b**	**78**
3	 **46c**	 **47a**	 **48c**	**84**
4	 **46d**	 **47a**	 **48d**	**62**
5	 **46e**	 **47a**	 **48e**	**74**
6	 **46f**	 **47a**	 **48f**	**79**
7	 **46g**	 **47a**	 **48g**	**58**
8	 **46h**	 **47a**	 **48h**	**54**

Table 2.2. Continues…….

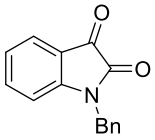
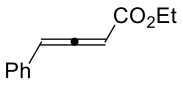
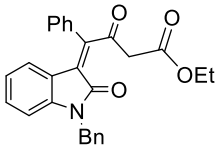
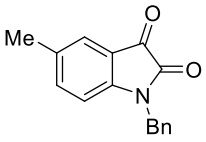
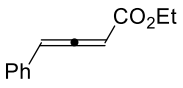
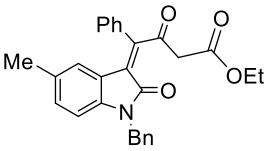
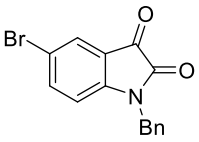
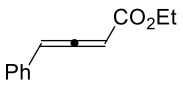
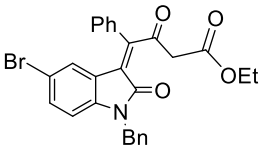
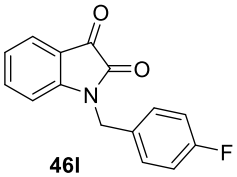
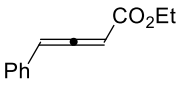
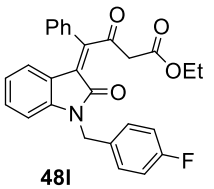
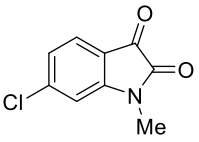
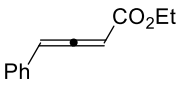
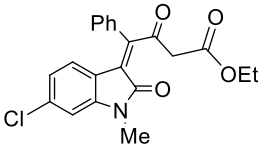
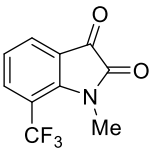
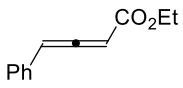
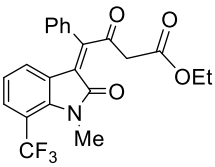
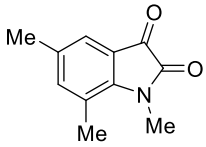
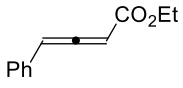
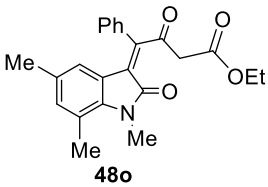
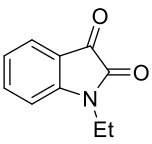
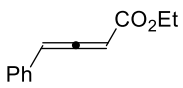
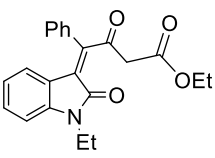
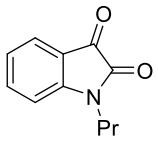
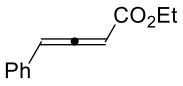
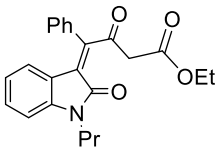
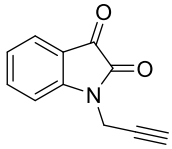
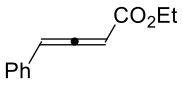
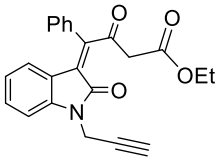
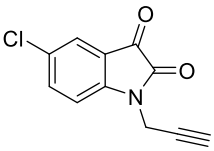
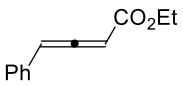
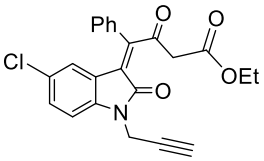
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
9	 **46i**	 **47a**	 **48i**	**65**
10	 **46j**	 **47a**	 **48j**	**63**
11	 **46k**	 **47a**	 **48k**	**61**
12	 **46l**	 **47a**	 **48l**	**56**
13	 **46m**	 **47a**	 **48m**	**72**
14	 **46n**	 **47a**	 **48n**	**58**
15	 **46o**	 **47a**	 **48o**	**trace**
16	 **46p**	 **47a**	 **48p**	**77**

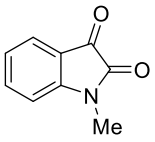
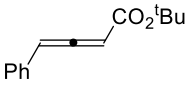
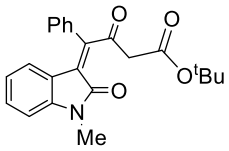
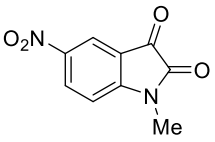
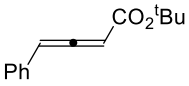
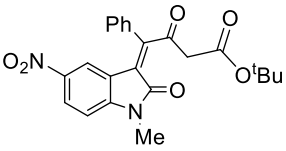
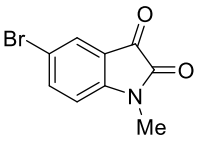
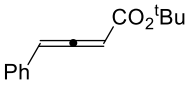
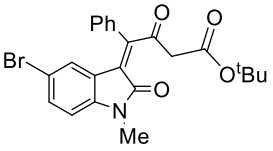
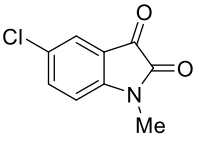
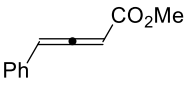
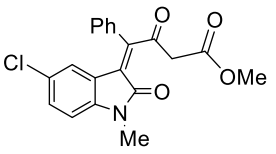
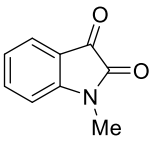
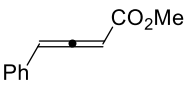
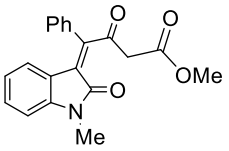
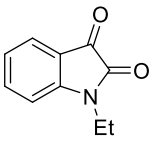
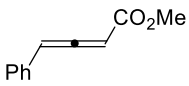
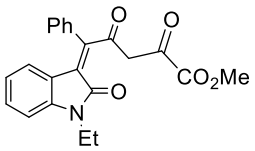
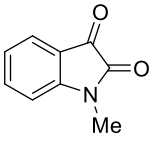
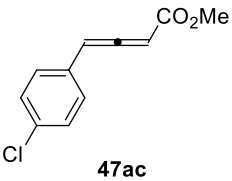
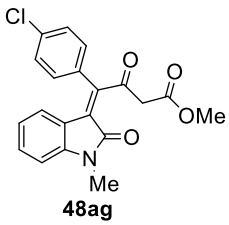
Table 2.2. Continues…….

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
17	 **46q**	 **47a**	 **48q**	71
18	 **46r**	 **47a**	 **48r**	72
19	 **46s**	 **47a**	 **48s**	69

Reaction conditions: 1 equiv. of isatins **46** (50 mg) & 1.5 equiv. of allenoate (**47a**) and 1.5 equiv. of TBD in acetonitrile (3 mL) at room temperature for 1 h

The scope of the protocol was subsequently extended by employing diverse aryl allenoates **47** (**Table 2.3**). The results indicated that aryl allenoates with different substituents on the phenyl ring as well as various ester substituents efficiently underwent reaction with *N*-methyl isatin (**46a**) and its derivatives furnishing the respective products in moderate to good yields. Nonetheless, the aryl allenoates with smaller ester groups such as -CO_2Me (**Table 2.2**, 47 - 84%) exhibited higher yields compared to the bulkier -CO_2Bn (**Table 2.2**, 52 - 64%) and -$CO_2{}^t$Bu (**Table 2.2**, 53 - 67%). The γ-thiophene allenoate resulted in the product only in trace (**48ao**). Furthermore, the furyl allenoate failed to yield the product (**48ap**), probably because the heteroaromatic ring reduced the resonance stabilisation of the zwitterionic intermediate **A**. The 3-methyl allenoate also was unsuccessful in delivering the product **48aq**.

Table 2.3. Scope of the reaction to the diversity of allenoates

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1	 **46a**	 **47aa**	 **48aa**	**67**
2	 **46g**	 **47aa**	 **48ab**	**53**
3	 **46f**	 **47aa**	 **48ac**	**59**
4	 **46e**	 **47ab**	 **48ad**	**77**
5	 **46a**	 **47ab**	 **48ae**	**80**
6	 **46p**	 **47ab**	 **48af**	**79**
7	 **46a**	 **47ac**	 **48ag**	**67**

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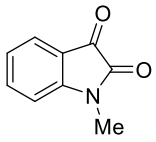
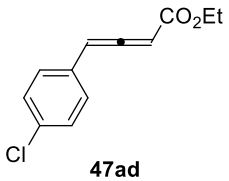
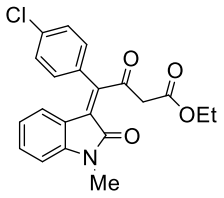
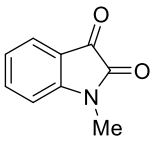
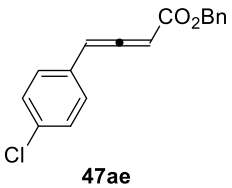
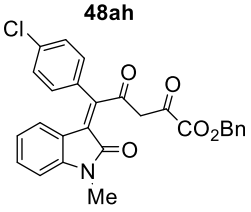
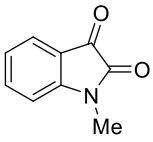
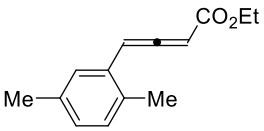
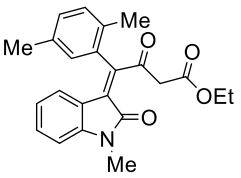
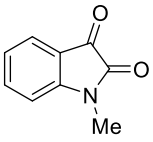
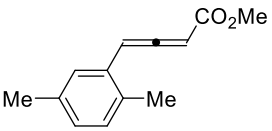
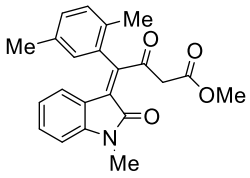
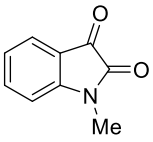
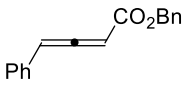
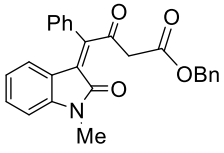
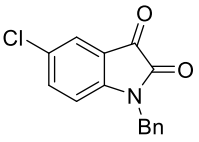
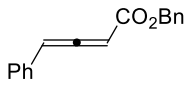
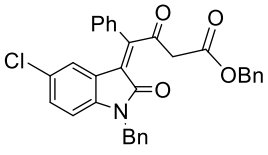
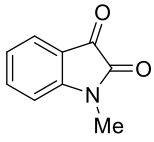
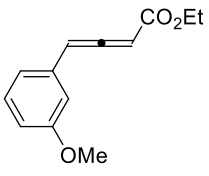
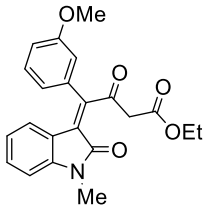
8	 **46a**	 **47ad**	 **48ah**	60
9	 **46a**	 **47ae**	 **48ai**	58
10	 **46a**	 **47af**	 **48aj**	45
11	 **46a**	 **47ag**	 **48ak**	47
12	 **46a**	 **47ah**	 **48al**	64
13	 **46t**	 **47ah**	 **48am**	52
14	 **46a**	 **47ai**	 **48an**	67

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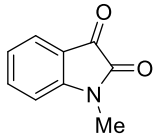
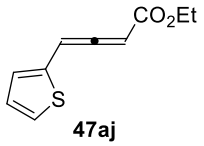
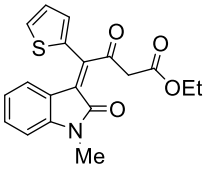
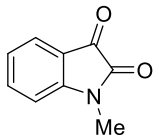
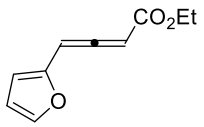
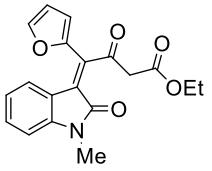
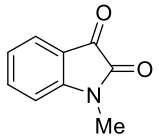
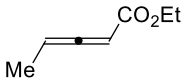
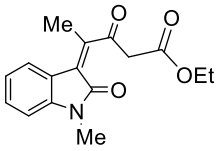
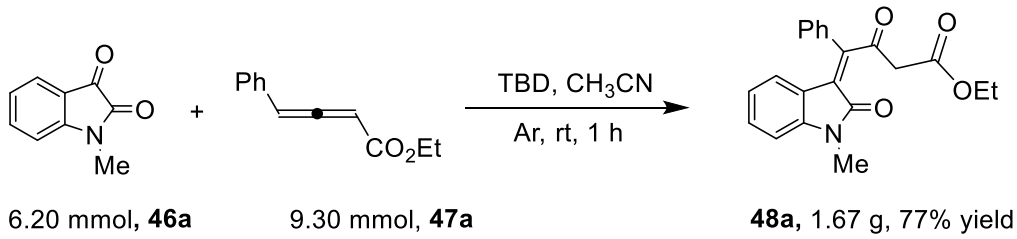
15	 **46a**	 **47aj**	 **48ao**	trace
16	 **46a**	 **47ak**	 **48ap**	ND
17	 **46a**	 **47al**	 **48aq**	ND

Reaction conditions: 1 equiv. of isatins **46** (50 mg) & 1.5 equiv. of allenoates (**47**) and 1.5 equiv. of TBD in acetonitrile (3 mL) at room temperature for 1 h

To demonstrate the efficiency and practicality of the developed protocol, a gram-scale reaction was carried out using 6.20 mmol of *N*-methyl isatin (**46a**) and 9.30 mmol of ethyl 4-phenylbuta-2,3-dienoate (**47a**), affording the corresponding product **48a** in 77% yield (1.67 g) (**Scheme 2.14**).

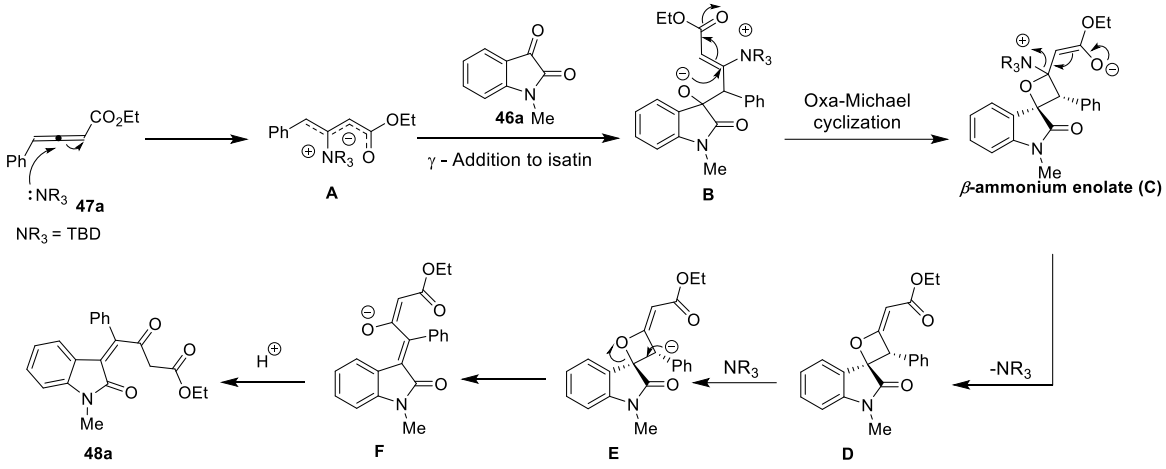


Scheme 2.14. Gram-scale synthesis of 3-alkenyl-2-oxindole

2.5. Plausible mechanism

Based upon the above results and literature precedents,[25,27] a plausible mechanism for the synthesis of 3-alkenyl-2-oxindole is proposed in **Scheme 2.15**. The first step involves the nucleophilic attack of the Lewis base (NR_3) at the β-carbon of γ-aryl allenoate, generating a zwitterionic intermediate **A**. The generated zwitterion **A** then undergoes γ-addition to *N*-

protected isatin **1** resulting in intermediate **B**. The subsequent oxo-Michael cyclization of intermediate **B** generates *β*-ammonium intermediate **C**. This follows the removal of the Lewis base catalyst, which delivers spiro-oxetane oxindole **D**. Subsequently, the presence of excess Lewis base promotes ring cleavage of intermediate **D** at the C–O bond, leading to the formation of intermediate **E**, which then undergoes isomerization to yield the stable acyclic product, *β*-keto ester **48a**.

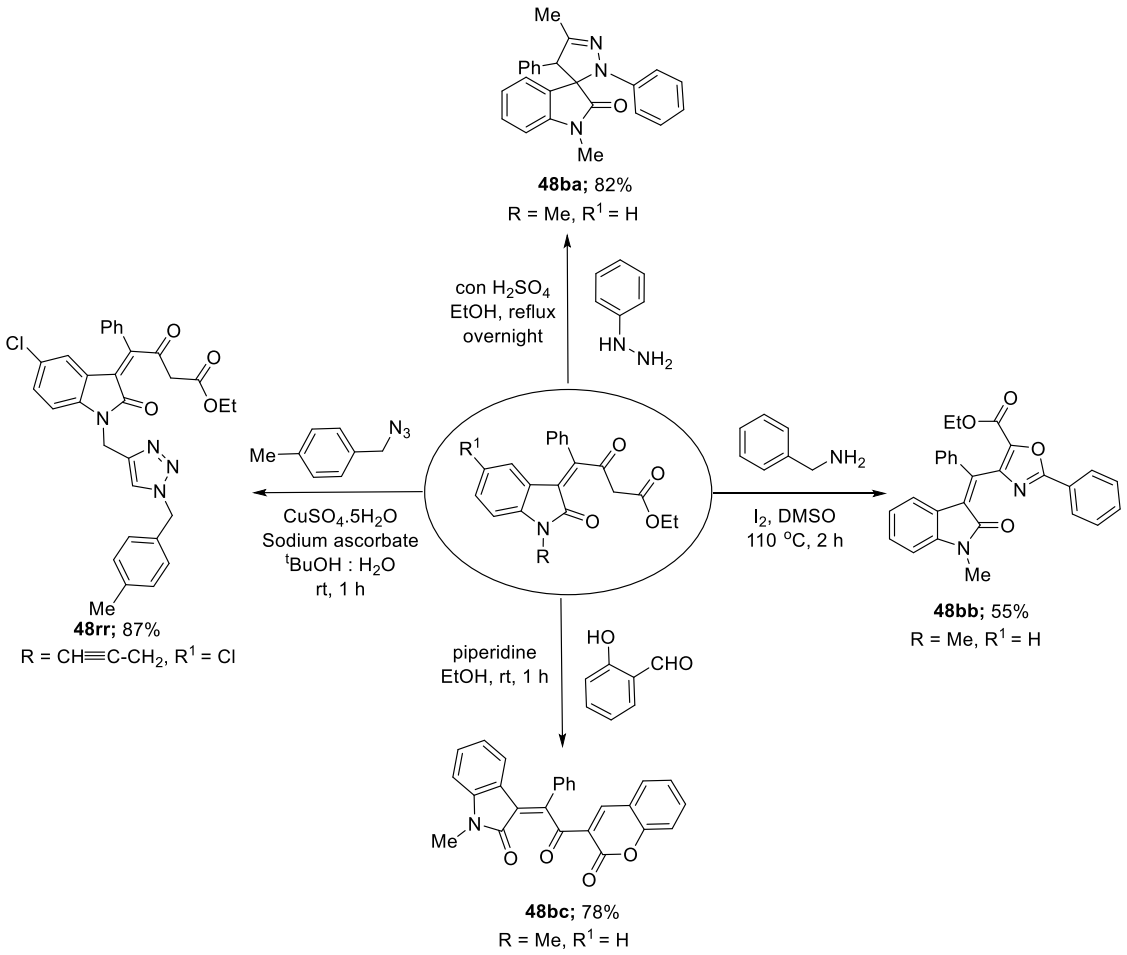


Scheme 2.15. Proposed mechanistic pathway

2.6. Last stage functionalization of 3-alkenyl-2-oxindoles

The significance of *β*-dicarbonyl compounds as an important precursor employed in synthetic organic chemistry cannot be overstated. 1,3-dicarbonyls are frequently used as versatile synthons in multistep and complex chemical synthesis to construct a broad diversity of heterocycles.[28] Furthermore, heterocyclic analogues of oxindoles have revealed a fascinating array of pharmacological activities *viz.* anti-HIV, anti-TB, antibacterial, anticonvulsant, anticancer, anti-inflammatory, and antidiabetic properties[29] (**Figure 2.1**). In this assessment, we aimed to explore the synthetic utility of the obtained 3-alkenyl-2-oxindoles (**48**) by transforming them into novel heterocyclic compounds (**Scheme 2.16**). First, we successfully synthesized the biologically significant dihydrospiro[indoline-3,3'-pyrazol]-2-one (**48ba**), by reacting ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (**48a**) with phenylhydrazine in ethanol under reflux temperature affording **48ba** in 82% yield. When the 3-alkenyl-2-oxindoles (**48a**) are treated with benzylamine under an I_2 /DMSO mediated reaction afforded the 2-oxoindolinylidene oxazole-carboxylate (**48bb**) in 55% yield. Furthermore, 2-oxo-2H-chromen-3-yl-phenylethylidene indolin-2-one (**48bc**) was obtained from 3-alkenyl-2-oxindoles (**48a**) by

reacting with salicylaldehyde in ethanol under basic media in a 78% yield. In addition, we demonstrated the synthetic applicability of compound **48r**, which underwent a Click reaction to afford the oxindole-appended triazole **48rr** in 87% yield. Hence, the established synthetic transformations further signify the importance of 3-alkenyl-2-oxindoles and the protocol reporting herein.



Scheme 2.16. Synthetic utility of 3-alkenyl-2-oxindoles

2.7. Conclusion

In conclusion, we have established an effective approach to the stereoselective synthesis of functionalized 3-alkenyl-2-oxindoles by the TBD-mediated tandem reaction of isatins and aryl-allenoates. This protocol employs widely accessible substrates, *viz.* isatins and aryl-allenoates that gave the corresponding products in substantial yields under mild reaction conditions with wide substrate scope and high functional group tolerance. Furthermore, it is the first protocol to utilize allenoate reactivity to build structurally varied 3-alkenyl-2-oxindole motifs. Additionally, this approach enables us to reduce the synthesis path that previously demanded multiple steps into a single one. We have also demonstrated the

synthetic utility of 3-alkenyl-2-oxindoles to convert them into novel oxindole-appended heterocyclic scaffolds. Hence, we believe that the obtained 3-alkenyl-2-oxindoles might draw the attention of synthetic and medicinal chemists for the rapid and efficient syntheses of hitherto unattainable highly functionalized target molecules for therapeutic uses.

2.8. General methods

All the chemicals and solvents (anhydrous) were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out under an argon atmosphere unless otherwise noted. Column chromatography was performed using silica gel (100-200 mesh), and a hexane-ethyl acetate mixture was used for elution. NMR spectra were recorded at 500 (^{1}H) and 125 (^{13}C) MHz on a Bruker ASCEND^{TM} spectrometer by using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) for ^{1}H NMR spectra are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 7.27, singlet). Coupling constants (*J*) are given in Hertz (Hz), and multiplicities were represented as s, d, t, q, m, and dd for singlet, doublet, triplet, quartet, multiplet, and doublet of a doublet, respectively. Chemical shifts (δ) for ^{13}C NMR are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 77.03, triplet). Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive mass spectrometer. Melting points were determined on a Buchi melting point apparatus and were uncorrected. All the substituted allenoates were synthesized using known procedures.[30] The *N*-protection of isatins was carried out using literature reports.[31]

2.9. General experimental procedure

2.9.1. Procedure for the *N*-protection of isatins (46)[31]

A solution of isatin (50 mg,1.0 equiv.) in DMF (10 mL) was cooled to 0 °C and NaH (60% dispersion in mineral oil, 2.0 equiv.) was added slowly. After stirring for 15 min at 0 °C, alkyl halide/ benzyl halide (1.2 equiv.) was added *via* syringe while maintaining the reaction mixture at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the slow addition of sat. NH_4Cl solution (5 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: 100 - 200 mesh) using ethyl acetate and hexane as the eluent.

2.9.2. Procedure for the synthesis of allenoates (47)[30]

A 250 mL three-necked round-bottomed flask is equipped with a nitrogen inlet, a 100 mL pressure-equalizing dropping funnel fitted with a gas outlet, and a Teflon-coated magnetic stirring bar. The flask is charged with 20 mL of dichloromethane and 5.0 g (1 equiv.) of (carbethoxymethylene)triphenylphosphorane and flushed with nitrogen. The yellow solution is stirred at 25 °C as a solution of triethylamine (1.2 equiv.) in 10 mL of dichloromethane is added dropwise over 5 min. After 10 min, acyl chloride (1.2 equiv.) in 10 mL of dichloromethane is added dropwise to the vigorously stirred solution over 15 min. Stirring is continued for an additional 0.5 h, after which 100 mL of diethyl ether was added and kept at 0 °C overnight. The precipitate is removed by filtration through a coarse, sintered-glass Buchner funnel, and the filtrates are combined and concentrated at reduced pressure. The product was then purified by column chromatography (silica gel: 100 - 200 mesh) using ethyl acetate and hexane as the eluent.

2.9.3. General experimental procedure for the synthesis of 3-alkenyl-2-oxindoles (48)

A mixture of isatin (50 mg, 1.0 equiv.) and the aryl allenoate (1.5 equiv.) in acetonitrile (2 mL) was taken in an oven-dried 20 mL reaction tube (Carousel 12 Plus Reaction station) under Argon atmosphere, stirred for about 5 min at room temperature. To this solution, 1.5 equiv. of TBD was added and continued stirring for 1 h. After completion of the reaction, the product was extracted with ethyl acetate (3 x 10mL) and evaporated in *vacuo*. Then, the obtained residue was purified by using silica column chromatography (100 – 200 mesh) using a mixture of hexane and ethyl acetate (85:15) as eluent afforded 3-alkenyl-2-oxindole.

2.9.4. Procedure for gram-scale synthesis of 3-alkenyl-2-oxindoles (48a)

A mixture of *N*-methyl isatin **46a** (1 g, 6.20 mmol.) and ethyl 4-phenylbuta-2,3-dienoate **47a** (1.75 g, 9.30 mmol.) in acetonitrile (5 mL) was taken in an oven-dried 20 mL reaction tube (Carousel 12 Plus Reaction station) under Argon atmosphere, stirred for about 5 min at room temperature. To this solution, TBD (1.29 g, 9.30 mmol) was added and continued stirring for 1 h. After completion of the reaction, the product was extracted with ethyl acetate (3 x 10mL) and evaporated in *vacuo*. Then, the obtained residue was purified by using silica column chromatography (100 – 200 mesh) using a mixture of hexane and ethyl

acetate (85:15) as eluent afforded ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (**48a**) in 77% (1.67 g) yield.

2.10. Experimental procedures for late-stage diversification

2.10.1. General experimental procedure for the synthesis of 1,5'-dimethyl-2',4'-diphenyl 2',4'-dihydrospiro[indoline-3,3'-pyrazol]-2-one (48ba)

The compound **48a** (50 mg, 0.143 mmol) and phenyl hydrazine (14.1 µL,0.143 mmol) were dissolved in 2 mL of EtOH and added 1 drop of conc. H_2SO_4. The mixture was then refluxed overnight in an oil bath. The white precipitate formed was filtered, washed with EtOH and dried to obtain **48ba** (43 mg) in 82% yield.

2.10.2. General experimental procedure for the synthesis of ethyl (*Z*)-4-((1-methyl-2-oxoindolin-3-ylidene)(phenyl)methyl)-2-phenyloxazole-5-carboxylate (48bb)

A solution of **48a** (50 mg, 0.143 mmol) and iodine (36 mg, 0.143 mmol) in DMSO (2 mL) was allowed to stir at 110 ^oC in an oil bath. After 1 h benzylamine (19.0 µL, 0.172 mmol) was added to the above mixture and continued stirring at 110 ^oC for 2 h. After completion of the reaction, the content was extracted with ethyl acetate, washed with brine and the compound was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **48bb** (35 mg, 55%) was isolated as a yellow gummy liquid by column chromatography (silica gel: 100 – 200 mesh) using ethyl acetate: hexane (30: 70) as the eluent.

2.10.3. General experimental procedure for the synthesis of (*Z*)-1-methyl-3-(2-oxo-2-(2-oxo-2H-chromen-3-yl)-1-phenylethylidene)indolin-2-one (48bc)

A mixture of **48a** (50 mg, 0.143 mmol), salicylaldehyde (14.9 µL, 0.143 mmol and piperidine (1.4 µL, 10 mol%) in EtOH (2 mL) was stirred at room temperature for 15 min. The orange precipitate formed was filtered, washed with EtOH and dried to obtain **48bc** (45 mg) in 78% yield.

2.10.4. General experimental procedure for the synthesis of ethyl (*Z*)-4-(5-chloro-1-((1-(4-methylbenzyl)-1H-1,2,3-triazol-5-yl)methyl)-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48rr)

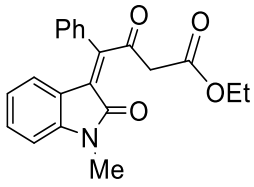
To a solution of 4-methyl benzyl azide (18 mg, 0.123 mmol) and compound **48r** (50 mg, 0.123 mmol) in ^{t}BuOH - water (1:2) mixture, $CuSO_4.5H_2O$ (3 mg, 0.0123 mmol) and

sodium ascorbate (6.1 mg, 0.031 mmol) were added and the reaction mixture was allowed to stir at room temperature, progress of the reaction was monitored by TLC. After completion of the reaction, the content was extracted with ethyl acetate, washed with brine and the compound was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **48rr** (59 mg, 87%) was isolated as a yellow gummy liquid by column chromatography (silica gel: 100 – 200 mesh) using ethyl acetate : hexane (30 : 70) as the eluent.

2.11. Characterization data of 3-alkenyl-2-oxindoles (48a - 48aq)

Ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48a)

The compound **48a** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), ethyl 4-phenylbuta-2,3-dienoate (88 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48a** was obtained as a yellow gummy liquid in 79% (86 mg) yield.



48a

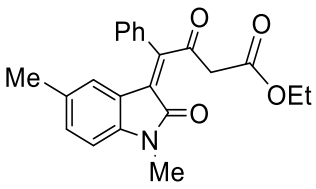
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.42 (s, 3H), 7.17 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.68 (t, *J* = 7.0 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 3.16 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.1, 166.7, 166.6, 149.0,144.8, 132.4, 130.4, 130.0, 129.2, 128.3, 125.3, 123.3, 122.1, 120.4, 108.4, 61.2, 48.8, 26.0, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{19}NO_4Na, M+Na]^+$: 372.1206; **Found**: 372.1217.

Ethyl (*Z*)-4-(1,5-dimethyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48b)

The compound **48b** was synthesized following the procedure described in **section 2.9** using 1,5-dimethylindoline-2,3-dione (50 mg, 0.28 mmol), ethyl 4-phenylbuta-2,3-dienoate (81 mg, 0.42 mmol) and TBD (60 mg, 0.42 mmol) in acetonitrile (3 mL) at room temperature. The product **48b** was obtained as a yellow gummy liquid in 78% (81 mg) yield.



48b

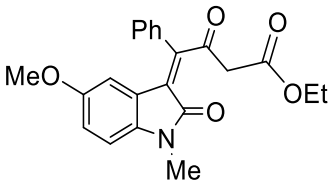
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.49 (m, 2H), 7.41 – 7.32 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 3.14 (s, 3H), 2.02 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.1, 166.8, 166.6, 148.7, 142.6, 132.4, 131.4, 130.8, 130.0, 129.1, 128.4, 125.5, 124.1, 120.4, 108.1, 61.2, 48.8, 26.0, 21.0, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{21}NO_4Na, M+Na]^+$: 386.1363; **Found**: 386.1362.

Ethyl (*Z*)-4-(5-methoxy-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48c)

The compound **48c** was synthesized following the procedure described in **section 2.9** using 5-methoxy-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), ethyl 4-phenylbuta-2,3-dienoate (74 mg, 0.39 mmol) and TBD (55 mg, 0.39 mmol) in acetonitrile (3 mL) at room temperature. The product **48c** was obtained as a yellow gummy liquid in 84% (83 mg) yield.



43c

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (s, 2H), 7.49 (s, 3H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 1H), 6.36 (s, 1H), 4.06 (q, *J* = 6.5 Hz, 2H), 3.85 (s, 2H), 3.53 (s, 3H), 3.20 (s, 3H), 1.14 (t, *J* = 6.5 Hz, 3H).

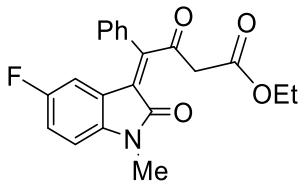
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.0, 166.6, 155.2, 149.1, 138.7, 132.3, 130.1, 129.2, 128.3, 125.7, 121.2, 115.4, 110.1, 108.7, 61.2, 55.5, 48.8, 26.0, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{21}NO_5Na, M+Na]^+$: 402.1312; **Found**: 402.1312.

Ethyl (*Z*)-4-(5-fluoro-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48d)

The compound **48d** was synthesized following the procedure described in **section 2.9** using 5-fluoro-1-methylindoline-2,3-dione (50 mg, 0.27 mmol), ethyl 4-phenylbuta-2,3-dienoate (79 mg, 0.41 mmol) and TBD (58 mg, 0.41 mmol) in acetonitrile (3 mL) at room

temperature. The product **48d** was obtained as a yellow gummy liquid in 62% (63 mg) yield.



48d

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (m, 5H), 6.97 (t, *J* = 8.5 Hz,1H), 6.72 – 6.75 (m, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 2H), 3.24 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H).

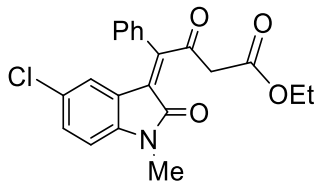
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.7, 166.6, 166.5, 159.4 (d, *J* = 237.5 Hz), 150.4, 140.9, 131.8, 130.4, 129.4, 128.1, 124.9, 121.5, (d, *J* = 8.7 Hz), 21.4, 116.7 (d, *J* = 23.7 Hz), 111.1 (d, *J* = 26.2 Hz), 108.7 (d, *J* = 8.7 Hz), 61.3, 48.7, 26.1, 13.9.

^{19}F NMR (371 MHz, $CDCl_3$): δ 120.5.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}FNO_4Na, M+Na]^+$: 390.1112; **Found**: 390.1114.

Ethyl (*Z*)-4-(5-chloro-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48e)

The compound **48e** was synthesized following the procedure described in **section 2.9** using 5-chloro-1-methylindoline-2,3-dione (50 mg, 0.25 mmol), ethyl 4-phenylbuta-2,3-dienoate (72 mg, 0.38 mmol) and TBD (53 mg, 0.38 mmol) in acetonitrile (3 mL) at room temperature. The product **48e** was obtained as a yellow solid in 74% (73 mg) yield.



48e

Mp: 130 - 131 ^{o}C

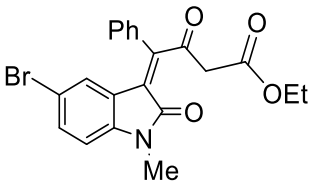
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 5H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.64 – 6.68 (m, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 3.15 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 197.6, 166.4, 166.4, 150.6, 143.2, 131.8, 130.5, 130.0, 129.3, 128.2, 127.5, 124.4, 123.4, 121.8, 109.2, 61.2, 48.7, 26.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}ClNO_4Na, M+Na]^+$: 406.0817, **Found**: 406.0834.

Ethyl (*Z*)-4-(5-bromo-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48f)

The compound **48f** was synthesized following the procedure described in **section 2.9** using 5-bromo-1-methylindoline-2,3-dione (50 mg, 0.20 mmol), ethyl 4-phenylbuta-2,3-dienoate (59 mg, 0.31 mmol) and TBD (43 mg, 0.31 mmol) in acetonitrile (3 mL) at room temperature. The product **48f** was obtained as a yellow gummy liquid in 79% (70 mg) yield.



48f

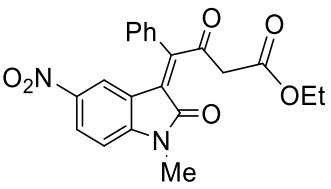
^{1}H NMR (500 MHz, $CDCl_3$): 7.52 (s, 5H), 7.37 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.05 (q, *J* = 6.0 Hz, 2H), 3.82 (s, 2H), 3.21 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.6, 166.4, 166.3, 150.6, 143.6, 132.9, 131.7, 130.5, 129.3, 128.2, 126.1, 124.2, 122.2, 114.7, 109.8, 61.3, 48.7, 26.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}BrNO_4Na, M+Na]^+$: 450.0311; **Found**: 450.0300.

Ethyl (*Z*)-4-(1-methyl-5-nitro-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48g)

The compound **48g** was synthesized following the procedure described in **section 2.9** using 1-methyl-5-nitroindoline-2,3-dione (50 mg, 0.24 mmol), ethyl 4-phenylbuta-2,3-dienoate (68 mg, 0.36 mmol) and TBD (51 mg, 0.36 mmol) in acetonitrile (3 mL) at room temperature. The product **48g** was obtained as a yellow solid in 58% (55 mg) yield.



43g

Mp: 126 - 128 °C

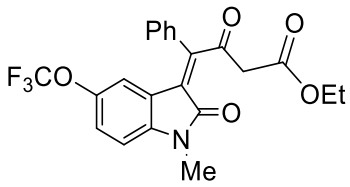
^{1}H NMR (500 MHz, $CDCl_3$): 8.15 (d, *J* = 8.5 Hz, 1H), 7.65 (s, 1H), 7.49 – 7.51 (m, 5H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 3.24 (s, 3H), 1.08 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.2, 166.9, 166.3, 152.7, 149.3, 143.0, 131.2, 131.1, 129.6, 128.1, 126.7, 123.1, 120.8, 118.7, 108.0, 61.4, 48.6, 26.5, 13.97.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}N_2O_6Na, M+Na]^+$: 417.1057; **Found**: 417.1065.

Ethyl (*Z*)-4-(1-methyl-2-oxo-5-(trifluoromethoxy)indolin-3-ylidene)-3-oxo-4-phenyl butanoate (48h)

The compound **48h** was synthesized following the procedure described in **section 2.9** using 1-methyl-5-(trifluoromethoxy)indoline-2,3-dione (50 mg, 0.20 mmol), ethyl 4-phenylbuta-2,3-dienoate (57 mg, 0.30 mmol) and TBD (42 mg, 0.30 mmol) in acetonitrile (3 mL) at room temperature. The product **48h** was obtained as a yellow gummy liquid in 54% (48 mg) yield.



48h

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (m, 5H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.57 (s, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 3.16 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

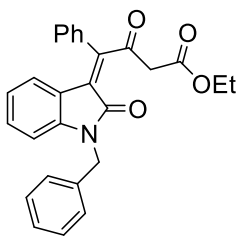
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 166.5, 166.4, 150.9, 144.0, 143.2, 131.7, 130.5, 129.3, 128.1, 124.4, 123.2, 121.4, 121.3, 119.3, 116.9, 108.7, 61.3, 48.6, 26.1, 13.9.

^{19}F NMR (371 MHz, $CDCl_3$): δ 58.6.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{18}F_3NO_5Na, M+Na]^+$: 456.1029; **Found**: 456.1049.

Ethyl (*Z*)-4-(1-benzyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48i)

The compound **48i** was synthesized following the procedure described in **section 2.9** using 1-benzylindoline-2,3-dione (50 mg, 0.21 mmol), ethyl 4-phenylbuta-2,3-dienoate (59 mg, 0.31 mmol) and TBD (44 mg, 0.31 mmol) in acetonitrile (3 mL) at room temperature. The product **48i** was obtained as a yellow gummy liquid in 65% (58 mg) yield.



48i

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.52 (m, 2H), 7.42 – 7.43 (m, 3H), 7.24 – 7.25 (m, 4H), 7.18 – 7.21 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.61 – 6.66 (m, 2H), 4.85 (s, 2H), 3.98 (q, *J* = 6.5 Hz, 2H), 3.79 (s, 2H), 1.06 (t, *J* = 7.0 Hz, 3H).

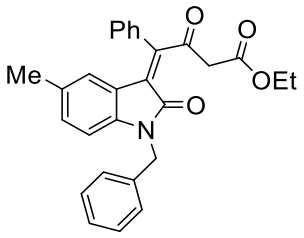
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.1, 166.8, 166.6, 149.2, 143.9, 135.5, 132.4, 130.3, 130.0, 129.2, 128.8, 128.3,

127.7, 127.3, 125.1, 123.4, 122.1, 120.5, 109.4, 61.2, 48.8, 43.7, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{27}H_{23}NO_4Na, M+Na]^+$: 448.1519; **Found**: 448.1538.

Ethyl (*Z*)-4-(1-benzyl-5-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48j)

The compound **48j** was synthesized following the procedure described in **section 2.9** using 1-benzyl-5-methylindoline-2,3-dione (50 mg, 0.20 mmol), ethyl 4-phenylbuta-2,3-dienoate (56 mg, 0.30 mmol) and TBD (41 mg, 0.30 mmol) in acetonitrile (3 mL) at room temperature. The product **48j** was obtained as a yellow gummy liquid in 63% (55 mg) yield.



48j

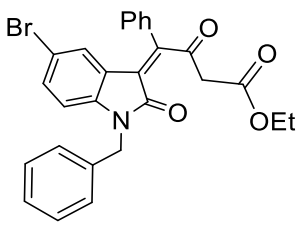
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.51 (m, 2H), 7.42 – 7.43 (m, 3H), 7.22 – 7.26 (m, 4H), 7.17 – 7.19 (m, 1H), 6.84 – 6.86 (d, *J* = 8.0 Hz, 1H), 6.48 – 6.52 (m, 2H), 4.83 (s, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 2H), 1.98 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.2, 166.8, 166.6, 148.9, 141.8, 135.6, 132.5, 131.5, 130.7, 130.0, 129.1, 128.7, 128.4, 127.6, 127.3, 125.4, 124.1, 120.5, 109.1, 61.2, 48.9, 43.6, 21.0, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{28}H_{25}NO_4Na, M+Na]^+$: 462.1676; **Found**: 462.1685.

Ethyl (*Z*)-4-(1-benzyl-5-bromo-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48k)

The compound **48k** was synthesized following the procedure described in **section 2.9** using 1-benzyl-5-bromoindoline-2,3-dione (50 mg, 0.16 mmol), ethyl 4-phenylbuta-2,3-dienoate (45 mg, 0.24 mmol) and TBD (33 mg, 0.24 mmol) in acetonitrile (3 mL) at room temperature. The product **48k** was obtained as a yellow gummy liquid in 61% (49 mg) yield.



48k

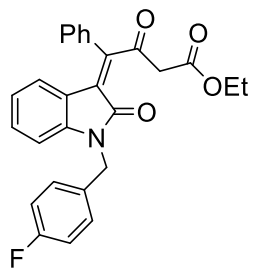
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 – 7.49 (m, 2H), 7.46 (s, 3H), 7.24 – 7.27 (m, 2H), 7.21 (s, 1H), 7.19 – 7.20 (m , 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.82 (s, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 4.84 (s, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 1.06 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.7, 166.5, 166.3, 150.9, 142.7, 135.1, 132.8, 131.8, 130.5, 129.4, 128.9, 128.2, 127.8, 127.3, 126.2, 124.1, 122.4, 114.8, 110.8, 61.3, 48.7, 43.7, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{27}H_{22}BrNO_4Na, M+Na]^+$: 526.0624; **Found**: 526.0625.

Ethyl (Z)-4-(1-(4-fluorobenzyl)-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48l)

The compound **48l** was synthesized following the procedure described in **section 2.9** using 1-(4-fluorobenzyl)indoline-2,3-dione (50 mg, 0.19 mmol), ethyl 4-phenylbuta-2,3-dienoate (55 mg, 0.29 mmol) and TBD (41 mg, 0.29 mmol) in acetonitrile (3 mL) at room temperature. The product **48l** was obtained as a yellow gummy liquid in 56% (49 mg) yield.



48l

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.50 (m, 2H), 7.42 – 7.43 (m, 3H), 7.21 - 7.24 (m, 2H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 4.82 (s, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 2H), 1.06 (t, *J* = 7.0 Hz, 3H).

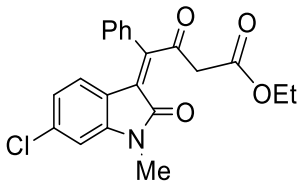
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.0, 166.8, 166.5, 163.2 (d, *J* = 245.0 Hz), 149.4, 143.7, 132.4, 131.3, 130.3 (d, *J* = 28.75 Hz), 129.2, 129.1 (d, *J* = 7.5 Hz), 128.3, 125.0, 123.5, 122.2, 120.6, 115.8 (d, *J* = 21.25 Hz), 109.2, 61.2, 48.8, 43.0, 13.9.

^{19}F NMR (371MHz, $CDCl_3$): δ 114.5.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{27}H_{22}FNO_4Na, M+Na]^+$: 466.1425; **Found**: 466.1431.

Ethyl (*Z*)-4-(6-chloro-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48m)

The compound **48m** was synthesized following the procedure described in **section 2.9** using 6-chloro-1-methylindoline-2,3-dione (50 mg, 0.25 mmol), ethyl 4-phenylbuta-2,3-dienoate (72 mg, 0.38 mmol) and TBD (53 mg, 0.38 mmol) in acetonitrile (3 mL) at room temperature. The product **48m** was obtained as a yellow solid in 72% (71 mg) yield.



48m

Mp: 95 - 97 ^{o}C

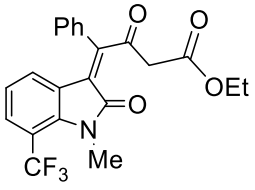
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44 – 7.45 (m, 2H), 7.42 (s, 3H), 6.72 (s, 1H), 6.67 (q, *J* = 8.5 Hz, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 3.14 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 197.8, 166.7, 166.5, 149.5, 145.8, 136.2, 132.1, 130.2, 129.3, 128.2, 124.3, 124.1, 122.0, 118.9, 109.1, 61.2, 48.7, 26.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}ClNO_4Na, M+Na]^+$: 406.0817; **Found**: 406.0824.

Ethyl (*Z*)-4-(1-methyl-2-oxo-7-(trifluoromethyl)indolin-3-ylidene)-3-oxo-4-phenyl butanoate (48n)

The compound **48n** was synthesized following the procedure described in **section 2.9** using 1-methyl-7-(trifluoromethyl)indoline-2,3-dione (50 mg, 0.22 mmol), ethyl 4-phenylbuta-2,3-dienoate (62 mg, 0.33 mmol) and TBD (45 mg, 0.33 mmol) in acetonitrile (3 mL) at room temperature. The product **48n** was obtained as a yellow gummy liquid in 58% (53 mg) yield.



48n

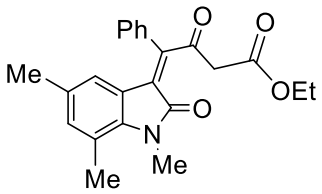
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44 (s, 6H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 1H), 3.75 (s, 2H), 3.37 (s, 3H), 1.08 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 197.6, 167.5, 166.4, 150.9, 142.3, 132.0, 130.3, 129.4, 128.1, 127.9 (q, *J* = 5.9 Hz).126.4, 122.9 (d, *J* = 17.5 Hz), 121.3, 113.0, 61.3, 48.5, 13.9.

^{19}F NMR (371MHz, $CDCl_3$): δ 53.3.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{18}F_3NO_4Na, M+Na]^+$: 440.1080; **Found**: 440.1081.

Ethyl (*Z*)-3-oxo-4-phenyl-4-(1,5,7-trimethyl-2-oxoindolin-3-ylidene)butanoate (48o)



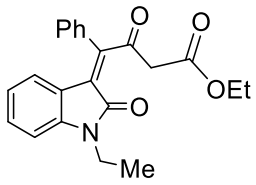
48o

.

Yield: Product obtained in trace.

Ethyl (*Z*)-4-(1-ethyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48p)

The compound **48p** was synthesized following the procedure described in **section 2.9** using 1-ethylindoline-2,3-dione (50 mg, 0.28 mmol), ethyl 4-phenylbuta-2,3-dienoate (81 mg, 0.42 mmol), and TBD (60 mg, 0.42 mmol) in acetonitrile (3 mL) at room temperature. The product **48p** was obtained as a white solid in 77% (80 mg) yield.



48p

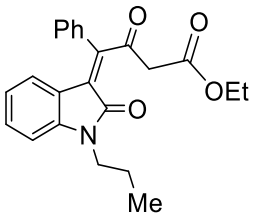
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 2H), 7.41 (s, 3H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.71 – 6.75 (m, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 3.98 (q, *J* = 6.8 Hz, 2H), 3.77 (s, 2H), 3.73 (q, *J* = 7.0 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.2, 166.6, 166.3, 148.8, 143.9, 132.5, 130.3, 129.9, 129.2, 128.3, 125.4, 123.5, 121.9, 120.6, 108.5, 61.2, 48.8, 34.6, 13.9, 12.7.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{21}NO_4Na, M+Na]^+$: 386.1363; **Found**: 386.1418.

Ethyl (*Z*)-3-oxo-4-(2-oxo-1-propylindolin-3-ylidene)-4-phenylbutanoate (48q)

The compound **48q** was synthesized following the procedure described in **section 2.9** using 1-propylindoline-2,3-dione (50 mg, 0.26 mmol), ethyl 4-phenylbuta-2,3-dienoate (75 mg, 0.39 mmol), and TBD (55 mg, 0.39 mmol) in acetonitrile (3 mL) at room temperature. The product **48q** was obtained as a yellow gummy liquid in 71% (71 mg) yield.



48q

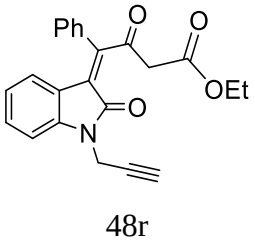
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 2H), 7.14 (s, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.72 (t, *J* = 8.5 Hz, 2H), 6.66 (t, *J* = 7.5 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 2H), 3.61 (t, *J* = 7.0 Hz, 1H), 1.62 – 1.67 (m, 2H), 1.06 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.2, 166.7, 166.6, 148.8, 144.3, 132.5, 130.3, 129.9, 129.2, 128.3, 125.4, 123.5, 121.8, 120.5, 108.6, 61.2, 48.8, 41.5, 20.9, 13.9, 11.4.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for [$C_{23}H_{23}NO_4Na$, $M+Na]^+$: 400.1519; **Found**: 400.1533.

Ethyl (*Z*)-3-oxo-4-(2-oxo-1-(prop-2-yn-1-yl)indolin-3-ylidene)-4-phenylbutanoate (48r)

The compound **48r** was synthesized following the procedure described in **section 2.9** using 1-(prop-2-yn-1-yl)indoline-2,3-dione (50 mg, 0.27 mmol), ethyl 4-phenylbuta-2,3-dienoate (76 mg, 0.40 mmol), and TBD (56 mg, 0.40 mmol) in acetonitrile (3 mL) at room temperature. The product **48r** was obtained as a yellow solid in 72% (72 mg) yield.



48r

Mp: 93 - 94 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 2H), 7.43 (s, 3H), 7.19 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.73 (q, *J* = 7.5 Hz, 2H), 4.46 (s, 2H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 2.18 (s, 1H), 1.08 (t, *J* = 7.0 Hz, 3H).

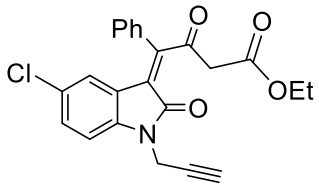
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.9, 166.5, 165.8, 149.7, 142.8, 132.2, 130.4, 130.1, 129.2, 128.3, 124.8, 123.5, 122.5, 120.5, 109.4, 76.6, 72.5, 61.3, 48.7, 29.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for [$C_{23}H_{19}NO_4Na$, $M+Na]^+$: 396.1206; **Found**: 396.1204.

Ethyl (*Z*)-4-(5-chloro-2-oxo-1-(prop-2-yn-1-yl)indolin-3-ylidene)-3-oxo-4-phenyl butanoate (48s)

The compound **48s** was synthesized following the procedure described in **section 2.9** using 5-chloro-1-(prop-2-yn-1-yl)indoline-2,3-dione (50 mg, 0.23 mmol), ethyl 4-phenylbuta-

2,3-dienoate (64 mg, 0.34 mmol), and TBD (47 mg, 0.34) in acetonitrile (3 mL) at room temperature. The product **48s** was obtained as a yellow gummy liquid in 69% (64 mg) yield.



48s

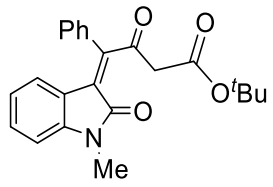
^{1}H NMR (500 MHz, $CDCl_3$): 7.46 (s, 5H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.70 (s, 1H), 4.44 (s, 2H), 3.99 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 2H), 2.19 (s, 1H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 166.3, 165.4, 151.3, 141.2, 131.6, 130.6, 130.1, 129.4, 128.1, 127.9, 123.9, 123.5, 121.9, 110.4, 76.2, 72.8, 61.3, 48.6, 29.2, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{23}H_{18}ClNO_4Na, M+Na]^+$: 430.0817; **Found**: 430.0833.

***Tert*-butyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48aa)**

The compound **48aa** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), *tert*-butyl 4-phenylbuta-2,3-dienoate (101 mg, 0.46 mmol), and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48aa** was obtained as a yellow gummy liquid in 67% (78 mg) yield.



48aa

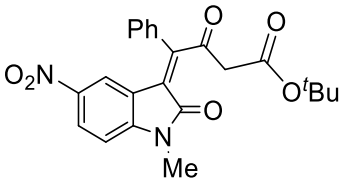
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (s, 2H), 7.51 (s, 3H), 7.24 – 7.28 (m, 1H), 6.76 – 6.82 (m, 3H), 3.78 (s, 2H), 3.25 (s, 3H), 1.34 (s, 9H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.6, 166.7, 165.7, 149.3, 144.7, 132.5, 130.3, 129.9, 129.2, 128.4, 125.1, 123.3, 122.0, 120.5, 108.3, 81.7, 50.1, 27.7, 26.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{23}H_{23}NO_4Na, M+Na]^+$: 400.1519; **Found**: 400.1539.

***Tert*-butyl (*Z*)-4-(1-methyl-5-nitro-2-oxoindolin-3-ylidene)-3-oxo-4-phenyl butanoate (48ab)**

The compound **48ab** was synthesized following the procedure described in **section 2.9** using 1-methyl-5-nitroindoline-2,3-dione (50 mg, 0.24 mmol), *tert*-butyl 4-phenylbuta-2,3-dienoate (79 mg, 0.36 mmol), and TBD (51 mg, 0.36 mmol) in acetonitrile (3 mL) at room temperature. The product **48ab** was obtained as a yellow solid in 53% (54 mg) yield.



48ab

Mp: 148 - 149 °C

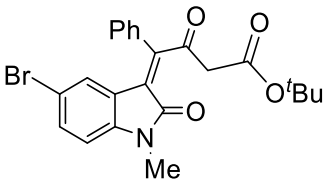
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.5 Hz, 1H), 7.63 (s, 1H), 7.49 – 7.52 (m, 5H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.68 (s, 2H), 3.24 (s, 3H), 1.26 (s, 9H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.7, 166.8, 165.3, 153.1, 149.3, 143.0, 131.3, 131.0, 129.6, 128.1, 126.6, 123.0, 120.9, 118.8, 107.9, 82.0, 49.9, 27.7, 26.4.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{23}H_{22}N_2O_6Na, M+Na]^+$: 445.1370; **Found**: 445.1362.

***Tert*-butyl (*Z*)-4-(5-bromo-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenyl butanoate (48ac)**

The compound **48ac** was synthesized following the procedure described in section 2.9 using 5-bromo-1-methylindoline-2,3-dione (50 mg, 0.20 mmol), *tert*-butyl 4-phenylbuta-2,3-dienoate (68 mg, 0.31 mmol) and TBD (43 mg, 0.31 mmol) in acetonitrile (3 mL) at room temperature. The product **48ac** was obtained as a yellow gummy liquid in 59% (56 mg) yield.



48ac

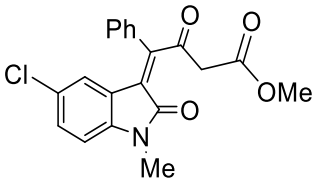
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 – 7.47 (m, 5H), 7.29 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 3.67 (s, 2H), 3.13 (s, 3H), 1.25 (s, 9H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.1, 166.2, 165.5, 151.0, 143.6, 132.8, 131.9, 130.4, 129.3, 128.2, 126.1, 124.1, 122.3, 114.7, 109.7, 81.7, 50.0, 27.7, 26.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{23}H_{22}BrNO_4Na, M+Na]^+$: 478.0624; **Found**: 478.0624.

Methyl (*Z*)-4-(5-chloro-1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48ad)

The compound **48ad** was synthesized following the procedure described in **section 2.9** using 5-chloro-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), methyl 4-phenylbuta-2,3-dienoate (67 mg, 0.38 mmol) and TBD (53 mg, 0.38 mmol) in acetonitrile (3 mL) at room temperature. The product **48ad** was obtained as a yellow solid in 77% (73 mg) yield.



48ad

Mp: 158 - 159 ^{o}C

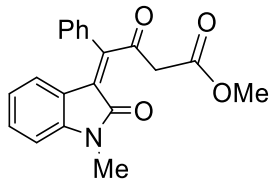
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.45 (s, 5H), 7.14 – 7.16 (m, 1H), 6.69 (s, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 2H), 3.54 (s, 3H), 3.15 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 197.5, 166.9, 166.4, 150.5, 143.2, 131.7, 130.6, 130.1, 129.4, 128.1, 127.5, 124.4, 123.4, 121.7, 109.3, 52.3, 48.3, 26.1.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{20}H_{16}ClNO_4Na, M+Na]^+$: 392.0660; **Found**: 392.0653.

Methyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48ae)

The compound **48ae** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), methyl 4-phenylbuta-2,3-dienoate (81 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48ae** was obtained as a yellow gummy liquid in 80% (83 mg) yield.



48ae

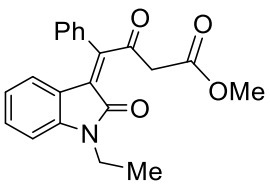
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46 – 7.47 (m, 2H), 7.42 – 7.43 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.72 – 6.73 (m, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 2H), 3.54 (s, 3H), 3.17 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 197.9, 167.0, 166.7, 148.9, 144.8, 132.3, 130.4, 130.1, 129.2, 128.3, 125.3, 123.3, 122.1, 120.4, 108.4, 52.2, 48.4, 26.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{20}H_{17}NO_4Na, M+Na]^+$: 358.1050; **Found**: 358.1060.

Methyl (*Z*)-4-(1-ethyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48af)

The compound **48af** was synthesized following the procedure described in **section 2.9** using 1-ethylindoline-2,3-dione (50 mg, 0.28 mmol), methyl 4-phenylbuta-2,3-dienoate (75 mg, 0.43 mmol) and TBD (60 mg, 0.43 mmol) in acetonitrile (3 mL) at room temperature. The product **48af** was obtained as a yellow solid in 79% (79 mg) yield.



48af

Mp: 158 - 160 °C

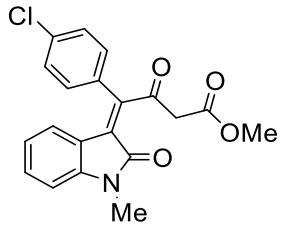
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.47 – 7.48 (m, 2H), 7.42 – 7.43 (m, 3H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 2H), 3.74 (q, *J* = 7.0 Hz, 2H), 3.54 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 198.0, 167.1, 166.3, 148.7, 143.9, 132.3, 130.4, 130.0, 129.2, 128.3, 125.4, 123.6, 121.9, 120.6, 108.5, 52.2, 48.4, 34.6, 12.7.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{19}NO_4Na, M+Na]^+$: 372.1206; **Found**: 372.1214.

Methyl (*Z*)-4-(4-chlorophenyl)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoate (48ag)

The compound **48ag** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), methyl 4-(4-chlorophenyl)buta-2,3-dienoate (97 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48ag** was obtained as a yellow gummy liquid in 67% (77 mg) yield.



48ag

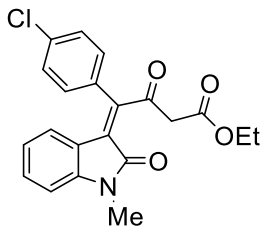
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39 – 7.44 (m, 4H), 7.19 – 7.21 (m, 1H), 6.71 – 6.77 (m, 3H), 3.78 (s, 2H), 3.55 (s, 3H), 3.16 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): δ 197.9, 167.0, 166.6, 147.3, 144.9, 136.3, 130.8, 130.7, 129.8, 129.6, 125.7, 123.3, 122.2, 120.1, 108.6, 52.3, 48.4, 26.1.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{20}H_{16}ClNO_4Na, M+Na]^+$: 392.0660; **Found**: 392.0673.

Ethyl (*Z*)-4-(4-chlorophenyl)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoate (48ah)

The compound **48ah** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), ethyl 4-(4-chlorophenyl)buta-2,3-dienoate (104 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48ah** was obtained as a yellow gummy liquid in 60% (71 mg) yield.



48ah

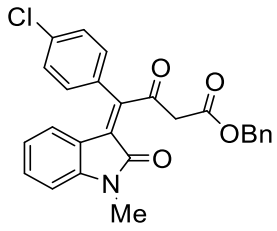
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (s, 5H), 6.91 (t, *J* = 8.5 Hz, 1H), 6.64 – 6.67 (m, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 3.14 (s, 3H), 1.08 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.6, 166.5, 166.4, 159.4, 157.5, 148.9, 141.0, 136.73, 130.2, 129.7, 125.3, 125.2, 121.2, 121.1, 117.0, 116.8, 111.0, 110.8, 109.0, 108.9, 61.3, 48.7, 26.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{21}H_{18}ClNO_4Na, M+Na]^+$: 406.0817; **Found**: 406.0822.

Ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48ai)

The compound **48ai** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), benzyl 4-(4-chlorophenyl)buta-2,3-dienoate (132 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48ai** was obtained as a white solid in 58% (80 mg) yield.



48ai

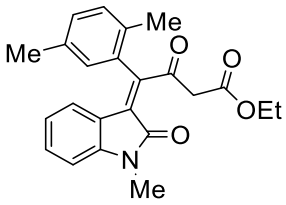
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 7.5, 16.5 Hz, 4H), 7.25 – 7.28 (m, 6H), 6.78 (s, 3H), 5.03 (s, 2H), 3.89 (s, 2H), 3.20 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.7, 166.6, 166.4, 147.3, 144.9, 136.2, 135.2, 130.7, 129.8, 129.5, 128.4, 128.33, 128.30, 125.8, 123.3, 122.2, 120.1, 108.5, 67.0, 48.7, 26.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{26}H_{20}ClNO_4Na, M+Na]^+$: 468.0973; **Found**: 468.0994.

Ethyl (*Z*)-4-(2,5-dimethylphenyl)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoate (48aj)

The compound **48aj** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), ethyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (101 mg, 0.46 mmol) and DBU (65 mg, 046 mmol) in acetonitrile (3 mL) at room temperature. The product **48aj** was obtained as a yellow solid in 45% (53 mg) yield.



48aj

Mp: 117 - 119 °C

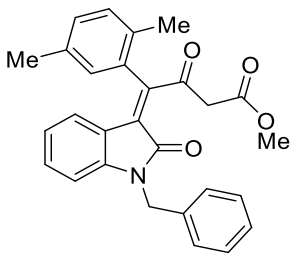
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 – 7.17 (m, 2H), 7.08 – 7.10 (m, 2H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.67 (t, *J* = 8.0 Hz, 1H), 6.21 (d, *J* = 8.0 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 3.87 (d, *J* = 15.5 Hz, 1H), 3.76 (d, *J* = 15.5 Hz, 1H), 3.16 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 166.4, 166.3, 148.5, 144.6, 136.4, 132.9, 132.0, 130.9, 130.4, 130.3, 127.7, 126.2, 123.3, 122.5, 120.8, 108.2, 61.3, 48.5, 26.0, 20.9, 19.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{23}H_{23}NO_4Na, M+Na]^+$: 400.1519; **Found**: 400.1520.

Methyl (*Z*)-4-(1-benzyl-2-oxoindolin-3-ylidene)-4-(2,5-dimethylphenyl)-3-oxobutanoate (48ak)

The compound **48ak** was synthesized following the procedure described in **section 2.9** using 1-benzylindoline-2,3-dione (50 mg, 0.21 mmol), methyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (64 mg, 0.31 mmol) and TBD (44 mg, 0.31 mmol) in acetonitrile (3 mL) at room temperature. The product **48ak** was obtained as a yellow solid in 47% (64 mg) yield.



48ak

Mp: 109 - 111 °C

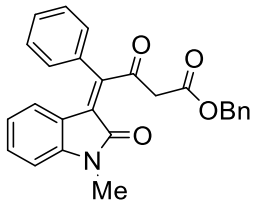
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 4H), 7.18 – 7.19 (m, 1H), 7.14 – 7.16 (m, 1H), 7.11 (s, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.58 – 6.64 (m, 2H), 6.21 (d, *J* = 7.5 Hz, 1H), 4.94 (d, *J* = 16.0 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.79 (d, *J* = 16.0 Hz, 1H), 3.60 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.4, 167.0, 166.4, 148.6, 143.8, 136.5, 135.5, 132.9, 132.0, 130.9, 130.4, 130.3, 128.8, 127.74, 127.72, 127.4, 127.3, 126.1, 123.4, 122.5, 120.9, 109.3, 52.3, 48.2, 43.7, 20.9, 19.2.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{28}H_{25}NO_4Na, M+Na]^+$: 462.1676; **Found**: 462.1679.

Benzyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48al)

The compound **48al** was synthesized following the procedure described in **section 2.9** using *N*-methyl isatin (50 mg, 0.31 mmol), benzyl 4-phenylbuta-2,3-dienoate (116 mg, 0.46 mmol) and TBD (65 mg,0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48al** was obtained as a yellow gummy liquid in 64% (82 mg) yield.



48al

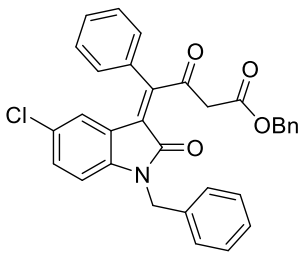
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.44 (m, 2H), 7.33 – 7.38 (m, 3H), 7.15 – 7.22 (m, 6H), 6.66 – 6.71 (m, 3H), 4.96 (s, 2H), 3.81 (s, 2H), 3.13 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.8, 166.7, 166.4, 148.8, 144.8, 135.4, 132.3, 130.4, 130.0, 129.2, 128.4, 128.3, 128.29, 128.20, 125.43, 123.3, 122.1, 120.4, 108.4, 108.2, 66.9, 48.6, 26.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{26}H_{21}NO_4Na, M+Na]^+$: 434.1363; **Found**: 434.1361.

Benzyl (*Z*)-4-(1-benzyl-5-chloro-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (48am)

The compound **48am** was synthesized following the procedure described in **section 2.9** using 1-benzyl-5-chloroindoline-2,3-dione (50 mg, 0.18 mmol), benzyl 4-phenylbuta-2,3-dienoate (69 mg, 0.27 mmol) and TBD (38 mg, 0.27 mmol) in acetonitrile (3 mL) at room temperature. The product **48am** was obtained as a yellow gummy liquid in 52% (69 mg) yield.



48am

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 5H), 7.36 (s, 1H), 7.29 – 7.33 (m, 2H), 7.25 – 7.27 (m, 7H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 2H), 4.88 (s, 2H), 3.89 (s, 2H).

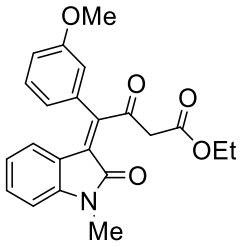
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 166.5, 166.3, 150.7, 142.3, 135.3, 135.1, 131.7, 130.5, 130.0, 129.4,

128.9, 128.5, 128.4, 128.3, 128.28, 128.22, 127.9, 127.5, 127.3, 127.0, 124.3, 123.5, 121.9, 110.3, 67.0, 48.6, 43.8.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{32}H_{24}ClNO_4Na, M+Na]^+$: 544.1286; **Found**: 544.1240.

Ethyl (*Z*)-4-(3-methoxyphenyl)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoate (48an)

The compound **48an** was synthesized following the procedure described in section 2.9 using *N*-methyl isatin (50 mg, 0.31 mmol), ethyl 4-(3-methoxyphenyl)buta-2,3-dienoate (102 mg, 0.46 mmol) and TBD (65 mg, 0.46 mmol) in acetonitrile (3 mL) at room temperature. The product **48an** was obtained as a yellow gummy liquid in 67% (79 mg) yield.



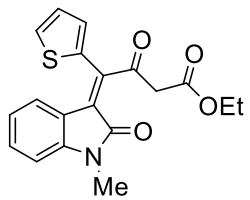
48an

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (t, *J* = 8.0 Hz, 1H), 7.24 – 7.28 (m, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.78 – 6.82 (m, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 2H), 3.83 (s, 3H), 3.24 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.9, 166.5, 160.1, 148.8, 144.8, 133.5, 130.4, 130.3, 125.3, 123.5, 122.1, 120.6, 120.4, 116.1, 113.0, 108.4, 61.2, 55.4, 48.7, 26.0, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{22}H_{21}NO_5Na, M+Na]^+$: 402.1312; **Found**: 402.1336.

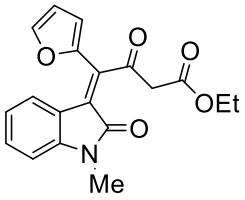
Ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-(thiophen-2-yl)butanoate (48ao)



48ao

Yield: Obtained in trace amount.

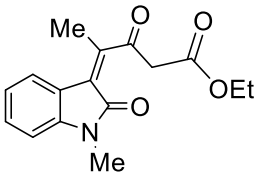
Ethyl (*Z*)-4-(furan-2-yl)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoate (48ap)



48ap

Yield: Product not obtained.

Ethyl (Z)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxopentanoate (48aq)



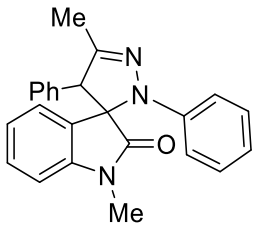
48aq

Yield: Product not obtained.

2.12. Characterization data of products (48ba - 48bc, 48rr)

Dimethyl-2',4'-diphenyl-2',4'-dihydrospiro[indoline-3,3'-pyrazol]-2-one (48ba)

The compound **48ba** was synthesized following the procedure described in **section 2.11.1** using **48a** (50 mg, 0.143 mmol) and phenylhydrazine (14.1 µL,0.143 mmol) in 2 mL of EtOH and 1 drop of conc. H_2SO_4. The product **48ba** was obtained as white precipitate in 82% (43 mg) yield.



48ba

Mp: 236 – 237 ^oC

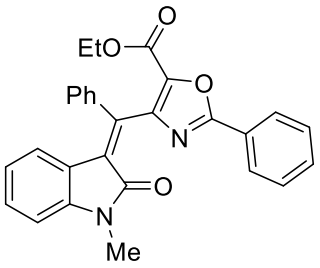
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 3H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 2H), 6.93 (s, 2H), 6.72 – 6.76 (m, 3H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 4.64 (s, 1H), 3.19 (s, 3H), 2.11 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 176.5, 149.9, 144.9, 142.7, 133.5, 129.4, 129.3, 128.8, 128.4, 127.9, 126.1, 125.3, 122.3, 120.6, 115.2, 108.2, 76.7, 66.4, 26.4, 15.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{24}H_{21}N_3ONa, M+Na]^+$: 390.1577; **Found**: 390.1577.

Ethyl (*Z*)-4-((1-methyl-2-oxoindolin-3-ylidene)(phenyl)methyl)-2-phenyloxazole-5-carboxylate (48bb)

The compound **48bb** was synthesized following the procedure described in **section 2.11.2** using **48a** (50 mg, 0.143 mmol), iodine (36 mg, 0.143 mmol), benzylamine (19.0 µL, 0.172 mmol) in DMSO (2 mL). The product **48bb** was obtained as a yellow gummy liquid in 55% (35 mg) yield.



48bb

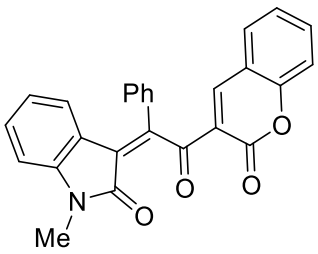
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.44 – 7.45 (m, 2H), 7.38 – 7.40 (m, 3H), 7.34 – 7.36 (m, 3H), 7.17 (d, *J* = 6.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.65 – 6.69 (m, 2H), 4.19 (q, *J* = 7.5 Hz, 2H), 3.12 (s, 3H), 1.10 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 165.8, 161.5, 161.4, 152.7, 144.5, 136.6, 134.8, 131.9, 130.9, 130.6, 130.3, 129.7, 129.3, 128.9, 128.6, 127.0, 126.6, 123.8, 121.7, 121.6, 108.0, 61.0, 25.9, 14.0.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{28}H_{22}N_2O_4Na, M+Na]^+$: 473.1472; **Found**: 473.1486.

(*Z*)-1-Methyl-3-(2-oxo-2-(2-oxo-2H-chromen-3-yl)-1-phenylethylidene)indolin-2-one (48bc)

The compound **48bc** was synthesized following the procedure described in **section 2.11.3** using **48a** (50 mg, 0.143 mmol), salicylaldehyde (14.9 µL, 0.143) mmol and piperidine (1.4 µL, 10 mol%) in EtOH (2 mL). The product **48bc** was obtained as orange precipitate in 78% (45 mg) yield.



48bc

Mp: 258 - 259 °C

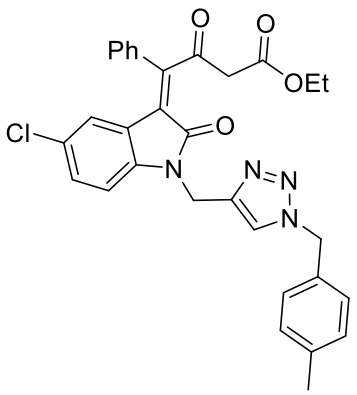
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 7.77 (d, *J* = 5.0 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.47 (s, 3H), 7.29 – 7.32 (m, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.80 (d, *J* = 7.0 Hz, 2H), 3.19 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 191.8, 167.3, 158.5, 155.4, 149.5, 147.8, 144.7, 134.4, 132.3, 130.4, 129.8, 129.7, 129.2, 128.9, 125.5, 124.8, 123.0, 122.8, 122.0, 121.1, 118.6, 116.6, 108.3, 25.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{26}H_{17}NO_4Na, M+Na]^+$: 430.1050; **Found**: 430.1059.

Ethyl (*Z*)-4-(5-chloro-1-((1-(4-methylbenzyl)-1H-1,2,3-triazol-5-yl)methyl)-2-oxoindolin -3-ylidene)-3-oxo-4-phenylbutanoate (48rr)

The compound **48rr** was synthesized following the procedure described in **section 2.11.4** using 4-methyl benzyl azide (18 mg, 0.123 mmol), compound **48r** (50 mg, 0.123 mmol), $CuSO_4.5H_2O$ (3 mg, 0.0123 mmol) and sodium ascorbate (6.1 mg, 0.031 mmol). The product **48rr** was obtained as a as a yellow gummy liquid in 87% (59 mg) yield.



48rr

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (s, 5H), 7.39 (s, 1H), 7.07 – 7.11 (m, 5H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.64 (s, 1H), 5.35 (s, 2H), 4.89 (s, 2H), 3.95 (q, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 2.27 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 197.6, 166.3, 166.0, 150.7, 141.9, 138.8, 131.7, 131.1, 130.6, 130.2, 129.8, 129.4, 128.3, 128.1, 127.7, 124.2, 123.3, 122.6, 121.6, 110.9, 61.3, 54.1, 48.6, 35.3, 21.1, 13.9.

HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $[C_{31}H_{27}ClN_4O_4Na, M+Na]^+$: 577.1613; **Found**: 577.1623.

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Chapter 3

Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines *via* Tandem Reaction of Allenoates and Cyclic Amidines

3.1. Abstract

A tandem reaction of easily accessible allenoates and cyclic amidines for the synthesis of functionalized tricyclic pyridopyrimidines is reported herein. The annulation featured a broad substrate scope with good functional group tolerance under very mild conditions (35 examples, 32 – 85% yields). The pyridopyrimidines were obtained in an exceptionally short reaction time (1 min), at room temperature under neat conditions, which offering a sustainable and efficient approach for the synthesis of functionalized pyridopyrimidines. The scalability of the developed protocol was further demonstrated through a gram-scale synthesis.

3.2. Introduction

Bicyclic amidines, DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which are "non-nucleophilic strong bases", are widely used in organic synthesis.[1] Though often regarded as hindered and non-nucleophilic strong bases, DBU and DBN nonetheless exhibit nucleophilic behavior, mediating organic reactions and potentially leading to the formation of compounds bearing DBU and DBN scaffolds.[2] So far, significant efforts have been devoted to the development of synthetic strategies which demonstrate the nucleophilic properties of these amidines.[3] Among these, the synthesis of fused tricyclic pyridopyrimidines is currently attracting attention.[4]

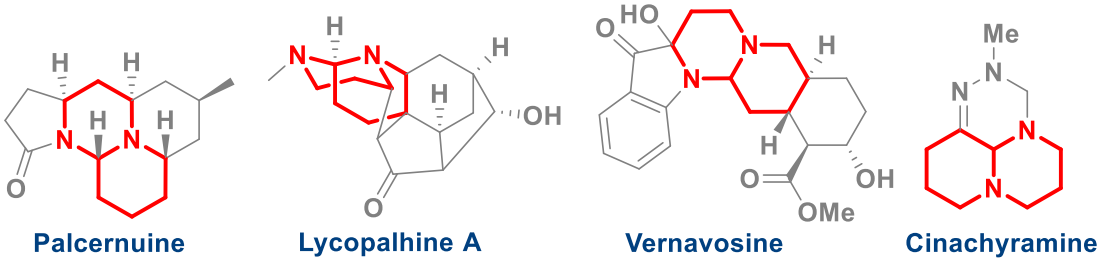


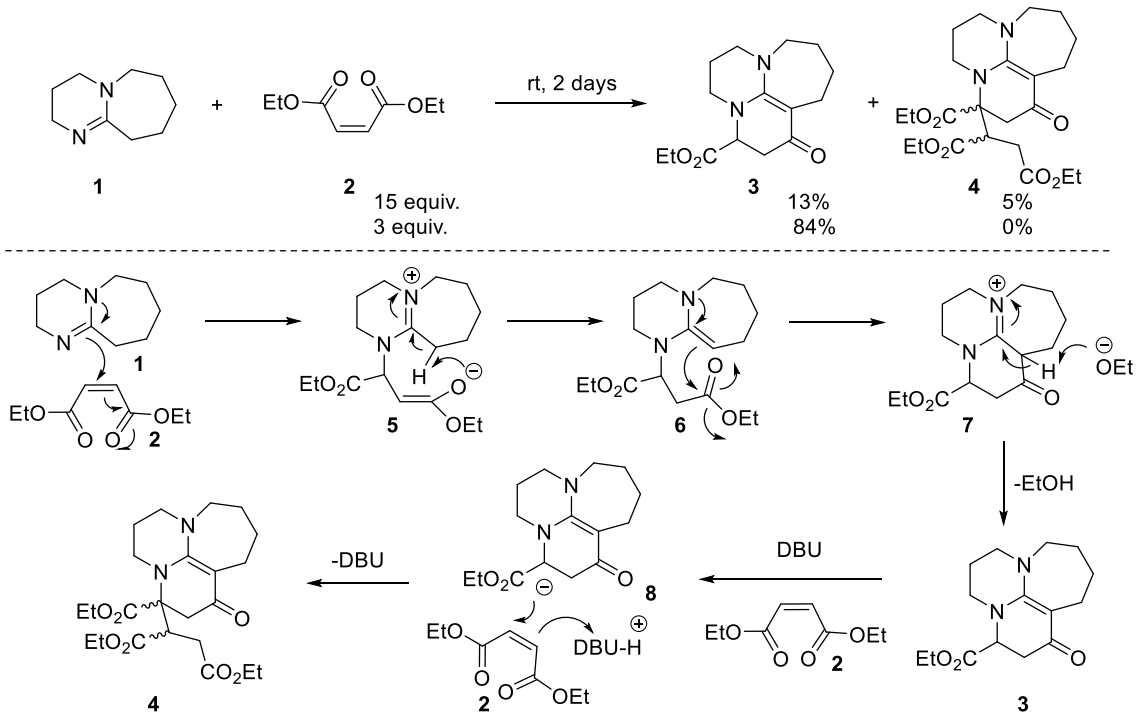
Figure 3.1. Natural products containing pyridopyrimidine core

These structures have gained significant pharmaceutical relevance, as it is present in compounds with antibacterial,[5] antipyretic,[6] antihistaminic,[7] and anti-inflammatory profiles.[8] Pyridopyrimidines are known to be potent inhibitors of dihydrofolate reductase,[9] cyclin-dependent kinase 4[10] and tyrosine kinases of the epidermal growth factor receptor family.[11] Pyridopyrimidine core is found in the skeletons of many natural products (**Figure 3.1**).[12]

Hexahydropyrimidine derivatives are also reported to have diverse pharmacological activities.[13] Hexetidine, a hexahydropyrimidine-based drug molecule has promising deodorant, anaesthetic and astringent effects.[14] *N*-Substituted hexahydropyrimidines constitute a key synthetic intermediate for nitroimidazole-spermidine drug used in the treatment of A549 lung carcinoma.[15] Recently, hexahydropyrimidines bearing suitable substitutions have been identified as potent inhibitors of the *Plasmodium falciparum* parasite in human blood, highlighting their potential as pharmaceutical agents for the treatment of malaria.[16]

3.2.1. Synthetic approaches towards tricyclic pyridopyrimidines

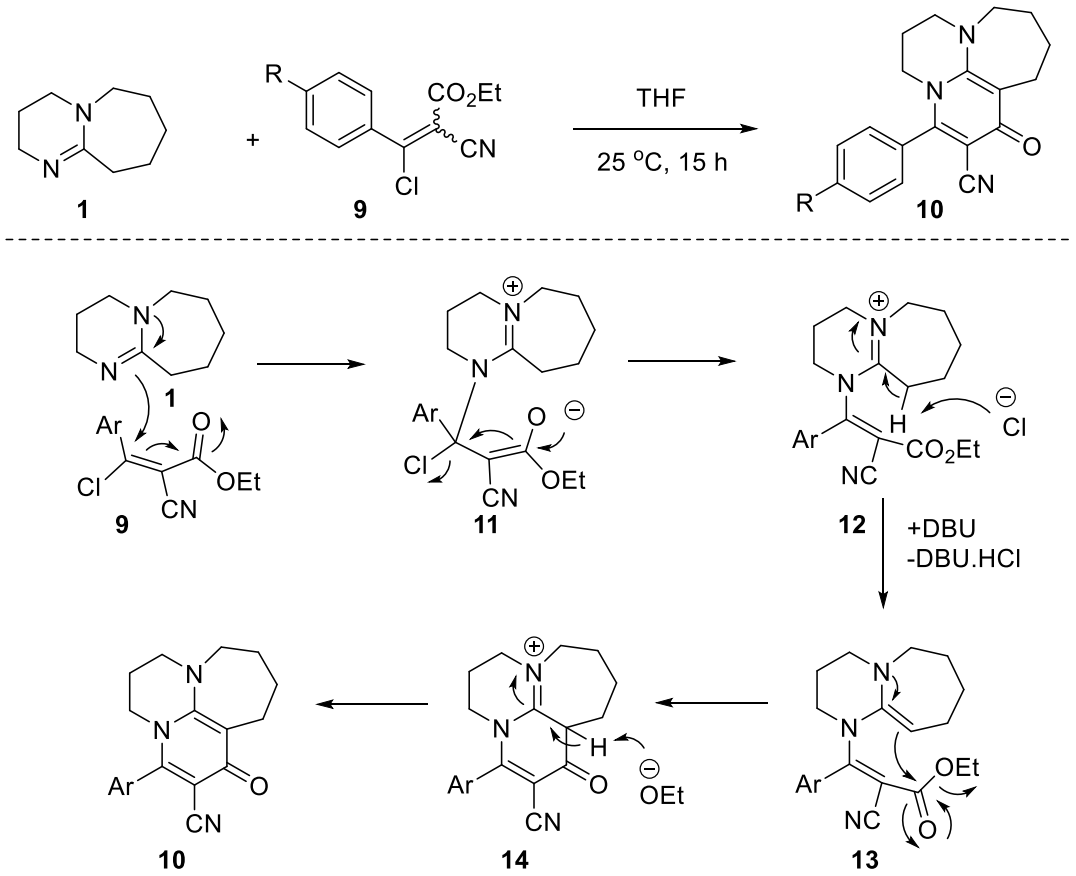
Although the extensive medicinal significance is well appreciated by pharmacologists, the construction of this fused tricyclic pyridopyrimidines has sporadically been explored. In 1993 Lucas and co-workers reported the reaction of DBU and diethyl maleate to the



Scheme 3.1. Michael addition of DBU to diethyl maleate

synthesis of tricyclic derivatives **3** and **4**. The reaction commences with the Michael addition, resulting in enolate **5**. Subsequent intramolecular protonation and nucleophilic addition affords **7**. Ethylate-mediated H-6 abstraction provides **3**, which then reacts with a second molecule of diethyl maleate results in **4** (**Scheme 3.1**).[17]

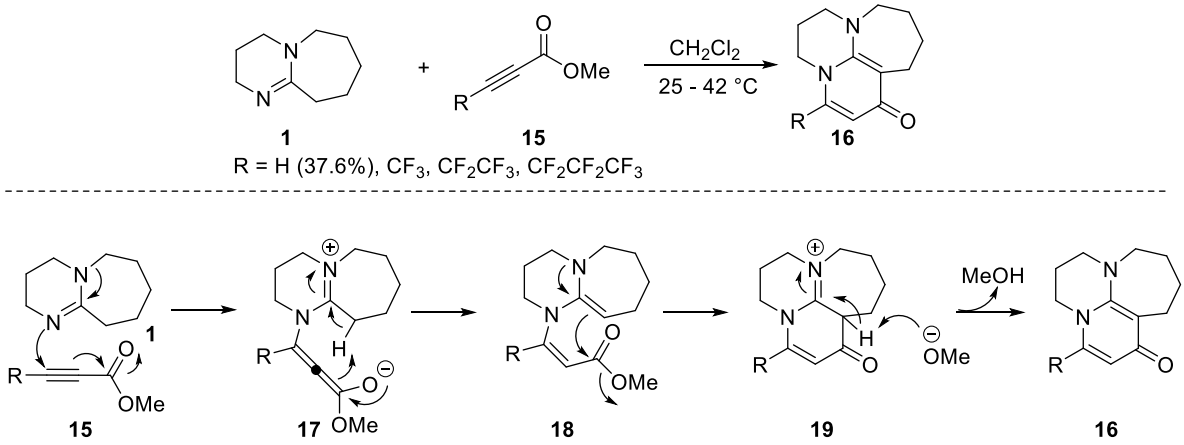
In 2000, Lönnqvist and Jalander synthesised a tricyclic compound **10** by coupling DBU with ethyl 3-chloro-2-cyano-3-arylacrylates. This tricyclic derivative is formed *via* a Michael addition, resulting in intermediate **11**. Subsequent retro-reaction cleaves the C-Cl bond producing **12**. Sequential H-6 proton abstraction generates **13**, which undergoes nucleophilic addition to the ester, forming a cyclic intermediate **14**. Finally, the loss of the second H-6 proton liberates product **10** (**Scheme 3.2**).[18]



Scheme 3.2. Michael reaction of DBU with ethyl 3-chloro-2-cyano-3-aryl acrylates

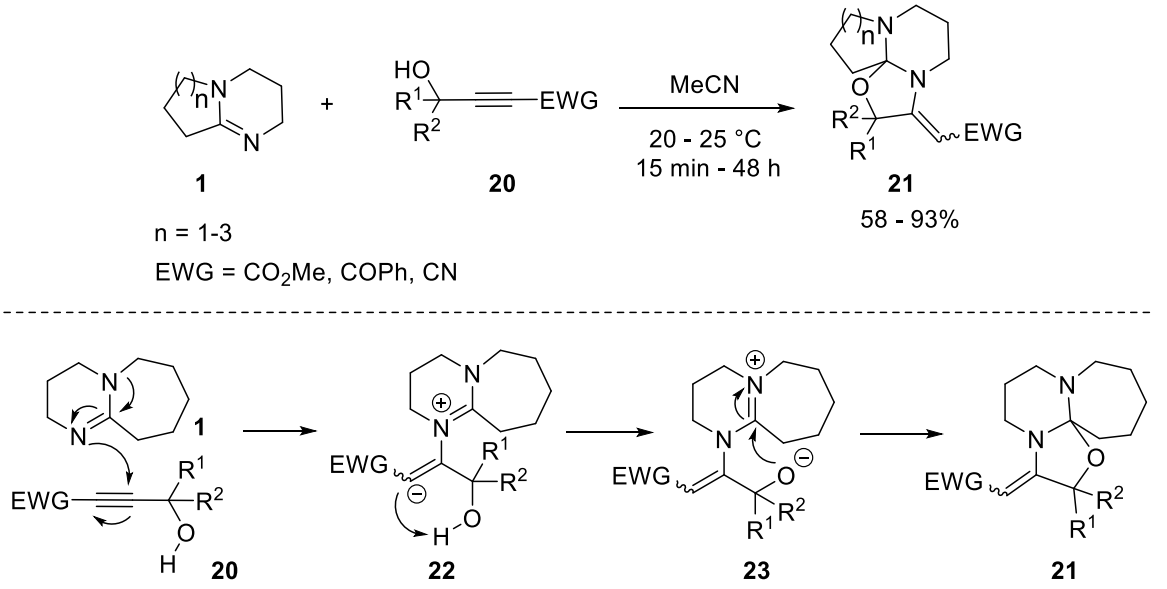
In 2002, Shi and co-workers reported the synthesis of substituted pyridinones **16** from the reaction of DBU with methyl alkynoates. The mechanism involves the initial Michael addition, forming zwitterion intermediate **17**, which undergoes H-6 proton abstraction to

generate **18**. Subsequent ring closure and a proton abstraction lead to the product **16** (**Scheme 3.3**).[19]



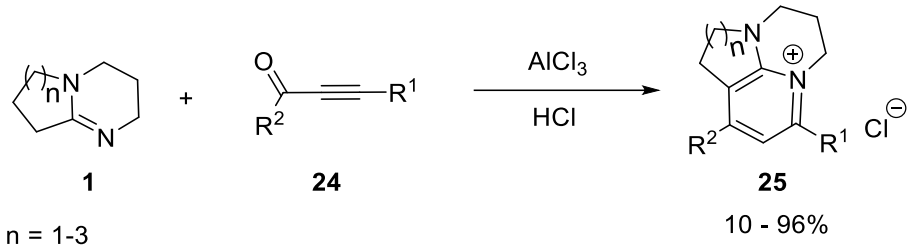
Scheme 3.3. DBU addition to alkynoates

In 2016, Trofimov's group demonstrated the annulation of DBU and DBN with propargylic alcohols bearing electron-withdrawing groups (-CN, -COPh, or -CO_2Me) which led to functionalized Oxazolopyrrolohexahydropyrimidine and Oxazolohexahydropyrimidoazepine scaffolds respectively. Mechanistically, the reaction proceeds through zwitterion intermediate **22**, which undergoes a proton transfer from the hydroxy group to quench the carbanionic (α-position to the EWG) to form the thermodynamically more stable oxygen-centred anion **23**, which undergoes subsequent cyclization to afford product **21** (**Scheme 3.4**).[20]



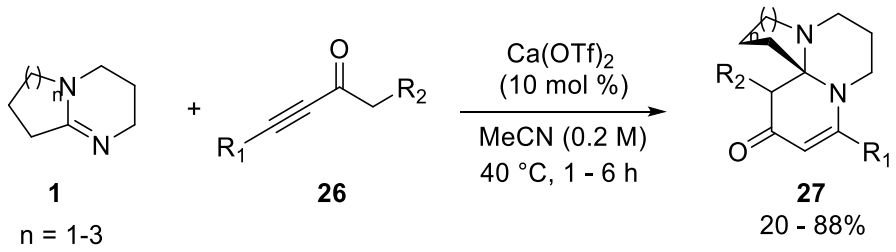
Scheme 3.4. Amphibilic insertion of cyclic amidines into propargylic alcohols

In 2018, Muller's group reported the synthesis of tricyclic 2-amino pyridinium salts **25** *via* a (3+3) annulation of alkynones and cyclic amidines. The developed class of 2-aminopyridinium salts exhibited remarkable emission in dichloromethane, water, as well as in the solid state (**Scheme 1b**).[21]



Scheme 3.5. (3+3) annulation of alkynones and cyclic amidines

In 2020, Ramachary's group disclosed a $Ca(OTf)_2$ promoted formal [4+2] cycloaddition reaction between ynones and cyclic amidines. This approach provides a regioselective route to highly functionalized tricyclic azepines **27** in good yields (up to 88%) (**Scheme 1c**).[22]

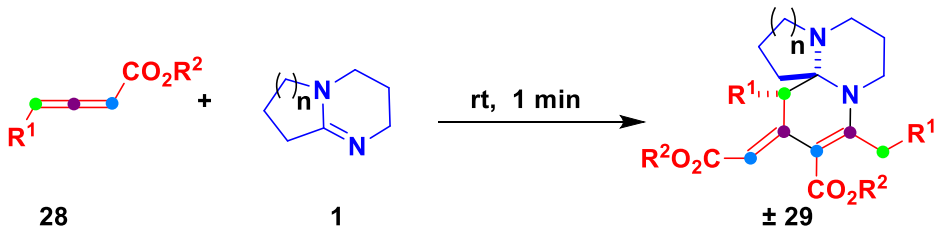


Scheme 3.6. [4+2] cycloaddition of ynones with cyclic amidines

3.3. Background to the present work

While employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in consecutive transformations of allenoates,[23] we serendipitously discovered an intriguing product, which prompted a more detailed investigation of the reaction. Further studies revealed the product to be a tricyclic pyridopyrimidine moiety, formed *via* a (2+2+2) annulation between the allenoate and DBU. Hence, given these exciting observations and in continuation to our recent efforts in the construction of new heterocyclic hybrids,[24] herein we report a 100% atom economic unprecedented novel annulation principle of allenoates[25] and cyclic amidines that leads directly to the formation of pyridopyrimidines fused with functionalized heterocyclic systems; octahydro-6*H*,10*H*-pyrido[2',1':2,3]pyrimido[1,2-*a*]azepine and hexahydro-1*H*,5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*b*]pyrimidine (**Scheme 3.7**). This approach, for the first time, exploits the reactivity of DBU and DBN with readily accessible allenoates for the synthesis of tricyclic pyridopyrimidine scaffolds. Such unusual

reactivity is the outcome of the fact that, following the Michael addition by N-8 of DBU (N-6 of DBN) on allenoates, the resulting zwitterion can be neutralized either by proton loss from C-6 of DBU (C-4 of DBN) or by the nucleophilic attack on the iminium carbon. These stabilization pathways impart nucleophilic behaviour on cyclic amidines and eventually lead to their incorporation into allenoates.



Scheme 3.7. Synthesis of Fused Tricyclic Pyridopyrimidines

3.4. Results and discussion

We commenced our study by reacting 1.0 equiv. of DBU **1** and 1.0 equiv. of ethyl 4-phenylbuta-2,3-dienoate **28a** (0.26 mmol) at room temperature in acetonitrile. To our delight, the (*E*)- isomer of product **29a** was obtained as the sole product with a 30% yield within 1.0 h (**Table 3.1**, entry 1). This diastereoselectivity can be rationalized by assuming

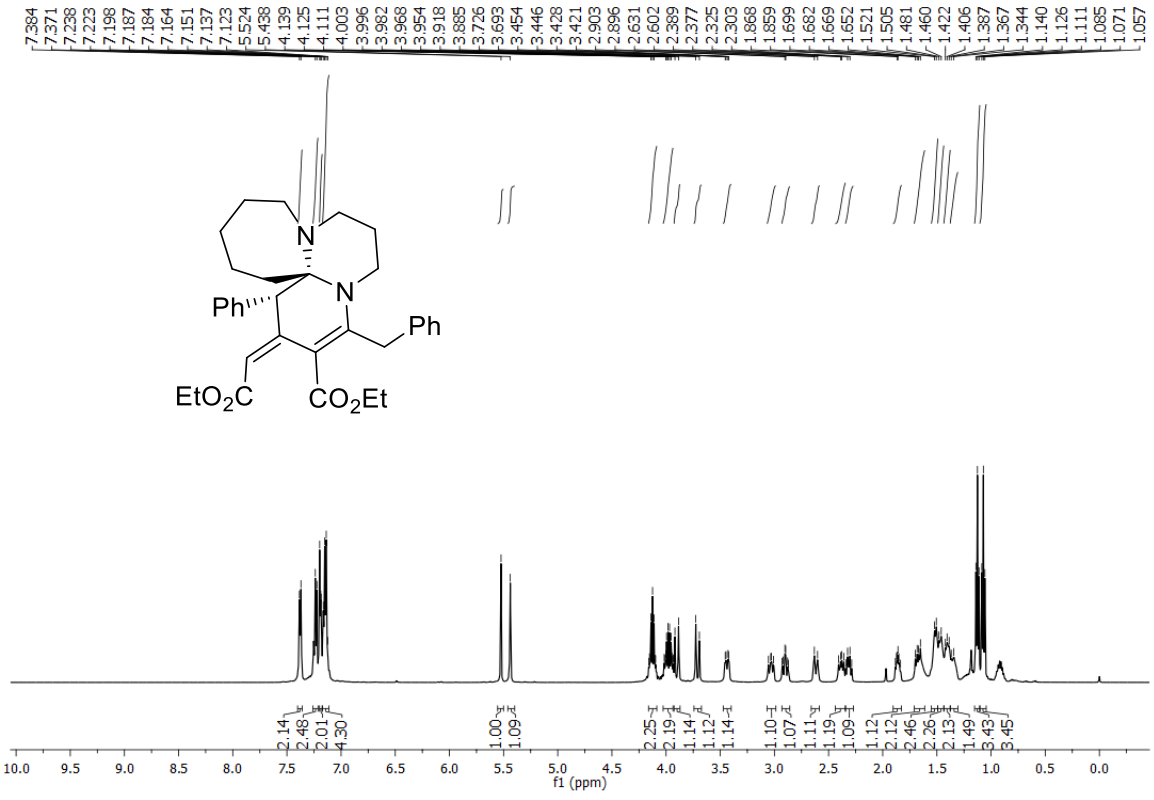


Figure 3.2. ^{1}H NMR (500 MHz, $CDCl_3$) of **29a**

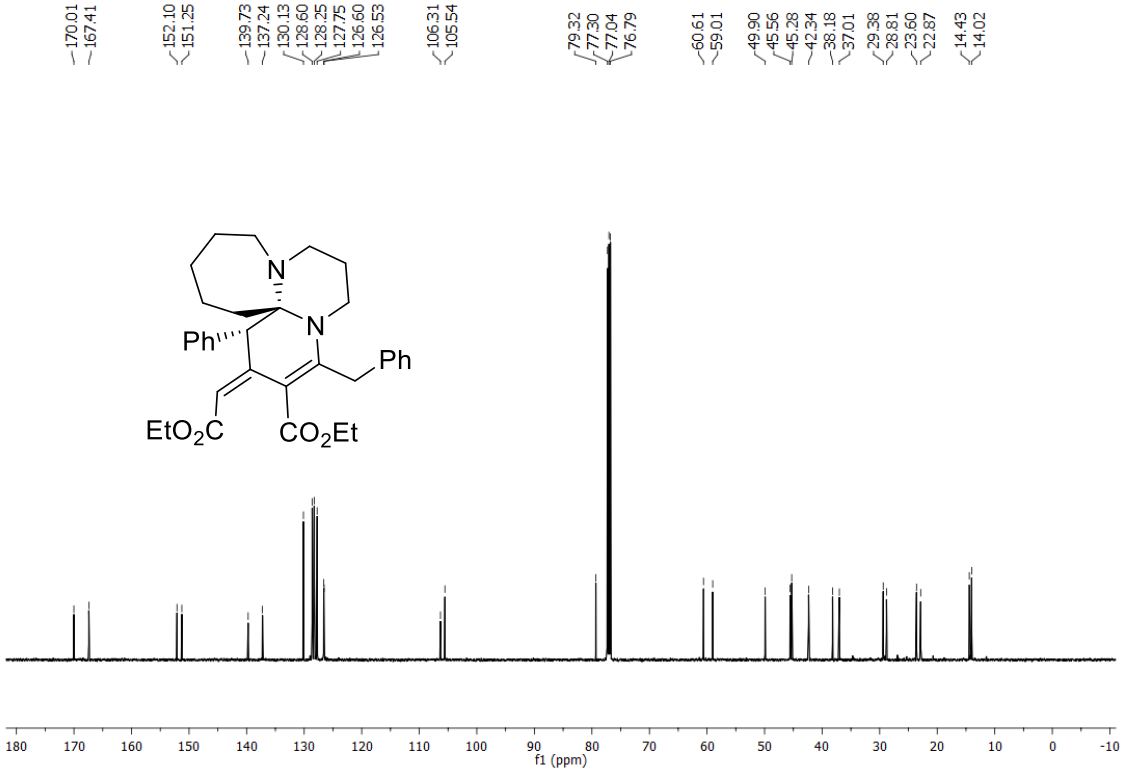


Figure 3.3. $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) of **29a**

that the Zwitterion intermediate **A** is approaching from the less hindered side of the allenoate to reduce the steric hindrance caused by the proximity between two ester groups, favouring (*E*)- isomer (**Scheme 3.9)**.

Its molecular structure and relative stereochemistry were established by Nuclear Magnetic Resonance (NMR), High-Resolution Mass (HRM) spectrometry and further confirmed *via* single-crystal X-ray analysis of **29a**.

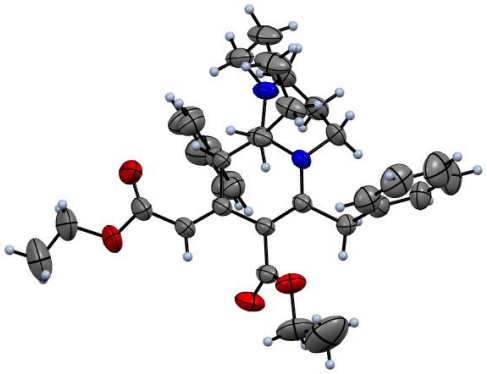
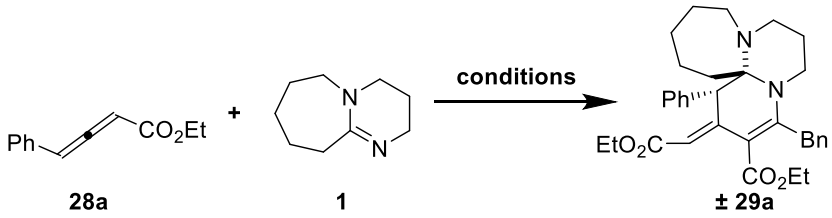


Figure 3.4. Single crystal X-ray structure of **29a** (**CCDC 2154687**)

The reaction parameters were then screened to improve the yield and overall process; the results are summarized in **Table 3.1**. Firstly, we tuned the stoichiometric ratio of substrates;

an attempt to improve the yield by increasing the equiv. of **1** to 2.0 was successful, resulting in a 50% yield of **29a** (**Table 3.1**, entry 2). Hence the formation of **29a** might be attributable to the dual character of DBU **1** as a base and nucleophile. Next, an increase in

Table 3.1. Optimization of the reaction[a]



28a **1** **± 29a**

Entry	**1** (equiv.)	Solvent	Temp (°C)	Time	Yield (%)[b]
1	1.0	Acetonitrile	rt	1 h	30
2	2.0	Acetonitrile	rt	1 h	50
3	3.0	Acetonitrile	rt	1 h	50
4	2.0	Acetonitrile	rt	1 min	50
5	2.0	Acetonitrile	0-5	1 min	48
6	2.0	Acetonitrile	50	1 min	45
7	2.0	THF	rt	1 min	45
8	2.0	DMF	rt	1 min	57
9	2.0	DMSO	rt	1 min	Trace
10	2.0	Ethanol	rt	1 min	ND
11	2.0	Ethyl acetate	rt	1 min	ND
12	2.0	1,4- Dioxane	rt	1 min	51
13	2.0	Toluene	rt	1 min	55
14	2.0	Ether	rt	1 min	58
15	2.0	Chloroform	rt	1 min	48
16	2.0	DCE	rt	1 min	82
17	2.0	DCM	rt	1 min	73
18	**2.0**	**Neat**	**rt**	**1 min**	**82**

[a]All the reactions were conducted with 1.0 equiv. of **28a** (0.26 mmol) in solvent (2 mL), [b]Yield of isolated product

the amount of DBU loading from 2.0 equiv. did not show any increase in yield (**Table 3.1**, entry 3). Gratifyingly, evaluation of the reaction time demonstrated that the product is formed in a period of 1 min with same yield of 50% (**Table 3.1**, entry 4). Further assessment of the variation of reaction temperature resulted in decreased yields, confirming that room temperature is more favourable for the reaction (**Table 3.1**, entries 5, 6). Subsequently, an extensive solvent screening was carried out (**Table 3.1**, entries 7 - 17). To begin, polar aprotic solvents like THF, and DMF furnished **29a** in moderate yields of 45% and 57% respectively (**Table 3.1**, entries 7, 8), DMSO in poor yield (**Table 3.1**, entry 9), and no reaction was observed in ethanol and ethyl acetate (**Table 3.1**, entries 10, 11). These observations directed our investigation towards non-polar aprotic solvents like 1,4-dioxane, toluene, ether, chloroform, DCE and DCM which resulted in **29a** in 51%, 55%, 58%, 48%, 82% and 73% respectively (**Table 3.1**, entries 12 - 17), indicating DCE as the most suitable solvent for the desired transformation. Finally, we were pleased to observe that the highest yield of 82% could also be achieved under a solvent-free condition (**Table 3.1**, entry 18). Based on these experimental results, the best reaction condition was confirmed to be 1.0 equiv. of allenoate, 2.0 equiv. of DBU under neat conditions at room temperature for 1 min.

With the optimal reaction conditions in hand, we next explored the scope of the reaction using various substituted allenoates (**Table 3.2)**. In all the experiments, the reaction proceeded smoothly and furnished the anticipated products in moderate to good yields. However, the highest yield of 85% was noticed for compound **29b**. Moreover, it was found that allenoates having smaller ester substituents such as -CO_2Me and -CO_2Et attributed comparatively higher yield than bulkier -CO_2Bn and -$CO_2{}^t$Bu groups. The yields appear to decrease slightly with the introduction of substituents on the allenoate. The thienyl allenoates resulted in comparatively less yield (**29o** and **29p**). Furthermore, the furyl allenoate failed to furnish the product (**29q**), likely due to the decreased resonance stabilization of the zwitterionic intermediate **A** by the heteroaromatic ring (**Scheme 3.9**). The alkyl derivative, ethyl penta-2,3-dienoate and ethyl octa-2,3-dienoate also furnished the corresponding products **29r** and **29s** in 55% and 48% yield respectively.

Table 3.2. Substrate scope of allenoates with DBU

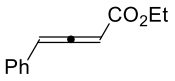
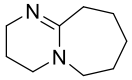
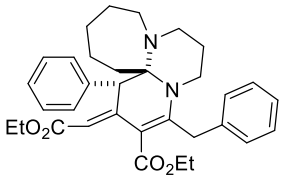
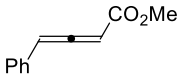
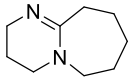
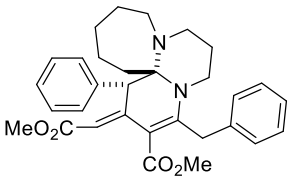
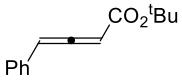
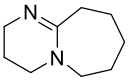
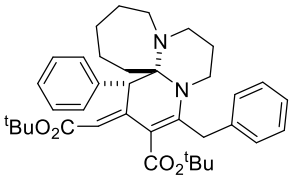
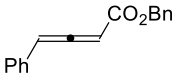
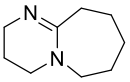
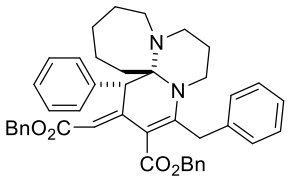
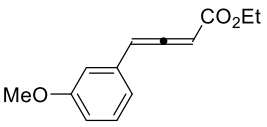
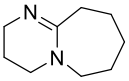
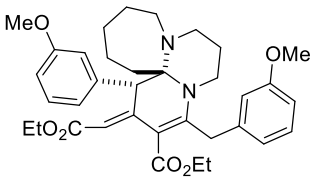
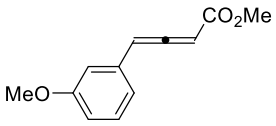
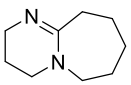
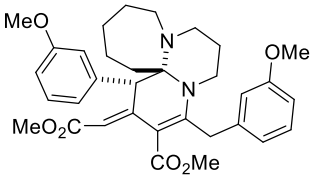
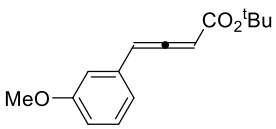
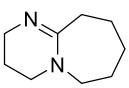
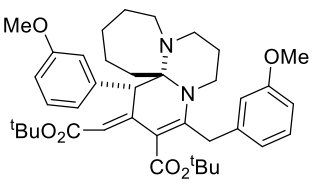
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1				82
	28a	**1**	**± 29a**	
2				85
	28b	**1**	**± 29b**	
3				81
	28c	**1**	**± 29c**	
4				79
	28d	**1**	**± 29d**	
5				71
	28e	**1**	**± 29e**	
6				78
	28f	**1**	**± 29f**	
7				68
	28g	**1**	**± 29g**	

Table 3.2. Continues…….

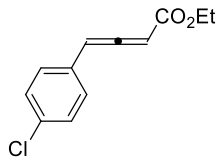
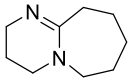
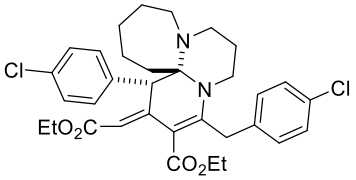
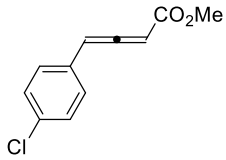
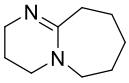
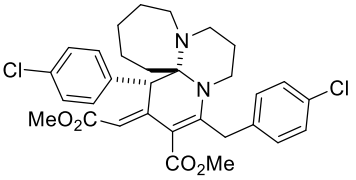
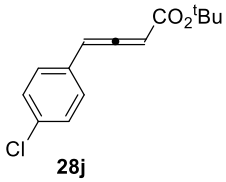
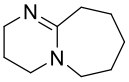
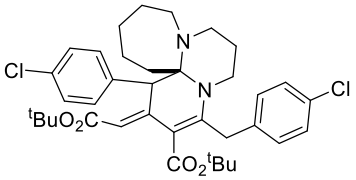
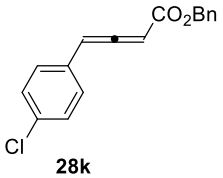
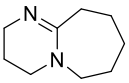
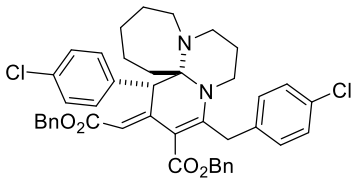
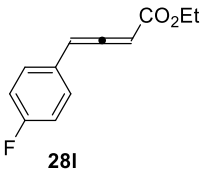
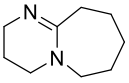
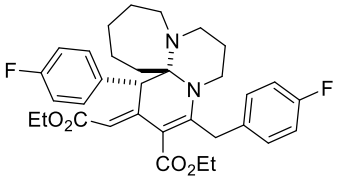
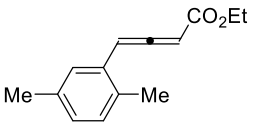
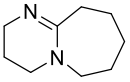
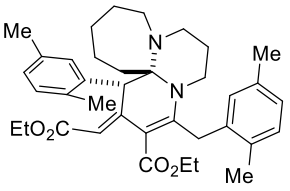
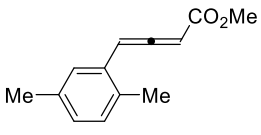
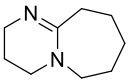
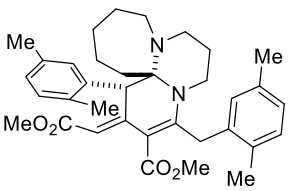
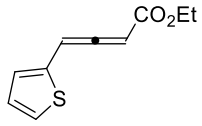
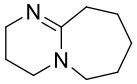
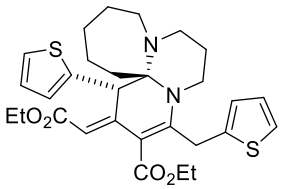
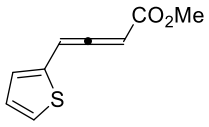
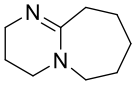
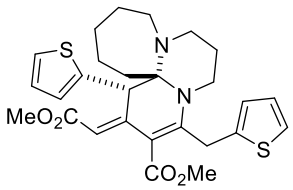
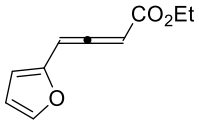
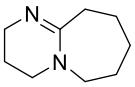
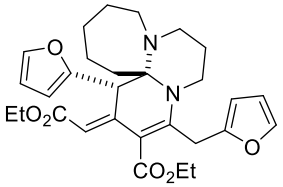
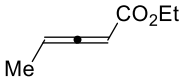
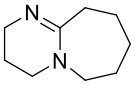
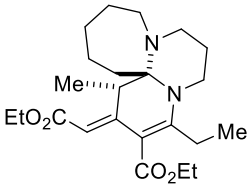
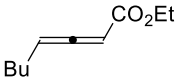
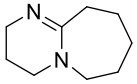
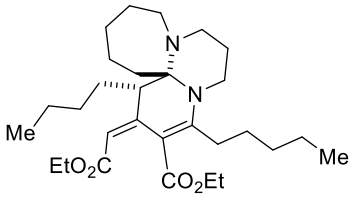
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
8	 **28h**	 **1**	 **± 29h**	73
9	 **28i**	 **1**	 **± 29i**	76
10	 **28j**	 **1**	 **± 29j**	66
11	 **28k**	 **1**	 **± 29k**	69
12	 **28l**	 **1**	 **± 29l**	76
13	 **28m**	 **1**	 **± 29m**	67
14	 **28n**	 **1**	 **± 29n**	72

Table 3.2. Continues…….

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
15				trace
	28o	**1**	**± 29o**	
16				36
	28p	**1**	**± 29p**	
17				ND
	28q	**1**	**± 29q**	
18				55
	28r	**1**	**± 29r**	
19				48
	28s	**1**	**± 29s**	

Reaction conditions: 1 equiv. of allenoate **28** (50 mg) & 2.0 equiv. of DBU (**1**) at room temperature for 1 min

The scope of the protocol was further expanded by utilizing 1,5-diazabicyclo[4.3.0]non-5-ene amidine base, DBN **30**, in reaction with a variety of allenoates, delivering products **31a - 31q** in satisfactory yields (**Table 3.3**). The highest yield of 81% was observed for compound **31b**. The allenoates with smaller ester substituents like -CO_2Me and -CO_2Et

Table 3.3. Substrate scope of allenoates with DBN

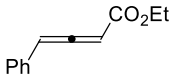
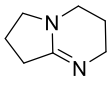
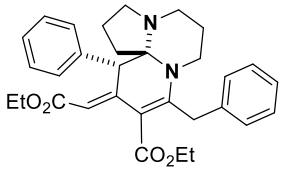
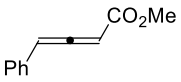
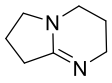
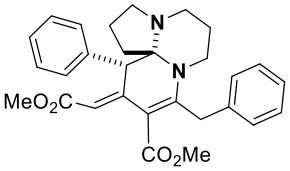
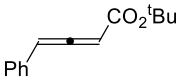
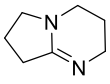
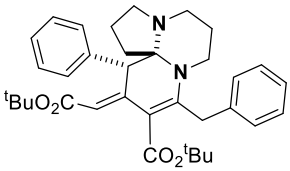
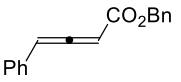
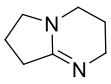
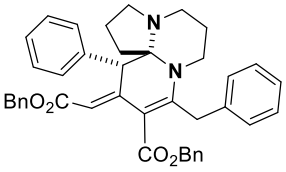
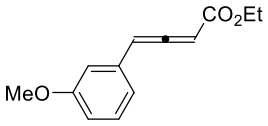
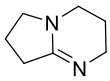
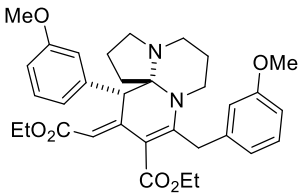
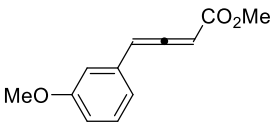
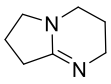
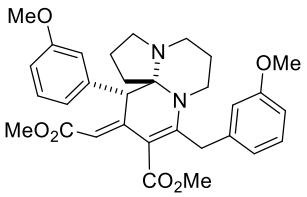
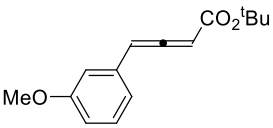
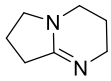
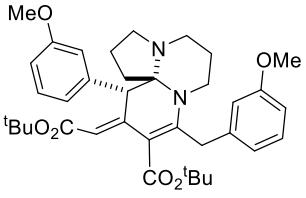
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1				78
	28a	**30**	**± 31a**	
2				81
	28b	**30**	**± 31b**	
3				76
	28c	**30**	**±31c**	
4				74
	28d	**30**	**± 31d**	
5				68
	28e	**30**	**±31e**	
6				75
	28f	**30**	**± 31f**	
7				66
	28g	**30**	**± 31g**	

Table 3.3. Continues…….

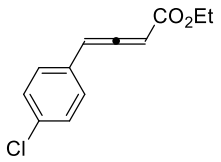
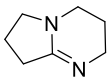
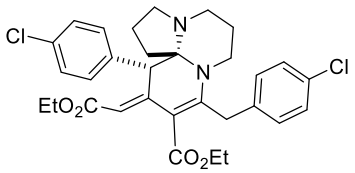
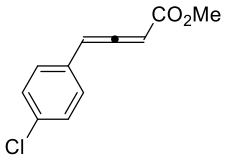
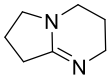
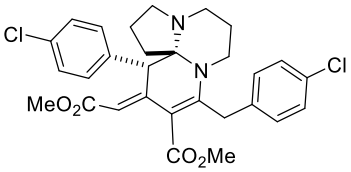
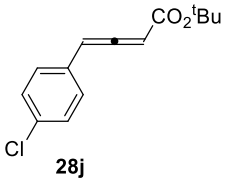
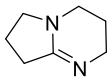
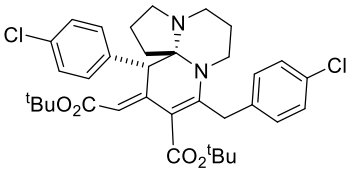
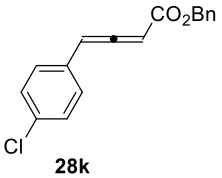
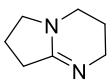
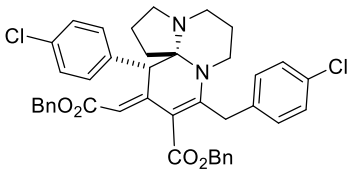
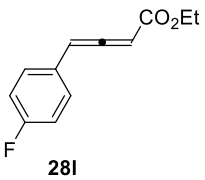
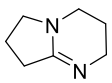
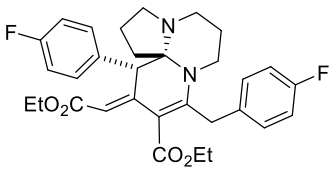
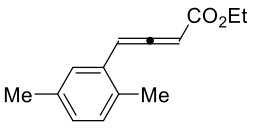
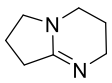
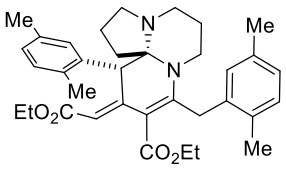
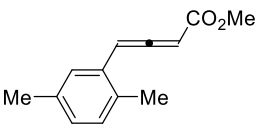
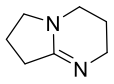
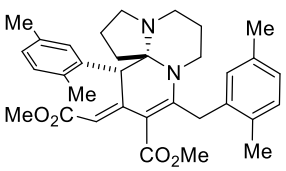
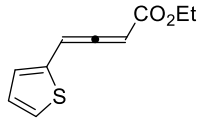
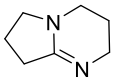
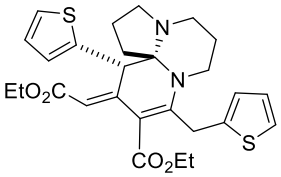
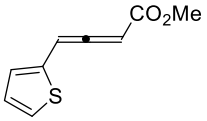
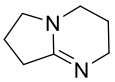
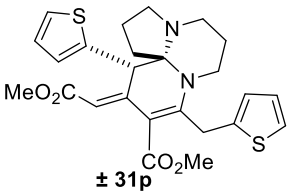
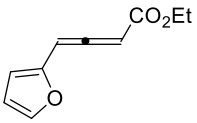
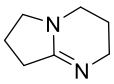
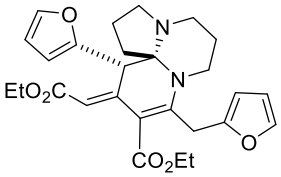
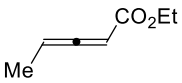
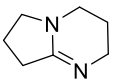
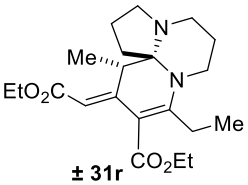
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
8	 **28h**	 **30**	 **± 31h**	**73**
9	 **28i**	 **30**	 **± 31i**	**75**
10	 **28j**	 **30**	 **± 31j**	**63**
11	 **28k**	 **30**	 **± 31k**	**67**
12	 **28l**	 **30**	 **± 31l**	**72**
13	 **28m**	 **30**	 **± 31m**	**63**
14	 **28n**	 **30**	 **± 31n**	**67**

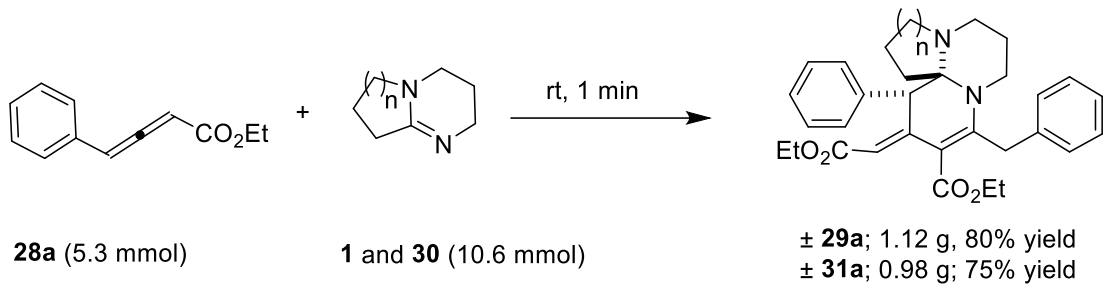
Table 3.3. Continues…….

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
15	 **28o**	 **30**	 **± 31o**	**32**
16	 **28p**	 **30**	 **± 31p**	**34**
17	 **28q**	 **30**	 **± 31q**	**ND**
18	 **28r**	 **30**	 **± 31r**	**48**

Reaction conditions: 1 equiv. of allenoate **28** (50 mg) & 2.0 equiv. of DBN (**30**) at room temperature for 1 min

resulted in comparatively higher yields than bulkier -CO_2Bn and -$CO_2{}^t$Bu groups. Moreover, the yields decreased slightly with substitutions on the allenoates, following a similar trend observed with DBU. With DBN, thiophenyl allenoates also resulted in comparatively lower yields (**31o** and **31p**). The furyl allenoate did not furnish the product (**31q**). The alkyl derivative, ethyl penta-2,3-dienoate afforded the product **31r** in 47% yield.

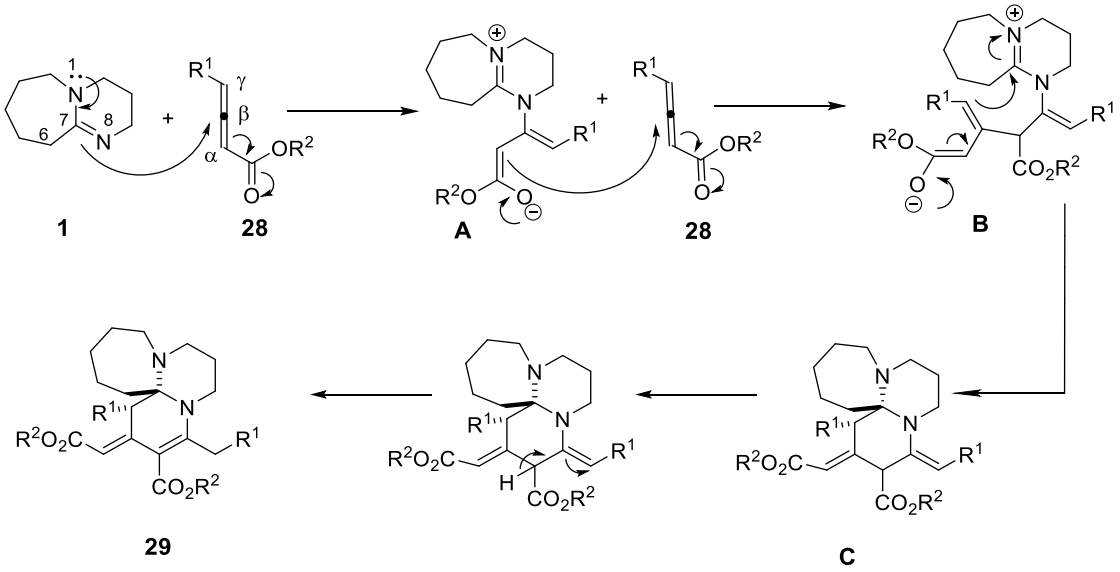
The protocol was also performed on a gram scale using 5.3 mmol of ethyl 4-phenylbuta-2,3-dienoate (**28a**), 10.6 mmol of DBU (**1**), and 10.6 mmol of DBN (**30**), affording the corresponding products **29a** with 80% yield and **31a** with 75% isolated yield (**Scheme 3.8**). This signifies the efficiency and practical applicability of the developed annulation protocol.



Scheme 3.8. Gram-scale synthesis of fused tricyclic pyridopyrimidines

3.5. Plausible Mechanism

Considering of the crystal structure of **29a** and previously reported mechanisms,[2a,4a,22] we have proposed the plausible mechanistic pathway for the formation of fused tricyclic pyridopyrimidines as depicted in **Scheme 3.9**. The reaction seems to proceed *via* the initial nucleophilic addition of DBU **1,** at the *β* position of the allenoate **28** forming stabilized *β*-ammonium enolate **A**. The *β*-ammonium enolate **A** thus formed can easily add to another molecule of allenoate resulting in intermediate **B**, which upon intra-molecular cyclization followed by isomerization furnishes the final conjugated ene system **29**.

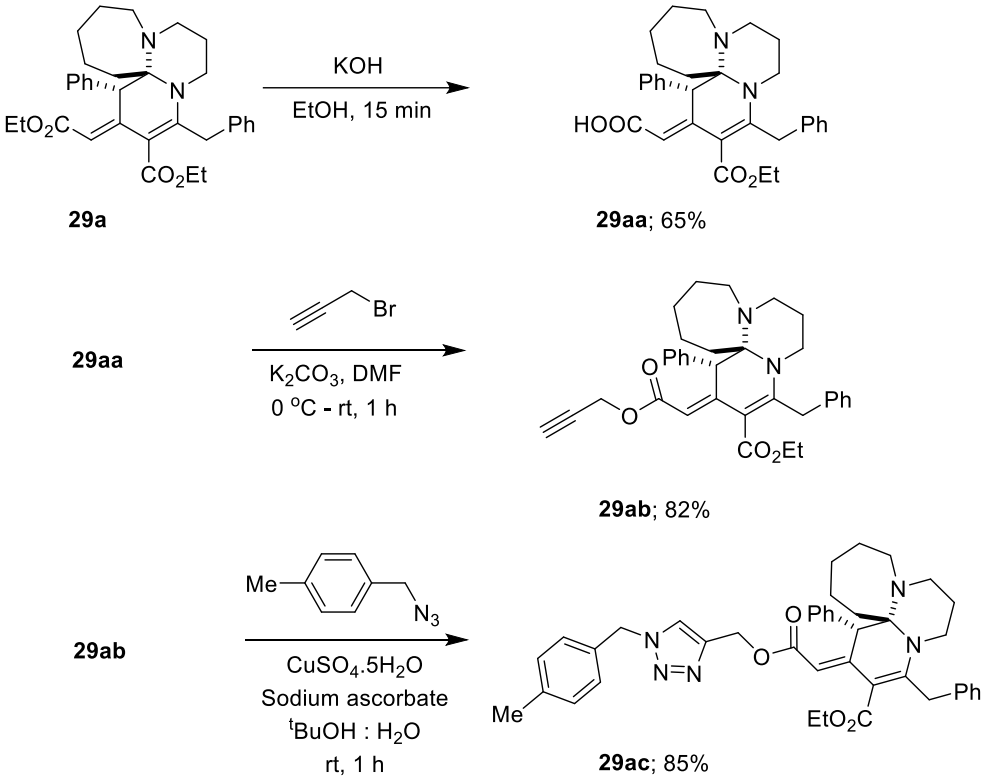


Scheme 3.9. Proposed mechanism

3.6. Last stage functionalization of tricyclic pyridopyrimidines

In addition, we have also demonstrated the late-stage diversification of the obtained tricyclic pyridopyrimidines (**29a**) (**Scheme 3.10**). We successfully attempted the synthesis of biologically relevant triazole **29ac** *via* Click reaction, utilizing **29ab**, which is obtained

by the propargylation of **29aa**, the acid-hydrolysed product of **29a**. The pyridopyrimidine derivatives **29aa** and **29ab** with the free reactive acid and propargyl groups respectively, could generate a lot of interest among synthetic and medicinal chemists for further modifications in generating pyridopyrimidine hybrids of medicinal relevance.



Scheme 3.10. Late-stage diversification of tricyclic pyridopyrimidines

3.7. Conclusion

In summary, an unprecedented 100% atom-economical annulation of allenoates with cyclic amidines has been achieved for the synthesis of functionalized tricyclic pyridopyrimidine scaffolds. High reaction efficiency, ease of operation, very short time, mild and solvent-free reaction conditions, with wide substrate scope are the key advantages of the present annulation protocol. This is the first approach that exploits the reactivity of allenoates to construct the structurally diverse motifs of tricyclic pyridopyrimidines.

3.8. General Methods

All the chemicals (**1** and **30**) and solvents (anhydrous) were commercially purchased from Sigma-Aldrich and used without further purification. Column chromatography was performed using silica gel (100-200 mesh), and a mixture of hexane-ethyl acetate was used for elution. NMR spectra were recorded at 500 (^{1}H) and 125 (^{13}C) MHz on a Bruker ASCEND^{TM} spectrometer by using $CDCl_3$ and CD_3COCD_3 as solvents and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) for ^{1}H NMR spectra are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 7.27, singlet) and CD_3COCD_3 (δ 2.05, quintet). Coupling constants (*J*) are given in Hertz (Hz), and multiplicities were represented as s, d, t, q, m, and dd for singlet, doublet, triplet, quartet, multiplet, and doublet of a doublet, respectively. Chemical shifts (δ) for ^{13}C NMR are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 77.03, triplet) and CD_3COCD_3 (δ 206.68, singlet and δ 29.92, septet). Infrared spectra were recorded with a Bruker Alpha-T FT-IR spectrometer. Mass spectra were recorded under HRMS (ESI) using a Thermo Scientific Exactive mass spectrometer. Melting points were determined on a Buchi melting point apparatus and were uncorrected. All the substituted allenoates were synthesized using known procedures.[26]

3.9. General experimental procedure

3.9.1. Procedure for the synthesis of Fused Tricyclic pyridopyrimidines (29 & 31):

In an ordinary glass tube equipped with a magnetic stirring bar, allenoate **1** (50 mg, 0.26 mmol) was taken (except for **28d** and **28k,** which are dissolved in a minimum amount of DCE). To that, DBU/ DBN (0.53 mmol, 2 equiv.) was added and stirred for 1 min at room temperature. The progress of the reaction was monitored by running the TLC plate in 2 : 8 (EtOAc : Hexane) solution to view the product formation. After completion of the reaction, the reaction mixture was loaded on to a silica gel column (100 – 200 mesh) by dissolving it in a minimum amount of DCM and was purified by 2 : 8 (EtOAc : Hexane) as the eluent. Owing to the nature of the product sticking to silica gel, the column was completed in a time of 10 minutes to get maximum yield.

3.9.2. Procedure for the gram scale reaction

In an ordinary glass tube equipped with a magnetic stirring bar, a solution of allenoate **28a** (1 g, 5.31 mmol) was taken. To that, DBU/ DBN (10.62 mmol, 2 equiv.) was added and

stirred for 1 min at room temperature. The progress of the reaction was monitored by running the TLC plate in a 2 : 8 (EtOAc : Hexane) solution to view the yellow-coloured product formation. After completion of the reaction, the reaction mixture was loaded onto a silica gel column (100 – 200 mesh) by dissolving it in a minimum amount of DCM and was purified by 2: 8 (EtOAc: Hexane) as the eluent. Owing to the nature of the product sticking to silica gel, the column was completed in a period of 10 minutes to get maximum yield. The product **29a** was obtained in 80% yield (1.12 g) as a yellow gummy solid. The product **31a** was obtained in 75% yield (0.98 g) as a yellow gummy solid.

3.10. Experimental procedures for late-stage diversification

3.10.1. Procedure for the synthesis of (*E*)-2-(4-benzyl-3-(ethoxycarbonyl)-1-phenyl-7,8,11,12,13,14-hexahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepin-2(1H)-ylidene)acetic acid (29aa)[27]

Add KOH (174 mg, 3.09 mmol) to a solution of **29a** (50 mg, 0.094 mmol) in 4 mL of EtOH. Stir the resulting solution for 15 minutes at reflux. The solvent was removed and the compound was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **29aa** (31 mg, 65%) was isolated as a yellow gummy liquid by column chromatography (silica gel: 100 - 200 mesh) using ethyl acetate: hexane (30 : 70) as the eluent.

3.10.2. Procedure for the synthesis of Ethyl (*E*)-4-benzyl-2-(2-oxo-2-(prop-2-yn-1-yloxy)ethylidene)-1-phenyl-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido [2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29ab)[28]

The propargyl bromide (11.9 mg, 0.09 mmol) was added dropwise to a solution of **29aa** (50 mg, 0.09 mmol) in DMF at 0 ^oC. K_2CO_3 (21 mg, 0.15 mmol) was added and allowed to stir at room temperature until the completion of the reaction monitored by TLC. The compound was extracted with ethyl acetate, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **29ab** (44 mg, 82%) was isolated as a yellow gummy liquid by column chromatography (silica gel: 100 - 200 mesh) using ethyl acetate : hexane (15 : 85) as the eluent.

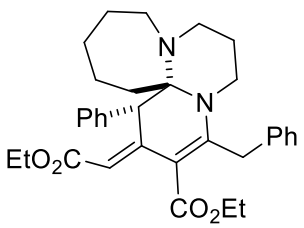
3.10.3. Procedure for the synthesis of Ethyl (*E*)-4-benzyl-2-(2-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-oxoethylidene)-1-phenyl-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29ac)[28]

To a solution of 4-methyl benzyl azide (11 mg, 0.074 mmol) and compound **29ab** (40 mg, 0.074 mmol) in ^{t}BuOH - water (1:2) mixture, $CuSO_4.5H_2O$ (2 mg, 0.0074 mmol) and sodium ascorbate (3.7 mg, 0.0185 mmol) were added and the reaction mixture was allowed to stir at room temperature, progress of the reaction was monitored by TLC. After completion of the reaction, the content was extracted with ethyl acetate, washed with brine and the compound was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **29ac** (43 mg, 85%) was isolated as a yellow gummy liquid by column chromatography (silica gel: 100 – 200 mesh) using ethyl acetate : hexane (30 : 70) as the eluent.

3.11. Characterization data of fused tricyclic pyridopyrimidines (29a – 29s, 31a – 31r)

Ethyl (*E*)-4-benzyl-2-(2-ethoxy-2-oxoethylidene)-1-phenyl-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29a)

The compounds **29a** was synthesized following the procedure described in section **3.9.1** using ethyl 4-phenylbuta-2,3-dienoate (50 mg, 0.26 mmol), DBU (79 µL, 0.53 mmol) at room temperature. The product **29a** was obtained as a yellow gummy solid in 82% (58 mg) yield.



29a

Mp: 148 – 150 ^{o}C.

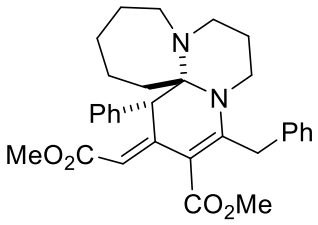
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 6.5 Hz, 2H), 7.22 – 7.25 (m, 2H), 7.19 – 7.18 (m, 2H), 7.16 – 7.12 (m, 4H), 5.52 (s, 1H), 5.44 (s, 1H), 4.09 – 4.15 (m, 2H), 3.93 – 4.02 (m, 2H), 3.92 (d, *J* = 16.5 Hz, 1H), 3.72 (d, *J* = 16.5 Hz, 1H), 3.45 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.00 – 3.05 (m, 1H), 2.87 – 2.92 (m, 1H), 2.60 – 2.63 (m, 1H), 2.36 – 2.40 (m, 1H), 2.28 – 2.34 (m, 1H), 1.83 – 1.88 (m, 1H), 1.65 – 1.69 (m, 1H), 1.32 – 1.55 (m, 8H), 1.13 (t, *J* = 7.0 Hz, 3H), 1.07 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 167.4, 152.1, 151.2, 139.7, 137.2, 130.1, 128.6, 128.2, 127.7, 126.6, 126.5, 106.3, 105.5, 79.3, 60.6, 59.0, 49.9, 45.5, 45.2, 42.3, 38.2, 37.0, 29.38, 28.8, 23.6, 22.9, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{33}H_{41}N_2O_4$: 529.3061; Found: 529.3061.

Methyl (*E*)-4-benzyl-2-(2-methoxy-2-oxoethylidene)-1-phenyl-1,2,7,8,11,12, 13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29b)

The compounds **29b** was synthesized following the procedure described in section **3.9.1** using methyl 4-phenylbuta-2,3-dienoate (50 mg, 0.29 mmol), DBU (86 µL, 0.57 mmol) at room temperature. The product **29b** was obtained as a yellow gummy liquid in 85% (61 mg) yield.



29b

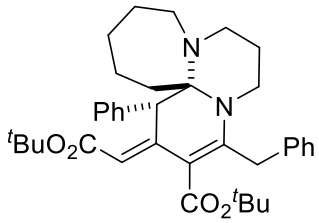
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.23 – 7.26 (m, 2H), 7.18 – 7.19 (m, 3H), 7.13 – 7.16 (m, 3H), 5.46 (s, 1H), 5.43 (s, 1H), 3.92 (d, *J* = 16.5 Hz, 1H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.65 (s, 3H), 3.52 (s, 3H), 3.47 (m, 1H), 3.05 – 3.00 (m, 1H), 2.87 – 2.93 (m, 1H), 2.63 (d, *J* = 15.0 Hz, 1H), 2.34 – 2.39 (m, 1H), 2.29 – 2.32 (m, 1H), 1.83 – 1.88 (m, 1H), 1.63 – 1.68 (m, 1H), 1.35 – 1.56 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 167.7, 152.5, 151.8, 139.6, 137.2, 130.0, 128.7, 128.2, 127.81, 126.6, 126.5, 105.9, 105.0, 79.3, 51.7, 50.5, 49.9, 45.5, 45.3, 42.4, 38.1, 37.1, 29.3, 28.8, 23.5, 22.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{37}N_2O_4$: 501.2748; Found: 501.2724.

***Tert*-butyl (*E*)-4-benzyl-2-(2-(tert-butoxy)-2-oxoethylidene)-1-phenyl-1,2,7,8, 11,12, 13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29c)**

The compounds **29c** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-phenylbuta-2,3-dienoate (50 mg, 0.23 mmol), DBU (69 µL, 0.46 mmol) at room temperature. The product **29c** was obtained as a yellow gummy liquid in 81% (55 mg) yield.



29c

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.28 – 7.32 (m, 4H), 7.22 – 7.25 (m, 4H), 5.50 (s, 2H), 3.97 (d, *J* = 16.5 Hz, 1H), 3.79 (d, *J* = 16.5 Hz, 1H), 3.48 (d, *J* = 8.5 Hz, 1H), 3.09 – 3.14 (m, 1H), 2.92 (t, *J* = 11.5 Hz, 1H), 2.71 (d, *J* = 15.0 Hz, 1H), 2.37 – 2.42 (m, 2H), 1.95 – 1.99 (m, 1H), 1.78 – 1.83 (m, 1H), 1.45 – 1.55 (m, 8H), 1.42 (s, 9H), 1.41 (s, 9H).

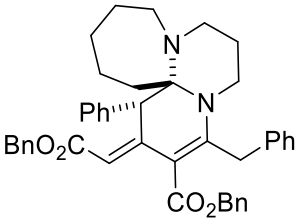
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.6, 166.9, 150.5, 148.6, 140.1, 137.3, 130.1, 128.5, 128.3, 127.5, 126.4, 126.3, 108.2, 107.7, 80.7, 79.1, 78.5, 49.9, 45.6, 44.6, 41.8, .37.9, 35.9, 29.2, 28.6, 28.3, 28.0, 27.9, 23.6, 22.6.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{37}H_{49}N_2O_4$: 585.3687; Found: 585.3680.

Benzyl (*E*)-4-benzyl-2-(2-(benzyloxy)-2-oxoethylidene)-1-phenyl-1,2,7,8,11, 12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29d)

The compounds **29d** was synthesized following the procedure described in section **3.9.1** using benzyl 4-phenylbuta-2,3-dienoate (50 mg, 0.20 mmol), DBU (60 µL, 0.40 mmol) at room temperature. The product **29d** was obtained as a yellow gummy liquid in 79% (52 mg) yield.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46 – 7.47 (m, 2H), 7.34 – 7.38 (m, 4H), 7.29 – 7.32 (m, 4H), 7.24 – 7.25 (m, 4H), 7.19 – 7.22 (m, 6H), 5.70 (s, 1H), 5.53 (s, 1H), 5.27 (d, *J* = 12.5 Hz, 1H), 5.09 – 5.14 (m, 2H), 5.05 (d, *J* = 12.5 Hz, 1H), 3.97 (d, *J* = 17.0 Hz, 1H), 3.77 (d, *J* = 17.0



29d

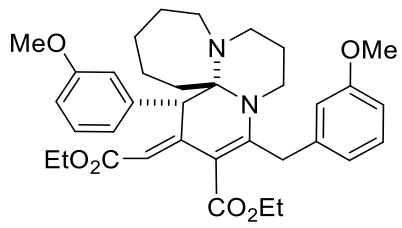
Hz, 1H), 3.49 – 3.53 (m, 1H), 3.12 – 3.08 (m, 1H), 2.96 – 3.02 (m, 1H), 2.73 (d, *J* = 15.0 Hz, 1H), 2.39 – 2.50 (m, 2H), 1.92 – 1.97 (m, 1H), 1.75 – 1.79 (m, 1H), 1.46 – 1.59 (m, 8H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.7, 167.1, 152.5, 151.8, 139.5, 137.0, 136.8, 135.7, 130.1, 128.69, 128.63, 128.37, 128.33, 128.1, 128.0, 127.9, 127.79, 127.77, 126.6, 126.5, 105.8, 105.3, 79.4, 66.6, 65.0, 49.9, 45.5, 45.4, 42.3, 38.0, 37.0, 29.4, 28.9, 23.5, 22.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{43}H_{45}N_2O_4$: 653.3374; Found: 653.3410.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-4-(3-methoxybenzyl)-1-(3-methoxy phenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29e)

The compounds **29e** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBU (68 µL, 0.46 mmol) at room temperature. The product **29e** was obtained as a yellow gummy solid in 71% (48 mg) yield.



29e

Mp: 115 – 117 ^{o}C.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.14 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.98 – 7.01 (m, 2H), 6.75 – 6.77 (m, 2H), 6.69 – 6.70 (m, 2H), 5.51 (s, 1H), 5.44 (s, 1H), 4.11 – 4.15 (m, 2H), 3.95 – 4.02 (m, 2H), 3.86 – 3.89 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.64 – 3.67 (m, 1H), 3.44 – 3.46 (m, 1H), 3.01 – 3.06 (m, 1H), 2.91 – 2.96 (m, 1H), 2.62 – 2.65 (d, *J* = 14.5 Hz, 1H), 2.33 – 2.38 (m, 2H), 1.94 – 1.99 (m, 1H), 1.65 – 1.70 (m, 1H), 1.50 – 1.52 (m, 2H), 1.36 – 1.47 (m, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H).

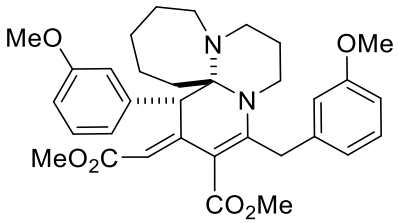
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.9, 167.4, 159.8, 159.0, 151.8, 150.9, 141.2, 138.7, 129.5, 128.5, 122.9, 120.5, 115.7, 113.6, 112.1, 112.0, 106.2, 105.7, 79.3,

60.6, 59.0, 55.18, 55.13, 49.9, 45.6, 44.9, 42.3, 38.1, 36.9, 29.3, 28.8, 23.7, 22.8, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{35}H_{45}N_2O_6$: 589.3272; Found: 589.3253.

Methyl (*E*)-2-(2-methoxy-2-oxoethylidene)-4-(3-methoxybenzyl)-1-(3-methoxyphenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29f)

The compounds **29f** was synthesized following the procedure described in section **3.9.1** using methyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBU (73 µL, 0.48 mmol) at room temperature. The product **29f** was obtained as a yellow gummy solid in 78% (53 mg) yield.



29f

Mp: 122 – 124 ^oC.

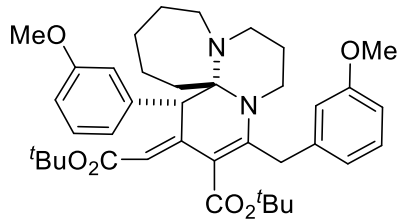
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (t, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.98 - 7.00 (m, 2H), 6.75 – 6.76 (m, 2H), 6.69 (t, *J* = 7.0 Hz, 2H), 5.45 (s, 1H), 5.43 (s, 1H), 3.89 (d, *J* = 16.5 Hz, 1H), 3.78 (d, *J* = 17.0 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.53 (s, 3H), 3.46 – 3.49 (m, 2H), 3.01 – 3.05 (m, 1H), 2.91 – 2.97 (m, 1H), 2.65 (d, *J* = 15.0 Hz, 1H), 2.33 – 2.38 (m, 2H), 1.94 – 1.99 (m, 1H), 1.63 – 1.68 (m, 2H), 1.35 – 1.47 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 167.6, 159.9, 159.0, 152.3, 151.5, 141.0, 138.6, 129.6, 128.5, 122.8, 120.5, 115.8, 113.7, 112.1, 111.9, 105.8, 105.2, 79.4, 55.18, 55.13, 51.7, 50.5, 49.9, 45.6, 45.0, 42.4, 38.0, 37.1, 29.3, 28.8, 23.6, 22.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{33}H_{41}N_2O_6$: 561.2959; Found: 561.2919.

***Tert*-butyl (*E*)-2-(2-(tert-butoxy)-2-oxoethylidene)-4-(3-methoxybenzyl)-1-(3-methoxyphenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]azepine-3-carboxylate (29g)**

The compounds **29g** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.20 mmol), DBU (60 µL, 0.40 mmol) at room temperature. The product **29g** was obtained as a yellow gummy liquid in 68% (45 mg) yield.



29g

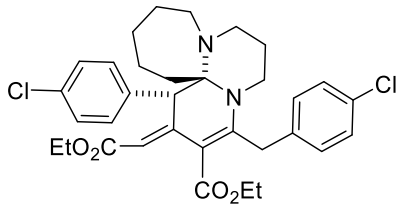
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.13 (t, *J* = 8.0 Hz, 1H), 7.03 – 7.04 (m, 3H), 6.76 (s, 2H), 6.68 (t, *J* = 9.0 Hz, 2H), 5.43 (s, 1H), 5.39 (s, 1H), 3.85 (d, *J* = 17.0 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.65 (d, *J* = 17.0 Hz, 1H), 3.38 – 3.41 (m, 1H), 3.00 – 3.05 (m, 1H), 2.83 – 2.89 (m, 1H), 2.63 (d, *J* = 15.0 Hz, 1H), 2.33 – 2.39 (m, 1H), 2.25 – 2.29 (m, 1H), 1.97 – 2.01 (m, 1H), 1.69 – 1.74 (m, 1H), 1.53 (s, 3H), 1.41 – 1.45 (m, 5H), 1.34 (s, 9H), 1.32 (s, 9H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.5, 166.9, 159.8, 158.9, 150.2, 148.3, 141.7, 138.9, 129.4, 128.2, 122.9, 120.7, 115.5, 113.7, 112.1, 112.0, 108.2, 108.0, 80.7, 79.1, 78.5, 55.18, 55.14, 49.9, 45.7, 44.3, 41.9, 37.9, 29.1, 28.5, 28.4, 28.0, 23.8, 22.6.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{39}H_{53}N_2O_6$: 645.3898; Found: 645.3952.

Ethyl (*E*)-4-(4-chlorobenzyl)-1-(4-chlorophenyl)-2-(2-ethoxy-2-oxoethylidene)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29h)

The compounds **29h** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.22 mmol), DBU (67 µL, 0.44 mmol) at room temperature. The product **29h** was obtained as a yellow gummy liquid in 73% (49 mg) yield.



29h

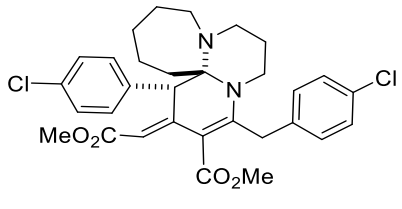
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 7.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 3H), 7.13 (d, *J* = 8.5 Hz, 3H), 5.51 (s, 1H), 5.44 (s, 1H), 4.11 – 4.16 (m, 2H), 3.97 – 4.02 (m, 2H), 3.86 (d, *J* = 17 Hz, 1H), 3.66 (d, *J* = 17.5 Hz, 1H), 3.38 – 3.39 (m, 1H), 2.97 – 3.02 (m, 1H), 2.84 – 2.89 (m, 1H), 2.64 (d, *J* = 14.5 Hz, 1H), 2.35 – 2.40 (m, 1H), 2.26 – 2.30 (m, 1H), 1.93 – 1.96 (m, 1H), 1.65 – 1.70 (m, 1H), 1.41 – 1.50 (m, 6H), 1.18 – 1.24 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 167.3, 151.2, 150.5, 138.3, 135.5, 132.5, 132.4, 131.3, 129.5, 128.8, 127.9, 106.3, 106.2, 79.3, 60.7, 59.1, 49.9, 45.6, 44.3, 42.2, 37.5, 36.2, 29.10, 28.5, 23.6, 22.7, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{33}H_{39}Cl_2N_2O_4$: 597.2281; Found: 597.2290.

Methyl (*E*)-4-(4-chlorobenzyl)-1-(4-chlorophenyl)-2-(2-methoxy-2-oxoethylid ene)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]aze pine-3-carboxylate (29i)

The compounds **29i** was synthesized following the procedure described in section **3.9.1** using methyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBU (73 µL, 0.48 mmol) at room temperature. The product **29i** was obtained as a yellow gummy liquid in 76% (52 mg) yield.



29i

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 4H), 5.45 (s, 1H), 5.43 (s, 1H), 3.86 (d, *J* = 16.5 Hz, 1H), 3.65 (s, 3H), 3.63 (s, 1H), 3.53 (s, 3H), 3.39 – 3.45 (m, 1H), 2.97 – 3.02 (m, 1H), 2.85 – 2.90 (m, 1H), 2.61 – 2.64 (d, 1H), 2.35 – 2.41 (m, 1H), 2.25 – 2.29 (m, 1H), 1.93 – 1.97 (m, 1H), 1.64 - 1.69 (m, 2H), 1.47 – 1.51 (m, 2H), 1.41 – 1.43 (m, 3H).

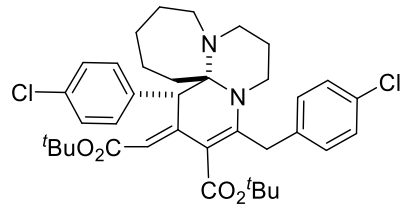
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 167.6, 151.6, 151.1, 138.2, 135.5, 132.54, 132.51, 131.2, 129.5,

128.9, 127.9, 105.9, 105.8, 79.4, 51.8, 50.7, 49.9, 45.6, 44.4, 42.3, 37.5, 36.3, 31.6, 29.1, 28.6, 23.5, 22.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{35}Cl_2N_2O_4$: 569.1968; Found: 569.1961.

***Tert*-butyl (*E*)-2-(2-(tert-butoxy)-2-oxoethylidene)-4-(4-chlorobenzyl)-1-(4-chlorophenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]azepine-3-carboxylate (29j)**

The compounds **29j** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.20 mmol), DBU (59 µL, 0.40 mmol) at room temperature. The product **29j** was obtained as a yellow gummy liquid in 66% (43 mg) yield.



29j

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.20 (m, 2H), 7.12 (t, *J* = 8.5 Hz, 4H), 5.42 (s, 1H), 5.39 (s, 1H), 3.78 (d, *J* = 16.5 Hz, 1H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.31 – 3.34 (m, 1H), 2.97 – 3.02 (m, 1H), 2.77 – 2.82 (m, 1H), 2.59 – 2.62 (m, 1H), 2.36 – 2.41 (m, 1H), 2.17 – 2.22 (m, 1H), 1.96 – 1.98 (m, 1H), 1.69 -1.73 (m, 2H), 1.46 – 1.48 (m, 4H), 1.39 – 1.42 (m, 3H), 1.33 (s, 9H), 1.32 (s, 9H).

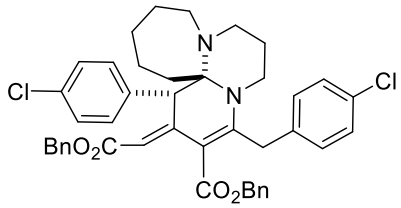
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.3, 166.8, 149.7, 147.9, 138.7, 135.7, 132.3, 132.0, 131.3, 129.7, 128.7, 127.6, 108.5, 108.2, 81.0, 79.1, 78.7, 49.9, 45.7, 43.6, 41.8, 37.2, 35.1, 28.8, 28.3, 28.2, 28.1, 28.0, 23.7, 22.4.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{37}H_{47}Cl_2N_2O_4$: 653.2907; Found: 653.2907.

Benzyl (*E*)-2-(2-(benzyloxy)-2-oxoethylidene)-4-(4-chlorobenzyl)-1-(4-chlorophenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]azepine-3-carboxylate (29k)

The compounds **29k** was synthesized following the procedure described in section **3.9.1** using benzyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.17 mmol), DBU (52 µL, 0.35

mmol) at room temperature. The product **29k** was obtained as a yellow gummy liquid in 69% (44 mg) yield.



29k

^{1}H NMR (500 MHz, $CDCl_3$):) δ 7.36 – 7.39 (m, 4H), 7.32 – 7.34 (m, 3H), 7.24 – 7.26 (m, 2H), 7.21 – 7.22 (m, 3H), 7.18 – 7.19 (m, 4H), 7.09 – 7.11 (d, *J* = 8.0 Hz, 2H), 5.69 (s, 1H), 5.52 (s, 1H), 5.26 (d, *J* = 12.0 Hz, 1H), 5.11 (d, *J* = 13.0 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H), 3.87 (d, *J* = 17.0 Hz, 1H), 3.69 (d, *J* = 17.0 Hz, 1H), 3.43 – 3.47 (m, 1H), 3.04 – 3.09 (m, 1H), 2.93 – 2.99 (m, 1H), 2.74 (d, *J* = 15.0 Hz, 1H), 2.43 – 2.48 (m, 1H), 2.34 – 2.39 (m, 1H), 2.00 – 2.05 (m, 1H), 1.75 – 1.79 (m, 1H), 1.51 – 1.59 (m, 4H), 1.46 – 1.52 (m, 4H).

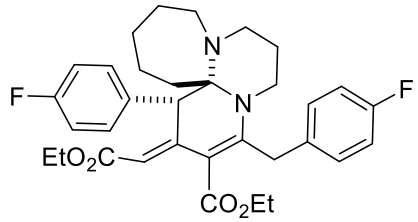
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.0, 151.6, 151.1, 138.1, 136.6, 135.4, 135.3, 132.5, 132.4, 131.3, 129.4, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 106.0, 105.7, 79.4, 66.8, 65.2, 50.0, 45.6, 44.5, 42.2, 37.4, 36.2, 29.1, 28.6, 23.5, 22.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{43}H_{43}Cl_2N_2O_4$: 721.2594; Found: 721.2616.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-4-(4-fluorobenzyl)-1-(4-fluorophenyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29l)

The compounds **29l** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(4-fluorophenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBU (72 µL, 0.48 mmol) at room temperature. The product **29l** was obtained as a yellow gummy liquid in 76% (52 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.34 (dd, *J* = 6.0, 7.5 Hz, 2H), 7.14 – 7.16 (m, 2H), 6.92 (t, *J* = 8.5 Hz, 2H), 6.84 (t, *J* = 9.0 Hz, 1H), 5.51 (s, 1H), 5.42 (s, 1H), 4.09 – 4.16 (m, 2H), 3.92 – 4.01 (m, 2H), 3.85 (d, *J* = 16.5 Hz, 1H), 3.67 (d, *J* = 16.5 Hz, 1H), 3.38



29l

– 3.42 (m, 1H), 2.97 – 3.02 (m, 1H), 2.84 - 2.90 (m, 1H), 2.63 (d, *J* = 14.5 Hz, 1H), 2.28 – 2.39 (m, 2H), 1.87 – 1.92 (m, 1H), 1.63 – 1.68 (m, 1H), 1.45 – 1.49 (m, 4H), 1.39 – 1.40 (m, 4H), 1.12 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H).

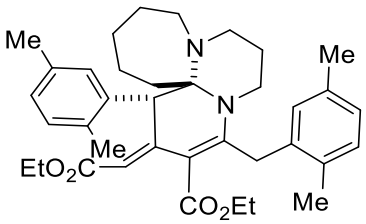
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.8, 167.3, 162.8 (d, *J* = 242.5 Hz), 162.6 (d, *J* = 243.7 Hz), 151.7, 150.9, 135.4 (d, *J* = 3.0 Hz), 132.8 (d, *J* = 3.1 Hz), 131.4 (d, *J* = 7.6 Hz), 129.8 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 21.2 Hz), 114.6 (d, *J* = 20.5 Hz), 106.2, 105.9, 79.2, 60.7, 59.1, 49.9, 45.5, 44.3, 42.2, 37.3, 36.5, 29.2, 28.6, 23.6, 22.7, 14.4, 14.0.

^{19}F NMR (371MHz, CDCl$_3$): δ 116.14, 116.43.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ for $C_{33}H_{39}F_2N_2O_4$: 565.2873; Found: 565.2878.

Ethyl (*E*)-4-(2,5-dimethylbenzyl)-1-(2,5-dimethylphenyl)-2-(2-ethoxy-2-oxoethyl idene)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]azepine-3-carboxylate (29m)

The compounds **29m** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBU (70 µL, 0.46 mmol) at room temperature. The product **29m** was obtained as a yellow gummy liquid in 67% (45 mg) yield.



29m

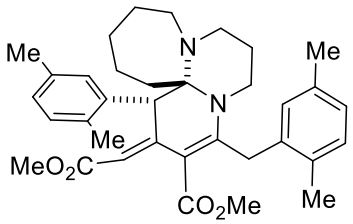
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29 (s, 1H), 6.98 (d, *J* = 7.0 Hz, 1H), 6.92 – 6.94 (m, 2H), 6.84 – 6.88 (m, 2H), 5.69 (s, 1H), 5.53 (s, 1H), 4.05 – 4.09 (m, 2H), 3.91 – 4.00 (m, 2H), 3.56 – 3.67 (m, 2H), 3.12 – 3.16 (m, 1H), 2.92 – 2.98 (m, 1H), 2.81 – 2.85 (m, 1H), 2.64 (s, 3H), 2.31 – 2.37 (m, 2H), 2.23 – 2.29 (m, 1H), 2.19 (s, 9H), 2.13 – 2.16 (m, 2H), 1.96 – 2.02 (m, 2H), 1.91 – 1.94 (m, 1H), 1.67 – 1.70 (m, 1H), 1.48 – 1.50 (m, 2H), 1.41 (s, 2H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 167.3, 153.1, 152.0, 138.3, 136.1, 135.5, 135.3, 134.3, 131.7, 130.3, 129.8, 129.3, 128.3, 127.1, 106.8, 105.4, 80.6, 60.3, 58.8, 52.6, 45.6, 41.3, 41.2, 35.4, 30.7, 29.9, 23.3, 22.9, 21.5, 21.1, 20.4, 19.3, 19.0, 14.4, 13.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{37}H_{49}N_2O_4$: 585.3687; Found: 585.3676.

Methyl (*E*)-4-(2,5-dimethylbenzyl)-1-(2,5-dimethylphenyl)-2-(2-methoxy-2-oxo ethylidene)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido [1,2-a]azepine-3-carboxylate (29n)

The compounds **29n** was synthesized following the procedure described in section **3.9.1** using methyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBU (74 µL, 0.49 mmol) at room temperature. The product **29n** was obtained as a yellow gummy liquid in 72% (50 mg) yield.



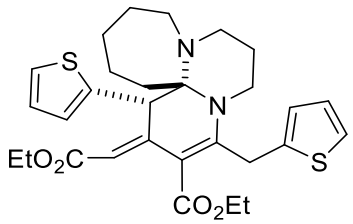
29n

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 6.5 Hz, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 5.65 (s, 1H), 5.45 (s, 1H), 3.69 (d, *J* = 16.5 Hz, 1H), 3.61 (s, 3H), 3.59 (d, *J* = 17.5 Hz, 1H), 3.50 (s, 3H), 3.10 – 3.15 (m, 1H), 2.84 – 2.95 (m, 2H), 2.76 – 2.81 (m, 1H), 2.64 (s, 3H), 2.32 – 2.37 (m, 1H), 2.23 – 2.26 (m, 2H), 2.19 (s, 9H), 2.15 – 2.17 (m, 2H), 1.96 – 2.02 (m, 1H), 1.88 – 1.93 (m, 1H), 1.65 – 1.71 (m, 2H), 1.45 – 1.49 (m, 2H), 1.40 – 1.44 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 167.6, 153.5, 152.5, 138.0, 136.0, 135.7, 135.2, 131.8, 130.4, 129.9, 129.1, 128.0, 127.2, 106.5, 105.0, 80.6, 52.6, 51.6, 50.5, 45.6, 41.3, 35.1, 30.6, 29.9, 26.9, 25.2, 23.3, 22.9, 21.5, 21.2, 20.4, 19.3.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{35}H_{45}N_2O_4$: 557.3374; Found: 557.3348.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-1-(thiophen-2-yl)-4-(thiophen-2-ylmethyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29o)

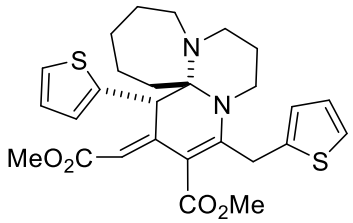


29o

Yield: Obtained in trace amount

Methyl (*E*)-2-(2-methoxy-2-oxoethylidene)-1-(thiophen-2-yl)-4-(thiophen-2-ylmethyl)-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29p)

The compounds **29p** was synthesized following the procedure described in section **3.9.1** using methyl 4-(thiophen-2-yl)buta-2,3-dienoate (50 mg, 0.28 mmol), DBU (83 µL, 0.55 mmol) at room temperature. The product **29p** was obtained as a yellow gummy liquid in 36% (26 mg) yield.



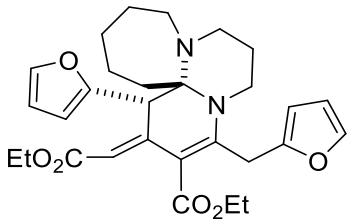
29p

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 – 7.09 (m, 2H), 6.98 (s, 1H), 6.81 – 6.82 (m, 2H), 6.58 (s, 1H), 6.11 (s, 1H), 5.59 (s, 1H), 3.91 (s, 2H), 3.65 (s, 3H), 3.59 (s, 3H), 3.14 – 3.19 (m, 1H), 2.96 – 3.01 (m, 1H), 2.70 – 2.73 (m, 2H), 2.40 – 2.44 (m, 1H), 2.01 – 2.06 (m, 1H), 1.83 – 1.86 (m, 1H), 1.74 (s, 1H), 1.58 – 1.61 (m, 2H), 1.46 – 1.51 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 167.9, 151.6, 151.3, 140.5, 139.2, 126.8, 126.4, 125.5, 125.4, 125.0, 124.0, 106.8, 103.7, 78.8, 51.7, 50.7, 49.2, 45.2, 42.5, 39.3, 33.2, 32.4, 27.8, 26.3, 23.5, 21.6.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_4S_2$: 513.1876; Found: 513.1900.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-1-(furan-2-yl)-4-(furan-2-ylmethyl)-1,2,7,8, 11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29q)

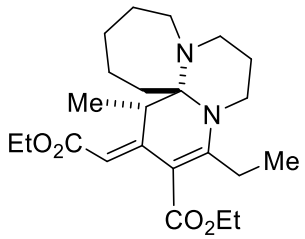


29q

Yield: Product not obtained

Ethyl (*E*)-2-(2-ethoxy-2-oxoethylidene)-4-ethyl-1-methyl-1,2,7,8,11,12,13,14-octa hydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29r)

The compounds **29r** was synthesized following the procedure described in section **3.9.1** using ethyl penta-2,3-dienoate (50 mg, 0.40 mmol), DBU (118 µL, 0.79 mmol) at room temperature. The product **29r** was obtained as a yellow gummy liquid in 55% (44 mg) yield.



29r

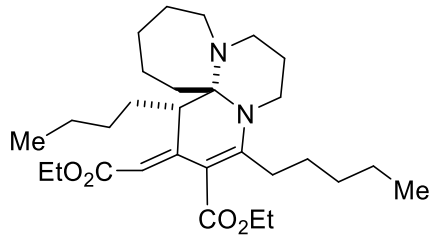
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.32 (s, 1H), 4.66 – 4.67 (m, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.61 (d, *J* = 12.0 Hz, 1H), 3.04 – 3.13 (m, 2H), 2.97 – 3.01 (m, 1H), 2.68 – 2.71 (m, 2H), 2.18 – 2.31 (m, 2H), 1.78 – 1.88 (m, 2H), 1.67 – 1.74 (m, 4H), 1.41 – 1.46 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 167.9, 155.8, 153.9, 103.0, 78.1, 60.4, 58.9, 48.8, 45.3, 31.5, 29.5, 25.1, 24.9, 20.6, 14.4, 14.3, 14.2, 12.9.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{23}H_{37}N_2O_4$: 405.2748; Found: 405.2763.

Ethyl (*E*)-1-butyl-2-(2-ethoxy-2-oxoethylidene)-4-pentyl-1,2,7,8,11,12,13,14-octa hydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29s)

The compounds **29s** was synthesized following the procedure described in section **3.9.1** using ethyl octa-2,3-dienoate (50 mg, 0.30 mmol), DBU (89 µL, 0.59 mmol) at room temperature. The product **29s** was obtained as a yellow gummy liquid in 48% (35 mg) yield.



29s

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.43 (s, 1H), 4.65 (d, *J* = 8.5 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.55 (d, *J* = 13.0 Hz, 1H), 3.12 (t, *J* = 12.0 Hz, 1H), 2.97 – 3.04 (m, 2H), 2.67 – 2.70 (m, 2H), 2.25 – 2.31 (m, 1H), 2.12 – 2.18 (m, 1H), 1.82 - 1.87 (m, 1H), 1.70 – 1.72 (m, 3H), 1.62 – 1.64 (m, 2H), 1.40 -1.41 (m, 2H), 1.22 – 1.25 (m, 9H), 1.17 – 1.19 (m, 5H), 0.80 – 0.81 (m, 3H), 0.78 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 168.1, 154.1, 152.9, 106.4, 103.1, 78.7, 60.3, 58.9, 48.6, 45.4, 41.4, 35.8, 31.7, 31.30, 30.0, 28.4, 28.1, 27.5, 26.6, 25.3, 25.0, 23.4, 22.4, 20.5, 14.4, 14.2, 14.1, 13.9.

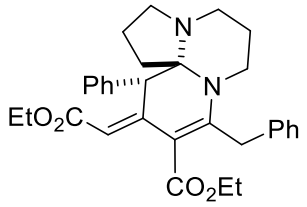
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{29}H_{49}N_2O_4$: 489.3687; Found: 489.3683.

Ethyl (*E*)-9-benzyl-11-(2-ethoxy-2-oxoethylidene)-12-phenyl-2,3,6,7,11,12-hexahydro -1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31a)

The compounds **31a** was synthesized following the procedure described in section **3.9.1** using ethyl 4-phenylbuta-2,3-dienoate (50 mg, 0.26 mmol), DBN (65 µL, 0.53 mmol) at room temperature. The product **31a** was obtained as a yellow gummy solid in 78% (52 mg) yield.

Mp: 134 – 136 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.0 Hz, 1H), 7.20 – 7.27 (m, 4H), 7.11 – 7.19 (m, 5H), 5.52 (s,



31a

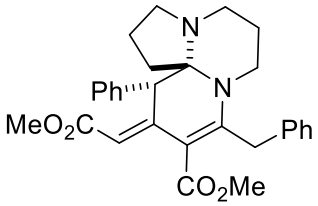
1H), 4.81 (s, 1H), 4.11 – 4.17 (m, 2H), 3.91 – 4.01 (m, 2H), 3.87 (d, *J* = 16.5 Hz, 1H), 3.71 (d, *J* = 16.5 Hz, 1H), 3.42 (m, 1H), 2.96 (t, *J* = 7.5 Hz, 1H), 2.79 – 2.84 (m, 1H), 2.61 – 2.67 (m, 1H), 2.27 – 2.23 (m, 1H), 2.15 – 2.19 (m, 1H), 1.65 – 1.84 (m, 3H), 1.43 – 1.51 (m, 3H), 1.07 – 1.13 (m, 6H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.9, 167.0, 152.3, 152.1, 138.7, 136.9, 130.0, 128.6, 128.2, 127.5, 126.6, 126.4, 107.1, 106.1, 81.2, 60.7, 59.0, 54.4, 50.2, 40.2, 39.6, 37.8, 37.7, 22.5, 20.7, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{37}N_2O_4$: 501.2748; Found: 501.2727.

Methyl (*E*)-9-benzyl-11-(2-methoxy-2-oxoethylidene)-12-phenyl-2,3,6,7,11,12-hexa hydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31b)

The compounds **31b** was synthesized following the procedure described in section **3.9.1** using methyl 4-phenylbuta-2,3-dienoate (50 mg, 0.29 mmol), DBN (70 µL, 0.57 mmol) at room temperature. The product **31b** was obtained as a yellow gummy liquid in 81% (55 mg) yield.



31b

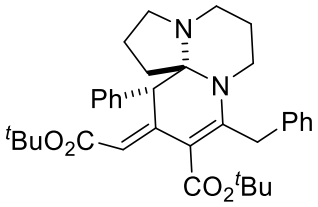
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.12 – 7.17 (m, 4H), 5.47 (s, 1H), 4.80 (s, 1H), 3.88 (d, *J* = 16.0 Hz, 1H), 3.71 (s, 1H), 3.67 (s, 3H), 3.51 (s, 3H), 3.39 – 3.44 (m, 1H), 2.97 (t, *J* = 7.5 Hz, 1H), 2.80 – 2.85 (m, 1H), 2.62 – 2.68 (m, 1H), 2.15 – 2.25 (m, 2H), 1.65 – 1.84 (m, 4H), 1.43 – 1.47 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 170.4, 167.3, 152.9, 152.6, 138.5, 136.8, 130.0, 128.7, 128.1, 127.6, 126.6, 126.5, 106.7, 105.6, 81.2, 54.5, 51.8, 50.5, 50.2, 40.1, 39.6, 37.9, 37.6, 22.5, 20.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{29}H_{33}N_2O_4$: 473.2435; Found: 473.2419.

***Tert*-butyl (*E*)-9-benzyl-11-(2-(tert-butoxy)-2-oxoethylidene)-12-phenyl-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31c)**

The compounds **31c** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-phenylbuta-2,3-dienoate (50 mg, 0.23 mmol), DBN (57 µL, 0.46 mmol) at room temperature. The product **31c** was obtained as a yellow gummy liquid in 76% (48 mg) yield.



31c

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.23 (s, 4H), 7.12 – 7.16 (m, 4H), 5.42 (s, 1H), 4.78 (s, 1H), 3.83 (d, *J* = 16.5 Hz, 1H), 3.68 (d, *J* = 16.5 Hz, 1H), 3.30 – 3.34 (m, 1H), 2.95 (t, *J* = 7.0 Hz, 1H), 2.78 – 2.83 (m, 1H), 2.57 – 2.63 (m, 1H), 2.22 – 2.26 (m, 1H), 2.14 – 2.18 (m, 1H), 1.78 – 1.83 (m, 1H), 1.65 – 1.76 (m, 2H), 1.41 – 1.52 (m, 3H), 1.33 (s, 9H), 1.31 (s, 9H).

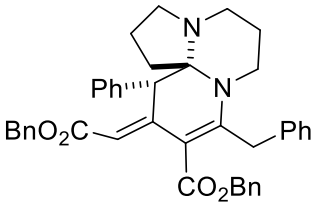
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.4, 166.6, 150.5, 149.6, 139.1, 137.1, 130.1, 128.5, 128.3, 127.3, 126.5, 126.1, 109.3, 108.4, 81.1, 80.8, 78.6, 54.0, 49.7, 40.5, 39.3, 37.4, 37.0, 28.3, 27.9, 22.5, 20.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{35}H_{45}N_2O_4$: 557.3374; Found: 557.3355.

Benzyl (*E*)-9-benzyl-11-(2-(benzyloxy)-2-oxoethylidene)-12-phenyl-2,3,6,7, 11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31d)

The compounds **31d** was synthesized following the procedure described in section **3.9.1** using benzyl 4-phenylbuta-2,3-dienoate (50 mg, 0.20 mmol), DBN (50 µL, 0.40 mmol) at room temperature. The product **31d** was obtained as a yellow gummy liquid in 74% (46 mg) yield.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.20 – 7.27 (m, 7H), 7.13 – 7.15 (m, 7H), 7.08 – 7.11 (m, 4H), 5.59 (s, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.06 (d, *J* = 12.0 Hz, 1H), 4.99 (d, *J* = 12.5 Hz, 1H),



31d

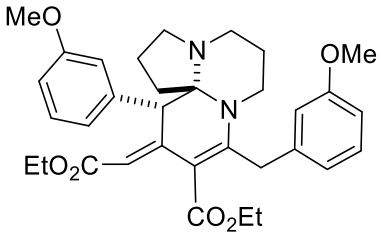
4.92 (d, *J* = 12.5 Hz, 1H), 4.82 (s, 1H), 3.82 (d, *J* = 16.5 Hz, 1H), 3.65 (d, *J* = 16.5 Hz, 1H), 3.35 – 3.39 (m, 1H), 2.96 (t, *J* = 7.0 Hz, 1H), 2.79 – 2.84 (m, 1H), 2.59 – 2.66 (m, 1H), 2.23 – 2.26 (m, 1H), 2.15 – 2.20 (m, 1H), 1.66 – 1.83 (m, 4H), 1.42 – 1.49 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.6, 166.7, 152.9, 152.7, 138.5, 136.8, 136.7, 135.7, 130.1, 128.7, 128.6, 128.37, 128.35, 128.1, 128.0, 127.9, 127.7, 127.6, 126.5, 126.5, 106.6, 105.7, 81.2, 66.7, 65.0, 54.4, 50.3, 40.1, 39.6, 37.9, 37.6, 22.5, 20.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{41}H_{41}N_2O_4$: 625.3061; Found: 625.3037.

Ethyl (*E*)-11-(2-ethoxy-2-oxoethylidene)-9-(3-methoxybenzyl)-12-(3-methoxyphenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31e)

The compounds **31e** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBN (57 µL, 0.46 mmol) at room temperature. The product **31e** was obtained as a yellow gummy liquid in 68% (44 mg) yield.



31e

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.16 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.01 – 7.02 (m, 2H), 6.78 – 6.79 (m, 2H), 6.69 (t, *J* = 9.0 Hz, 2H), 5.51 (s, 1H), 4.81 (s, 1H), 4.12 – 4.16 (m, 2H), 3.91 – 4.02 (m, 2H), 3.82 -3.85 (d, *J* = 16.5 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.65 (d, *J* = 16.5 Hz, 1H), 3.38 – 3.43 (m, 1H), 2.97 (t, *J* = 6.5 Hz, 1H), 2.81 – 2.85 (m, 1H), 2.64 – 269 (m, 1H), 2.20 – 2.25 (m, 2H), 1.72 – 1.82 (m, 2H), 1.58 – 1.67 (m, 4H), 1.14 (t, *J* = 7.5 Hz, 3H), 1.10 (t, *J* = 7.5 Hz, 3H).

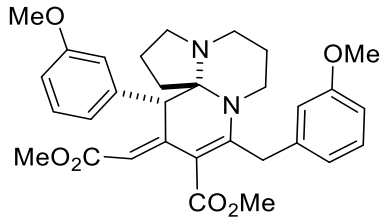
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.8, 167.0, 159.9, 152.0, 140.2, 138.4, 129.6, 128.3, 122.9, 120.5, 115.6, 113.6, 112.2, 111.9, 106.3, 81.2, 60.6, 59.0, 55.18,

55.15, 54.3, 50.0, 40.3, 39.6, 37.7, 37.6, 22.5, 20.8, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{33}H_{41}N_2O_6$: 561.2959; Found: 561.2958.

Methyl (*E*)-11-(2-methoxy-2-oxoethylidene)-9-(3-methoxybenzyl)-12-(3-methoxy phenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b] pyrimidine-10-carboxylate (31f)

The compounds **31f** was synthesized following the procedure described in section **3.9.1** using methyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBN (60 µL, 0.48 mmol) at room temperature. The product **31f** was obtained as a yellow gummy solid in 75% (49 mg) yield.



31f

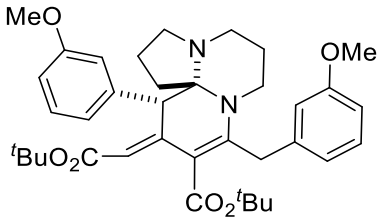
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.77 – 6.79 (m, 2H), 6.69 (t, *J* = 9.0 Hz, 2H), 5.46 (s, 1H), 4.80 (s, 1H), 3.86 (d, *J* = 16.5 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.65 (d, *J* = 17.0 Hz, 1H), 3.51 (s, 3H), 3.40 – 3.45 (m, 1H), 2.96 – 2.99 (m, 1H), 2.82 – 2.86 (m, 1H), 2.64 – 2.70 (m, 1H), 2.21 – 2.25 (m, 2H), 1.74 – 1.82 (m, 2H), 1.66 – 1.71 (m, 2H), 1.58 – 1.64 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 167.3, 159.9, 159.0, 152.6, 152.4, 140.1, 138.4, 129.7, 128.3, 122.8, 120.4, 115.7, 113.6, 112.2, 111.8, 106.7, 105.8, 81.2, 55.18, 55.16, 54.4, 51.8, 50.5, 50.0, 40.2, 39.6, 37.9, 37.6, 22.5, 20.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{37}N_2O_6$: 533.2646; Found: 533.2659.

***Tert*-butyl (*E*)-11-(2-(tert-butoxy)-2-oxoethylidene)-9-(3-methoxybenzyl)-12-(3-methoxyphenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31g)**

The compounds **31g** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-(3-methoxyphenyl)buta-2,3-dienoate (50 mg, 0.20 mmol), DBN (50 µL, 0.40 mmol) at room temperature. The product **31g** was obtained as a yellow gummy liquid in 66% (41 mg) yield.



31g

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.15 (t, *J* = 8.1 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.02 (s, 2H), 6.79 (s, 2H), 6.68 (dd, *J* = 12.8, 8.3 Hz, 2H), 5.41 (s, 1H), 4.79 (s, 1H), 3.80 (d, *J* = 16.4 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.62 (d, *J* = 16.5 Hz, 1H), 3.34 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.96 (t, *J* = 7.1 Hz, 1H), 2.82 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.25 – 2.17 (m, 2H), 1.82 – 1.72 (m, 2H), 1.67 (d, *J* = 8.3 Hz, 3H), 1.50 (ddd, *J* = 24.6, 14.5, 8.2 Hz, 2H), 1.34 (s, 8H), 1.32 (s, 8H).

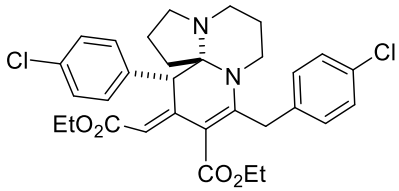
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.3, 166.6, 159.8, 158.9, 150.3, 149.4, 140.7, 138.6, 129.5, 128.1, 122.9, 120.6, 115.4, 113.6, 112.1, 112.0, 109.3, 108.5, 81.1, 80.86, 78.67, 55.17, 54.0, 49.5, 40.6, 39.3, 37.4, 36.9, 28.3, 28.0, 22.4, 20.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{37}H_{49}N_2O_6$: 617.3585; Found: 617.3628.

Ethyl (*E*)-9-(3-chlorobenzyl)-12-(4-chlorophenyl)-11-(2-ethoxy-2-oxoethylid ene)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31h)

The compounds **31h** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.22 mmol), DBN (54 µL, 0.44 mmol) at room temperature. The product **31h** was obtained as a yellow gummy liquid in 73% (47 mg) yield.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.31 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.12 – 7.17 (m, 4H), 5.51



31h

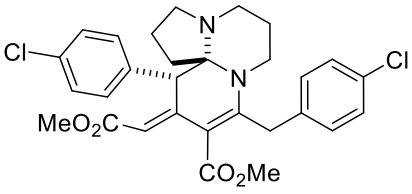
(s, 1H), 4.77 (s, 1H), 4.11 – 4.17 (m, 2H), 3.92 – 4.01 (m, 2H), 3.78 (t, *J* = 16.5 Hz, 1H), 3.64 (d, *J* = 16.5 Hz, 1H), 3.31 – 3.35 (m, 1H), 2.95 – 2.98 (m, 1H), 2.80 – 2.83 (m, 1H), 2.60 – 2.65 (m, 1H), 2.20 – 2.22 (m, 2H), 1.77 – 1.80 (m, 1H), 1.64 – 1.69 (m, 2H), 1.49 – 1.51 (m, 3H), 1.09 – 1.14 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 166.9, 151.6, 151.3, 137.3, 135.2, 132.5, 132.3, 131.3, 129.5, 128.9, 127.7, 107.2, 106.7, 81.1, 60.8, 59.1, 54.3, 49.5, 40.4, 39.6, 37.5, 37.0, 22.53, 20.7, 14.3, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{35}Cl_2N_2O_4$: 569.1968; Found: 569.1979.

Methyl (*E*)-9-(3-chlorobenzyl)-12-(4-chlorophenyl)-11-(2-methoxy-2-oxo ethylidene)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b] pyrimidine-10-carboxylate (31i)

The compounds **31i** was synthesized following the procedure described in section **3.9.1** using methyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBN (59 µL, 0.48 mmol) at room temperature. The product **31i** was obtained as a yellow gummy liquid in 75% (49 mg) yield.



31i

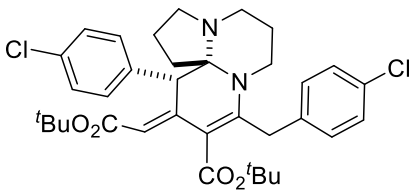
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.0 Hz, 4H), 5.46 (s, 1H), 4.76 (s, 1H), 3.82 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H), 3.64 (d, *J* = 16.5 Hz, 1H), 3.51 (s, 3H), 3.32 – 3.37 (m, 1H), 2.95 – 2.98 (m, 1H), 2.82 – 2.83 (m, 1H), 2.61 – 2.67 (m, 1H), 2.18 – 2.26 (m, 2H), 1.78 – 1.82 (m, 1H), 1.64 – 1.70 (m, 2H), 1.54 – 1.56 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 167.2, 152.2, 151.7, 137.1, 135.2, 132.6, 132.4, 131.3, 129.5, 129.0, 127.8, 106.7, 106.3, 81.2, 54.3, 51.9, 50.6, 49.5, 40.3, 39.6, 37.6, 37.0, 22.5, 20.6.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{29}H_{31}Cl_2N_2O_4$: 541.1655; Found: 541.1687.

***Tert*-butyl (*E*)-11-(2-(tert-butoxy)-2-oxoethylidene)-9-(3-chlorobenzyl)-12-(4-chlorophenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b] pyrimidine-10-carboxylate (31j)**

The compounds **31j** was synthesized following the procedure described in section **3.9.1** using *tert*-butyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.20 mmol), DBN (49 µL, 0.40 mmol) at room temperature. The product **31j** was obtained as a yellow gummy solid in 63% (39 mg) yield.



31j

Mp: 160 – 162 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.41 (s, 1H), 4.75 (s, 1H), 3.77 (d, *J* = 16.5 Hz, 1H), 3.62 (d, *J* = 16.5 Hz, 1H), 3.24 – 3.28 (m, 1H), 2.93 – 2.96 (m, 1H), 2.78 – 2.81 (m, 1H), 2.56 – 2.61 (m, 1H), 2.19 – 2.21 (m, 2H), 1.78 – 1.79 (m, 1H), 1.54 – 1.68 (m, 5H), 1.35 (s, 9H), 1.31 (s, 9H).

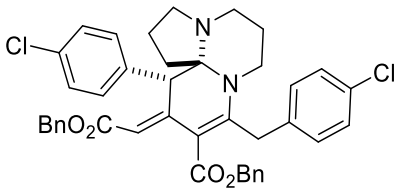
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 166.4, 149.7, 149.0, 137.7, 135.4, 132.4, 132.0, 131.3, 129.6, 128.8, 128.7,127.5, 109.3, 109.0, 81.2, 81.0, 78.8, 53.9, 48.9, 40.7, 39.3, 36.8, 36.7, 28.3, 28.0, 22.4, 20.7.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{35}H_{43}Cl_2N_2O_4$: 625.2594; Found: 625.2608.

Benzyl (*E*)-11-(2-(benzyloxy)-2-oxoethylidene)-9-(3-chlorobenzyl)-12-(4-chlorophenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31k)

The compounds **31k** was synthesized following the procedure described in section **3.9.1** using benzyl 4-(4-chlorophenyl)buta-2,3-dienoate (50 mg, 0.17 mmol), DBN (43 µL, 0.35

mmol) at room temperature. The product **31k** was obtained as a yellow gummy liquid in 67% (41 mg) yield.



31k

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.30 (m, 2H), 7.27 (s, 2H), 7.24 – 7.25 (m, 2H), 7.20 – 7.22 (m, 2H), 7.16 – 7.17 (m, 2H), 7.10 – 7.13 (m, 6H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.58 (s, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1H), 4.96 (d, *J* = 17.0 Hz, 1H), 4.77 (s, 1H), 4.63 (s, 1H), 3.73 (d, *J* = 16.5 Hz, 1H), 3.57 (d, *J* = 16.5 Hz, 1H), 3.27 – 3.32 (m, 1H), 2.94 – 2.97 (m, 1H), 2.79 - 2.83 (m, 1H), 2.59 – 2.64 (m, 1H), 2.20 – 2.23 (m, 2H), 1.75 – 1.81 (m, 1H), 1.63 – 1.69 (m, 3H), 1.52 – 1.55 (m, 2H).

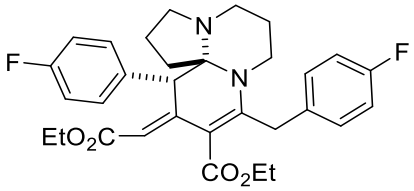
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 166.6, 152.3, 151.8, 137.1, 136.6, 135.4, 135.0, 132.5, 132.4, 131.3, 129.4, 128.87, 128.80, 128.5, 128.4, 128.1, 128.0, 127.87, 127.80, 127.6, 127.0, 106.6, 106.4, 81.2, 66.9, 65.4, 65.2, 54.3, 49.6, 40.4, 39.6, 37.6, 36.9, 22.5, 20.6.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{41}H_{39}Cl_2N_2O_4$: 693.2281; Found: 693.2286.

Ethyl (*E*)-11-(2-ethoxy-2-oxoethylidene)-9-(3-fluorobenzyl)-12-(4-fluoro phenyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31l)

The compounds **31l** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(4-fluorophenyl)buta-2,3-dienoate (50 mg, 0.24 mmol), DBN (60 µL, 0.48 mmol) at room temperature. The product **31l** was obtained as a yellow gummy liquid in 72% (47 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.5, 6.0 Hz, 1H), 7.27- 7.29 (m, 2H), 6.95 (t, *J* = 8.5 Hz, 2H), 6.85 (t, *J* = 8.5 Hz, 2H), 5.59 (s, 1H), 4.86 (s, 1H), 4.19 – 4.26 (m, 2H), 4.00 – 4.09 (m, 2H), 3.89 (d, *J* = 16.5 Hz, 1H), 3.74 (d, *J* = 16.0 Hz, 1H), 3.43– 3.47



31l

(m, 1H), 3.05 (t, *J* = 7.5 Hz, 1H) 2.89 – 2.93 (m, 1H), 2.69 – 2.75 (m, 1H), 2.27 – 2.32 (m, 2H), 1.84 – 1.90 (m, 1H), 1.74 – 1.81 (m, 2H), 1.56 – 1.63 (m, 3H), 1.18 – 1.22 (m, 6H).

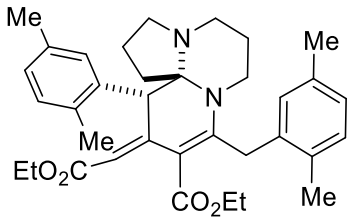
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 166.9, 162.8 (d, *J* = 242.5 Hz), 162.6 (d, *J* = 243.75 Hz), 152.0, 151.8, 134.4 (d, *J* = 2.8 Hz), 132.4 (d, *J* = 2.8 Hz), 131.4 (d, *J* = 7.7 Hz), 129.7 (d, *J* = 7.8 Hz),115.6 (d, *J* = 21.2 Hz), 114.4 (d, *J* = 20.7 Hz), 107.0, 106.4, 81.1, 60.8, 59.1, 54.3, 49.4, 40.3, 39.5, 37.5, 36.8, 22.5, 20.7, 14.3, 14.0.

^{19}F NMR (371MHz, $CDCl_3$): δ 115.99, 116.67.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{35}F_2N_2O_4$: 537.2559; Found: 537.2557.

Ethyl(*E*)-9-(2,5-dimethylbenzyl)-12-(2,5-dimethylphenyl)-11-(2-ethoxy-2-oxoethylidene)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31m)

The compounds **31m** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBN (57 µL, 0.46 mmol) at room temperature. The product **31m** was obtained as a yellow gummy liquid in 63% (40 mg) yield.



31m

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 1H), 6.98 (d, *J* = 7.0 Hz, 3H), 6.92 (s, 1H), 6.84 – 6.88 (m, 2H), 6.80 (s, 1H), 5.69 (s, 1H), 5.53 (s, 1H), 4.05 – 4.11 (m, 2H), 3.92 – 4.00 (m, 2H), 3.57 – 3.63 (m, 2H), 3.12 – 3.16 (m, 1H), 2.92 - 298 (m, 1H), 2.81 – 2.85 (m, 1H), 2.64 (s, 3H), 2.32 – 2.34 (m, 1H), 2.21 – 2.23 (m, 4H), 2.19 (s, 9H), 2.13 – 2.14 (m, 2H), 1.91 – 2.02 (m, 2H), 1.55 – 1.73 (m, 3H), 1.40 – 1.42 (m, 1H), 1.11 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H).

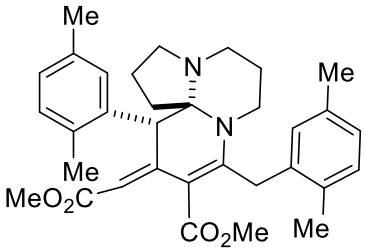
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 167.0, 152.5, 137.5, 136.7, 135.5, 135.0, 134.2, 131.8, 129.99,

129.94, 128.5, 128.1, 127.1, 126.9, 108.0, 106.0, 81.7, 60.4, 58.8, 54.2, 45.5, 39.3, 38.4, 34.9, 23.0, 21.5, 21.1, 20.9, 20.0, 19.3, 14.3, 13.8.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{35}H_{45}N_2O_4$: 557.3374; Found: 557.3351.

Methyl (*E*)-9-(2,5-dimethylbenzyl)-12-(2,5-dimethylphenyl)-11-(2-methoxy-2-oxoethylidene)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31n)

The compounds **31n** was synthesized following the procedure described in section **3.9.1** using methyl 4-(2,5-dimethylphenyl)buta-2,3-dienoate (50 mg, 0.23 mmol), DBN (61 µL, 0.49 mmol) at room temperature. The product **31n** was obtained as a yellow gummy liquid in 67% (44 mg) yield.



31n

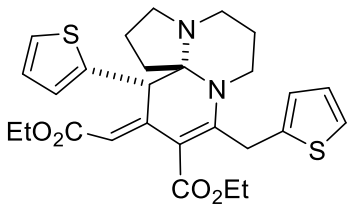
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 5.48 (s, 1H), 5.19 (s, 1H), 3.63 (s, 3H), 3.59 (s, 2H), 3.49 (s, 3H), 3.06 – 3.10 (m, 1H), 2.91 – 2.94 (m, 1H), 2.84 – 2.88 (m, 1H), 2.63 – 2.69 (m, 1H), 2.56 (s, 3H), 2.29 – 2.30 (m, 1H), 2.19 (s, 9H), 1.85 – 1.87 (m, 2H), 1.71 (s, 1H), 1.58 – 1.64 (m, 2H), 1.48 – 1.52 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 167.4, 153.1, 152.9, 137.4, 136.7, 135.7, 135.0, 134.3, 131.9, 130.1, 130.0, 128.4, 127.9, 127.2, 127.1, 107.7, 105.7, 81.8, 54.3, 51.7, 50.5, 45.7, 39.4, 39.3, 38.5, 34.8, 29.7, 22.9, 21.5, 21.2, 20.9, 20.0, 19.3.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{33}H_{41}N_2O_4$: 529.3061; Found: 529.3058.

Ethyl (*E*)-11-(2-ethoxy-2-oxoethylidene)-12-(thiophen-2-yl)-9-(thiophen-2-ylmethyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31o)

The compounds **31o** was synthesized following the procedure described in section **3.9.1** using ethyl 4-(thiophen-2-yl)buta-2,3-dienoate (50 mg, 0.26 mmol), DBN (64 µL, 0.51 mmol) at room temperature. The product **31o** was obtained as a yellow gummy liquid in 32% (21 mg) yield.



31o

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (t, *J* = 6.5 Hz, 2H), 7.00 (s, 1H), 6.86 – 6.87 (m, 1H), 6.83 – 6.84 (m, 1H), 6.79 (s, 1H), 5.59 (s, 1H), 5.33 (s, 1H), 4.12 – 4.16 (m, 2H), 3.99 – 4.02 (m, 3H), 3.92 (d, *J* = 16.5 Hz, 1H), 3.58 – 3.63 (m, 1H), 3.05 (s, 1H), 2.79 – 2.89 (m, 2H), 2.35 – 2.39 (m, 1H), 2.11 – 2.16 (m, 1H), 1.92 – 1.97 (m, 1H), 1.75 – 1.81 (m, 3H), 1.58 – 1.61 (m, 1H), 1.36 – 1.38 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.0 Hz, 3H).

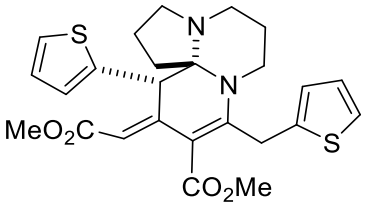
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.1, 152.2, 151.4, 140.4, 139.1, 126.8, 126.5, 125.8, 125.5, 124.5, 124.0, 107.4, 104.3, 81.3, 60.6, 59.2, 54.2, 44.5, 41.8, 40.0, 35.68, 32.2, 22.1, 21.1, 14.4, 14.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{27}H_{33}N_2O_4S_2$: 513.1876; Found: 513.1891.

Methyl (*E*)-11-(2-methoxy-2-oxoethylidene)-12-(thiophen-2-yl)-9-(thiophen-2-ylmethyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31p)

The compounds **31p** was synthesized following the procedure described in section **3.9.1** using methyl 4-(thiophen-2-yl)buta-2,3-dienoate (50 mg, 0.28 mmol), DBN (68 µL, 0.55 mmol) at room temperature. The product **31p** was obtained as a yellow gummy liquid in 34% (23 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 11.0, 5.0 Hz, 2H), 7.00 (s, 1H), 6.87 (t, *J* = 3.5 Hz, 1H), 6.83 – 6.84 (m, 1H), 6.79 (s, 1H), 5.55 (s, 1H), 5.32 (s, 1H),



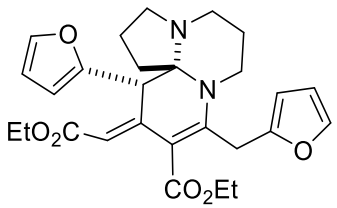
31p

4.05 (d, *J* = 16.5 Hz, 1H), 3.93 (d, *J* = 16.5 Hz, 1H), 3.67 (s, 3H), 3.56 (s, 3H), 3.02 – 3.06 (m, 1H), 2.81 – 2.90 (m, 2H), 2.36 – 2.41 (m, 1H), 2.13 (d, *J* = 5.0 Hz, 1H), 1.91 – 1.96 (m, 1H), 1.73 – 1.81 (m, 4H), 1.59 – 1.64 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 169.8, 167.4, 152.9, 151.8, 140.3, 139.2, 126.9, 126.6, 125.9, 125.5, 124.6, 124.2, 107.0, 103.5, 81.3, 54.3, 51.7, 50.7, 44.6, 41.5, 40.0, 36.0, 32.2, 22.2, 21.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{25}H_{29}N_2O_4S_2$: 485.1563; Found: 485.1583.

Ethyl (*E*)-11-(2-ethoxy-2-oxoethylidene)-12-(furan-2-yl)-9-(furan-2-ylmethyl)-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31q)



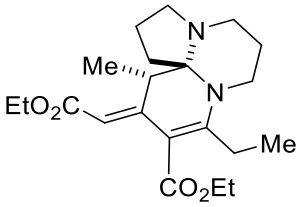
31q

Yield: Product not obtained

Ethyl (*E*)-11-(2-ethoxy-2-oxoethylidene)-9-ethyl-12-methyl-2,3,6,7,11,12-hexahydro-1H,5H-pyrido[1,2-a]pyrrolo[2,1-b]pyrimidine-10-carboxylate (31r)

The compounds **31r** was synthesized following the procedure described in section **3.9.1** using ethyl penta-2,3-dienoate (50 mg, 0.40 mmol), DBN (98 µL, 0.79 mmol) at room temperature. The product **31r** was obtained as a yellow gummy liquid in 48% (36 mg) yield.

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.32 (s, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.85 (s, 1H), 3.59 – 3.62 (m,1H), 2.98 - 3.04 (m, 3H), 2.83 – 2.88 (m,1H), 2.67 - 2.72 (m, 1H), 2.22 – 2.33 (m, 2H), 1.92



31r

– 1.95 (m, 1H), 1.84 – 1.88 (m, 1H), 1.74 (s, 2H), 1.60 – 1.62 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 6.5 Hz, 3H), 1.07 – 1.09 (m, 6H).

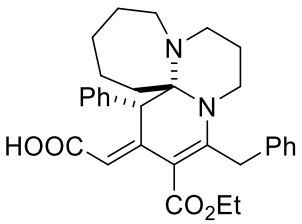
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.9, 167.5, 156.1, 155.0, 104.1, 102.8, 81.4, 60.4, 58.9, 53.3, 44.8, 39.3, 37.9, 29.6, 24.5, 22.5, 21.3, 14.5, 14.4, 14.2, 14.0, 13.0.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{21}H_{33}N_2O_4$: 377.2435; Found: 377.2468.

3.12. Characterization data of products (29aa – 29ac)

(*E*)-2-(4-benzyl-3-(ethoxycarbonyl)-1-phenyl-7,8,11,12,13,14-hexahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepin-2(1H)-ylidene)acetic acid (29aa)

The compounds **29aa** was synthesized following the procedure described in section **3.10.1** using **29a** (50 mg, 0.094 mmol) and KOH (174 mg, 3.09 mmol) in 4 mL of EtOH at reflux temperature. The product **29aa** was obtained as a yellow gummy liquid in 65% (31 mg) yield.



29aa

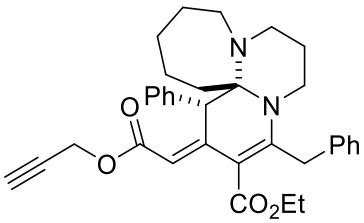
^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 7.37 (d, *J* = 6.5 Hz, 1H), 7.18 – 7.25 (m, 4H), 7.13 (t, *J* = 6.5 Hz, 1H), 7.05 – 7.06 (m, 3H), 5.62 (s, 1H), 5.44 (s, 1H), 4.02 – 4.04 (m, 2H), 3.86 (d, *J* = 17.0 Hz, 1H), 3.82 (d, *J* = 17.0 Hz, 1H), 3.57 (d, *J* = 13.5 Hz, 2H), 2.98 (t, *J* = 13.5 Hz, 1H), 2.84 (t, *J* = 12.0 Hz, 1H), 2.56 (d, *J* = 15.0 Hz, 1H), 2.29 – 2.38 (m, 2H), 1.86 (s, 1H), 1.61 – 1.66 (m, 1H), 1.48 – 1.51 (m, 3H), 1.39 (s, 3H), 1.31 – 1.33 (m, 1H), 1.00 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 169.4, 167.9, 151.8, 150.8, 140.3, 137.6, 130.2, 128.4, 128.3, 127.3, 126.34, 126.30, 106.3, 105.6, 79.0, 59.9, 49.6, 45.4, 44.2, 42.1, 37.4, 36.0, 23.5, 22.5, 13.6, 13.4.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{31}H_{37}N_2O_4$: 501.2748; Found: 501.2753.

Ethyl(*E*)-4-benzyl-2-(2-oxo-2-(prop-2-yn-1-yloxy)ethylidene)-1-phenyl-1,2,7,8,11,12,13, 14-octahydro-6H,10H-pyrido[2',1':2,3]pyrimido[1,2-a]azepine-3-carboxylate (29ab)

The compounds **29ab** was synthesized following the procedure described in section **3.10.2** using propargyl bromide (11.9 mg, 0.09 mmol), **29aa** (50 mg, 0.09 mmol), K_2CO_3 (21 mg, 0.15 mmol) in DMF at room temperature. The product **29ab** was obtained as a yellow gummy liquid in 82% (44 mg) yield.



29ab

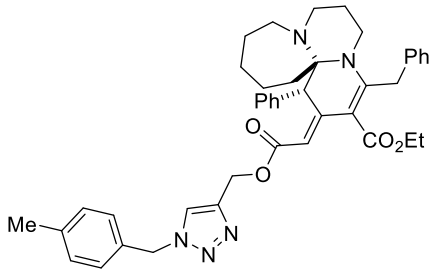
^{1}H NMR (500 MHz, CD_3COCD_3): δ 7.49 (d, *J* = 6.0 Hz, 2H), 7.35 – 7.38 (m, 4H), 7.22 – 7.27 (m, 4H), 5.56 (s, 2H), 4.59 – 4.73 (m, 2H), 4.19 (t, *J* = 6.5 Hz, 2H), 4.04 (d, *J* = 17.0 Hz, 1H), 3.99 (d, *J* = 17.0 Hz, 1H), 3.74 (d, *J* = 13.0 Hz, 1H), 3.09 – 3.15 (m, 1H), 3.02 (t, *J* = 12.0 Hz, 1H), 2.93 (s, 1H), 2.76 (d, *J* = 14.5 Hz, 1H), 2.47 – 2.54 (m, 2H), 1.95 – 1.98 (m, 1H), 1.74 – 1.78 (m, 1H), 1.63 (s, 3H), 1.52 – 1.53 (m, 5H), 1.14 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CD_3COCD_3): δ 169.1, 165.6, 153.8, 152.4, 139.6, 137.4, 130.2, 128.4, 127.4, 126.6, 126.4, 106.3, 102.8, 79.2, 78.9, 74.6, 60.1, 49.9, 49.7, 45.4, 45.2, 42.3, 37.5, 36.5, 23.2, 22.6, 13.4.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{34}H_{39}N_2O_4$: 539.2904; Found: 539.2923.

Ethyl (*E*)-4-benzyl-2-(2-((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-oxoethylidene)-1-phenyl-1,2,7,8,11,12,13,14-octahydro-6H,10H-pyrido[2',1':2,3] pyrimido[1,2-a]azepine-3-carboxylate (29ac)

The compounds **29ac** was synthesized following the procedure described in section **3.10.3** using 4-methyl benzyl azide (11 mg, 0.074 mmol), compound **29ab** (40 mg, 0.074 mmol), $CuSO_4.5H_2O$ (2 mg, 0.0074 mmol) and sodium ascorbate (3.7 mg, 0.0185 mmol) in ^{t}BuOH - water (1:2) mixture at room temperature. The product **29ac** was obtained as a yellow gummy liquid in 85% (43 mg) yield.



29ac

^{1}H NMR (500 MHz, CD_3COCD_3): δ 7.69 (s, 1H), 7.31 (s, 2H), 7.22 (s, 4H), 7.11 – 7.12 (m, 3H), 7.06 (s, 5H), 5.36 – 5.44 (m, 4H), 4.97 (d, *J* = 12.5 Hz, 1H), 4.93 (d, *J* = 13.0 Hz, 1H), 4.00 (m, 2H), 3.87 (d, *J* = 17.0 Hz, 1H), 3.81 (d, *J* = 16.5 Hz, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 2.92 – 2.97 (m, 1H), 2.82 – 2.87 (m, 2H), 2.58 (d, *J* = 14.5 Hz, 1H), 2.30 – 2.34 (m, 2H), 2.18 (s, 3H), 1.81 – 1.83 (m, 1H), 1.57 – 1.61 (m,1H), 1.45 (s, 3H), 1.36 (s, 4H), 0.95 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, CD_3COCD_3): δ 169.1, 166.3, 153.1, 151.9, 143.5, 139.8, 137.9, 137.4, 133.0, 130.2, 129.3, 128.44, 128.41, 128.0, 127.4, 126.5, 126.4, 123.6, 106.2, 103.7, 79.2, 60.0, 56.2, 53.0, 49.7, 45.4, 45.1, 42.1, 37.5, 36.3, 23.3, 22.6, 20.2, 13.4.

HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{42}H_{48}N_5O_4$: 686.3701; Found: 686.3714.

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Chapter 4

Multicomponent Synthesis of Spirooxindoles Incorporating 2-Amino pyran-3-carbonitrile Unit *via* Cascade Spiro Cyclization of Knoevenagel /Aza-Michael adducts and Hydrolysis

4.1. Abstract

A simple one-pot synthesis of spirooxindoles incorporating a 2-amino pyran-3-carbonitrile unit *via* readily available isatin, malononitrile, allenoate, and alkyl amine is described. The metal/organocatalyst-free, Et_3N-catalyzed tandem reaction is proposed to proceed through cascade spiro-cyclization of *in situ* generated Knoevenagel/aza-Michael adducts and imine hydrolysis. This strategy is highly efficient, allowing the mild synthesis of spiro[4H-pyran-oxindole] with a wide substrate scope and good functional group compatibility (32 examples, up to 85% yields). Additionally, we have demonstrated the late-stage transformations of the developed spiro[4H-pyran-oxindole] motif for the synthesis of several complex molecules.

4.2. Introduction

Spiro-oxindoles are versatile structural motifs with widespread occurrence in natural products and synthetic compounds of pharmacological relevance.[1] For instance, the macroline-related oxindole, Alstonisine which is extracted from *Alstonia muelleriana* Domin exhibits antimalarial activity.[2] Pteropodine, a heterohimbine-type oxindole alkaloid isolated from 'Cat's Claw' has shown antimutagenic and anti-inflammatory properties.[3] Rhynchophylline is a tetracyclic oxindole alkaloid component of *Uncaria* species. It is a non-competitive NMDA antagonist and a calcium channel blocker.[4] A simple alkaloid Horsfiline shows analgesic properties. This compound is isolated from the leaves of *Horsfildea Superba,* a tree indigenous to Malaysia[5] **(Figure 4.1)**. The majority of biologically relevant spirooxindole molecules contain a spiro ring fused with various heterocyclic rings at the C3 position of the oxindole.[6] Among this, spirooxindoles with 2-amino pyran-3-carbonitrile on position C3 have drawn a lot of interest.[7] The 2-amino pyran-3-carbonitrile is a core class of valuable compounds with an extensive array of therapeutic activities including analgesic, cardiovascular, antimicrobial, anticancer, antibacterial, and anti-inflammatory properties **(Figure 4.1)**.

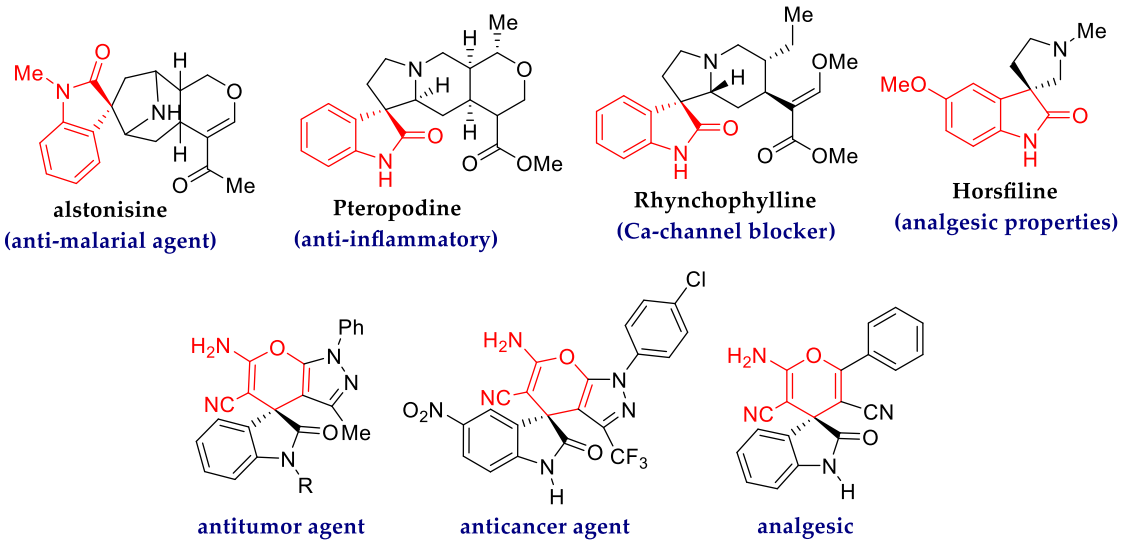
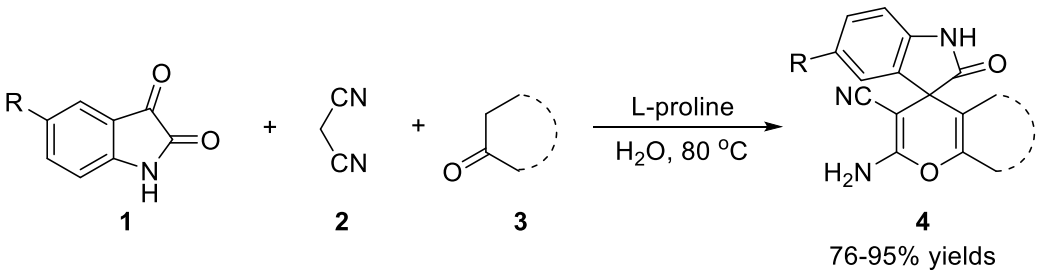


Figure 4.1. Bioactive compounds containing spiro-oxindole core

4.2.1. Synthetic approaches towards spiro pyran-oxindoles

Numerous strategies toward the synthesis of spirooxindoles incorporating 2-amino-4H-pyran-3-carbonitriles in racemic or enantiomerically pure form have been developed. Among these approaches, the most useful and preferred method for the construction of these spirooxindoles is the multicomponent reaction (MCR) of isatin with malononitrile and *β*-ketoesters/ diverse enolizable C-H activated acidic compounds in the presence or absence of a catalyst.

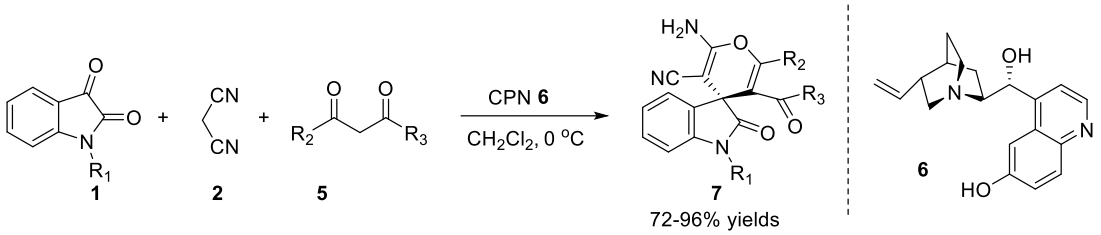
In 2010, Shunjun et al. employed L-proline to synthesize spirooxindole derivatives **4** in good to-high yields (76–95%) *via* one pot three-component reaction of isatins **1**, malononitrile **2** and 1,3-dicarbonyl compounds **3** in water (**Scheme 4.1**).[8]



Scheme 4.1. Synthesis of spirooxindole pyrans catalyzed by L-proline

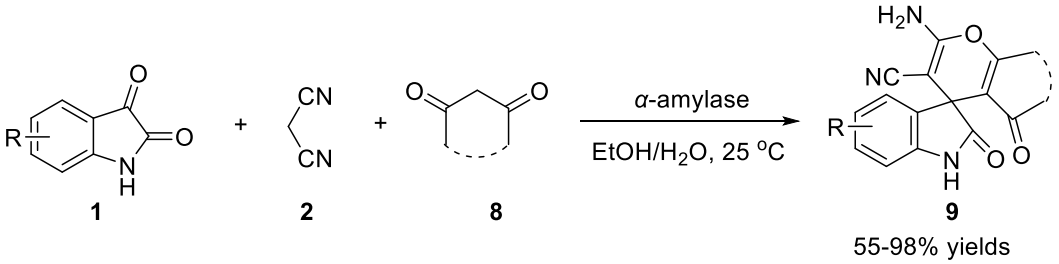
In 2010, Cheng and co-workers developed the first enantioselective organocatalytic three-component reaction, employing a domino Knoevenagel/Michael/cyclization sequence. The method utilized cupreine (CPN) **6** as an organocatalyst to synthesize enantiopure spiro[*4H*-

pyran-3,3′ -oxindoles] **7** by the reaction of isatins **1,** malononitrile **2** and 1,3-diones **5** (**Scheme 4.2**).[9]



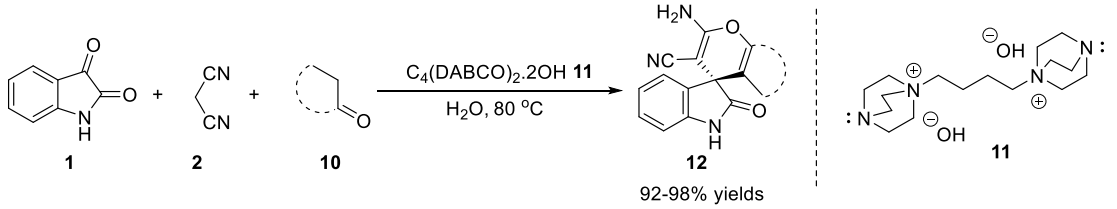
Scheme 4.2. Synthesis of optically active spirooxindole pyrans catalyzed by cupreine

In 2015, Guan and co-workers developed an efficient synthesis of spirooxindole pyrans **9** through a one-pot, three-component reactions between isatins **1**, malononitrile **2** and active methylene compounds **8** in ethanol/water mixture using *α*-amylase as a catalyst. The approach provided spirooxindole derivatives *via* Knoevenagel/Michael/cyclization reactions with good to excellent yields of up to 98% (**Scheme 4.3**).[10]



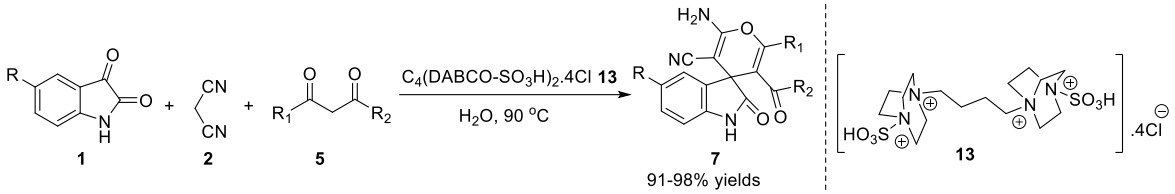
Scheme 4.3. Synthesis of spirooxindole pyrans catalyzed by *α*-amylase

In 2016, Seddighi and group developed an efficient protocol for the synthesis of spiro-4*H*-pyrans **12** through a one-pot, three-component reactions. The method employed a novel catalyst, 1,1'-(butane-1,4-diyl)bis(1,4-diazabicyclo[2.2.2]octan-1-ium) hydroxide **11** and featured a domino Knoevenagel/Michael/cyclization sequence. The catalyst showed excellent recyclability, retaining its catalytic activity even after being reused up to 10 times (**Scheme 4.4**).[11]



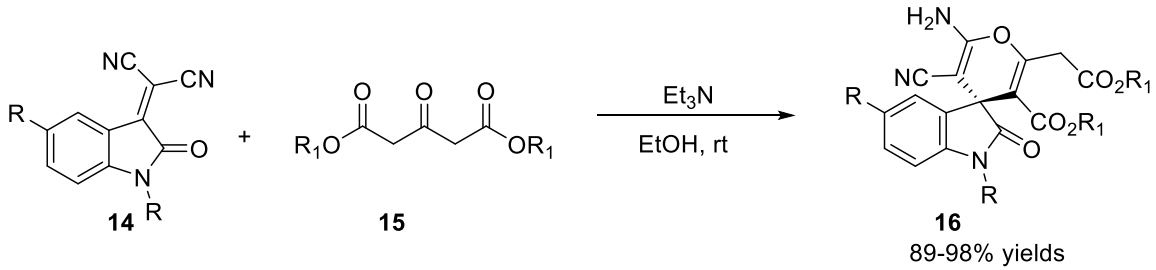
Scheme 4.4. Synthesis of spirooxindole pyrans catalyzed by $C_4(DABCO)_2.2OH$

Later in 2016, Seddighi successfully applied C_4(DABCO-$SO_3H)_2$.4Cl **13** as a nano Bronsted acidic catalyst for the one-pot synthesis of functionalized 2-amino-3-cyano-4H-pyrans incorporating spirooxindole pyran **7** in water (**Scheme 4.5**).[12]



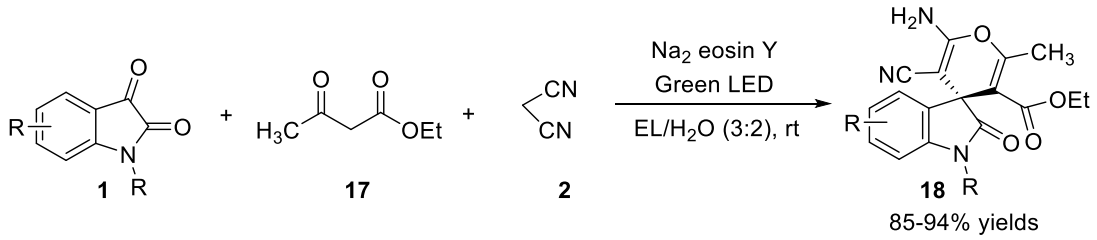
Scheme 4.5. Synthesis of spirooxindole pyrans catalyzed by C_4(DABCO-$SO_3H)_2$.4Cl

In 2018, Ani Deepthi et al. described a route to spirooxindoles incorporating 2-amino pyran-3-carbonitrile unit **16** from the reaction of isatilidenes **14** and diethyl 1,3-acetone dicarboxylates **15** in the presence of triethylamine. The desired products **16** were isolated in good-to-excellent yields. Additionally, a one-pot reaction involving diethyl 1,3-acetone dicarboxylate **15**, isatin **1** and malononitrile **2** was successful, producing the same product **16** (**Scheme 4.6**).[13]



Scheme 4.6. Synthesis of spirooxindole pyrans catalyzed by triethylamine

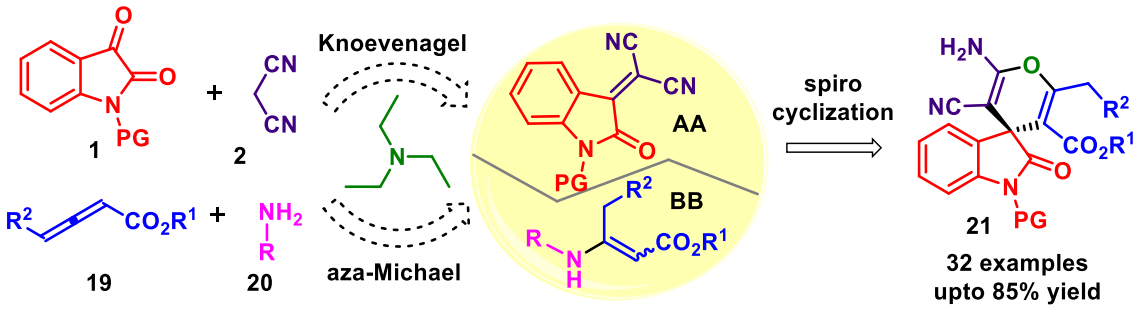
In 2020, Zhang and co-workers developed a synthetic method for the preparation of spiro[oxindole-3,4'-(4'H-pyran)] derivatives **18** *via* visible light-mediated one-pot, three-component reactions of isatins **1**, 1,3-dicarbonyl compounds **17** and malononitrile **2**. The reaction proceeds smoothly in the presence of organic dye Na_2 eosin Y, as the photocatalyst in aqueous ethyl lactate under green LED irradiation under an air atmosphere, generating the desired products in high to excellent yields (**Scheme 4.7**).[14]



Scheme 4.7. Eosin Y-catalyzed synthesis of spiropyran oxindoles under visible-light

4.3. Background to the present work

Although the approaches discussed in section **4.2.1** have facilitated the synthesis of spiro pyran-oxindoles, they possessed several shortcomings concerning high temperature, expensive reagents, complex catalyst preparation, use of hazardous solvents, or limited substrate scope. Therefore, the development of more facile, reliable, and economical methods using readily accessible starting materials to synthesize functionalized spiro[4H-pyran-oxindole] is highly desirable. Recently, multicomponent reactions (MCRs) involving isatin and allenoates have gained significant attention due to their remarkable reactivity in the synthesis of various carbocycles and heterocycles.[15] The multicomponent reactions allow for more atom-efficient, convergent, and straightforward methods to build intricate molecular structures out of readily accessible substrates.[16] Inspired by the aforementioned results and continuing our research in the area of spiro-oxindole frameworks,[17] herein we propose a one pot, four-component reaction of isatin (**1**), malononitrile (**2**), allenoate (**19**), and alkyl amine (**20**), leading to the synthesis of functionalized spiro[4H-pyran-oxindole] (**21**) (**Scheme 4.8**). The developed metal/organocatalyst-free, Et_3N-mediated protocol involves Knoevenagel condensation, aza-Michael addition, imine hydrolysis and spiro-cyclization sequence.



Scheme 4.8. One-pot multicomponent approach for the spiro pyran-oxindoles

4.4. Results and discussion

We have recently reported an efficient, one-pot multicomponent synthesis of spiro-dihydropyridine oxindoles from isatin, malononitrile, allenoate, and aniline.[18] During the study we found that when alkyl amines were used instead of anilines, the reaction failed to generate spiro-dihydropyridine and instead produced a new spot in the TLC. This finding has driven us to investigate the reaction in further depth. After isolating the newly generated product, its molecular geometry was identified *via*

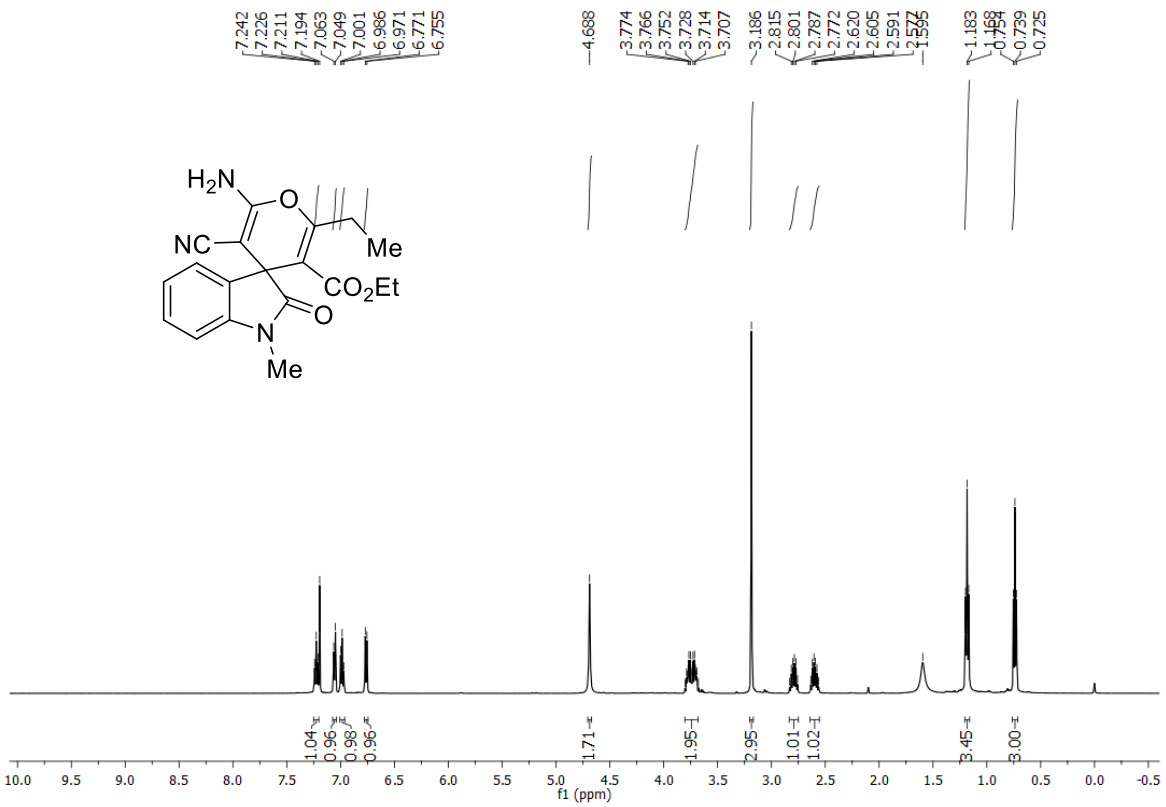


Figure 4.2. ^{1}H NMR (500 MHz, $CDCl_3$) of **21a**

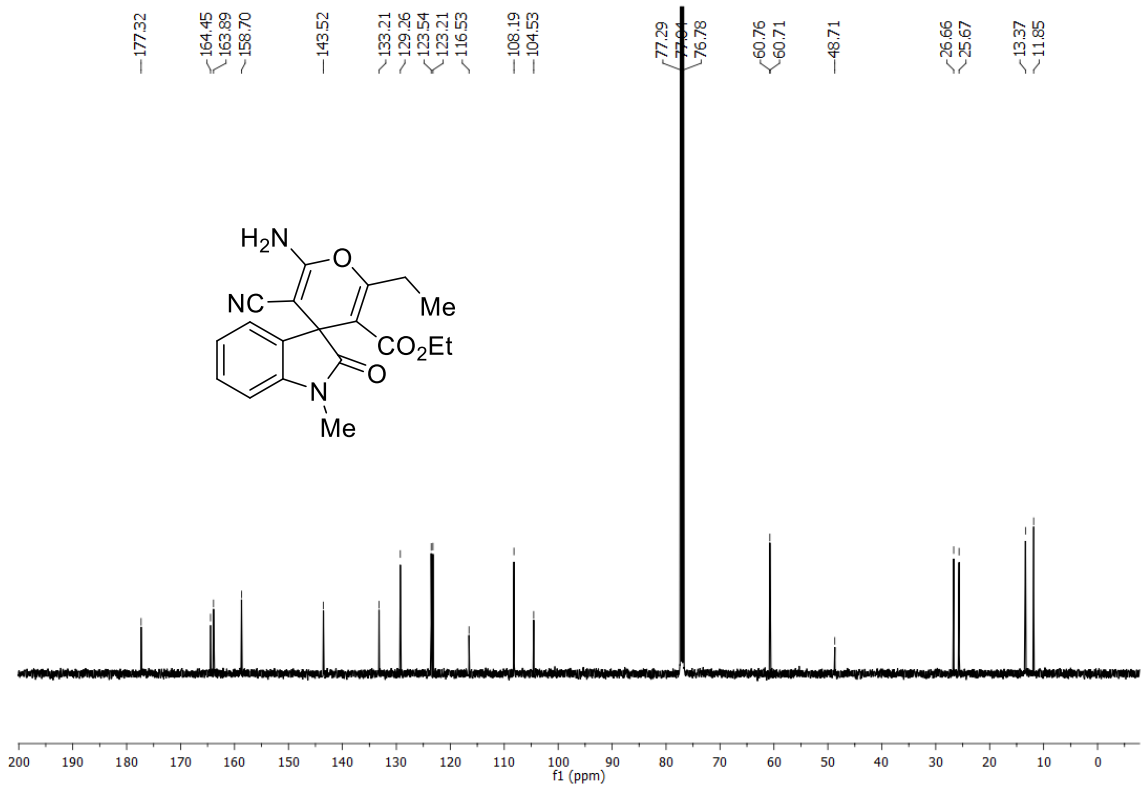


Figure 4.3. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) of **21a**

Nuclear Magnetic Resonance (NMR) and High-Resolution Mass (HRM) spectrometry as ethyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate, **21a**.

The relative stereochemistry was further validated with a single-crystal X-ray study of **21a** (**Figure 4.4**).

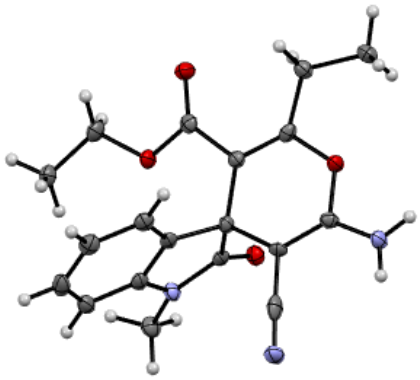
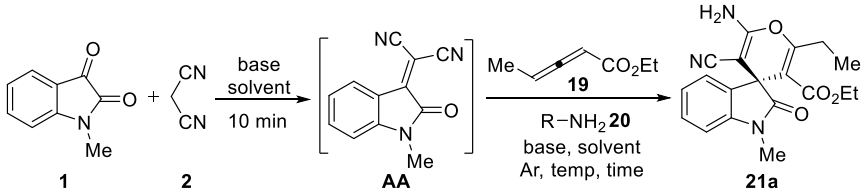


Figure 4.4. Single crystal X-ray structure of **21a** (**CCDC 2395543**)

In our initial experiment, a solution of 1 equiv. of *N*-methyl isatin **1a** (0.31 mmol) and 1 equiv. of malononitrile **2** in EtOH was stirred for 10 minutes in the presence of 1.0 equiv. of Et_3N under an argon atmosphere at room temperature. Subsequently, a mixture of 1.0 equiv. of 3-methyl allenoate **19a** and 1.0 equiv. of propylamine **20** in EtOH was added and stirred for 1 h. To our astonishment, ethyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate, **21a** was obtained in 36% yield (**Table 4.1**, entry 1). The reaction conditions were subsequently optimized to improve the yield of the process and the results are depicted in **Table 4.1**. We initially screened the stoichiometric ratio of substrates; our effort to improve the yield by increasing the equiv. of **19a** to 1.5 was effective, resulting in a 55% yield of **21a** (**Table 4.1**, entry 2). An excess of allenoate was found to negatively affect the yield (**Table 4.1**, entry 3). Furthermore, increasing the loading of propylamine and Et_3N to 1.2 equiv. showed an improvement in yield (**Table 4.1**, entries 4, 6). However, further increase in loading of propylamine and Et_3N from 1.2 equiv. did not yield any beneficial results (**Table 4.1**, entries 5, 7). Screening of various alkyl amines, including ethylamine and butylamine, identified propylamine as the most effective choice (**Table 4.1**, entries 8, 9). The reaction times between 0.5 h to 2 h were also evaluated, but no improvements in yield were observed (**Table 4.1**, entries 10, 11). The examination of the variation in reaction temperature proved

Table 4.1. Optimization of the reaction[a]



Entry	19 (equiv.)	20 (equiv.)	Base (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)[f]
1	1	1	Et_3N (1.0)	EtOH	rt	1	36
2	1.5	1	Et_3N (1.0)	EtOH	rt	1	55
3	2	1	Et_3N (1.0)	EtOH	rt	1	47
4	1.5	1.2	Et_3N (1.0)	EtOH	rt	1	63
5	1.5	1.5	Et_3N (1.0)	EtOH	rt	1	56
6	1.5	1.2	Et_3N (1.2)	EtOH	rt	1	77
7	1.5	1.2	Et_3N (1.5)	EtOH	rt	1	75
8[b]	1.5	1.2	Et_3N (1.2)	EtOH	rt	1	57
9[c]	1.5	1.2	Et_3N (1.2)	EtOH	rt	1	65
10	1.5	1.2	Et_3N (1.2)	EtOH	rt	30	70
11	1.5	1.2	Et_3N (1.2)	EtOH	rt	2	77
12	1.5	1.2	Et_3N (1.2)	EtOH	0 - 5	1	32
13	1.5	1.2	Et_3N (1.2)	EtOH	50	1	ND
14	1.5	1.2	L-Proline (1.2)	EtOH	rt	1	75
15	1.5	1.2	DBU (1.2)	EtOH	rt	1	Trace
16	1.5	1.2	DABCO (1.2)	EtOH	rt	1	ND
17	1.5	1.2	DMAP (1.2)	EtOH	rt	1	ND
18	1.5	1.2	K_2CO_3 (1.2)	EtOH	rt	1	ND
19	1.5	1.2	NaH (1.2)	EtOH	rt	1	ND
20	1.5	1.2	Et_3N (1.2)	MeOH	rt	1	12
21	1.5	1.2	Et_3N (1.2)	*tert*-BuOH	rt	1	74
22	1.5	1.2	Et_3N (1.2)	Propanol	rt	1	65
23	1.5	1.2	Et_3N (1.2)	Butanol	rt	1	62
24	1.5	1.2	Et_3N (1.2)	DCM	rt	1	ND
25	1.5	1.2	Et_3N (1.2)	DMF	rt	1	ND
26	1.5	1.2	Et_3N (1.2)	EtOH	rt	1	60[d], 66[e]

[a]All the reactions were conducted with 1.0 equiv. of **1** (50 mg, 0.31 mmol), **2** (0.31 mmol), 3-methyl allenoate (**19**), propylamine (**20**) and base in solvent (3 mL), [b]With 1.2 equiv. of ethylamine, [c]With 1.2 equiv. of butylamine, [d]With 1.0 equiv. of water, [e]With 0.5 equiv. of water, [f]Isolated yield.

detrimental, confirming that the reaction is more favourable at room temperature (**Table 4.1**, entries 12, 13). Following the screening of several organic and inorganic bases comprising L-proline, DBU, DABCO, DMAP, K_2CO_3, and NaH revealed Et_3N as the optimal candidate for carrying out the reaction (**Table 4.1,** entries 14 to 19). The assessment of various solvents confirmed that EtOH was the solvent of choice generating **21a** in 77% yield, while in other organic solvents, **21a** was afforded lower yields (**Table 4.1**, entries 20 - 25). We have also performed the reaction with different equivalents of water, which resulted in decreased yields of **21a** (**Table 4.1**, entry 26). Following these experimental results, the optimal condition for the transformation was determined to be 1 equiv. of *N*-methyl isatin, 1 equiv. of malononitrile, 1.5 equiv. of allenoate, 1.2 equiv. of propylamine and 1.2 equiv. of Et_3N in EtOH at room temperature for 1 h. **(Table 4.1,** entry 6**)**.

With the optimized reaction condition determined, we next evaluated the generality of different substituted isatins (**Table 4.2)**. The process worked readily with isatins having both electron-donating (EDG) and electron-withdrawing groups (EWG). The isatins bearing electron-donating groups such as -Me and -OMe was successfully transformed into the corresponding products (**21b**, **21c**) with yields of 73 and 86% respectively. With 5,7-dimethyl substituted isatin the corresponding product **21h** was afforded in 70% yield. The isatins with halo substituents like -F, -Cl and -Br resulted in the target products (**21d**, **21e**, **21f**, **21j**) in 52 - 69% yields. Further, isatin with electron-withdrawing groups such as -NO_2, and -OCF_3 was tolerated well, leading to the desired products (**21g**, **21i**) in satisfying yields (39 - 42%). The observed substitution effect on the isatin ring for delivering the corresponding products is -H > -EDG > -Halo > -EWG. Gratifyingly, various *N*-benzyl substituted isatins also underwent reaction smoothly to afford corresponding products in good yields (**21k - 21n**). However, *N*-ethyl and *N*-propargyl substituted isatins yielded only trace amounts of products (**21o**, **21p**).

Table 4.2. Substrate scope for various *N*-substituted isatins

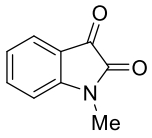
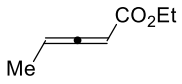
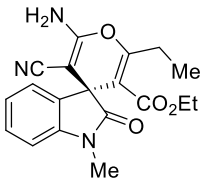
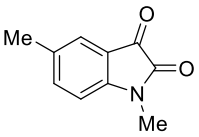
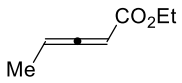
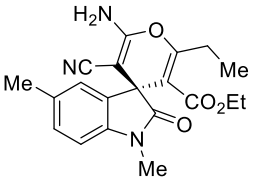
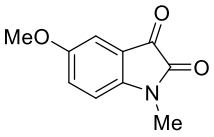
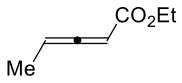
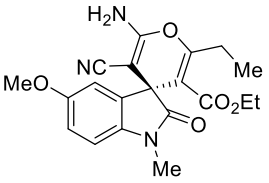
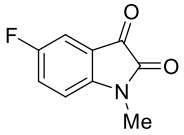
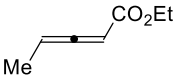
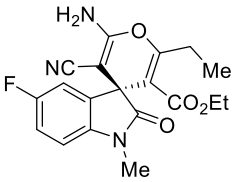
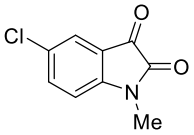
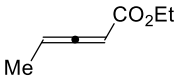
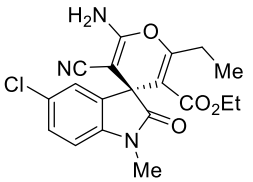
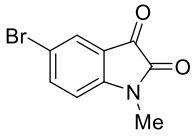
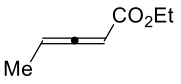
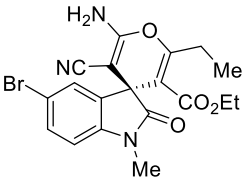
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1	 **1a**	 **19a**	 **21a**	77
2	 **1b**	 **19a**	 **21b**	73
3	 **1c**	 **19a**	 **21c**	76
4	 **1d**	 **19a**	 **21d**	69
5	 **1e**	 **19a**	 **21e**	66
6	 **1f**	 **19a**	 **21f**	52

Table 4.2. Continues…….

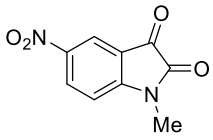
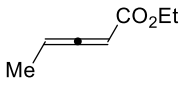
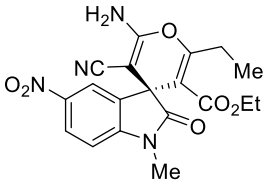
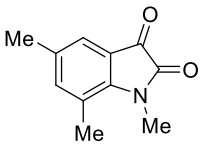
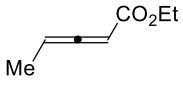
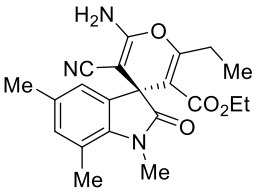
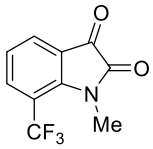
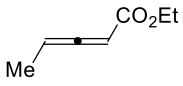
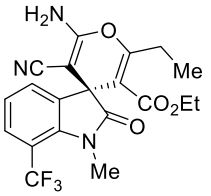
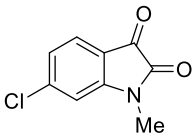
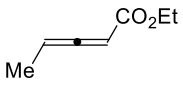
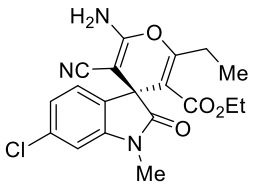
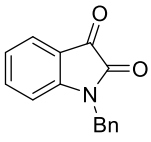
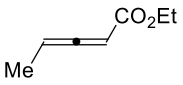
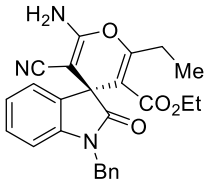
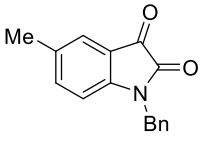
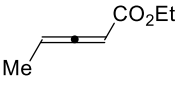
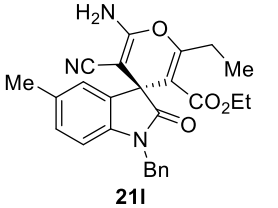
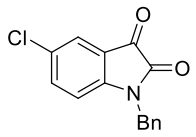
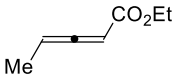
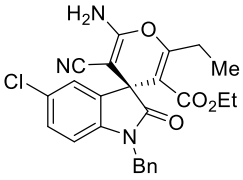
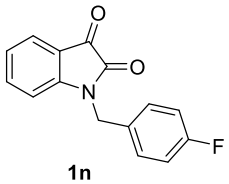
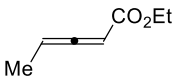
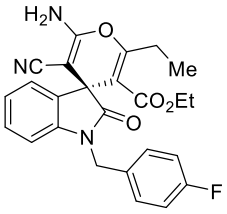
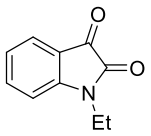
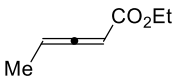
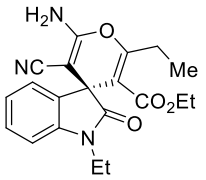
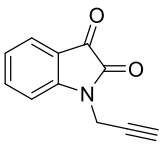
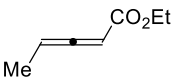
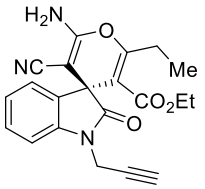
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
7	 **1g**	 **19a**	 **21g**	**39**
8	 **1h**	 **19a**	 **21h**	**70**
9	 **1i**	 **19a**	 **21i**	**42**
10	 **1j**	 **19a**	 **21j**	**59**
11	 **1k**	 **19a**	 **21k**	**68**
12	 **1l**	 **19a**	 **21l**	**65**

Table 4.2. Continues…….

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
13	 **1m**	 **19a**	 **21m**	**60**
14	 **1n**	 **19a**	 **21n**	**56**
15	 **1o**	 **19a**	 **21o**	**trace**
16	 **1p**	 **19a**	 **21p**	**trace**

Reaction conditions: 1 equiv. of isatins **1** (50 mg), 1 equiv. of malononitrile (**2**), 1.5 equiv. of 3-methyl allenoate (**19**), 1.2 equiv. of propylamine (**20**) and 1.2 equiv. of Et_3N in EtOH (3 mL) at room temperature for 1 h

The scope of the protocol was further extended by employing various substituted allenoates **19** (**Table 4.3**). The allenoates with smaller ester groups, such as -CO_2Me (47 - 85%), produced relatively higher yields than the bulkier -CO_2Et (76 - 80%), -CO_2Bn (55 - 64%) and -$CO_2{}^t$Bu (52 - 71%). Additionally, we investigated the reaction with different γ-substituted allenoates, which affords the intended products in moderate to good yields (**21ai - 21ap**). The yields seem to increase with the increase in the length of the alkyl chain at the γ position of allenoate (-butyl > -ethyl> -methyl).

Table 4.3. Substrate scope with respect to various allenoates

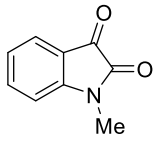
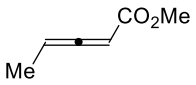
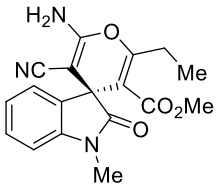
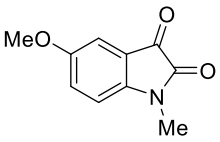
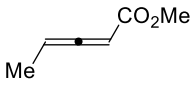
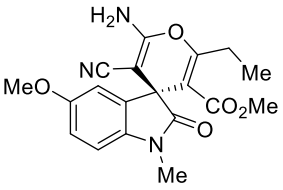
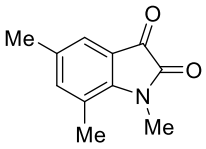
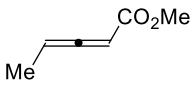
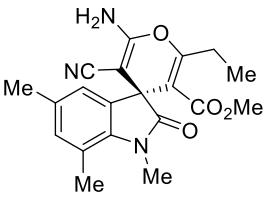
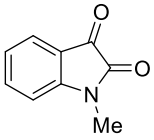
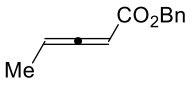
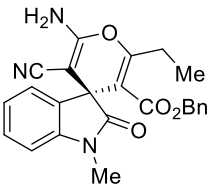
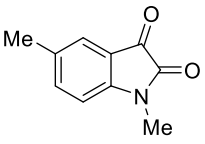
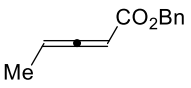
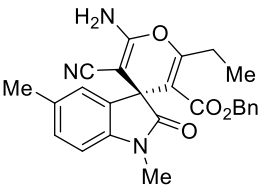
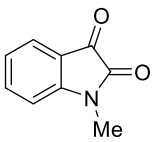
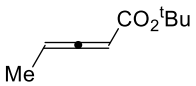
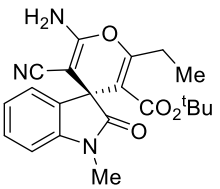
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
1	 **1a**	 **19b**	 **21aa**	**85**
2	 **1c**	 **19b**	 **21ab**	**81**
3	 **1h**	 **19b**	 **21ac**	**78**
4	 **1a**	 **19c**	 **21ad**	**59**
5	 **1b**	 **19c**	 **21ae**	**55**
6	 **1a**	 **19d**	 **21af**	**65**

Table 4.3. Continues…….

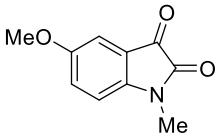
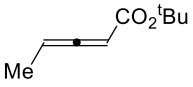
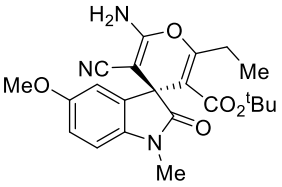
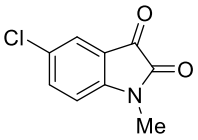
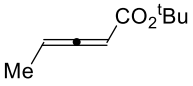
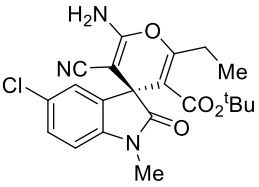
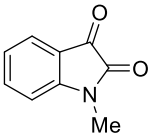
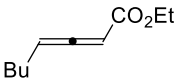
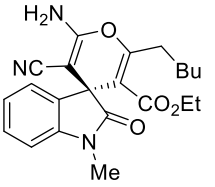
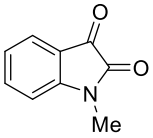
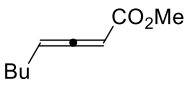
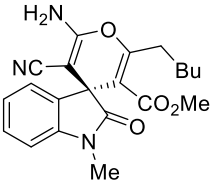
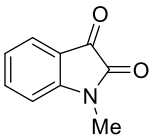
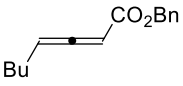
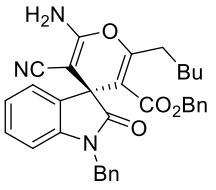
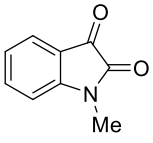
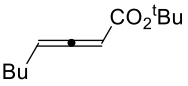
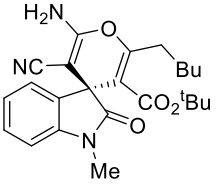
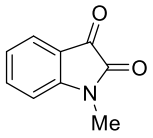
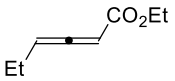
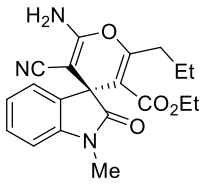
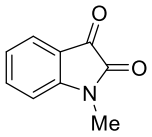
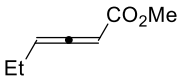
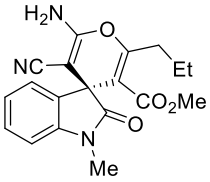
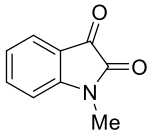
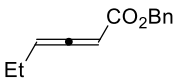
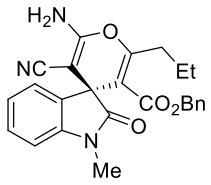
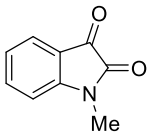
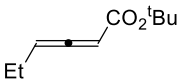
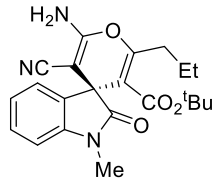
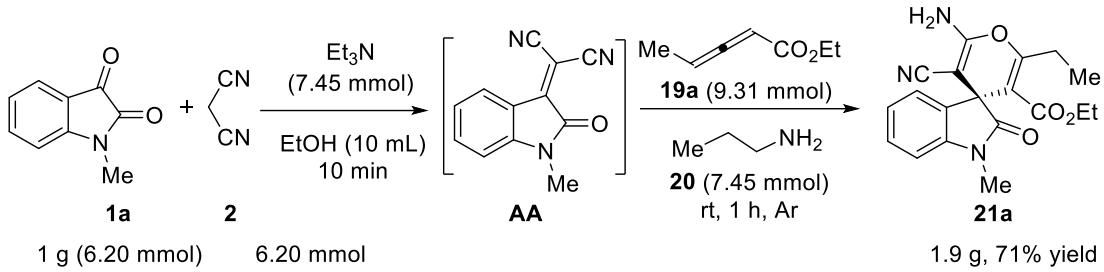
Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
7	 **1c**	 **19d**	 **21ag**	61
8	 **1e**	 **19d**	 **21ah**	52
9	 **1a**	 **19e**	 **21ai**	80
10	 **1a**	 **19f**	 **21aj**	82
11	 **1a**	 **19g**	 **21ak**	64
12	 **1a**	 **41a**	 **21al**	71

Table 4.3. Continues…….

Entry	*N*-Substituted isatins	Allenoate	Product	Yield (%)
13	 **1a**	 **19i**	 **21am**	**76**
14	 **1a**	 **19j**	 **21an**	**80**
15	 **1a**	 **19k**	 **21ao**	**58**
16	 **1a**	 **19l**	 **21ap**	**67**

Reaction conditions: 1 equiv. of isatins **1** (50 mg), 1 equiv. of malononitrile (**2**), 1.5 equiv. of allenoates (**19**), 1.2 equiv. of propylamine (**20**) and 1.2 equiv. of Et_3N in EtOH (3 mL) at room temperature for 1 h

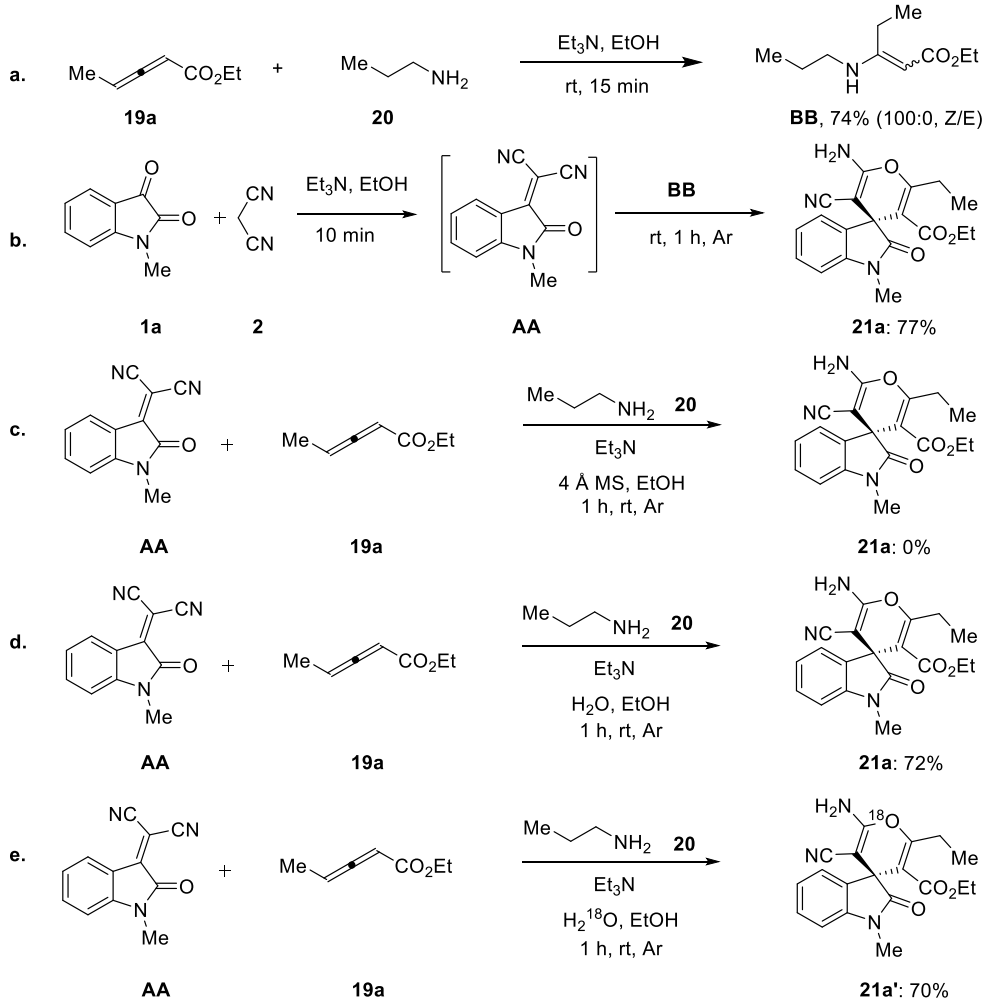
To demonstrate the efficiency and practicality of this protocol, a gram-scale reaction was performed using 6.20 mmol of isatin (**1a**) to synthesize compound **21a**. To our delight, the reaction proceeded smoothly and afforded the desired product in 71% yield.



Scheme 4.9. Gram-scale demonstration of spiro-pyran oxindole

4.5. Control experiments

Several control experiments were conducted under standard conditions to gain insight into the reaction pathway. The reaction between **19a** and **20** resulted in **BB** within 15 minutes with 74% yield (**Scheme 4.10.a**). Subsequently, **BB** was employed directly as the substrate to react with *in situ* generated **AA** under the same condition to yield the desired product **21a** in good yield (**Scheme 4.10.b**). To verify the role of water in the product formation,



Scheme 4.10. Control experiments

we carried out the reaction with 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile (**AA**) as starting material in freshly distilled EtOH in the presence of 4 Å molecular sieves under standard conditions. However, under this condition the reaction failed to deliver the product even in the trace, suggesting the source of oxygen in the pyran ring was water present in the reaction medium (**Scheme 4.10.c**). To confirm this, we performed the reaction between 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile **AA** and allenoate **19a** in the presence of water (3.0 equiv.), which resulted in the product **21a** in 72% yield (**Scheme 4.10.d**). An isotopic labelling experiment was also performed to further elucidate the role of water in the reaction mechanism (**Scheme 4.10.e**). Carrying out the reaction in the presence of $H_2{}^{18}O$ (3.0 equiv.) resulted in the generation of the corresponding product **21a'** in 70% yield (^{18}O determined by ESI-MS analysis).

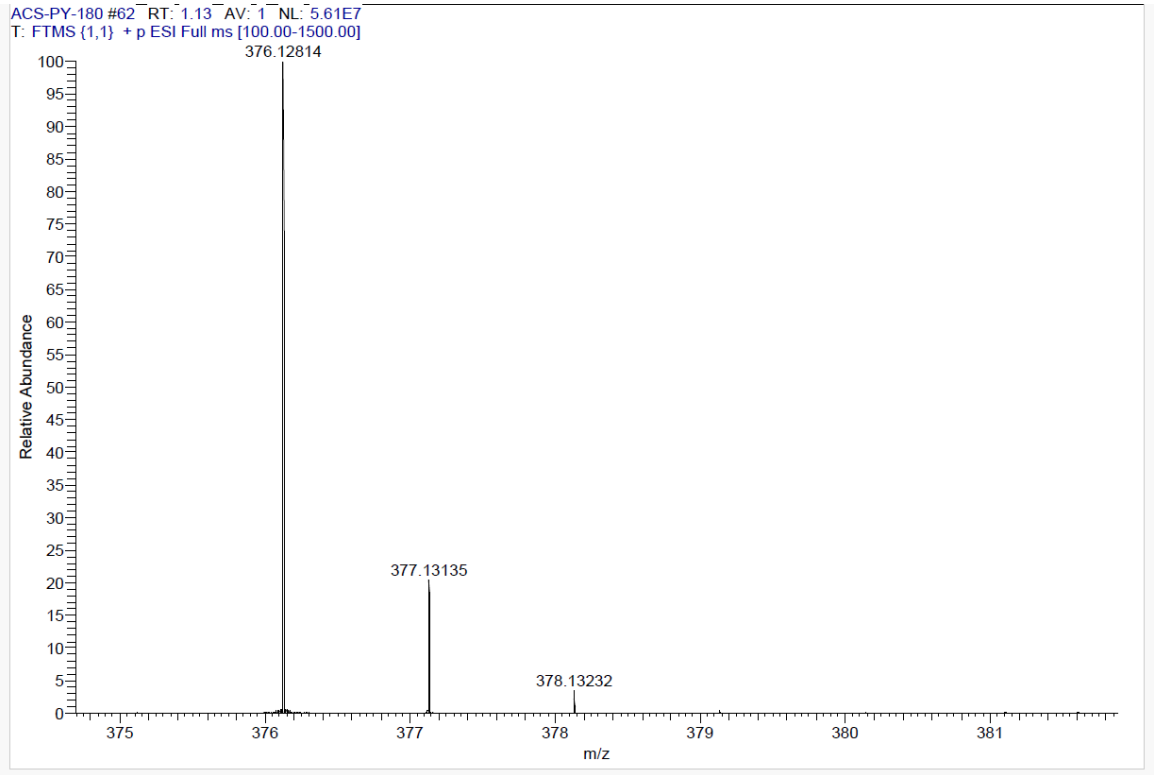
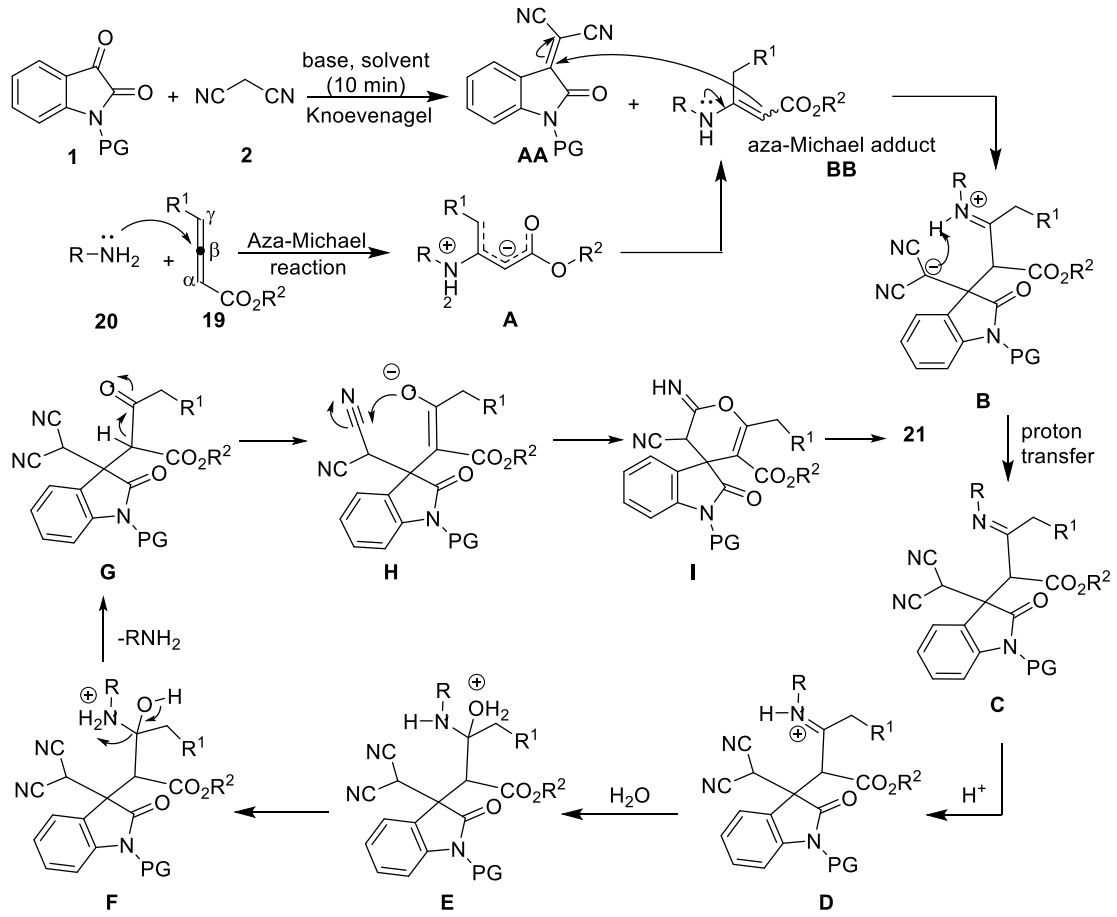


Figure 4.5. HRMS for **21a'** (^{18}O labelling product)

4.6. Plausible mechanism

Based on the control experiments (**Scheme 4.10**) and literature precedents,[18,19] a plausible mechanistic pathway for the formation of spiro[4H-pyran-oxindole] has been proposed, as illustrated in **Scheme 4.11**. Firstly, the alkyl amine (**20)** undergoes nucleophilic aza-

Michael addition at the *β*-carbon of the allenoate (**19)** forming stabilized zwitterionic intermediate **A**. The intermediate **A** is then protonated at the *γ*-carbon, affording the *α*,*β*-unsaturated adduct **BB** (aza-Michael adduct). The aza-Michael adduct **BB** thus formed adds to the *in situ* generated Knoevenagel adduct **AA** to form an intermediate **B**, which upon proton transfer leads to **C**. Subsequent protonation leads to intermediate **D**, which undergoes hydrolysis of the imine moiety to form ketone **G**.[20] The oxy-anion of intermediate **H** attacks one of the cyano groups, resulting in the unstable imine **I**. The latter on subsequent H-shift yields the product **21**. However, using aniline in the process leads to a more stable imine. As a result, the imine intermediate does not hydrolyse but rather undergoes proton transfer and intramolecular cyclisation, ultimately forming spiro-dihydropyridines.[18]

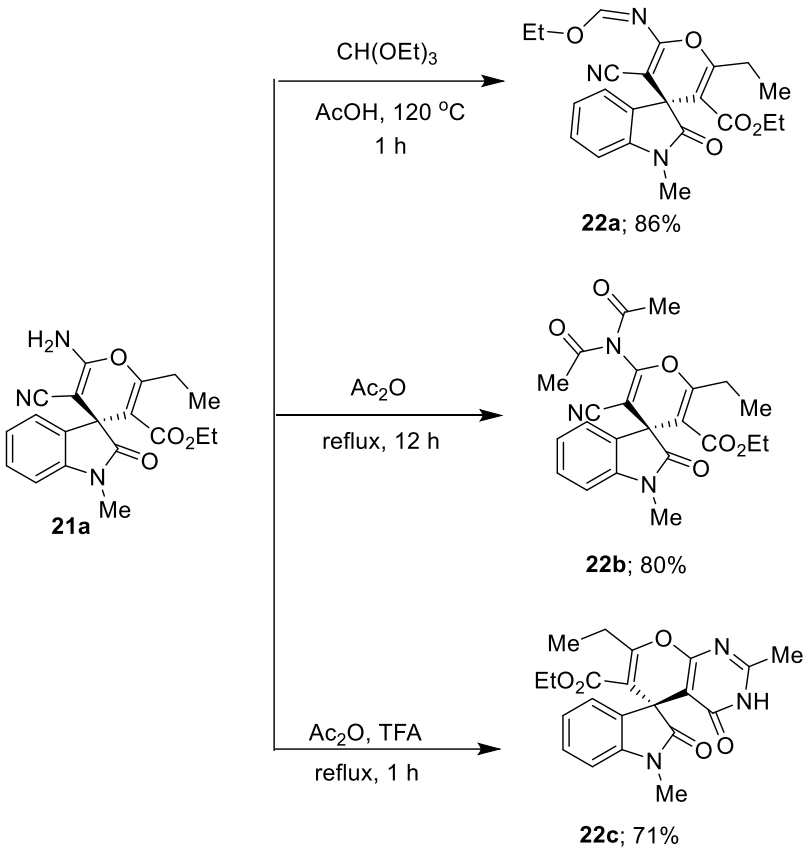


Scheme 4.11. Proposed mechanism for spiro[4H-pyran-oxindole]

4.7. Last stage functionalization of tricyclic pyridopyrimidines

Lastly, we became interested in the late-stage functionalization of synthesized spiro[4H-pyran-oxindole] **21** which enabled the construction of certain complex compounds. As demonstrated in **Scheme 4.12**, the transformation of the 2-amino functionality of **21a** into

imine works well by the addition of ethyl orthoformate in the presence of a few drops of glacial acetic acid at 120 °C, affording **22a** in 86% yield. The compound **21a** underwent *N*-acylation successfully with acetic anhydride under reflux conditions generating **22b** in 80% yield. The reaction of **21a** with acetic anhydride/trifluoro acetic acid under reflux conditions resulted in ethyl 7'-ethyl-1,2'-dimethyl-2,4'-dioxo-3',4'-dihydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carboxylate **22c** in 71% yield *via* Dimroth rearrangement. Hence, the synthesized compounds **21** serve as a versatile precursor for the synthesis of spiro[4H-pyran-oxindole] hybrids of medicinal relevance.



Scheme 4.12. Late-stage diversification of spiro[4H-pyran-oxindole]

4.8. Conclusion

In summary, a highly efficient multicomponent reaction for synthesizing functionalized spiro[4H-pyran-oxindole] scaffolds utilizing easily accessible isatin, malononitrile, allenoate, and alkyl amine has been developed. The Et_3N mediated reaction involves cascade spiro-cyclization of *in situ* generated Knoevenagel adduct and aza-Michael adduct. The developed protocol provides direct access to an array of functionalized spiro[4H-pyran-oxindole] scaffolds in good yields without the need for transition metal or

organocatalysts. Furthermore, the present method is scalable, offering a simple and alternative approach for the synthesis of functionalized spiro[4H-pyran-oxindole] frameworks in drug and bioactive molecule development. Additionally, this is the first approach to exploit the reactivity of allenoates for constructing structurally diverse motifs of spiro[4H-pyran-oxindole].

4.9.General Methods

All the chemicals were purchased from Sigma-Aldrich and used without further purification. All reactions were carried out under an argon atmosphere unless otherwise noted. Column chromatography was performed using silica gel (100-200 mesh), and a hexane-ethyl acetate mixture was used for elution. NMR spectra were recorded at 500 (^{1}H) and 125 (^{13}C) MHz on a Bruker ASCEND^{TM} spectrometer by using $CDCl_3$, CD_3SOCD_3, CD_3COCD_3 as solvents and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) for ^{1}H NMR spectra are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 7.27, singlet), CD_3SOCD_3 (δ 2.5, quintet), CD_3COCD_3 (δ 2.05, quintet). Coupling constants (*J*) are given in Hertz (Hz), and multiplicities were represented as s, d, t, q, m, and dd for singlet, doublet, triplet, quartet, multiplet, and doublet of a doublet, respectively. Chemical shifts (δ) for ^{13}C NMR are represented in parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of $CDCl_3$ (δ 77.03, triplet), CD_3SOCD_3 (δ 39.52, septet) and CD_3COCD_3 (δ 206.68, singlet and δ 29.92, septet). Mass spectra were recorded under HRMS (ESI) using Thermo Scientific Exactive mass spectrometer. Melting points were determined on a Buchi melting point apparatus and are uncorrected. All the substituted allenoates were synthesized using known procedures.[21] The *N*-protection of isatins was carried out using literature reports.[22]

4.10. General experimental procedure

4.10.1. General experimental procedure for the synthesis of Spiro[4H-pyran-oxindole] (21)

In a 10 mL round bottom flask, a solution of isatin **1** or its derivatives (50 mg, 1.0 equiv.), malononitrile **2** (1.0 equiv.) and triethylamine (1.2 equiv.) in ethanol (2 mL) was taken under an argon atmosphere and stirred at room temperature for 10-15 min. To the above solution, allenoate **19** (1.5 equiv.) and propylamine **20** (1.2 equiv.) in ethanol (1 mL) were added and stirred at room temperature for 1 h. After completing the reaction monitored by TLC, the compounds were extracted with EtOAc, dried over anhydrous Na_2SO_4, and the

solvent was removed in *vacuo*. The residue was purified by column chromatography using ethyl acetate and hexane as eluting solvents (silica gel-100-200 mesh) to give desired product **21**.

4.10.2. Procedure for the gram scale reaction

In a 10 mL round bottom flask, a solution of isatin **1a** (1 g, 6.20 mmol), malononitrile **2** (410 mg, 6.20 mmol) and triethylamine (1 mL, 7.45 mmol) in ethanol (8 mL) was taken under an argon atmosphere and stirred at room temperature for 10-15 min. To the above solution, allenoate **19a** (1.17 g, 9.31 mmol) and propylamine **20** (0.61 mL, 7.45 mmol) in ethanol (2 mL) were added and stirred at room temperature for 1 h. After completing the reaction monitored by TLC, the compounds were extracted with EtOAc, dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The residue was purified by column chromatography using ethyl acetate and hexane as eluting solvents (silica gel-100-200 mesh) to give desired product **21a** (1.9 g, 71% yield) as white solid.

4.11. Procedures for control experiments

4.11.1. Procedure for Scheme 4.10.a [19a]

In a 10 mL round bottom flask, a solution of 3-methyl allenoate **19a** (50 mg, 0.39 mmol) and propylamine **20** (39 µL, 0.48 mmol) in ethanol (1 mL) was taken under argon atmosphere and stirred at room temperature for 15 min. After completing the reaction monitored by TLC, the content was extracted with EtOAc, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The product **BB** (54 mg, 74% yield) was isolated as a colorless oil by column chromatography (silica gel-100-200 mesh) using ethyl acetate and hexane as the eluent.

4.11.2. Procedure for Scheme 4.10.b

In a 10 mL round bottom flask, a solution of isatin **1a** (50 mg, 0.31 mmol), malononitrile **2** (21 mg, 0.31 mmol) and triethylamine (0.05 mL, 0.37 mmol) in ethanol (2 mL) was taken under an argon atmosphere and stirred at room temperature for 10-15 min. To the above reaction, **BB** (77 mg, 0.45 mmol) in ethanol (1 mL) was added and stirred for 1 h at room temperature. After completing the reaction monitored by TLC, the compounds were extracted with EtOAc, dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The product **21a** (84, 77% yield) was isolated as a white solid by silica column

chromatography (100 – 200 mesh) using a mixture of hexane and ethyl acetate (60:40) as the eluent.

4.11.3. Procedure for Scheme 4.10.d

In a 10 mL round bottom flask, a solution of 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile **AA** (65 mg, 0.31 mmol) and triethylamine (0.05 mL, 0.37 mmol) in ethanol (2 mL) was taken under argon atmosphere and stirred at room temperature. To the above reaction mixture, allenoate **19a** (59 mg, 0.47 mmol), propylamine **20** (31 µL, 0.37 mmol) and H_2O (17 µL, 0.93 mmol) in ethanol (1 mL) were added and stirred at room temperature for 1 h. After completing the reaction monitored by TLC, the compounds were extracted with EtOAc, dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The product **21a** (79 mg, 72% yield), was purified using ethyl acetate and hexane (60:40) as eluting solvent by column chromatography (silica gel-100-200 mesh).

4.11.4. Procedure for Scheme 4.10.e

In a 10 mL round bottom flask, a solution of 2-(1-methyl-2-oxoindolin-3-ylidene)malononitrile **AA** (65 mg, 0.31 mmol) and triethylamine (0.05 mL, 0.37 mmol) in ethanol (2 mL) was taken under argon atmosphere and stirred at room temperature. To the above reaction mixture, allenoate **19a** (59 mg, 0.47 mmol), propylamine **20** (31 µL, 0.37 mmol) and $H_2{}^{18}O$ (19 µL, 0.93 mmol) in ethanol (1 mL) were added and stirred at room temperature for 1 h. After completing the reaction monitored by TLC, the compounds were extracted with EtOAc, dried over anhydrous Na_2SO_4, and the solvent was removed in *vacuo*. The product **21a** (77 mg, 70% yield), was purified using ethyl acetate and hexane (60:40) as eluting solvent by column chromatography (silica gel-100-200 mesh).

4.12. Experimental procedures for late-stage diversification (22a-22c)

4.12.1. Synthesis of ethyl 5'-cyano-6'-((ethoxymethylene)amino)-2'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-3'-carboxylate (22a)[23]

A mixture of **21a** (50 mg, 0.14 mmol), triethyl orthoformate (0.75 mL) and acetic acid (0.25 mL) was heated at reflux for 1 h. After completing the reaction monitored by TLC, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel-100-200mesh) using ethyl acetate and hexane as eluting solvents to give desired product **22a** (50 mg, 86% yield) as colourless oil.

4.12.2. Synthesis of ethyl 2'-(N-acetylacetamido)-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (22b)[24]

A solution of compound **21a** (50 mg, 0.14 mmol) in acetic anhydride (2 mL) was refluxed for 12 h. After the mixture was concentrated under reduced pressure, the residue was purified by column chromatography (silica gel-100-200mesh) using ethyl acetate and hexane as eluting solvents to give desired product **22b** (49 mg, 80% yield) as violet gummy liquid.

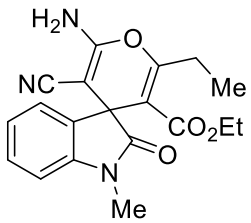
4.12.3. Synthesis of ethyl 7'-ethyl-1,2'-dimethyl-2,4'-dioxo-3',4'-dihydrospiro [indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carboxylate (22c)[25]

A mixture of **21a** (50 mg, 0.14mmol), acetic anhydride (1 mL) and trifluoroacetic acid (0.025 mL) was refluxed for 1 h. After the mixture was concentrated under reduced pressure, the residue was purified by column chromatography (silica gel-100-200mesh) using ethyl acetate and hexane as eluting solvents to give desired product **22c** (40 mg, 71% yield) as colorless oil.

4.13. Characterization data of products

Ethyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21a)

The compound **21a** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), ethyl penta-2,3-dienoate (59 mg, 0.47 mmol), propylamine (31 µL mg, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21a** was obtained as a white solid in 78% (85 mg) yield.



21a

Mp: 197 – 198 ^oC.

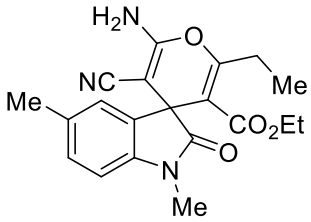
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.69 (s, 2H), 3.68 – 3.80 (m, 2H), 3.19 (s, 3H), 2.76 – 2.83 (m, 1H), 2.56 – 2.63 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 177.3, 164.4, 163.8, 158.7, 143.5, 133.2, 129.2, 123.5, 123.2, 116.5, 108.1, 104.5, 60.8, 60.7, 48.7, 26.6, 25.6, 13.3, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{19}N_3NaO_4, M+Na]^+$: 376.1268; Found: 376.1270.

Ethyl 2'-amino-3'-cyano-6'-ethyl-1,5-dimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21b)

The compound **21b** was synthesized following the procedure described in section **4.10.1** using 1,5-dimethylindoline-2,3-dione (50 mg, 0.28 mmol), malononitrile (19 mg, 0.28 mmol), ethyl penta-2,3-dienoate (43 mg, 0.34 mmol), propylamine (28 µL, 0.34 mmol) and Et_3N (0.05 mL, 0.34 mmol) in EtOH (3 mL) at room temperature. The product **21b** was obtained as a white solid in 73% (76 mg) yield.



21b

Mp: 257 – 258 °C.

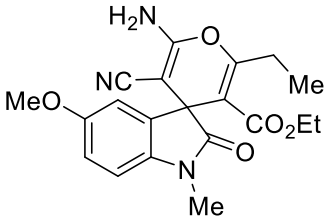
^{1}H NMR (500 MHz, DMSO): δ 7.28 (s, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 3.85 (q, *J* = 7.0 Hz, 2H), 3.20 (s, 3H), 2.74 – 2.82 (m, 2H), 2.36 (s, 3H), 1.27 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO): 177.2, 164.6, 163.3, 159.6, 141.6, 134.2, 132.0, 129.4, 124.1, 117.8, 108.4, 104.4, 60.6, 56.7, 49.0, 26.7, 25.4, 21.0, 13.6, 12.1.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{20}H_{21}N_3NaO_4, M+Na]^+$: 390.1424; Found: 390.1437.

Ethyl 2'-amino-3'-cyano-6'-ethyl-5-methoxy-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21c)

The compound **21c** was synthesized following the procedure described in section **4.10.1** using 5-methoxy-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), ethyl penta-2,3-dienoate (49 mg, 0.39 mmol), propylamine (26 µL, 0.31 mmol) and Et_3N (0.05 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **21c** was obtained as a white solid in 76% (76 mg) yield.



21c

Mp: 243 – 244 ºC.

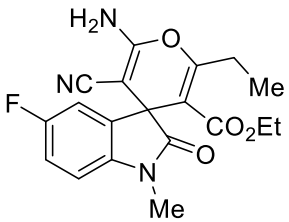
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 – 6.75 (m, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 4.71 (s, 2H), 3.79 (q, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 3.16 (s, 3H), 2.76 – 2.84 (m, 1H), 2.57 – 2.65 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 177.0, 164.3, 164.0, 158.6, 156.4, 137.0, 134.5, 116.5, 113.3, 111.0, 108.5, 104.4, 60.8, 60.7, 55.7, 49.1, 26.7, 25.6, 13.4, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{20}H_{21}N_3NaO_5, M+Na]^+$: 406.1373; Found: 406.1383.

Ethyl 2'-amino-3'-cyano-6'-ethyl-5-fluoro-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21d)

The compound **21d** was synthesized following the procedure described in section **4.10.1** using 5-fluoro-1-methylindoline-2,3-dione (50 mg, 0.28 mmol), malononitrile (18 mg, 0.28 mmol), ethyl penta-2,3-dienoate (53 mg, 0.42 mmol), propylamine (27 µL, 0.33 mmol) and Et_3N (0.05 mL, 0.33 mmol) in EtOH (3 mL) at room temperature. The product **21d** was obtained as a white solid in 69% (71 mg) yield.



21d

Mp: 237 – 238 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 – 6.95 (m, 1H), 6.81 – 6.82 (m, 1H), 6.68 – 6.70 (m, 1H), 4.68 (s, 2H), 3.73 – 3.85 (m, 2H), 3.18 (s, 3H), 2.77 – 2.84 (m, 1H), 2.59 – 2.66 (m, 1H), 1.19 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.0 Hz, 3H).

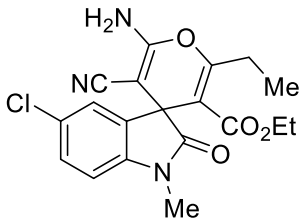
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 177.0, 164.3, 164.1, 160.5 (d, J_{C-F} = 238.7 Hz), 158.6, 139.5, 134.8 (d, J_{C-F} = 7.5 Hz), 116.1, 115.5 (d, J_{C-F} = 23.7 Hz, 1H), 111.8 (d, J_{C-F} = 25.0 Hz), 108.7 (d, J_{C-F} = 8.7 Hz), 104.1, 60.8, 60.5, 49.1, 29.6, 26.7, 25.7, 13.4, 11.7.

^{19}F{^{1}H} (371MHz, $CDCl_3$): δ -120.5.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{18}FN_3NaO_4, M+Na]^+$: 394.1174; Found: 394.1190.

Ethyl 2'-amino-5-chloro-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21e)

The compound **21e** was synthesized following the procedure described in section **4.10.1** using 5-chloro-1-methylindoline-2,3-dione (50 mg, 0.25 mmol), malononitrile (17 mg, 0.25 mmol), ethyl penta-2,3-dienoate (48 mg, 0.38 mmol), propylamine (25 µL, 0.31 mmol) and Et_3N (0.04 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **21e** was obtained as a white solid in 66% (65 mg) yield.



21e

Mp: 248 – 249 °C.

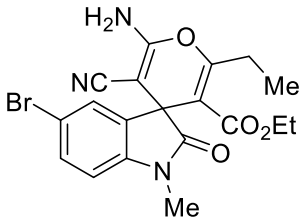
^{1}H NMR (500 MHz, DMSO): δ 7.38 (d, *J* = 8.5 Hz, 1H), 7.30 (s, 2H), 7.24 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 3.79 (q, *J* = 6.5 Hz, 2H), 3.14 (s, 3H), 2.73 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.77 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO): 177.1, 164.4, 164.3, 159.6, 142.8, 136.2, 129.0, 127.1, 123.7, 117.6, 110.3, 103.5, 60.8, 55.8, 49.2, 40.4, 40.3, 40.1, 39.9, 39.8, 39.6, 39.4, 26.9, 25.5, 13.6, 12.0.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{18}ClN_3NaO_4, M+Na]^+$: 410.0878; Found: 410.0902.

Ethyl 2'-amino-5-bromo-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21f)

The compound **21f** was synthesized following the procedure described in section **4.10.1** using 5-bromo-1-methylindoline-2,3-dione (50 mg, 0.21 mmol), malononitrile (14 mg, 0.21 mmol), ethyl penta-2,3-dienoate (39 mg, 0.31 mmol), propylamine (20 µL, 0.25 mmol) and Et_3N (0.03 mL, 0.25 mmol) in EtOH (3 mL) at room temperature. The product **21f** was obtained as a white solid in 52% (47 mg) yield.



21f

Mp: 263 – 264 °C.

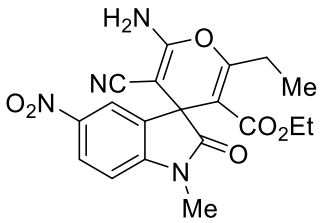
^{1}H NMR (500 MHz, DMSO): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.30 (s, 2H), 7.02 (d, *J* = 8.0 Hz, 1H), 3.79 (q, *J* = 6.5 Hz, 2H), 3.13 (s, 3H), 2.68 – 2.75 (m, 2H), 1.18 (t, *J* = 7.5 Hz, 3H), 0.77 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO): δ 177.0, 164.5, 164.3, 159.6, 143.2, 136.6, 131.9, 126.3, 117.6, 114.8, 110.8, 103.5, 60.8, 55.9, 49.1, 26.8, 25.5, 13.6, 12.0.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{18}BrN_3NaO_4, M+Na]^+$: 454.0373; Found: 454.0391.

Ethyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-5-nitro-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21g)

The compound **21g** was synthesized following the procedure described in section **4.10.1** using 1-methyl-5-nitroindoline-2,3-dione (50 mg, 0.24 mmol), malononitrile (16 mg, 0.24 mmol), ethyl penta-2,3-dienoate (45 mg, 0.36 mmol), propylamine (24 µL, 0.29 mmol) and Et_3N (0.04 mL, 0.29 mmol) in EtOH (3 mL) at room temperature. The product **21g** was obtained as a white solid in 47% (45 mg) yield.



21g

Mp: 235 – 236 °C.

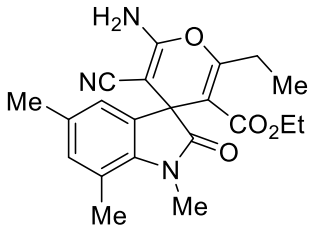
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.5 Hz, 1H), 8.04 (s, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.85 (s, 2H), 3.89 – 3.96 (m, 2H), 3.35 (s, 3H), 2.87 – 2.95 (m, 1H), 2.76 – 2.83 (m, 1H), 1.30 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 177.4, 165.2, 164.0, 158.6, 149.2, 143.8, 134.4, 126.4, 119.3, 115.8, 107.8, 103.5, 61.2, 59.6, 48.8, 27.0, 26.0, 13.5, 11.7.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{18}N_4NaO_6, M+Na]^+$: 421.1119; Found: 421.1123.

Ethyl 2'-amino-3'-cyano-6'-ethyl-1,5,7-trimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21h)

The compound **21h** was synthesized following the procedure described in section **4.10.1** using 1,5,7-trimethylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), ethyl penta-2,3-dienoate (50 mg, 0.40 mmol), propylamine (26 µL, 0.32 mmol) and Et_3N (0.04 mL, 0.32 mmol) in EtOH (3 mL) at room temperature. The product **21h** was obtained as a white solid in 70% (70 mg) yield.



21h

Mp: 270 – 271 °C.

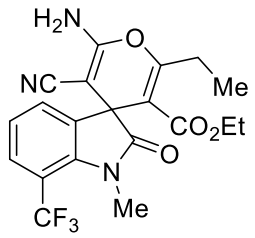
^{1}H NMR (500 MHz, DMSO): δ 7.15 (s, 2H), 6.85 (s, 1H), 6.72 (s, 1H), 3.76 – 3.78 (m, 2H), 3.37 (s, 3H), 2.63 – 2.71 (m, 2H), 2.50 (s, 3H), 2.20 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO): δ 177.9, 164.7, 163.1, 159.5, 139.1, 134.9, 133.1, 131.8, 122.1, 119.4, 117.9, 104.8, 60.6, 57.1, 48.5, 29.8, 25.4, 20.7, 18.7, 13.6, 12.1.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{21}H_{23}N_3NaO_4, M+Na]^+$: 404.1581; Found: 404.1590.

Ethyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxo-7-(trifluoromethyl)spiro[indoline-3,4'-pyran]-5'-carboxylate (21i)

The compound **21i** was synthesized following the procedure described in section **4.10.1** using 1-methyl-7-(trifluoromethyl)indoline-2,3-dione (50 mg, 0.22 mmol), malononitrile (14 mg, 0.22 mmol), ethyl penta-2,3-dienoate (41 mg, 0.33 mmol), propylamine (21 µL, 0.26 mmol) and Et_3N (0.04 mL, 0.26 mmol) in EtOH (3 mL) at room temperature. The product **21i** was obtained as a white solid in 42% (39 mg) yield.



21i

Mp: 177 – 178 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 4.79 (s, 2H), 3.79 – 3.89 (m, 2H), 3.48 (s, 3H), 2.87 – 2.95 (m, 1H), 2.69 – 2.77 (m, 1H), 1.28 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.0 Hz, 3H).

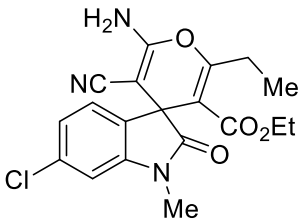
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 178.1, 164.6, 163.9, 158.6, 141.4, 135.9, 127.1, 127.1, 127.0, 124.5, 122.5, 116.0, 112.7, 112.4, 104.0, 60.9, 47.3, 29.4, 29.3, 25.6, 13.2, 11.8.

^{19}F{^{1}H} (371MHz, $CDCl_3$): δ -53.3.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{20}H_{18}F_3N_3NaO_4, M+Na]^+$: 444.1142; Found: 444.1147.

Ethyl 2'-amino-6-chloro-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21j)

The compound **21j** was synthesized following the procedure described in section **4.10.1** using 6-chloro-1-methylindoline-2,3-dione (50 mg, 0.25 mmol), malononitrile (17 mg, 0.25 mmol), ethyl penta-2,3-dienoate (48 mg, 0.38 mmol), propylamine (25 µL, 0.31 mmol) and Et_3N (0.04 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **2ij** was obtained as a white solid in 59% (58 mg) yield.



21j

Mp: 252 – 253 ^oC.

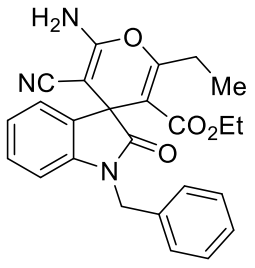
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (s, 2H), 6.86 (s, 1H), 4.74 (s, 2H), 3.90 (q, *J* = 7.0 Hz, 2H), 3.26 (s, 3H), 2.84 – 2.89 (m, 1H), 2.68 – 2.72 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.1, 164.2, 164.1, 158.61, 144.7, 135.0, 131.5, 124.4, 123.0, 116.2, 108.9, 104.1, 60.9, 60.4, 48.2, 26.7, 25.7, 13.5, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{18}ClN_3NaO_4, M+Na]^+$: 410.0878; Found: 410.0903.

Ethyl 2'-amino-1-benzyl-3'-cyano-6'-ethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21k)

The compound **21k** was synthesized following the procedure described in section **4.10.1** using 1-benzylindoline-2,3-dione (50 mg, 0.21 mmol), malononitrile (14 mg, 0.21 mmol), ethyl penta-2,3-dienoate (40 mg, 0.32 mmol), propylamine (21 µL, 0.25 mmol) and Et_3N (0.04 mL, 0.25 mmol) in EtOH (3 mL) at room temperature. The product **21k** was obtained as a white solid in 68% (61 mg) yield.



21k

Mp: 200 – 201 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.30 (s, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 6.5 Hz, 1H), 7.04 (t, *J* = 7.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 15.5 Hz, 1H), 4.82 (d, *J* = 15.5 Hz, 1H), 4.75 (s, 2H), 3.88 – 3.95 (m, 1H), 3.59 – 3.65 (m, 1H), 2.85 –

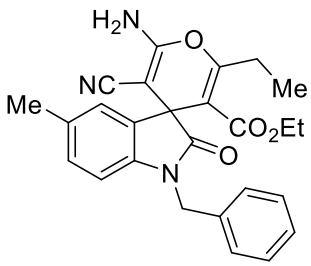
2.93 (m, 1H), 2.66 – 2.73 (m, 1H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.68 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 177.3, 164.4, 163.7, 158.7, 142.8, 135.5, 133.1, 129.1, 128.7, 127.7, 127.6, 123.6, 123.2, 116.6, 109.2, 104.7, 61.0, 60.7, 48.7, 44.6, 25.7, 13.2, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{25}H_{23}N_3NaO_4, M+Na]^+$: 452.1581; Found: 452.1573.

Ethyl 2'-amino-1-benzyl-3'-cyano-6'-ethyl-5-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21l)

The compound **21l** was synthesized following the procedure described in section **4.10.1** using 1-benzyl-5-methylindoline-2,3-dione (50 mg, 0.20 mmol), malononitrile (13 mg, 0.20 mmol), ethyl penta-2,3-dienoate (38 mg, 0.30 mmol), aniline (20 µL, 0.24 mmol) and Et_3N (0.03 mL, 0.24 mmol) in EtOH (3 mL) at room temperature. The product **21l** was obtained as a white solid in 65% (57 mg) yield.



21l

Mp: 208 – 209 °C.

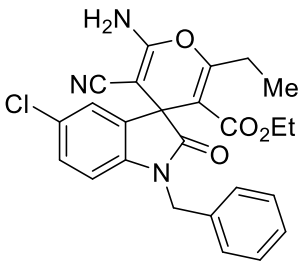
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.28 (s, 1H), 6.96 – 6.98 (m, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 5.12 (d, *J* = 15.5 Hz, 1H), 4.83 (s, 2H), 4.79 (d, *J* = 15.5 Hz, 1H), 3.90 – 3.93 (m, 1H), 3.62 – 3.66 (m, 1H), 2.86 – 2.91 (m, 1H), 2.67 – 2.71 (m, 1H), 2.29 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 0.69 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): 177.4, 164.6, 163.6, 158.8, 140.3, 135.6, 133.1, 132.8, 129.4, 128.6, 127.7, 127.6, 124.3, 116.8, 109.0, 104.7, 60.9, 60.7, 48.7, 44.6, 25.7, 21.0, 13.3, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{26}H_{25}N_3NaO_4, M+Na]^+$: 466.1737; Found: 466.1750.

Ethyl 2'-amino-1-benzyl-5-chloro-3'-cyano-6'-ethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21m)

The compound **21m** was synthesized following the procedure described in section **4.10.1** using 1-benzyl-5-chloroindoline-2,3-dione (50 mg, 0.18 mmol), malononitrile (12 mg, 0.18 mmol), ethyl penta-2,3-dienoate (35 mg, 0.28 mmol), propylamine (18 µL, 0.22 mmol) and Et_3N (0.03 mL, 0.22 mmol) in EtOH (3 mL) at room temperature. The product **21m** was obtained as a white solid in 60% (51 mg) yield.



21m

Mp: 218 – 219 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.13 (s, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.12 (d, *J* = 15.5 Hz, 1H), 4.79 (s, 2H), 4.77 – 4.78 (m, 1H), 3.94 – 4.01 (m, 1H), 3.68 – 3.75 (m, 1H), 2.87 – 2.94 (m, 1H), 2.69 – 2.76 (m, 1H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.0 Hz, 3H).

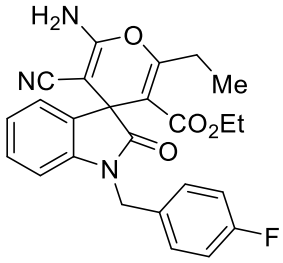
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.0, 164.4, 164.2, 158.6, 141.3, 135.0, 134.9, 129.0, 128.8, 128.5, 127.8, 127.6, 124.0, 116.4, 110.2, 104.1, 60.9, 60.5, 48.9, 44.7, 25.8, 13.4, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{25}H_{22}ClN_3NaO_4, M+Na]^+$: 486.1191; Found: 486.1203.

Ethyl 2'-amino-3'-cyano-6'-ethyl-1-(4-fluorobenzyl)-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21n)

The compound **21n** was synthesized following the procedure described in section **4.10.1** using 1-(4-fluorobenzyl)indoline-2,3-dione (50 mg, 0.20 mmol), malononitrile (13 mg, 0.20 mmol), ethyl penta-2,3-dienoate (37 mg, 0.29 mmol), propylamine (19 µL, 0.23 mmol) and Et_3N (0.03 mL, 0.23 mmol) in EtOH (3 mL) at room temperature. The product **21n** was obtained as a white solid in 56% (49 mg) yield.

Mp: 180 – 181 °C.



21n

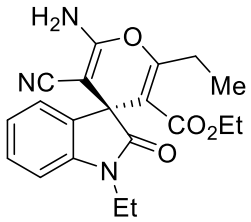
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.38 (m, 2H), 7.09 – 7.13 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.94 – 6.97 (m, 3H), 6.62 (d, *J* = 7.5 Hz, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 4.69 (s, 2H), 4.68 (d, *J* = 15.5 Hz, 1H), 3.80 – 3.86 (m, 1H), 3.53 – 3.59 (m, 1H), 2.76 – 2.83 (m, 1H), 2.56 – 2.63 (m, 1H), 1.19 (t, *J* = 7.5 Hz, 3H), 0.63 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.4, 164.4, 163.8, 158.7, 142.5, 133.1, 131.2, 129.4, 129.3, 129.1, 123.6, 123.3, 116.7, 115.7, 115.5, 109.1, 104.6, 60.7, 48.7, 43.8, 25.7, 13.3, 11.8.

^{19}F{^{1}H} (371MHz, $CDCl_3$): δ -114.5.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{25}H_{22}FN_3NaO_4, M+Na]^+$: 470.1487; Found: 470.1511.

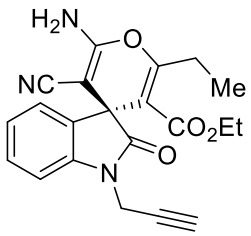
Ethyl -2'-amino-3'-cyano-1,6'-diethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21o)



21o

Yield: Obtained in trace amount.

Ethyl -2'-amino-3'-cyano-6'-ethyl-2-oxo-1-(prop-2-yn-1-yl)spiro[indoline-3,4'-pyran]-5'-carboxylate (21p)

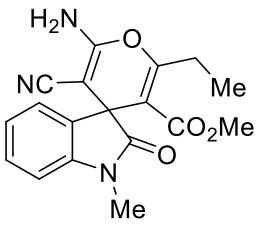


21p

Yield: Obtained in trace amount.

Methyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21aa)

The compound **21aa** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), methyl penta-2,3-dienoate (52 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21aa** was obtained as a white solid in 85% (89 mg) yield.



21aa

Mp: 229 – 230 °C.

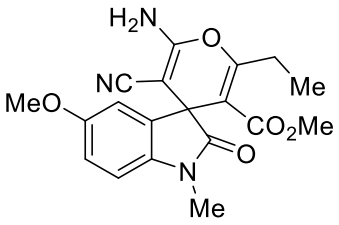
^{1}H NMR (500 MHz, DMSO): δ 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (s, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.01 – 7.04 (m, 2H), 3.31 (s, 3H), 3.15 (s, 3H), 2.51 – 2.71 (m, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO): 177.3, 165.3, 163.1, 159.7, 143.8, 133.9, 129.2, 123.5, 123.1, 117.8, 108.7, 104.7, 56.3, 52.0, 49.0, 40.4, 40.3, 40.1, 39.9, 39.8, 39.6, 39.4, 26.8, 25.6, 12.1.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{18}H_{17}N_3NaO_4, M+Na]^+$: 362.1111; Found: 362.1133.

Methyl 2'-amino-3'-cyano-6'-ethyl-5-methoxy-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ab)

The compound **21ab** was synthesized following the procedure described in section **4.10.1** using 5-methoxy-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), methyl penta-2,3-dienoate (44 mg, 0.39 mmol), propylamine (26 µL, 0.31 mmol) and Et_3N (0.04 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **21ab** was obtained as a white solid in 81% (78 mg) yield.



21ab

Mp: 248 – 249 °C.

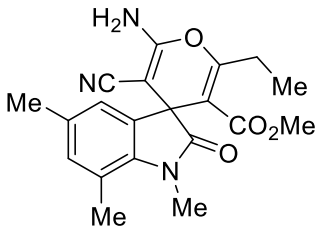
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 1H), 4.83 (s, 2H), 3.79 (s, 3H), 3.42 (s, 3H), 3.26 (s, 3H), 2.82 – 2.89 (m, 1H), 2.65 – 2.72 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 177.0, 164.9, 163.8, 158.6, 156.3, 136.9, 134.4, 116.5, 113.2, 111.0, 108.6, 104.6, 60.6, 55.7, 51.8, 49.2, 26.8, 25.8, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{19}N_3NaO_5, M+Na]^+$: 392.1217; Found: 392.1219.

Methyl 2'-amino-3'-cyano-6'-ethyl-1,5,7-trimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ac)

The compound **21ac** was synthesized following the procedure described in section **4.10.1** using 1,5,7-trimethylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), methyl penta-2,3-dienoate (44 mg, 0.40 mmol), propylamine (26 µL, 0.32 mmol) and Et_3N (0.04 mL, 0.32 mmol) in EtOH (3 mL) at room temperature. The product **21ac** was obtained as a white solid in 78% (75 mg) yield.



21ac

Mp: 260 – 261 °C.

^1H NMR (500 MHz, DMSO): δ 7.16 (s, 2H), 6.84 (s, 1H), 6.71 (s, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.69 (q, *J* = 7.5 Hz, 2H), 2.50 (s, 3H), 2.20 (s, 3H), 1.17 (t, *J* = 7.5 Hz, 3H).

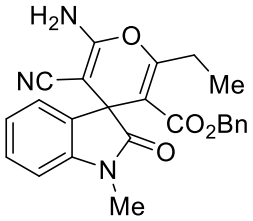
$^{13}C\{^1H\}$ NMR (125 MHz, DMSO): δ 178.0, 165.3, 162.9, 159.5, 139.1, 134.9, 133.2, 131.8, 122.1, 119.5, 117.8, 105.1, 57.0, 52.1, 48.6, 29.9, 25.6, 20.7, 18.7, 12.1.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{20}H_{21}N_3NaO_4, M+Na]^+$: 390.1424; Found: 390.1418.

Benzyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ad)

The compounds **21ad** were synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), benzyl penta-2,3-dienoate (88 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21ad** was obtained as a white solid in 59% (76 mg) yield.

Mp: 198 – 199 °C.



21ad

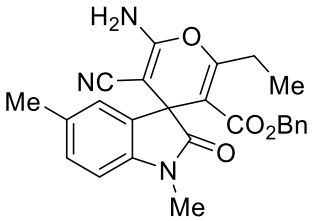
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 3H), 7.17 – 7.18 (m, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 2H), 6.46 (d, *J* = 7.5 Hz, 1H), 4.68 – 4.69 (m, 1H), 4.66 (s, 2H), 4.63 (d, *J* = 12.0 Hz, 1H), 2.80 – 2.87 (m, 1H), 2.63 (s, 3H), 2.56 – 2.61 (m, 1H), 1.18 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.0, 164.5, 164.3, 158.5, 143.1, 134.3, 133.1, 129.0, 129.0, 128.4, 128.4, 123.3, 123.0, 116.4, 108.7, 103.9, 67.2, 48.6, 26.0, 25.7, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{24}H_{21}N_3NaO_4, M+Na]^+$: 438.1424; Found: 438.1431.

Benzyl 2'-amino-3'-cyano-6'-ethyl-1,5-dimethyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ae)

The compound **21ae** was synthesized following the procedure described in section **4.10.1** using 1,5-dimethylindoline-2,3-dione (50 mg, 0.28 mmol), malononitrile (19 mg, 0.28 mmol), benzyl penta-2,3-dienoate (80 mg, 0.43 mmol), propylamine (28 µL, 0.34 mmol) and Et_3N (0.05 mL, 0.34 mmol) in EtOH (3 mL) at room temperature. The product **21ae** was obtained as a white solid in 55% (67 mg) yield.



21ae

Mp: 200 – 201 ^{o}C.

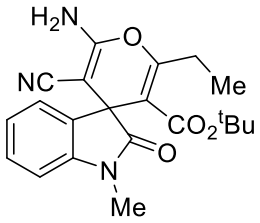
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 6.88 (d, *J* = 6.0 Hz, 2H), 6.46 (d, *J* = 7.0 Hz, 1H), 4.88 (s, 2H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 2.90 - 2.94 (m, 1H), 2.71 (s, 3H), 2.65 – 2.70 (m, 1H), 2.34 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.0, 164.4, 164.4, 158.5, 140.7, 134.3, 133.1, 132.6, 129.3, 128.9, 128.4, 128.4, 124.1, 116.5, 108.4, 104.0, 67.1, 60.9, 48.6, 26.0, 25.7, 21.1, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{25}H_{23}N_3NaO_4, M+Na]^+$: 452.1581; Found: 452.1568.

***Tert*-butyl 2'-amino-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21af)**

The compound **21af** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), *tert*-butyl penta-2,3-dienoate (72 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21af** was obtained as a white solid in 65% (77 mg) yield.



21af

Mp: 229 – 230 °C.

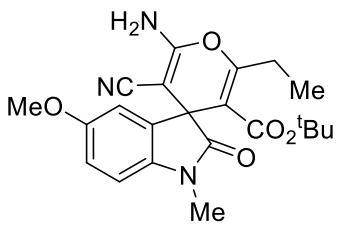
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.0 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.09 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 1H), 4.70 (s, 2H), 3.25 (s, 3H), 2.82 – 2.86 (m, 1H), 2.57 – 2.61 (m, 1H), 1.27 (t, *J* = 6.5 Hz, 3H), 1.04 (s, 9H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.1, 163.7, 162.4, 158.9, 143.6, 132.9, 129.2, 123.7, 123.1, 116.6, 108.1, 105.7, 81.8, 60.8, 48.6, 27.3, 26.5, 25.3, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{21}H_{23}N_3NaO_4, M+Na]^+$: 404.1581; Found: 404.1596.

***Tert*-butyl 2'-amino-3'-cyano-6'-ethyl-5-methoxy-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ag)**

The compound **21ag** was synthesized following the procedure described in section **4.10.1** using 5-methoxy-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), *tert*-butyl penta-2,3-dienoate (60 mg, 0.39 mmol), propylamine (26 µL, 0.31 mmol) and Et_3N (0.04 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **21ag** was obtained as a white solid in 61% (66 mg) yield.



21ag

Mp: 206 – 207 °C.

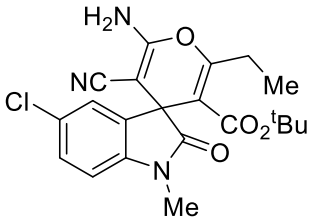
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 4.78 (s, 2H), 3.79 (s, 3H), 3.22 (s, 3H), 2.79 – 2.87 (m, 1H), 2.56 – 2.63 (m, 1H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.06 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): 176.9, 163.6, 162.6, 158.9, 156.5, 137.1, 134.2, 116.6, 113.6, 111.0, 108.5, 105.6, 81.8, 60.7, 55.9, 49.1, 27.4, 26.6, 25.3, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{22}H_{25}N_3NaO_5, M+Na]^+$: 434.1686; Found: 434.1705.

***Tert*-butyl 2'-amino-5-chloro-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (21ah)**

The compound **21ah** was synthesized following the procedure described in section **4.10.1** using 5-chloro-1-methylindoline-2,3-dione (50 mg, 0.26 mmol), malononitrile (17 mg, 0.26 mmol), *tert*-butyl penta-2,3-dienoate (59 mg, 0.39 mmol), propylamine (25 µL, 0.31 mmol) and Et_3N (0.04 mL, 0.31 mmol) in EtOH (3 mL) at room temperature. The product **21ah** was obtained as a white solid in 52% (55 mg) yield.



21ah

Mp: 203 – 204 °C.

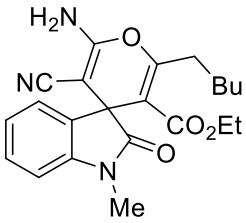
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 4.76 (s, 2H), 3.24 (s, 3H), 2.81 – 2.89 (m, 1H), 2.59 – 2.66 (m, 1H), 1.27 (t, *J* = 7.5 Hz, 3H), 1.09 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 176.7, 163.1, 158.9, 142.2, 134.7, 129.1, 128.4, 124.1, 116.3, 109.1, 105.0, 82.1, 60.2, 48.6, 27.5, 26.7, 25.5, 11.8.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{21}H_{22}ClN_3NaO_4, M+Na]^+$: 438.1191; Found: 438.1189.

Ethyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-pentylspiro[indoline-3,4'-pyran]-5'-carboxylate (21ai)

The compound **21ai** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), ethyl octa-2,3-dienoate (79 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21ai** was obtained as a white solid in 80% (98 mg) yield.



21ai

Mp: 210 – 211 °C.

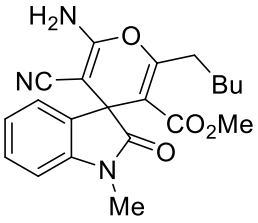
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 1H), 7.08 (t, *J* = 7.0 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 4.73 (s, 2H), 3.78 – 3.89 (m, 2H), 3.28 (s, 3H), 2.83 – 2.89 (m, 1H), 2.63 – 2.68 (m, 1H), 1.69 (s, 2H), 1.39 (s, 4H), 0.94 (s, 3H), 0.83 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 177.2, 164.4, 163.0, 158.6, 143.5, 133.2, 129.2, 123.5, 123.1, 116.5, 108.1, 104.9, 60.7, 48.7, 31.9, 31.4, 27.2, 26.6, 22.4, 13.9, 13.3.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{22}H_{25}N_3NaO_4, M+Na]^+$: 418.1737; Found: 418.1753.

Methyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-pentylspiro[indoline-3,4'-pyran]-5'-carboxylate (21aj)

The compound **21aj** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), methyl octa-2,3-dienoate (72 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21aj** was obtained as a white solid in 82% (97 mg) yield.



21aj

Mp: 204 – 205 °C.

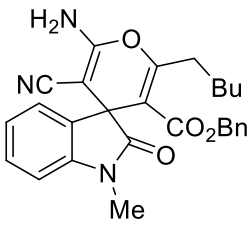
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.32 (m, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 4.87 (s, 2H), 3.38 (s, 3H), 3.28 (s, 3H), 2.79 – 2.86 (m, 1H), 2.59 – 2.65 (m, 1H), 1.67 – 1.68 (m, 2H), 1.38 (s, 4H), 0.94 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.4, 165.0, 162.8, 158.7, 143.4, 133.1, 129.2, 123.4, 123.2, 116.5, 108.2, 105.1, 60.2, 51.7, 48.8, 32.0, 31.3, 27.1, 26.7, 22.3, 13.9.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{21}H_{23}N_3NaO_4, M+Na]^+$: 404.1581; Found: 404.1594.

Benzyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-pentylspiro[indoline-3,4'-pyran]-5'-carboxylate (21ak)

The compound **21ak** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), benzyl penta-2,3-dienoate (88 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21ak** was obtained as a white solid in 64% (91 mg) yield.



21ak

Mp: 165 – 166 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ δ 7.28 – 7.33 (m, 4H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.0 Hz, 2H), 6.55 (d, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.73 (s, 2H), 4.72 (d, *J* = 12.5 Hz, 1H), 2.86 – 2.92 (m, 1H), 2.74 (s, 3H), 2.63 – 2.68 (m, 1H), 1.67 (s, 2H), 1.35 – 1.36 (d, *J* = 3.7 m, 4H), 0.93 (t, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 177.0, 164.4, 163.6, 158.4, 143.2, 134.3, 133.1, 129.0, 128.5, 128.4, 123.3, 123.0, 116.4, 108.6, 104.4, 60.9, 48.6, 32.0, 31.4, 27.2, 26.0, 22.4, 13.9.

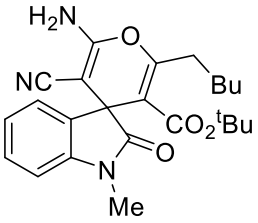
HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{27}H_{27}N_3NaO_4, M+Na]^+$: 480.1894; Found: 480.1921.

***Tert*-butyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-pentylspiro[indoline-3,4'-pyran]-5'-carboxylate (21al)**

The compound **21al** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), *tert*-butyl octa-2,3-dienoate (92 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21al** was obtained as a white solid in 71% (93 mg) yield.

Mp: 201 – 202 ^oC.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 4.77 (s, 2H), 3.24 (s, 3H), 2.73 – 2.79 (m, 1H), 2.58 –



21al

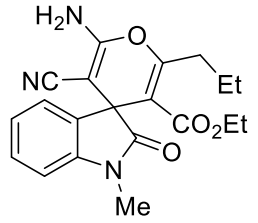
2.63 (m, 1H), 1.69 (s, 2H), 1.39 (s, 4H), 1.03 (s, 9H), 0.94 (s, 3H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 177.2, 163.7, 161.4, 159.0, 143.6, 132.9, 129.2, 123.7, 123.1, 116.7, 108.1, 106.1, 81.7, 60.5, 48.7, 31.5, 31.3, 27.3, 27.0, 26.5, 22.4, 13.9.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{24}H_{29}N_3NaO_4, M+Na]^+$: 446.2050; Found: 446.2062.

Ethyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-propylspiro[indoline-3,4'-pyran]-5'-carboxylate (21am)

The compound **21am** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), ethyl hexa-2,3-dienoate (66 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21am** was obtained as a white solid in 76% (87 mg) yield.



21am

Mp: 218 – 219 °C.

^1H NMR (500 MHz, $CDCl_3$): δ 7.21 – 7.24 (m, 1H), 7.05 (d, *J* = 6.0 Hz, 1H), 6.98 – 6.99 (m, 1H), 6.76 (d, *J* = 7.0 Hz, 1H), 4.67 (s, 2H), 3.71 – 3.77 (m, 2H), 3.19 (s, 3H), 2.75 – 2.77 (m, 1H), 2.56 – 2.58 (m, 1H), 1.59 – 1.65 (m, 1H), 0.96 (t, *J* = 6.5 Hz, 3H), 0.75 (t, *J* = 6.5 Hz, 3H).

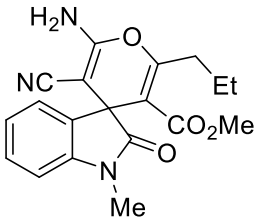
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 177.3, 164.4, 162.6, 158.6, 143.5, 133.2, 129.2, 123.5, 123.2, 116.5, 108.1, 105.1, 60.7, 48.7, 33.6, 26.6, 20.8, 13.6, 13.3.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{20}H_{21}N_3NaO_4, M+Na]^+$: 390.1424; Found: 390.1436.

Methyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-propylspiro[indoline-3,4'-pyran]-5'-carboxylate (21an)

The compound **21an** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), methyl hexa-2,3-dienoate (59 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL,

0.37 mmol) in EtOH (3 mL) at room temperature. The product **21an** was obtained as a white solid in 80% (88 mg) yield.



21an

Mp: 208 – 209 °C.

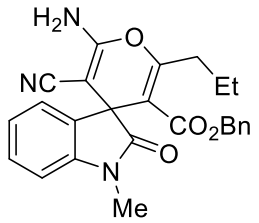
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 4.81 (s, 2H), 3.38 (s, 3H), 3.29 (s, 3H), 2.79 – 2.84 (m, 1H), 2.61 – 2.67 (m, 1H), 1.69 – 1.74 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.4, 165.0, 162.5, 158.7, 143.4, 133.1, 129.3, 129.2, 123.5, 123.4, 123.2, 116.5, 108.2, 108.1, 105.4, 60.4, 60.3, 51.7, 48.8, 33.7, 26.7, 20.8, 13.6.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{19}H_{19}N_3NaO_4, M+Na]^+$: 376.1268; Found: 376.1267.

Benzyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-propylspiro[indoline-3,4'-pyran]-5'-carboxylate (21ao)

The compound **21ao** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), benzyl hexa-2,3-dienoate (95 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21ao** was obtained as a white solid in 58% (77 mg) yield.



21ao

Mp: 231 – 232 °C.

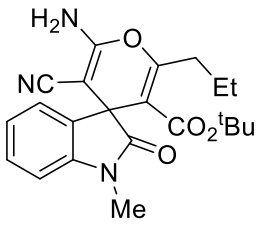
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.33 (m, 2H), 7.26 – 7.27 (m, 2H), 7.13 (d, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 2H), 6.55 (d, *J* = 7.5 Hz, 1H), 4.77 (s, 1H), 4.75 (s, 2H), 4.72 (d, *J* = 12.0 Hz, 1H), 2.86 – 2.91 (m, 1H), 2.73 (s, 3H), 2.63 – 2.69 (m, 1H), 1.69 – 1.76 (m, 2H), 1.01 (t, *J* = 7.5 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 177.0, 164.4, 163.3, 158.4, 143.2, 134.3, 133.1, 129.0, 128.5, 128.4, 123.3, 123.0, 116.4, 108.7, 104.6, 67.2, 60.8, 48.6, 33.6, 26.0, 20.8, 13.6.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{25}H_{23}N_3NaO_4, M+Na]^+$: 452.1581; Found: 452.1598.

***Tert*-butyl 2'-amino-3'-cyano-1-methyl-2-oxo-6'-propylspiro[indoline-3,4'-pyran]-5'-carboxylate (21ap)**

The compound **21ap** was synthesized following the procedure described in section **4.10.1** using *N*-methyl isatin (50 mg, 0.31 mmol), malononitrile (21 mg, 0.31 mmol), *tert*-butyl hexa-2,3-dienoate (79 mg, 0.47 mmol), propylamine (31 µL, 0.37 mmol) and Et_3N (0.05 mL, 0.37 mmol) in EtOH (3 mL) at room temperature. The product **21ap** was obtained as a white solid in 67% (82 mg) yield.



21ap

Mp: 201 – 202 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.72 (s, 2H), 3.25 (s, 3H), 2.73 – 2.78 (m, 1H), 2.59 – 2.65 (m, 1H), 1.69 – 1.74 (m, 2H), 1.04 (s, 9H).

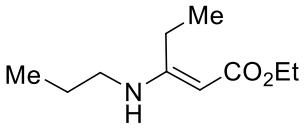
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): 176.6, 163.7, 161.0, 159.0, 143.9, 132.9, 129.2, 123.7, 123.1, 116.6, 116.1, 108.1, 106.5, 81.7, 60.8, 48.6, 33.2, 27.3, 26.5, 20.7, 13.5.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{22}H_{25}N_3NaO_4, M+Na]^+$: 418.1737; Found: 418.1736.

Ethyl 3-(propylamino)pent-2-enoate (BB)

The compound **BB** was synthesized following the procedure described in section **4.11.1** using ethyl penta-2,3-dienoate (50 mg, 0.39 mmol) and propylamine (39 µL, 0.48 mmol) in EtOH (2 mL) at room temperature. The product **BB** was obtained as a colorless oil in 74% (54 mg) yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 4.37 (s, 1H), 4.01 – 4.02 (m, 2H), 3.08 – 3.09 (m, 2H), 2.13 – 2.15 (m,



BB

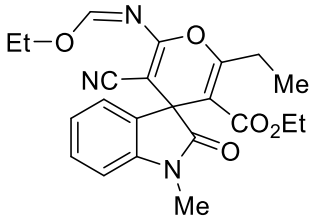
2H), 1.51 – 1.55 (m, 2H), 1.18 (t, *J* = 6.0 Hz, 3H), 1.06 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 6.5 Hz, 3H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 171.0, 167.1, 79.8, 58.2, 44.2, 25.3, 23.6, 14.6, 12.1, 11.3.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{10}H_{20}NO_2, M+H]^+$: 186.1489; Found: 186.1495.

Ethyl 5'-cyano-6'-((ethoxymethylene)amino)-2'-ethyl-1-methyl-2-oxospiro [indoline-3,4'-pyran]-3'-carboxylate (22a)

The compounds **22a** was synthesized following the procedure described in section **4.12.1** using **21a** (50 mg, 0.14 mmol), triethyl orthoformate (0.75 mL) and acetic acid (0.25 mL) at reflux temperature. The product **22a** was obtained as a colourless oil in 86% (50 mg) yield.



22a

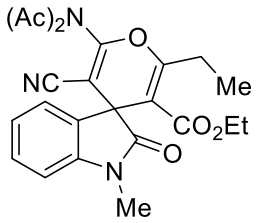
^1H NMR (500 MHz, CD_3COCD_3): δ 8.42 (s, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 4.22 – 4.25 (m, 2H), 3.66 – 3.71 (m, 2H), 3.12 (s, 3H), 2.72 – 2.78 (m, 1H), 2.65 – 2.71 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.13 (t, *J* = 7.5 Hz, 3H), 0.70 (t, *J* = 7.1 Hz, 3H).

$^3C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 175.8, 164.3, 164.1, 161.3, 157.1, 144.0, 133.1, 129.4, 123.6, 122.7, 114.4, 108.2, 103.7, 80.8, 64.1, 60.3, 50.3, 25.9, 25.2, 13.2, 12.8, 11.3.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{22}H_{23}N_3NaO_5, M+Na]^+$: 432.1530; Found: 432.1537.

Ethyl 2'-(N-acetylacetamido)-3'-cyano-6'-ethyl-1-methyl-2-oxospiro[indoline-3,4'-pyran]-5'-carboxylate (22b)

The compound **22b** was synthesized following the procedure described in section **4.12.2** using **21a** (50 mg, 0.14 mmol) and acetic anhydride (2 mL) at reflux temperature. The product **22b** was obtained as a violet gummy liquid in 80% (49 mg) yield.



22b

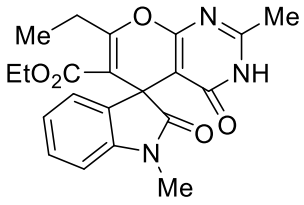
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.04 – 7.09 (m, 1H), 6.81 (d, *J* = 7.0 Hz, 1H), 3.78 – 3.83 (m, 2H), 3.21 (s, 3H), 2.77 – 2.84 (m, 1H), 2.59 – 2.66 (m, 1H), 2.42 (s, 6H), 1.18 (t, *J* = 6.5 Hz, 3H), 0.79 (t, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 175.3, 164.9, 163.7, 152.9, 143.3, 137.6, 131.4, 130.2, 126.7, 124.3, 123.9, 123.8, 112.0, 109.6, 108.4, 104.0, 93.5, 61.0, 50.9, 26.7, 25.6, 13.4, 11.7.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{23}H_{23}N_3NaO_6, M+Na]^+$: 460.1479; Found: 460.1482.

Ethyl 7'-ethyl-1,2'-dimethyl-2,4'-dioxo-3',4'-dihydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6'-carboxylate (22c)

The compound **22c** was synthesized following the procedure described in section **4.12.3** using **21a** (50 mg, 0.14mmol), acetic anhydride (1 mL) and trifluoroacetic acid (0.025 mL) at reflux temperature. The product **22c** was obtained as a colorless oil in 71% (40 mg) yield.



22c

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.76 (s, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.86 – 6.89 (m, 2H), 6.67 (d, *J* = 7.5 Hz, 1H), 3.75 – 3.85 (m, 2H), 3.16 (s, 3H), 2.75 – 2.80 (m, 1H), 2.63 – 2.69 (m, 1H), 2.06 (s, 3H), 1.23 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).

^{3}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 177.0, 164.7, 164.2, 163.5, 161.5, 158.7, 144.9, 133.0, 128.7, 123.4, 122.5, 106.8, 105.5, 99.5, 60.7, 48.2, 26.5, 26.4, 20.9, 13.5, 11.9.

HRMS (ESI-Orbitrap) m/z: $[M+Na]^+$ calcd for $[C_{21}H_{22}N_3O_5, M+H]^+$: 396.1554; Found: 396.1534.

4.14. References

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ABSTRACT

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Faculty of Study: Chemical Sciences Year of Submission: 2025
AcSIR academic centre/CSIR Lab: CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST) Name of the Supervisor: Dr. Sasidhar B. S.

Title of the thesis: **Exploring the Tertiary Amine-Mediated Reactivity of Allenoates: Efficient Access to 3-Alkenyl-2-oxindoles, Pyridopyrimidines and Spiropyran Frameworks**

Lewis base-mediated reactions of allenoates have been one of the most effective synthetic strategies for the construction of numerous valuable motifs, particularly in the construction of biologically active natural products and pharmaceuticals. Tertiary phosphine, NHC, and tertiary amine catalysts are often the most effective Lewis bases; of these, tertiary amine Lewis bases have demonstrated efficacy as catalysts for a variety of synthetic transformations. In recent decades, significant progress has been achieved in the construction of valuable motifs by the transformation of allenoates mediated by tertiary amines.

Chapter 1 will focus on the diverse reactivity, chemoselectivity and detailed reaction mechanisms of tertiary amine-mediated reactions of allenoates utilized for the synthesis of valuable carbocycles and heterocycles.

Chapter 2 describes an effective approach to the stereoselective synthesis of functionalized 3-alkenyl-2-oxindoles by the TBD-mediated tandem reaction of isatins and aryl allenoates. This protocol employs widely accessible substrates, viz., isatins and aryl-allenoates, that gave the corresponding products in substantial yields under mild reaction conditions with a wide substrate scope and high functional group tolerance. Additionally, this approach enables us to reduce the synthesis path that previously demanded multiple steps into a single one. We have also demonstrated the synthetic utility of 3-alkenyl-2-oxindoles to convert them into novel oxindole-appended heterocyclic scaffolds. Hence, we believe that the obtained 3- alkenyl-2-oxindoles might draw the attention of synthetic and medicinal chemists for the rapid and efficient syntheses of hitherto unattainable highly functionalized target molecules for therapeutic uses.

Chapter 3 explains an unprecedented 100% atom-economic annulation of allenoates with cyclic amidines for the synthesis of functionalized tricyclic pyridopyrimidine scaffolds. High reaction efficiency, ease of operation, very short time, mild and solvent-free reaction conditions, and wide substrate scope are the key advantages of the present annulation protocol. The scalability of the developed protocol is further demonstrated by a gram-scale synthesis. It is the first approach that exploits the reactivity of allenoates for constructing the structurally diverse motifs of tricyclic pyridopyrimidines.

A highly efficient multicomponent reaction for the synthesis of functionalized spiro[4H-pyran-oxindole] utilizing easily accessible isatin, malononitrile, allenoate, and alkyl amine is the subject matter of **Chapter 4**. The Et_3N-mediated reaction involves cascade spiro-cyclization of *in situ* generated Knoevenagel adduct and aza-Michael adduct. The developed protocol provides direct access to an array of functionalized spiro[4H-pyran-oxindole] scaffolds in good yields without the need for transition metal or organocatalysts. Further, this present method is scalable, providing a simple and alternative way for the synthesis of functionalized spiro[4H-pyran-oxindole] frameworks in drugs and bioactive molecules. Meanwhile, this is the first approach which exploits the reactivity of allenoates to build structurally varied motifs of spiro[4H-pyran-oxindole].

DETAILS OF PUBLICATIONS

List of Publications Emanating from the Thesis

1. **Athira, C. S**.; Basavaraja, D.; Geethu Venugopal.; Mohan Banyangala.; Ajay Krishna, M. S.; Sasidhar, B. S. TBD-Mediated Diastereoselective Access to Functionalized 3-Alkenyl-2-oxindoles *via* the Tandem Reaction of Isatins and Allenoates. *J. Org. Chem.,* **2024***, 89,* 19, 14021–14027. https://doi.org/10.1021/acs.joc.4c01427.

2. **Athira, C. S**.; Basavaraja, D.; Siddalingeshwar, V. D.; Aiswarya Siby.; Praveen, K. V.; Sasidhar, B. S. Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines *via* Tandem Cyclization of Allenoates and Cyclic Amidines. *Org. Lett.,* **2023,** *25,* 42, 7711−7715. https://doi.org/10.1021/acs.orglett.3c03053.

3. **Athira, C. S**.; Basavaraja, D.; Geethu Venugopal.; Sasidhar B. S. Multicomponent Synthesis of Spirooxindoles Incorporating 2-Amino pyran-3-carbonitrile unit *via* Cascade Spiro cyclization of Knoevenagel /aza-Michael adducts/hydrolysis [Manuscript to be communicated]

List of Publications not Related to Thesis Work

4. **Athira, C. S**.; Basavaraja, D.; Praveen K. V.; Shridevi D.; Sasidhar B. S. $Cu(OAc)_2$ Catalyzed Aerobic Oxidative 2-Aryl-3-acylquinoline Synthesis via Aza-Michael Addition and Aldol Condensation of *α, β*-unsaturated ketones and 2-Aminobenzyl alcohols. *Tetrahedron Letters,* **2022**, *104*, 154043. https://doi.org/10.1016/j.tetlet.2022.154043.

5. Basavaraja, D.; Ajay Krishna M. S.; Jagadeesh K.; **Athira C. S**.; Amrutha R. R.; Suresh, E.; Sasidhar, B. S. Base-enabled access to diastereoselective spirofuran oxindoles and γ-functionalized allenoates. *Chem. Commun.,* **2021**, *57*, 1746-1749. https://doi.org/10.1039/D0CC07715A.

6. Basavaraja.; D.; **Athira, C. S**.; Siddalingeshwar, V. D.; Ashitha, K. T.; Sasidhar, B. S. Multicomponent Synthesis of Spiro-dihydropyridine oxindoles via Cascade Spiro-cyclization of Knoevenagel /aza-Michael Adducts. *J. Org. Chem.*, **2022**, *87*, 21,13556–13563. https://doi.org/10.1021/acs.joc.2c01063.

7. Basavaraja, D.; **Athira C. S**.; Siddalingeshwar V. D.; Sasidhar B. S. DBU-Catalyzed Diastereo-/ Regiospecific Synthesis of Highly Substituted Spiro-oxetane oxindoles *via* [2+2] Cycloaddition of Isatins and 3-aryl allenoates. *J. Org. Chem.,* **2023**, *88*, 13, 8882–8888. https://doi.org/10.1021/acs.joc.3c00664.

8. Praveen, K. V.; **Athira C. S**.; Mohan Banyangala.; Priya, S.; Sasidhar, B. S. A selective photoinduced radical O-alkenylation of phenols and naphthols with terminal alkynes. *Chem. Commun*., **2024**, *60*, 9813-9816. https://doi.org/10.1039/D4CC02555E.

9. **Athira, C. S**.; Basavaraja, D.; Siddalingeshwar, V. D.; Aiswarya Siby.; Sreelakshmi V.; Ancy A.; Sasidhar B. S. Spiro-Heterocycles: Recent Advances in Biological Applications and Synthetic Strategies. *Tetrahedron* **2025**, 134468. https://doi.org/https://doi.org/10.1016/j.tet.2025.134468.

10. **Athira, C. S**.; Sasidhar B. S. Tertiary Amine Mediated Reactions of Allenoates for the Synthesis of Carbocycles and Heterocycles. [Manuscript to be communicated]

11. Mohan, B.; **Athira, C. S**.; Sasidhar B. S. Synthesis of 3-Substituted 4-Hydroxy Quinolines and Quinoline-2,4-diones *via* House-Meinwald Rearrangement Reaction of Oxindoles: Consequences of Unusual Amide Carbonyl Migration. [Manuscript to be communicated]

CONTRIBUTIONS TO ACADEMIC CONFERENCES

1. **Athira, C. S.** International Conference on Drug Discovery held at BITS-Pilani K K Birla Goa Campus on 10th & 11th November 2022. [Participated]
2. **Athira, C. S.** National Seminar on Recent Trends in Disease Prevention and Health Management at CSIR-National Institute for Interdisciplinary Science and Technology, Thiruvananthapuram, Kerala, 14 & 15 December 2022. [Participated]
3. Chemistry of Allenoates: A Simple Precursor to Specialty Chemicals of Medicinal and Material Relevance. **Athira, C. S**.; Sasidhar B. S. **Oral presentation** at the National Thematic Conclave on "SPECIALTY CHEMICALS AND SUSTAINABLE PACKAGING" (Theme: Chemicals (Incl. Leather) and Petrochemicals) and Visit to R&D Facilities, organized by CSIR- National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram on July 19, 2024.

The tandem reactions of easily accessible allenoate and isatin mediated by cyclic amidines for the synthesis of functionalized spiro-oxetane oxindoles, 3- alkenyl-2-oxindoles and tricyclic pyridopyrimidines are reported herein. The reactions featured a broad substrate scope with good functional group tolerance under very mild reaction conditions. The products were obtained in a very short reaction time, at room temperature, without the use of metal catalyst, which offers an alternative way for the sustainable synthesis of functionalized molecules. The developed class of molecules represent promising candidates of medicinal as well as material relevance. The synthetic utility of the developed molecules is also demonstrated in this work.

Keywords: Allenoate, Isatin, DBU

References:

(1) Santhoshkumar, A. C.; Durugappa, B.; Doddamani, S. V; Siby, A.; Valmiki, P. K.; Somappa, S. B. Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines via Tandem Cyclization of Allenoates and Cyclic Amidines. *Org. Lett.* **2023**, *25* (42), 7711–7715.
(2) Durugappa, B.; C S, A.; Doddamani, S. V; Somappa, S. B. DBU-Catalyzed Diastereo/Regioselective Access to Highly Substituted Spiro-Oxetane Oxindoles via Ring Annulation of Isatins and Allenoates. *J. Org. Chem.* **2023**, *88* (13), 8882–8888.

4. Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines *via* Tandem Reaction of Allenoates and Cyclic Amidines. **Athira, C. S**.; Sasidhar B. S. **Oral presentation** at 36th Kerala Science Congress at Government College, Kasaragod, Kerala, 9-11, February 2024.

Background: Bicyclic amidines, DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which are "non-nucleophilic strong bases", are widely used in organic synthesis. Though often considered as hindered and non-nucleophilic strong bases, they nonetheless uphold nucleophilic behaviour which mediate organic reactions and may lead to the formation of compounds containing DBU and DBN scaffolds. So far, significant efforts have been devoted to the development of synthetic strategies which demonstrate the nucleophilic properties of these amidines. Among these, the synthesis of fused tricyclic pyridopyrimidines is currently attracting attention.

Method: Herein we report a 100% atom economic unprecedented novel annulation principle of allenoates and cyclic amidines that leads directly to the formation of pyridopyrimidines fused with functionalized heterocyclic systems; octahydro-6*H*,10*H*-pyrido[2',1':2,3]pyrimido[1,2-*a*]azepine and hexahydro-1*H*,5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*b*]pyrimidine. This approach for the first time exploits the reactivity of DBU and DBN with easily accessible allenoates for the synthesis of tricyclic pyridopyrimidine scaffolds.

Results: The reaction products were obtained within a minute, at room temperature, under neat conditions, averting aqueous workup, which meets the sustainability in organic synthesis (35 examples, 32 – 85% yields). We have also demonstrated the synthetic utility of the protocol by performing late-stage diversification of the obtained pyridopyrimidines into new molecular hybrids of pharmaceutical relevance.

Conclusions: In summary, an unprecedented 100% atom economic annulation of allenoates with cyclic amidines has been achieved for the synthesis of functionalized tricyclic pyridopyrimidine scaffolds. High reaction efficiency, ease of operation, very

short time, mild and solvent-free reaction conditions, with wide substrate scope are the key advantages of the present annulation protocol.

Keywords: Pyridopyrimidines, allenoates, cyclic amidines

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Diastereoselective Synthesis of Fused Tricyclic Pyridopyrimidines via Tandem Cyclization of Allenoates and Cyclic Amidines

Athira C. Santhoshkumar, Basavaraja Durugappa, Siddalingeshwar V. Doddamani, Aiswarya Siby, Praveen K. Valmiki, and Sasidhar B. Somappa*

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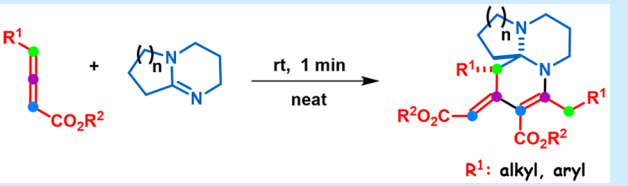
ABSTRACT: The tandem cyclization of easily accessible allenoates and cyclic amidines for the synthesis of functionalized tricyclic pyridopyrimidines is reported herein. The annulation featured a broad substrate scope with good functional group tolerance under very mild conditions (35 examples, 32−85% yields). The pyridopyrimidines were obtained in a very short reaction time (1 min), at room temperature, under neat conditions, which offers an alternative way to the sustainable synthesis of functionalized pyridopyrimidines. The scalability of the developed protocol is further demonstrated by a gram-scale synthesis.



Bicyclic amidines, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which are "non-nucleophilic strong bases", are widely used in organic synthesis.[1] Although often considered as hindered and non-nucleophilic strong bases, they nonetheless uphold nucleophilic behavior, which mediates organic reactions and may lead to the formation of compounds containing DBU and DBN scaffolds.[2] Thus far, significant efforts have been devoted to the development of synthetic strategies, which demonstrate the nucleophilic properties of these amidines.[3] Among these, the synthesis of fused tricyclic pyridopyrimidines is currently attracting attention.[4] These structures have gained significant pharmaceutical relevance, because they are present in compounds with antibacterial,[5] antipyretic,[6] antihistaminic,[7] and anti-inflammatory[8] profiles. Pyridopyrimidines are known to be potent inhibitors of dihydrofolate reductase,[9] cyclin-dependent kinase 4,[10] and tyrosine kinases of the epidermal growth factor receptor family.[11] The pyridopyrimidine core is found in the skeletons of many natural products (Figure 1).[12]

Hexahydropyrimidine derivatives are also reported to have diverse pharmacological activities.[13] Hexetidine, a hexahydropyrimidine-based drug molecule, has promising deodorant, anesthetic, and astringent effects.[14] N-Substituted hexahydropyrimidines constitute a key synthetic intermediate for a nitroimidazole−spermidine drug, which is used for the treatment of A549 lung carcinoma.[15] Recently, hexahydropyrimidines adorned with suitable substitutions were found to be potent inhibitors of the *Plasmodium falciparum* parasite in human blood and, thus, useful as pharmaceutical agents for the treatment of malaria.[16]

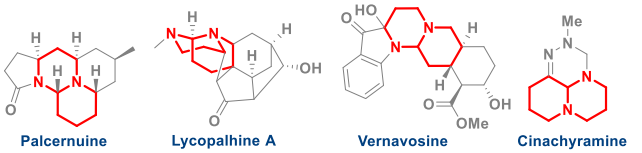


Figure 1. Natural products containing a pyridopyrimidine core.

Although the extensive medicinal significance is well-appreciated by pharmacologists, the construction of this fused tricyclic pyridopyrimidine has sporadically been explored. An effort was made in this direction recently, by Trofimov's group, wherein the annulation of DBU and DBN with propargylic alcohols bearing electron-withdrawing groups (−CN, −COPh, or $-CO_2Me$) led to functionalized oxazolopyrrolohexahydropyrimidine and oxazolohexahydropyrimidoazepine scaffolds, respectively (Scheme 1a).[17] In 2018, Muller's group reported the synthesis of tricyclic 2-amino pyridinium salts via a (3 + 3) annulation of alkynones and cyclic amidines (Scheme 1b).[18] A formal [4 + 2]-cycloaddition of ynones with cyclic amidines was reported for the construction of highly functionalized tricyclic azepines by Ramachary's group in 2020 (Scheme 1c).[19]

In view of these exciting observations and in continuation to our recent efforts in the construction of new heterocyclic hybrids,[20] herein, we report a 100% atom economic unprecedented novel annulation principle of allenoates[21] and cyclic amidines that leads directly to the formation of pyridopyrimidines fused with functionalized heterocyclic

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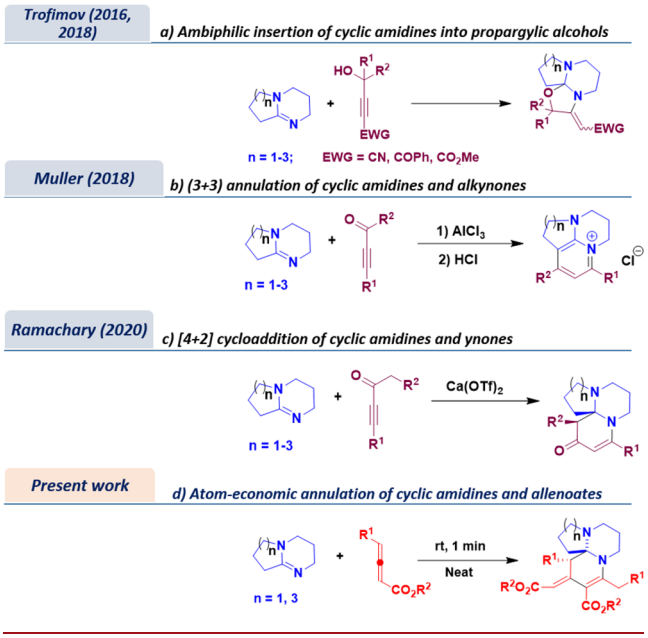
Scheme 1. Reaction Designs for the Synthesis of Tricyclic Pyridopyrimidines

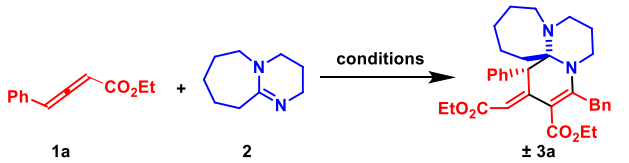


systems: octahydro-6*H*,10*H*-pyrido[2′,1′:2,3]pyrimido[1,2-*a*]-azepine and hexahydro-1*H*,5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*b*]-pyrimidine (Scheme 1d). The reaction products were obtained within 1 min, at room temperature, under neat conditions, averting aqueous workup, which meets the sustainability in organic synthesis. This approach for the first time exploits the reactivity of DBU and DBN with easily accessible allenoates for the synthesis of tricyclic pyridopyrimidine scaffolds. Such unusual reactivity is the outcome of the fact that, following the Michael addition by N-8 of DBU (N-6 of DBN) on allenoates, the resulting zwitterion can be neutralized by either proton loss from C-6 of DBU (C-4 of DBN) or the nucleophilic attack on iminium carbon. These stabilization pathways impart nucleophilic behavior on cyclic amidines and eventually lead to their incorporation into allenoates.

Upon employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in consecutive transformations of allenoates,[22] we serendipitously discovered an interesting product, which prompted us to investigate the reaction in more detail. We commenced our study by reacting 1.0 equiv of ethyl 4-phenylbuta-2,3-dienoate **1a** (0.26 mmol) and 1.0 equiv of DBU **2** at room temperature in acetonitrile. To our delight, the (*E*) isomer of product **3a** was obtained as the sole product with a 30% yield within 1.0 h (entry 1 in Table 1). This diastereoselectivity can be rationalized by assuming that the zwitterion intermediate **A** is approaching from the less hindered side of the allenoate to reduce the steric hindrance caused by the proximity between two ester groups, favoring the (*E*) isomer (Scheme 4). Its molecular structure and relative stereochemistry were established by nuclear magnetic resonance (NMR) and high-resolution mass spectrometry (HRMS) and further confirmed via single-crystal X-ray analysis of product **3a** (Supporting Information).

The reaction parameters were then screened to improve the yield and overall process; the results are summarized in Table 1. First, we tuned the stoichiometric ratio of substrates; an attempt to improve the yield by increasing the equiv of compound **2** to 2.0 was successful, resulting in a 50% yield of

Table 1. Optimization of the Reaction[a]



entry	2 (equiv)	solvent	temperature (°C)	time	yield (%)[b]
1	1.0	acetonitrile	rt	1 h	30
2	2.0	acetonitrile	rt	1 h	50
3	3.0	acetonitrile	rt	1 h	50
4	2.0	acetonitrile	rt	1 min	50
5	2.0	acetonitrile	0−5	1 min	48
6	2.0	acetonitrile	50	1 min	45
7	2.0	THF	rt	1 min	45
8	2.0	DMF	rt	1 min	57
9	2.0	DMSO	rt	1 min	trace
10	2.0	ethanol	rt	1 min	ND
11	2.0	ethyl acetate	rt	1 min	ND
12	2.0	1,4-dioxane	rt	1 min	51
13	2.0	toluene	rt	1 min	55
14	2.0	ether	rt	1 min	58
15	2.0	chloroform	rt	1 min	48
16	2.0	DCE	rt	1 min	82
17	2.0	DCM	rt	1 min	73
18	2.0	neat	rt	1 min	82

[a]All of the reactions were conducted with 1.0 equiv of compound **1a** (0.26 mmol) in solvent (2 mL). [b]Yield of isolated product.

product **3a** (entry 2 in Table 1). Hence, the formation of product **3a** might be attributable to the dual character of DBU **2** as a base and nucleophile. Next, an increase in the amount of DBU loading from 2.0 equiv did not show any increase in yield (entry 3 in Table 1). Gratifyingly, evaluation of the reaction time demonstrated that the product is formed in a time span of 1 min with the same yield of 50% (entry 4 in Table 1). Further assessment of the variation of the reaction temperature lowered the yields, which confirmed that room temperature is more favorable for the reaction (entries 5 and 6 in Table 1). An extensive solvent screening was then carried out (entries 7−17 in Table 1). To begin, polar aprotic solvents, like tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF), furnished product **3a** in moderate yields of 45 and 57%, respectively (entries 7 and 8 in Table 1); dimethyl sulfoxide (DMSO) furnished product **3a** in a poor yield (entry 9 in Table 1); and no reaction was observed in ethanol and ethyl acetate (entries 10 and 11 in Table 1) even after extending the reaction time to 1−2 h. These observations directed our investigation toward nonpolar aprotic solvents, like 1,4-dioxane, toluene, ether, chloroform, 1,2-dichloroethane (DCE), and dichloromethane (DCM), which resulted in product **3a** in 51, 55, 58, 48, 82, and 73%, respectively (entries 12−17 in Table 1), indicating DCE as the most suitable solvent for the desired transformation.

Finally, we were pleased to observe that the highest yield of 82% could also be achieved under a solvent-free condition (entry 18 in Table 1). On the basis of these experimental results, the best reaction condition was confirmed to be 1.0 equiv of allenoate and 2.0 equiv of DBU under neat conditions at room temperature for 1 min.

With the optimal reaction conditions in hand, we next investigated the scope of the reaction for various substituted

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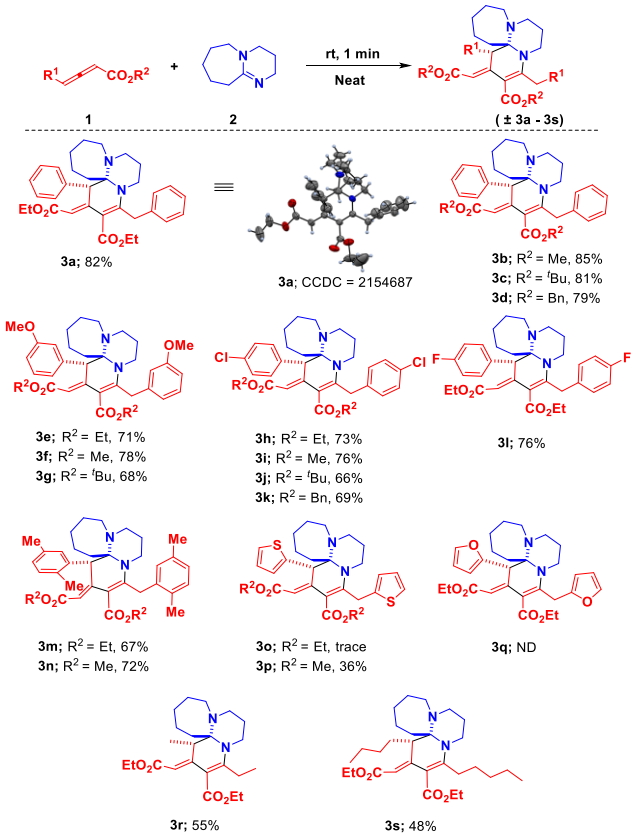
allenoates (Scheme 2). In all of the experiments, the reaction proceeded smoothly and furnished the anticipated products in

Scheme 2. Substrate Scope of Allenoates with DBU

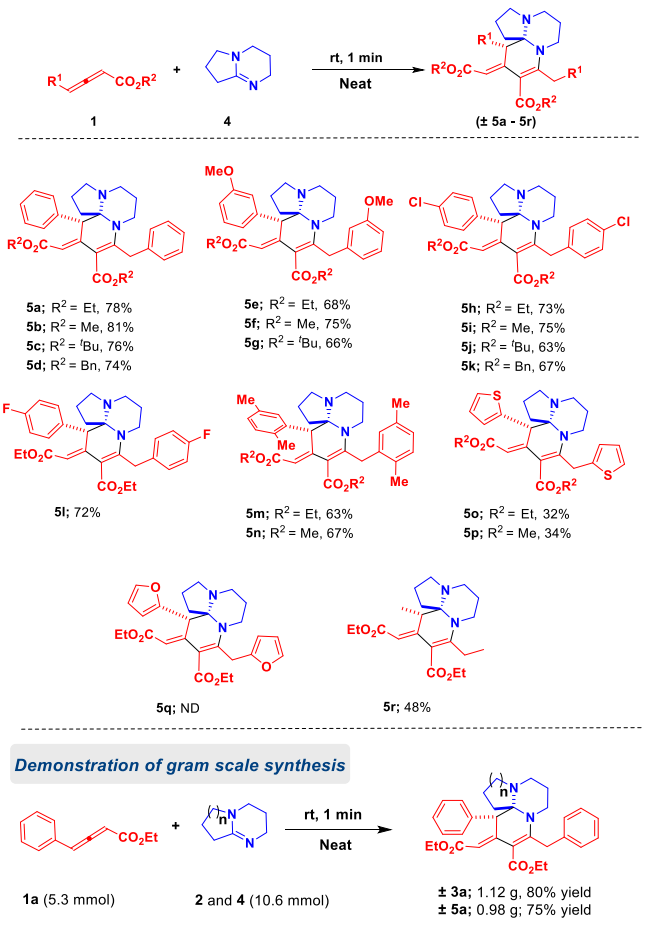


moderate to good yields. However, the highest yield of 85% was noticed for compound **3b**. Moreover, it was found that allenoates having smaller ester substituents, such as $-CO_2Me$ and $-CO_2Et$, attributed a comparatively higher yield than bulkier $-CO_2Bn$ and $-CO_2{}^tBu$ groups. The yields seem to decrease slightly with the introduction of substituents on allenoate. Thienyl allenoates resulted in comparatively lower yields (**3o** and **3p**). Furthermore, furyl allenoate failed to furnish the product (**3q**), which is probably due to the decreased resonance stabilization of zwitterionic intermediate **A** by the heteroaromatic ring (Scheme 4). The alkyl derivatives ethyl penta-2,3-dienoate and ethyl octa-2,3-dienoate also furnished the corresponding products **3r** and **3s** in 55 and 48% yield, respectively.

The scope of the protocol was further expanded by utilizing 1,5-diazabicyclo[4.3.0]non-5-ene amidine base (DBN) **4** in reaction with a handful of allenoates delivering the products **5a**−**5r** in satisfying yields (Scheme 3). The highest yield of 81% was observed for compound **5b**. Allenoates with smaller ester substituents, such as $-CO_2Me$ and $-CO_2Et$, resulted in comparatively higher yields than bulkier $-CO_2Bn$ and $-CO_2{}^tBu$ groups. Moreover, the yields decreased slightly with the substitutions on allenoates, similar to the trend followed with DBU. With DBN, thiophenyl allenoates resulted in comparatively lower yields (**5o** and **5p**). Furyl allenoate did not furnish the product (**5q**). The alkyl derivative ethyl penta-2,3-dienoate afforded the product **5r** in 48% yield.

The protocol is also executed on a gram scale by utilizing 5.3 mmol of ethyl 4-phenylbuta-2,3-dienoate **1a**, 10.6 mmol of

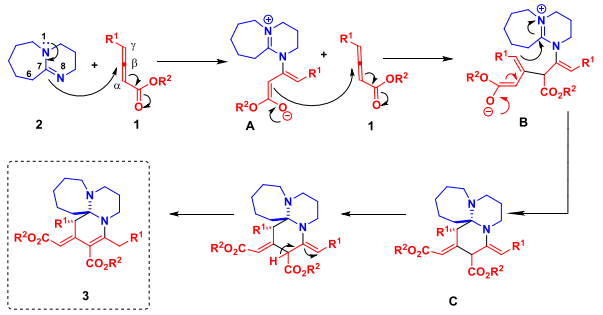
Scheme 3. Substrate Scope of Allenoates with DBN



DBU **2**, and 10.6 mmol of DBN **4**, affording the corresponding product **3a** with 80% isolated yield and product **5a** with 75% isolated yield (Scheme 3). This signifies the efficiency and practical applicability of the developed annulation protocol.

Taking cognizance of the crystal structure of product **3a** and the previously reported mechanisms,[2a,4a,19] we have proposed the plausible mechanistic pathway for the formation of fused tricyclic pyridopyrimidines as depicted in Scheme 4. The

Scheme 4. Proposed Mechanism



reaction seems to proceed via the initial nucleophilic addition of DBU **2** at the β position of allenoate **1**, forming stabilized β-ammonium enolate **A**. β-Ammonium enolate **A** thus formed can easily add to another molecule of allenoate, resulting in intermediate **B**, which upon intramolecular cyclization followed by isomerization furnishes the final conjugated ene system **3**.

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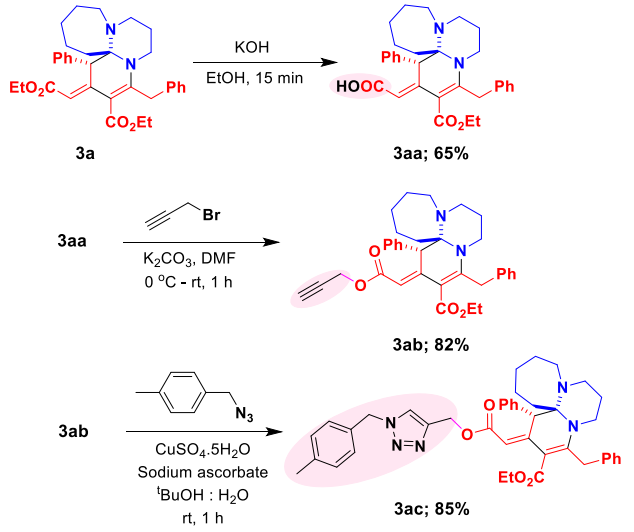
In addition, we have demonstrated the late-stage diversification of obtained tricyclic pyridopyrimidines (**3a**; Scheme 5).

Scheme 5. Late-Stage Diversification of Tricyclic Pyridopyrimidines



We successfully attempted the synthesis of biologically relevant triazole **3ac** via Click reaction, utilizing compound **3ab**, which is obtained by the propargylation of compound **3aa**, the acid hydrolyzed product of product **3a** (Scheme 5). The pyridopyrimidine derivatives **3aa** and **3ab** with the free reactive acid and propargyl group, respectively, could generate a lot of interest among synthetic and medicinal chemists for further modifications in generating pyridopyrimidine hybrids of medicinal relevance.

In summary, an unprecedented 100% atom economic annulation of allenoates with cyclic amidines has been achieved for the synthesis of functionalized tricyclic pyridopyrimidine scaffolds. High reaction efficiency, ease of operation, very short time, mild and solvent-free reaction conditions, and wide substrate scope are the key advantages of the present annulation protocol. It is the first approach that exploits the reactivity of allenoates for constructing the structurally diverse motifs of tricyclic pyridopyrimidines.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03053.

Details of experimental procedures and spectroscopic data for the products, NMR spectral data, and single-crystal X-ray data of compound **3a** (PDF)

Accession Codes

CCDC 2154687 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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DEDICATION

Dedicated to Prof. G Vijay Nair on the occasion of his 83rd birthday.

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TBD-Mediated Diastereoselective Access to Functionalized 3-Alkenyl-2-oxindoles via the Tandem Reaction of Isatins and Allenoates

Athira C. Santhoshkumar, Basavaraja Durugappa, Geethu Venugopal, Mohan Banyangala, Ajay Krishna M. S, and Sasidhar B. Somappa*

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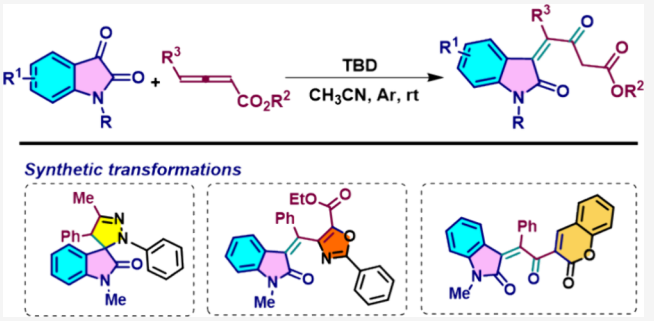
ABSTRACT: The 1,5,7-triazabicyclo[4.4.0]dec-5-ene−mediated tandem reaction of easily accessible isatins and allenoates to functionalized 3-alkenyl-2-oxindoles is disclosed. The reaction allows the synthesis of a wide range of 3-alkenyl-2-oxindoles in good yields with excellent functional group tolerance under mild reaction conditions (32 examples, up to 84% yields). The current strategy will provide a novel path for the sustainable synthesis of functionalized 3-alkenyl-2-oxindole derivatives. We have also demonstrated the significance of 3-alkenyl-2-oxindoles as key starting materials (KSMs) via their synthetic utility in producing oxindole-appended pyrazole, oxazole, and coumarin hybrids of medicinal relevance.



INTRODUCTION

3-Alkenyloxindoles are privileged frameworks that are present in a wide spectrum of biologically active candidates of synthetic and natural origin.[1] For instance, the FDA has approved Sunitinib (Sutent), a 3-alkenyl-2-oxindole derivative, as a multitargeted tyrosine kinase inhibitor for the treatment of advanced renal cell carcinoma and gastrointestinal cancer.[2] Soulieotine, extracted from *Souliea vaginata*, is utilized as an anti-inflammatory agent in traditional Chinese medicine.[3] The natural 3-alkenyloxindole derivative Indirubin has shown potent CDK inhibition.[4] Nintedanib is a clinically approved drug for the treatment of adenocarcinoma[5] (Figure 1).

Furthermore, the synthesis of natural products[6] including TMC-95[7] and Maremycins A[8] as well as several spirocyclic oxindoles[9] utilizes 3-alkenyl oxindoles as a versatile precursor. Owing to the diverse medicinal relevance and synthetic pertinence of 3-alkenyl-2-oxindole skeletons, the development of facile and novel routes for their synthesis has drawn considerable interest from chemists. Consequently, quite a few protocols have been developed. The target molecules are typically accessed via one of two approaches: (1) condensation reaction between preformed oxindole[10] (e.g., aldol condensations of unsubstituted oxindoles and Wittig-type reactions of isatins) (Scheme 1a); (2) tandem/telescoped routes utilizing anilines/*N*-substituted aniline, including carbonylative annulation of preformed aryl-alkynes,[11] arene−alkyne cyclization of arylpropionamides,[12] arene−alkene cyclization of *N*-acryloyl anilines,[13] Horner-Wadsworth-Emmons (HWE) strategy[14] and difluorocarbene enabled synthesis from *ortho*-amino aryl alkynone[15] (Scheme 1b). Despite of these advancements, many of these strategies have numerous shortcomings concerning the usage of extra carbonyl sources, expensive metal catalysts, and reagents and often result in 3-alkenyl-oxindoles as *E*/*Z*-mixtures. Therefore, the search for the development of new simple and reliable protocols from readily accessible starting materials to a series of structurally diverse 3-alkenyl-oxindoles is most valuable and appealing. Therefore, in continuation to our devoted efforts toward the novel routes,[16] herein, we report a tandem reaction between isatin and allenoates that leads to the diastereoselective synthesis of 3-alkenyl-2-oxindole functionalized with β-keto ester. For the first time, this approach harnesses the reactivity of isatins and allenoates to synthesize 3-alkenyl-2-oxindoles.

RESULTS AND DISCUSSION

Very recently our group devised an effective approach for the diastereo-/regiospecific synthesis of highly substituted spiro-oxetane oxindoles via DBU-catalyzed spiro annulation of isatins and aryl-allenoates (Scheme 1c left).[17] During the optimization studies of spiro-oxetane, we came across a serendipitous

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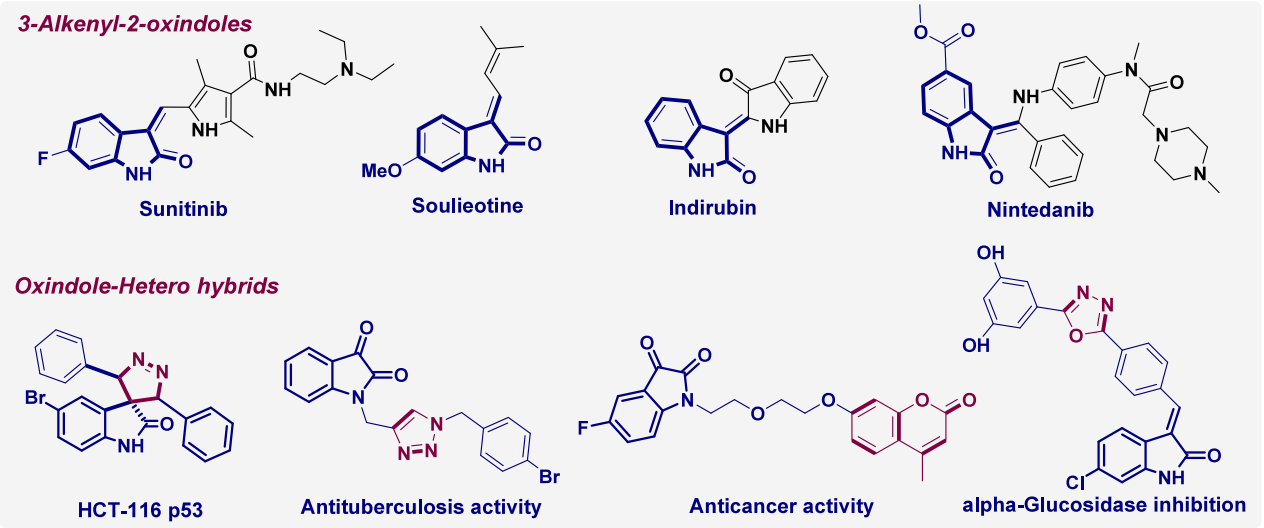
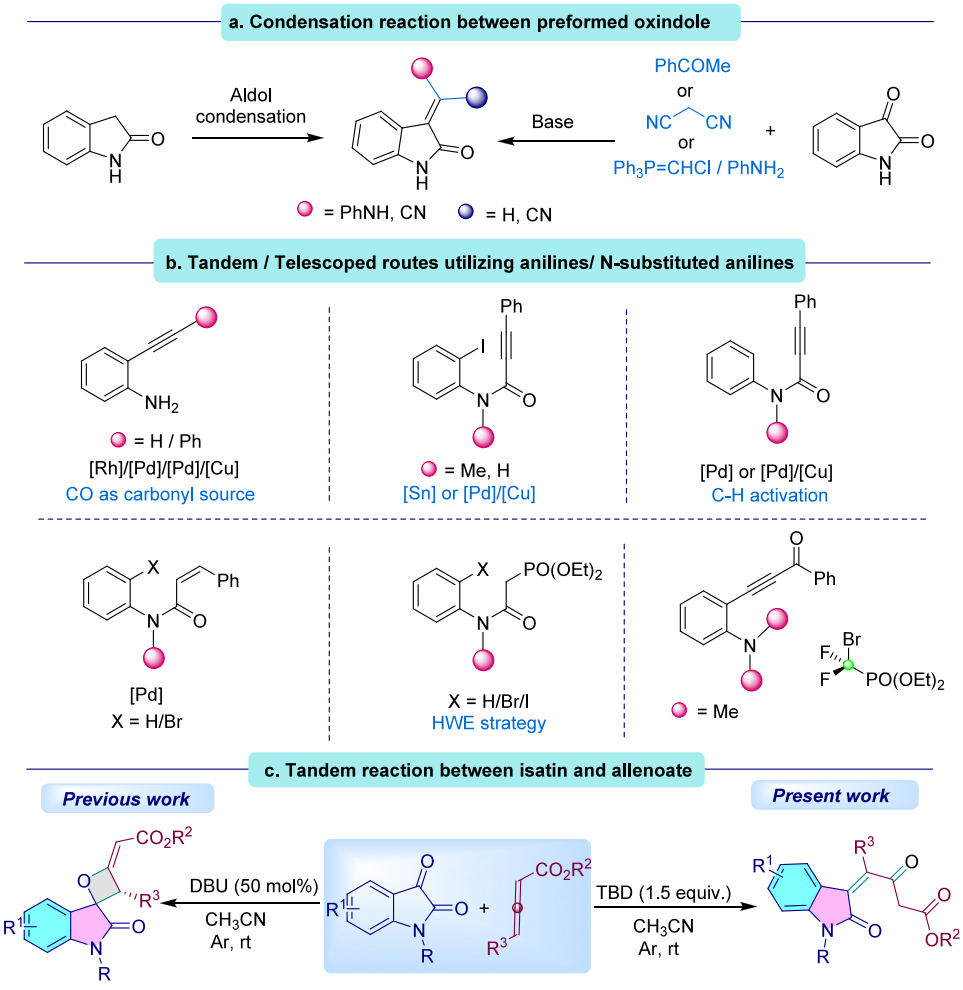


Figure 1. Representative biologically active compounds encompassing the oxindole skeleton.

Scheme 1. Reaction Strategies Toward 3-Alkenyl-2-oxindoles



observation. When the DBU loading was increased to 1.5 equiv., the TLC revealed a new product with a slight variation in retention factor (R_f) value.

This observation prompted us to study the reaction in more detail. The newly formed product was purified and characterized as ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate, **3a** via Nuclear Magnetic Resonance (NMR) and High-Resolution Mass (HRM) spectrometry. The single-crystal X-ray analysis of one of the derivatives, **3ad** provided further confirmation of the relative stereochemistry (Supporting Information).

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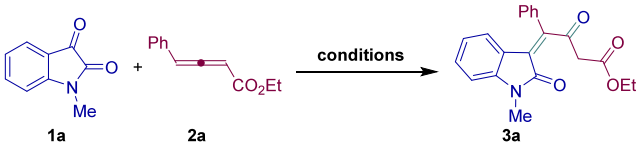
We started the investigation by reacting 1.0 equiv of *N*-methyl isatin **1a** (0.31 mmol) with 1.0 equiv of ethyl 4-phenylbuta-2,3-dienoate **2a** in the presence of 1.0 equiv of DBU in acetonitrile at room temperature under the Ar atmosphere for 1 h (Table 1, entry 1). To our delight, a single isomer of the anticipated product ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (**3a**), was obtained in 32% yield. Here the greater 1,3-allylic strain in the (*E*)-isomer will favor the formation of the (*Z*)-product over (*E*)-product, thus rationalizing the diastereoselectivity.[17,18]

Table 1. Optimization of the Reaction[a]



1a **2a** **3a**

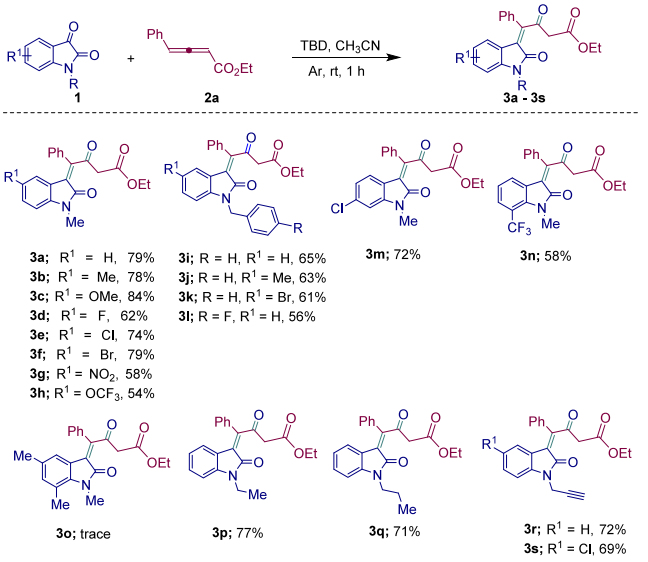
entry	**2a** (in eq.)	base (in eq.)	solvent	temp (°C)	time (h)	yield (%)[b]
1	1	DBU (1.0)	Acetonitrile	rt	1	32
2	1.5	DBU (1.0)	Acetonitrile	rt	1	45
3	2	DBU (1.0)	Acetonitrile	rt	1	36
4	1.5	DBU (1.2)	Acetonitrile	rt	1	54
5	1.5	DBU (1.5)	Acetonitrile	rt	1	62
6	1.5	DBU (2.0)	Acetonitrile	rt	1	56
7	1.5	DBU (1.5)	Acetonitrile	0 - 5	1	42
8	1.5	DBU (1.5)	Acetonitrile	50	1	18
9	1.5	DBU (1.5)	Acetonitrile	rt	0.5	38
10	1.5	DBU (1.5)	Acetonitrile	rt	2	57
11	1.5	DBU (1.5)	EtOH	rt	1	19
12	1.5	DBU (1.5)	DMF	rt	1	ND
13	1.5	DBU (1.5)	DCM	rt	1	trace
14	1.5	DBU (1.5)	Acetone	rt	1	trace
15	1.5	DBU (1.5)	Toluene	rt	1	ND
16	1.5	TBD (1.5)	Acetonitrile	rt	1	79
17	1.5	TBD (2.0)	Acetonitrile	rt	1	71
18	1.5	DBN (1.5)	Acetonitrile	rt	1	32
19	1.5	DABCO (1.5)	Acetonitrile	rt	1	trace
20	1.5	DMAP (1.5)	Acetonitrile	rt	1	trace
21	1.5	Et_3N (1.5)	Acetonitrile	rt	1	trace
22	1.5	PPh_3 (1.5)	Acetonitrile	rt	1	trace

[a]All the reactions were carried out with **1a** (0.31 mmol, 1.0 equiv) in solvent (2 mL) under the Ar atmosphere. [b]Yield of the isolated product. ND: Not detected.

The reaction parameters were then tuned in order to further enhance the yield of the process (Table 1). First, we screened the stoichiometric amount of the substrates (Table 1, entries 1−3); 1.0 equiv of *N*-methyl isatin **1a** and 1.5 equiv of 3-ethyl 4-phenylbuta-2,3-dienoate **2a** furnished 45% yield of **3a** (Table 1, entry 2). Further increase in the equiv of allenoate **2a** yielded unsatisfactory outcomes (Table 1, entry 3). To further enhance the yields, the loading of the base was carefully tested (Table 1, entries 4−6). Interestingly, an increased yield of 62% was obtained by the loading of 1.5 equiv of DBU. (Table 1, entry 5). Further assessment of reaction temperature lowered the yields, confirming that the reaction is more favorable at room temperature. (Table 1, entries 7, 8). The screening of the reaction time between 0.5 and 2 h did not give any positive results (Table 1, entries 9, 10). Then we screened various solvents (Table 1, entries 11−15), and found that acetonitrile was still the most effective one. In addition, we investigated the effect of several bases including TBD, DBN, DABCO, DMAP, Et_3N, and PPh_3 (Table 1, entries 16−22), which revealed that the TBD was the optimal candidate for conducting the reaction. Therefore, the optimized reaction condition identified was: 1.0 equiv of *N*-methyl isatin (**1a**), 1.5 equiv of allenoate (**2a**) and 1.5 equiv of TBD in acetonitrile at room temperature under the Ar atmosphere for 1 h (Table 1, entry 16).

After determining the optimal reaction conditions, we systematically examined the generality of the reaction. At the outset, we explored an array of isatins having various *N*-substituents, electron-releasing and electron-withdrawing groups, with aryl allenoate **2a** to generate the corresponding 3-alkenyl-2-oxindole **3** (Scheme 2). The substitution effect on isatin skeleton exhibited excellent functional group tolerance. The isatins with electron-donating substituents such as −Me and −OMe were successfully converted to the corresponding products (**3b**, **3c**) with yields of 78 and 84%, respectively. However, 5,7-dimethyl substituted isatin provided product **3o** only in the trace. The isatins with halo substituents like -F, -Cl, and -Br were also compatible with the reaction system to produce the desired products (**3d**−**3f**, **3m**) in good yields (62−79%), indicating that they can be used as a handle for further synthetic transformations. In addition, isatin with electron-withdrawing groups such as $-NO_2$, $-OCF_3$, $-CF_3$, tolerated well, leading to the expected products (**3g**, **3h**, **3n**) in satisfying yields (54−58%). To our delight, the reaction proceeded well on isatins with bulky *N*-substitutions such as ethyl, propyl, benzyl, and propargyl groups, yielding the targeted products (**3i**−**3l**, **3p**−**3s**) in 56−77% yields.

Scheme 2. Scope of the Reaction with Various Isatins



The scope of the protocol was subsequently extended by employing diverse aryl allenoates **2** (Scheme 3). The results indicated that aryl allenoates with different substituents on the phenyl ring as well as various ester substituents efficiently underwent reaction with *N*-methyl isatin (**1a**) and its derivatives furnishing the respective products in moderate to good yields. Nonetheless, the aryl allenoates with smaller ester groups such as $-CO_2Me$ (Scheme 3, 47−84%) exhibited higher yields compared to the bulkier $-CO_2Bn$ (Scheme 3, 52−64%) and $-CO_2{}^tBu$ (Scheme 3, 53−67%). The γ-thiophene allenoate

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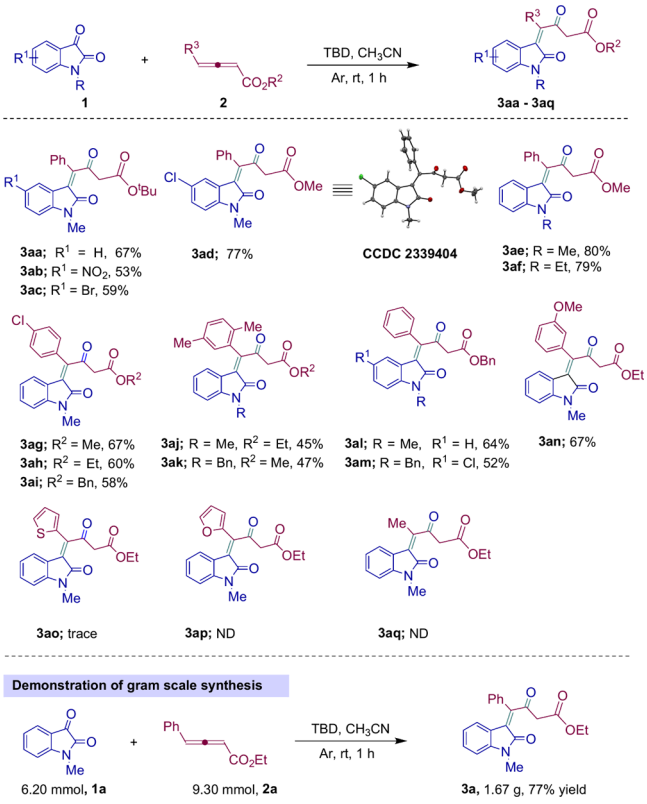
Scheme 3. Scope of the Reaction with Various Aryl Allenoates



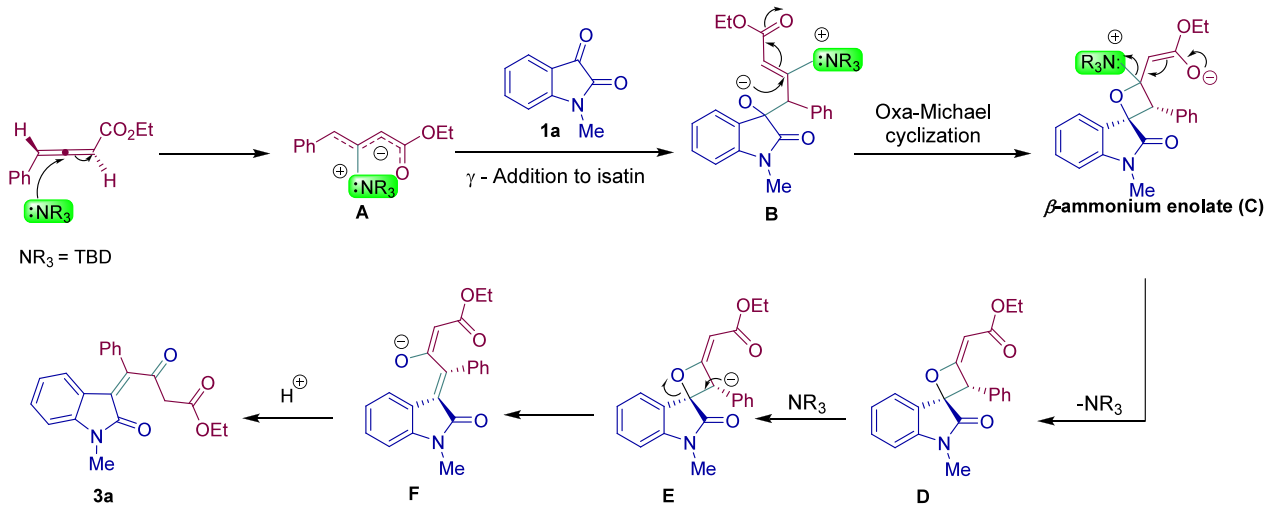
resulted in the product only in trace (**3ao**). Furthermore, the furyl allenoate failed to yield the product (**3ap**), probably because the heteroaromatic ring reduced the resonance stabilization of the zwitterionic intermediate **A**. The 3-methyl allenoate also was unsuccessful in delivering the product **3aq**.

To prove the efficiency and practicability of the developed protocol, we performed a gram-scale reaction by utilizing 6.20 mmol of *N*-methyl isatin **1a** and 9.30 mmol of ethyl 4-phenylbuta-2,3-dienoate **2a**, which affords the corresponding product **3a** with 77% yield (1.67 g) (Scheme 3).

Based upon the above results and literature precedents,[17,19] a plausible mechanism for the synthesis of 3-alkenyl-2-oxindole is proposed in Scheme 4. The first step involves the attack of the Lewis base (NR_3) at the β-carbon of γ-aryl allenoate generating a zwitterionic intermediate **A**. The generated zwitterion **A** then undergoes γ-addition to *N*-protected isatin **1** resulting in intermediate **B**. The subsequent oxa-Michael cyclization of intermediate **B** generates β-ammonium intermediate **C**. This follows the removal of the Lewis base catalyst, which delivers spiro-oxetane oxindole **D**. Later on, the presence of an excess of Lewis base causes **D** to undergo ring cleavage at the C−O bond, resulting in intermediate **E**. The intermediate **E** is thereafter isomerized to the stable acyclic product, β- keto ester **3a**.

The significance of β-dicarbonyl compounds as an important precursor employed in synthetic organic chemistry cannot be overstated. 1,3-dicarbonyls are frequently used as versatile synthons in multistep and complex chemical synthesis to construct a broad diversity of heterocycles.[20] Furthermore, heterocyclic analogues of oxindoles have revealed a fascinating array of pharmacological activities viz. anti-HIV, anti-TB, antibacterial, anticonvulsant, anticancer, anti-inflammatory, and antidiabetic properties[21] (Figure 1). In this assessment, we decided to explore the synthetic utility of the obtained 3-alkenyl-2-oxindoles **3** to transform them into novel heterocyclic compounds (Scheme 5). First, we successfully synthesized the biologically significant dihydrospiro[indoline-3,3′-pyrazol]-2-one (**3ba**), by reacting ethyl (*Z*)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxo-4-phenylbutanoate (**3a**) with phenylhydrazine in ethanol under reflux temperature affording **3ba** in 82% yield. When the 3-alkenyl-2-oxindoles (**3a**) are treated with benzylamine under an I_2/DMSO mediated reaction afforded the 2-oxoindolinylidene oxazole-carboxylate (**3bb**) in 55% yield. Furthermore, 2-oxo-2H-chromen-3-yl-phenylethylidene indolin-2-one (**3bc**) was obtained from 3-alkenyl-2-oxindoles (**3a**) by reacting with salicylaldehyde in ethanol under basic media in a 78% yield. In addition, we could also demonstrate the synthetic applicability of **3r**, which underwent Click reaction affording oxindole appended triazole (**3rr**) in 87% yield. Hence, the established synthetic transformations further signify the importance of 3-alkenyl-2-oxindoles and the protocol reporting herein.

Scheme 4. Proposed Mechanistic Pathway



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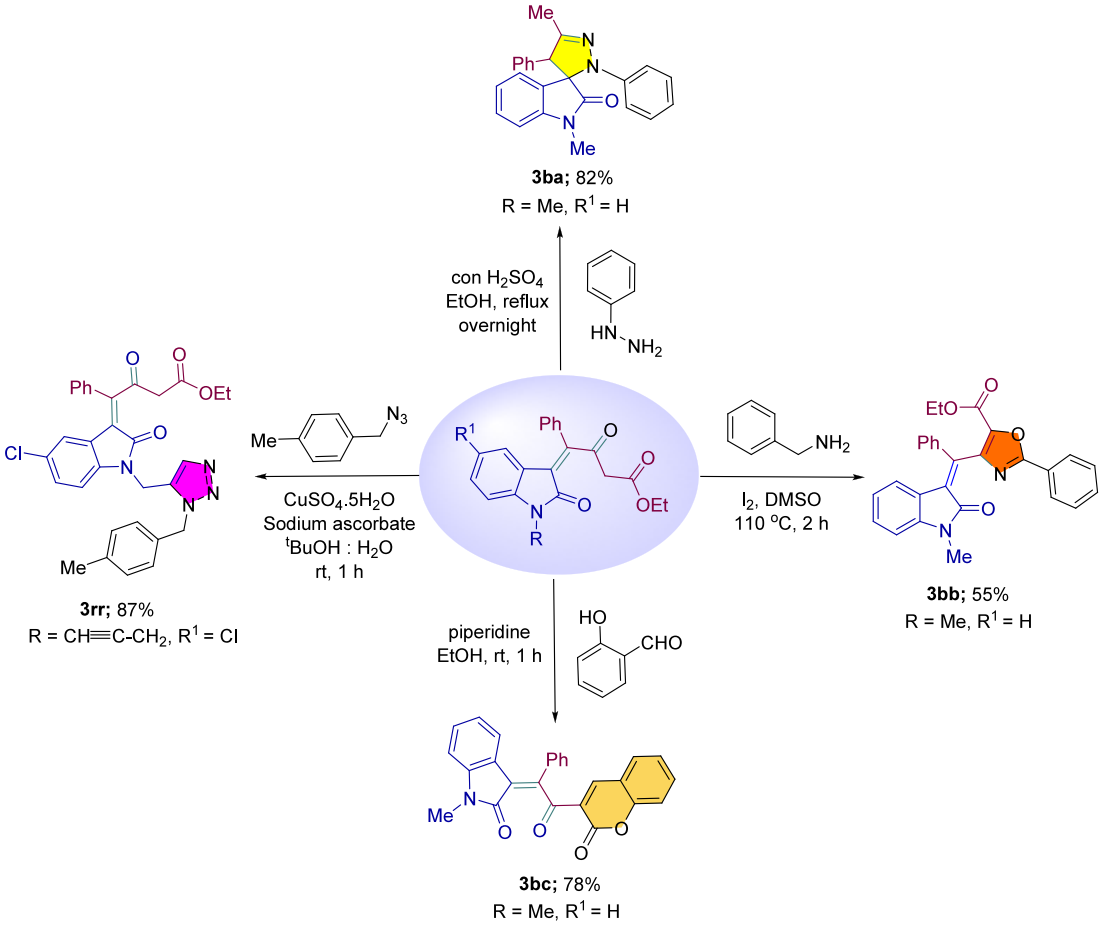
Scheme 5. Synthetic Utility of 3-Alkenyl-2-oxindoles



CONCLUSIONS

In conclusion, we have established an effective approach to the stereoselective synthesis of functionalized 3-alkenyl-2-oxindoles by the TBD-mediated tandem reaction of isatins and aryl-allenoates. This protocol employs widely accessible substrates, viz. isatins and aryl-allenoates that gave the corresponding products in substantial yields under mild reaction conditions with wide substrate scope and high functional group tolerance. Furthermore, it is the first protocol to utilize allenoate reactivity to build structurally varied 3-alkenyl-2-oxindole motifs. Additionally, this approach enables us to reduce the synthesis path that previously demanded multiple steps into a single one. We have also demonstrated the synthetic utility of 3-alkenyl-2-oxindoles to convert them into novel oxindole-appended heterocyclic scaffolds. Hence, we believe that the obtained 3-alkenyl-2-oxindoles might draw the attention of synthetic and medicinal chemists for the rapid and efficient syntheses of hitherto unattainable highly functionalized target molecules for therapeutic uses.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01427.

Details of experimental procedures and spectroscopic data for the products, NMR spectral data, and single-crystal X-ray data of compound **3ad** (CCDC 2339404)(PDF)

Accession Codes

CCDC 2339404 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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