Transition Metal Free Transformations of α,β-Unsaturated Ketones to Heterocycles of Medicinal Relevance

By

Ashitha K. T.

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Under the supervision of
Dr. Sasidhar B. S.

CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)
Thiruvananthapuram-695019

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC Campus
Sector 19, Kamla Nehru Nagar,
Ghaziabad, U.P.-201 002, India

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…..To My Parents and Teachers

CSIR-NATIONAL INSTITUTE FOR INTERDISCIPLINARY SCIENCE AND TECHNOLOGY (NIIST)

Council of Scientific & Industrial Research (CSIR), Govt. of India

Dr. Sasidhar B. S. *FICS*
Principal Scientist,
Organic Chemistry Section
Chemical Sciences and Technology Division

E mail: drsasidharbs@gmail.com
drsasidharbs@niist.res.in
Telephone: 09497260897 (Mob)
0471 2515416 (Off); Fax: +91 2491712

28 July 2022
Thiruvananthapuram

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled, "***Transition Metal Free Transformations of α,β-Unsaturated Ketones to Heterocycles of Medicinal Relevance***", submitted by ***Ms. Ashitha K. T.*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the ***Degree of Doctor of Philosophy in Sciences***, 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 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.

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Ashitha K. T.

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ABBREVIATIONS

Å	:	Angstrom
Ac	:	Acetyl
AcOH	:	Acetic acid
AcOI	:	Acetyl hypoiodite
Ar	:	Argon
Ar-	:	Aryl
Bn	:	Benzyl
BoC	:	*tert*-Butyloxycarbonyl
Calcd	:	Calculated
CCDC	:	Cambridge crystallographic data centre
CNTs	:	Carbon nanotubes
DABCO	:	1,4-Diazabicyclo[2.2.2]octane
DBN	:	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	:	Dichlorobenzene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
d	:	Doublet
dd	:	Doublet of doublets
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMA	:	*N*,*N*-Dimethylacetamide
DMAP	:	*N*,*N*-Dimethylpyridine-4-amine
DMF	:	*N*,*N*-Dimethylformamide
DMS	:	Dimethyl sulfide
DMSO	:	Dimethyl sulfoxide
dr	:	Diastereomeric ratio
dt	:	Doublet of triplets
ee	:	Enantiomeric excess

equiv	:	Equivalent
er	:	Enantiomeric ratio
ESI	:	Electron spray ionization
Et	:	Ethyl
Et_3N	:	Triethylamine
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
FT-IR	:	Fourier transform infrared spectroscopy
GO	:	Graphene oxide
h	:	Hour
HI	:	Hydroiodic acid
HRMS	:	High resolution mass spectrometry
Hz	:	Hertz
IPA	:	Isopropyl alcohol
J	:	Coupling constant
m	:	Multiplet
m	:	Meta
MCR	:	Multicomponent reaction
Me	:	Methyl
MeOH	:	Methanol
mg	:	Milligram
MHz	:	Mega hertz
min	:	Minutes
mL	:	Millilitre
mmol	:	Millimolar
mol%	:	Mole percent
MP	:	Melting point
MS	:	Molecular sieves
MW	:	Microwave
ND	:	Not detected
NHC	:	*N*-heterocyclic carbene

NIS	:	*N*-iodosuccinimide
NMM	:	*N*-methyl morpholine
NMR	:	Nuclear magnetic resonance
o	:	Ortho
p	:	Para
PET	:	Positron emission tomography
Ph	:	Phenyl
PIDA	:	Phenyliodine(III)diacetate
PNBA	:	*p*-Nitrobenzoic acid
PTSA	:	*p*-Toluenesulfonic acid
q	:	Quartet
rt	:	Room temperature
s	:	Singlet
t	:	Triplet
TBAI	:	Tetra-n-butylammonium iodide
TBHP	:	*tert*- Butyl hyrdoperoxide
tert	:	Tertiary
TfOH	:	Trifluoromethanesulfonic acid
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TMG	:	Tetramethylguanidine
TMEDA	:	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	:	Tetramethylsilane
Tol	:	Tolyl
Ts	:	Tosyl
δ	:	NMR chemical shift in parts per million

PREFACE

The word ‘Heterocycle’ is one of the most significant term that we come across in organic chemistry. It represents one of the largest classes of molecules that play undeniable role in the substance of life. Heterocycles have innumerable applications that are necessary for the smooth functioning of human society. Chief among them is the medicinal aspects. Numerous heterocyclic entities are endowed with broad spectrum of bioactivities that are beneficial in the development of pharmaceuticals. Hence development of new synthetic protocols to construct heterocyclic molecules is an ever expanding area of interest. So far a plethora of methods have been devised to synthesise diverse heterocyclic scaffolds. Among them transition metal catalyzed reaction have contributed to a large extent. Despite being a powerful synthetic tool, the inherent toxicity, requirement of drastic reaction conditions and the high cost of transition metal catalysts are topics of major concern. As a result, nowadays transition metal-free reactions are gaining more prominence over the transition metal catalyzed ones.

One of the challenges in organic synthesis is to develop reactions that makes use of easily accessible simple precursors. In this regard *α,β*-unsaturated ketones are valuable substrates. Molecules belonging to this class possess multiple reaction sites, including both electrophilic and nucleophilic centers. One of the prominent enone used as a valuable substrate in the synthesis of heterocycles is chalcone.

Overall, metal-free and operationally simple methodologies using easily accessible substrates such as *α,β*-unsaturated ketones for the synthesis of valuable heterocyclic cores of medicinal as well as industrial relevance are always desirable. In this context we have explored the chemical reactivity of *α,β*-unsaturated ketones under metal free condition towards the synthesis of heterocyclic entities of structural complexity and medicinal relevance.

The thesis is divided into four chapters. **Chapter 1** gives a brief introduction to importance of transition metal-free reactions in the synthesis of heterocycles. We have mainly focused on the reactions of *α,β*-unsaturated ketones, since these are one of the easily accessible substrates in organic synthesis. In this chapter we have documented various metal-free methodologies such as iodine/hypervalent iodine mediated reactions, organocatalytic reactions and Bronsted/Lewis acid mediated reactions developed in the recent years for the synthesis of various heterocyclic compounds.

The **Chapter 2** deals with the synthesis of *N*-substituted chromeno/pyrano fused pyridines in the presence of $BF_3.OEt_2$ from arylidenones, alkynes and nitriles. The reaction proceeds under mild conditions and has wide substrate scope. The method is also valid for the construction of thiochromeno[3,4-*c*]pyridines and thiopyrano[3,4-*c*]pyridine derivatives as well. In addition, a one-pot synthesis of 5*H*-chromeno[3,4-*c*]pyridines was successfully achieved.

Even though spiroheterocycles are considered as emerging drug candidates, synthesis of spiroaziridines has not been well explored so far. Hence, the main focus of **Chapter 3** is the synthesis of spiroaziridine under metal-free conditions. We have developed an I_2/TBHP mediated protocol for the synthesis of spiroaziridine from *α,β*-unsaturated ketones and primary amines. The reaction proceeds in a diastereoselective fashion under mild conditions. Notably, this protocol does not require pre functionalization of amine for the aziridination of *α,β*-unsaturated ketone. This protocol is valid for the synthesis of simple aziridine as well.

Synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole tethered with indole nucleus is the subject matter of **Chapter 4.** Benzo[*d*]imidazo[2,1-*b*]thiazoles are one of the important fused bicyclic scaffolds bearing sulphur and nitrogen atoms. Molecules bearing this core are associated with wide spectrum of biological properties. We have developed a one-pot, two step protocol for the synthesis of this tricyclic molecule from *α,β*-unsaturated ketones, indoles and 2-aminobenzothiazoles. The reaction proceeds under metal-free conditions and has wide substrate scope. Notably, this strategy gives access to benzo[*d*]imidazo[2,1-*b*]thiazoles tethered with indole ring at the C3 carbon atom. Interestingly, the reaction involves an unusual 1,2-indole migration and C_α-C_β bond cleavage.

Chapter 1

Transition Metal-free Synthesis of Heterocycles from *α,β*-Unsaturated Ketones

1.1. Abstract

Heterocyclic compounds are an inevitable part of our life. These important classes of molecules have a wide range of applications starting from life-sustaining drugs to agrochemicals. Numerous methods, including metal and non-metal mediated protocols, are documented to synthesise complex and straightforward heterocyclic entities. The metal-free protocols have more significance over the metal catalyzed ones when the toxicity associated with the metal catalyst is considered. On the other hand, *α,β*-unsaturated ketones are essential building blocks in synthetic organic chemistry. The presence of multiple reaction sites makes conjugated carbonyls suitable substrates for constructing a vast array of heterocycles.

1.2. Introduction

Heterocycles are one of the practical classes of organic molecules which play a pivotal role in the sustenance of life.[1] These are significant structural motifs found in various natural products and are known for a broad spectrum of biological properties.[2,3] Apart from the medicinal utility, numerous heterocyclic compounds are used as dyestuff, agrochemicals, antioxidants, sensitizers, copolymers and ligands.[1,4] Owing to the multifaceted applications, a plethora of protocols have been contributed by the scientific community towards the synthesis of various heterocycles. Synthesis and exploration of heterocycles for various applications are never ending area of fascination from the perspective of a researcher.

1.2.1. Pros and cons of transition metal catalyst

Transition metal catalysts have revolutionized the field of organic synthesis as it is highly beneficial in the straight forward construction of C-C and C-heteroatom bond.[5,6] The ability to exist in various oxidation states is the significant feature that makes transition metals better

catalyst for coupling reactions. In the last few decades, we have seen a substantial growth in the development of transition metal catalyzed protocols for various synthetic transformations.[7] Some of the synthetic strategies used in the synthesis of heterocycles are cycloaddition reactions, cycloisomerizations, metathesis reactions, C-H functionalization, multicomponent reactions and Sonogashira reactions. Various transition metals used in these protocols include palladium, silver, rhodium, ruthenium, cobalt, copper, gold and iron.[8]

Despite the benefits transition metal catalysts offer in the synthesis of various heterocyclic frameworks, transition metal-free reactions are gaining more attention nowadays. The quest to explore alternatives to transition metal catalysts is mainly attributed to the toxicity inherent with such systems, especially when it comes to synthesizing heterocycles of biological relevance. Moreover, the requirement of drastic reaction conditions, tedious purification procedures and high cost are some of the drawbacks of transition metal catalyzed protocols. Additionally, special additives, co-catalysts and pre functionalized starting materials are required in many cases.[9] Therefore protocols which are sustainable and proceed under metal-free conditions with good atom and step economy are always desirable.

1.2.2. *α,β*-unsaturated ketone: a valuable synthon

α,β-unsaturated ketones are important building blocks in synthetic organic chemistry.[10,11] Molecules of this class possess multiple reaction sites, including both electrophilic and nucleophilic centers **(Figure 1.1)**. Owing to the presence of a C=O and a C=C bond, enone undergoes reactions such as oxidation, reduction,[12,13] 1,2 addition, conjugate addition,[14,15] condensation and cycloaddition reactions.[16] Apart from its chemical reactivity, *α,β*-unsaturated ketones are readily available or can be easily synthesized. Some of the methods adopted for the synthesis of *α,β*-unsaturated ketones are Claisen – Schmidt condensation, Knoevenagel condensation, Wittig reaction, Peterson olefination and Horner-Wadsworth-Emmons reaction. Molecules of this class are utilized as necessary starting materials in various synthetic methodologies. One of the prominent enone used as a valuable substrate in the synthesis of heterocycles are chalcones.[17,18] These are molecules of natural origin, belonging to the family of flavonoid and are entities of biological significance. The medicinal aspects of the chalcones are fascinating as these are endowed with broad spectrum of biological properties, viz. anticancer, antitumor, anti- inflammatory, antibacterial, antifungal, antioxidant, antidiabetic

etc. The synthetic usefulness of this *α,β*-unsaturated ketone is evident in the nature itself, as it the precursor in the biosynthesis of flavonoids and isoflavonoids.[19]

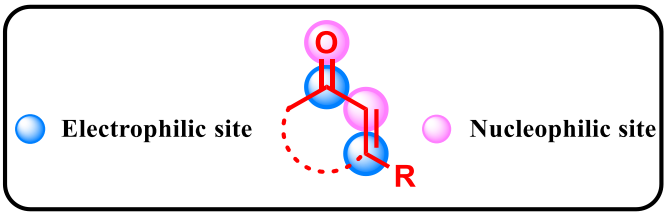


Figure 1.1. Reactive sites of *α,β*-unsaturated ketones.

The following sections in this chapter focuses on the recent advances in the transition metal-free synthesis of heterocycles using *α,β*-unsaturated ketones. We have documented some relevant methodologies developed during the period of 2009 to 2020 for the construction of nitrogen heterocycles, oxygen heterocycles and spiroheterocycles.

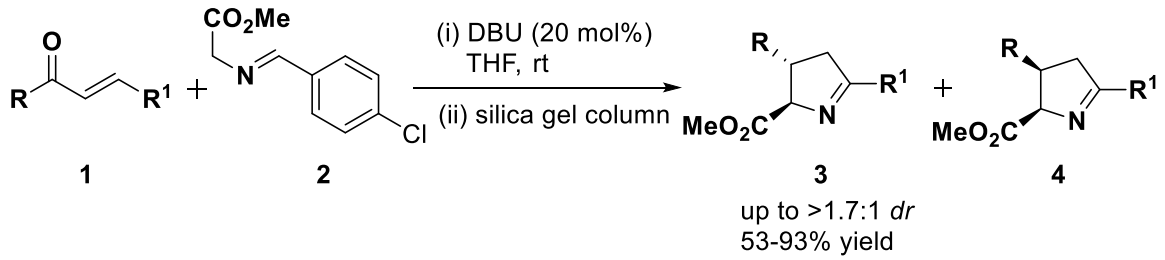
1.3. Synthesis of nitrogen containing heterocycles

Nitrogen containing molecules constitute one of the prominent class of structural scaffolds among various heterocycles. It is found that around 75% of the currently marketed drugs are nitrogen containing heterocyclic molecules.[20,21] Thus, synthesis of nitrogen heterocycles is an area of ever-growing interest among organic chemists. As a result, numerous protocols are being developed for accessing various nitrogen heterocycles.

1.3.1. Synthesis of five-membered nitrogen heterocycles

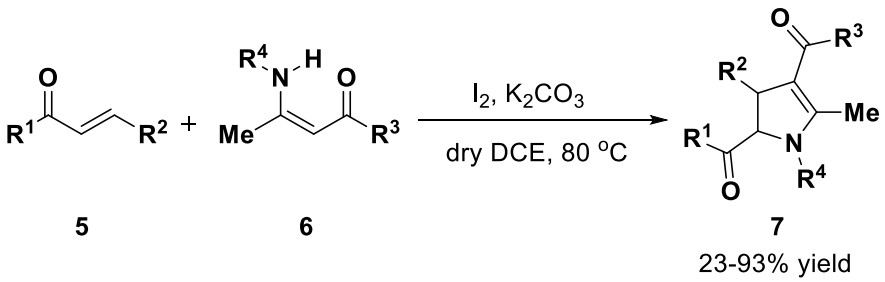
1.3.1.1. Pyrrole and its derivatives

Pyrrole is an important five-membered nitrogen containing heterocyclic compound. Like any other *N*-heterocyclic scaffold, pyrrole and its derivatives are endowed with valuable biological properties.[22,23] In 2012, Zhang *et al*. unravelled a single step, DBU catalyzed method for the synthesis of 3,4-dihydro-2*H*-pyrroles (**3** and **4**) using enone **1** and *N*-(4-chlorobenzylidene)-glycine methyl ester **2** as the substrates **(Scheme 1.1)**. This reaction involves the formation of a Michael adduct in the presence of catalytic amount of DBU. Further, conversion of the Michael adduct to the product as well as its purification occurs during silica gel column chromatography.[24]



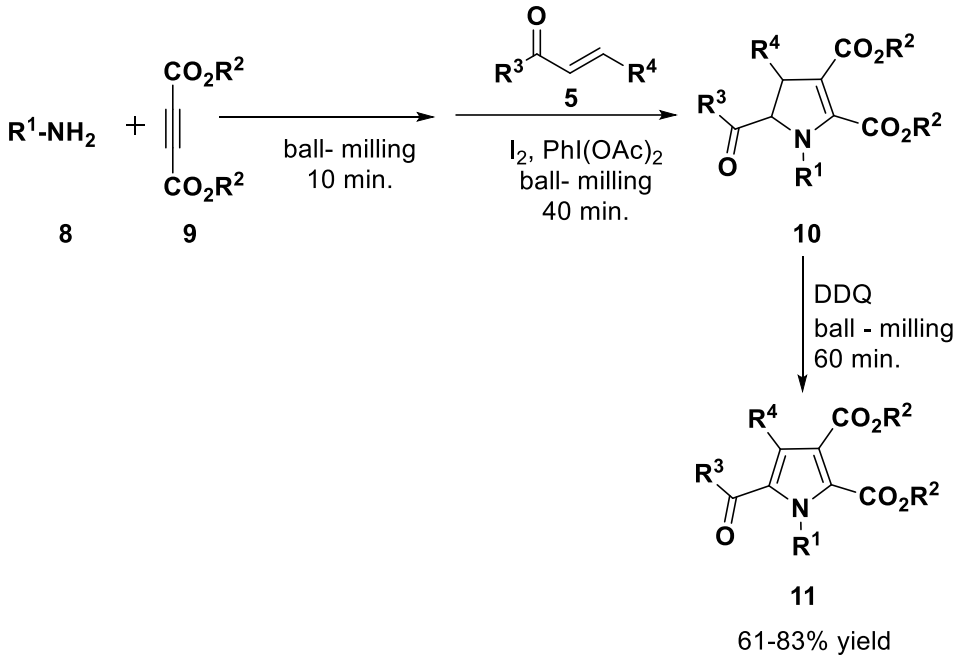
Scheme 1.1. DBU catalyzed single-step synthesis of 3,4-dihydro-2*H*-pyrroles.

Later, Li and co-workers reported an iodine mediated synthesis of polysubstituted *trans*-2,3-dihydropyrroles **7** in 2015 **(Scheme 1.2)**. The environmentally benign method utilises chalcones **5** and *β*-enamine ketones **6** as the starting materials.[25] The synthesis of 2,3-dihydropyrroles proceeds through molecular iodine mediated Michael addition of enamine to the chalcone followed by intramolecular cyclisation reaction.

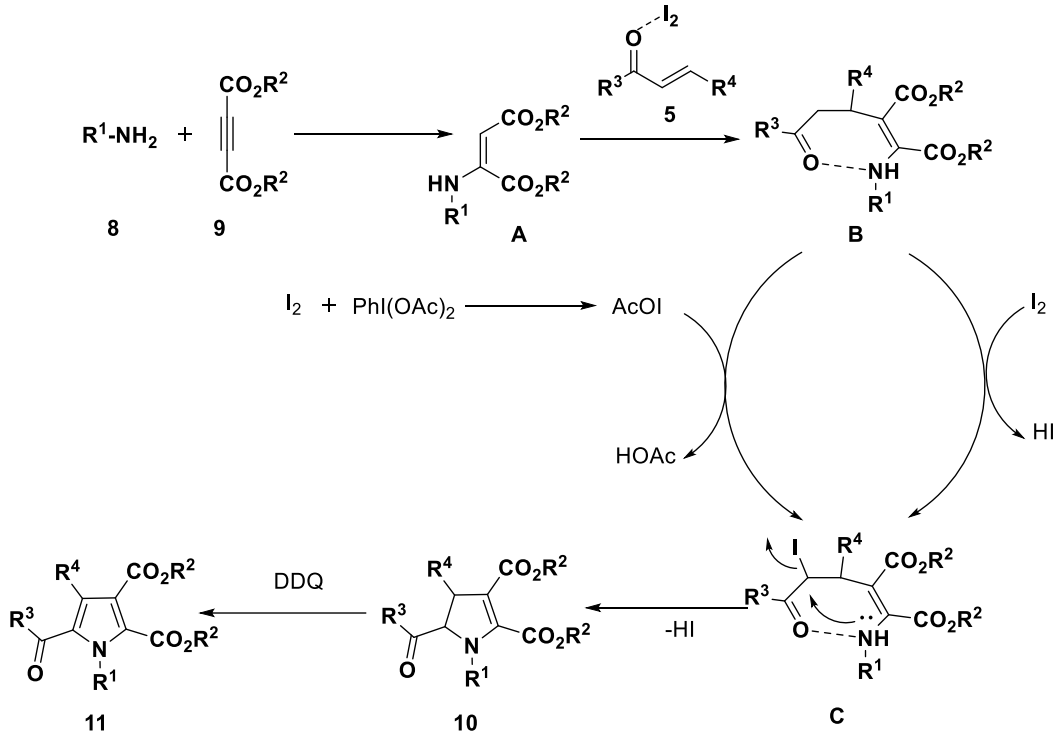


Scheme 1.2. Iodine mediated synthesis of polysubstituted *trans*-2,3-dihydropyrroles.

In 2018, a solvent-free ball milling method was introduced by Xu *et al*. using chalcone **5** as one of the reactants for the synthesis of polysubstituted dihydropyrroles **10 (Scheme 1.3)**. It is a metal-free I_2/PhI(OAc)$_2$ promoted multicomponent reaction.[26] One of the merits of the protocol is that 2,3-dihydropyrrole **10** can be transformed into the saturated counterpart **11** through a dehydrogenative aromatization in the presence of an oxidant such as DDQ in a one-pot fashion. In this reaction, initially the amine reacts with alkyne ester to form a *β*-enamino ester, which undergoes Michael addition with subsequently added chalcone, generating an intermediate **B**. In the presence of I_2 or AcOI generated in situ, the Michael adduct **B** forms the iodide intermediate **C,** which upon intramolecular cyclization affords the *trans*-2,3-dihydropyrrole **10**. Further, dehydrogenative aromatisation of dihydropyrrole in the presence of the DDQ affords the corresponding polysubstituted pyrrole **11 (Scheme 1.4)**.

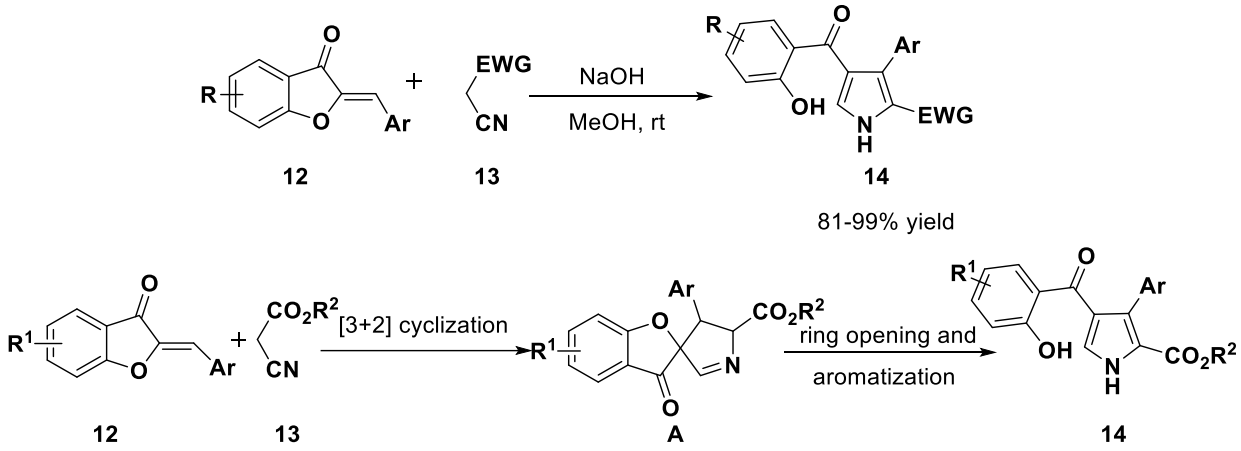


Scheme 1.3. $I_2/PhI(OAc)_2$ mediated one-pot MCR to synthesise polysubstituted dihydropyrroles.



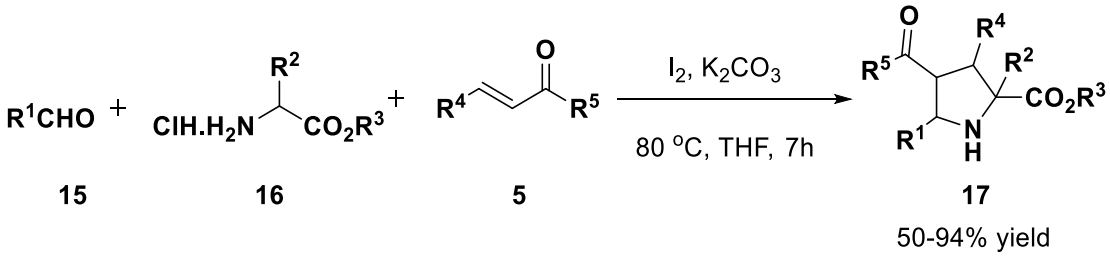
Scheme 1.4. Proposed mechanism for the synthesis of polysubstituted pyrroles.

In the same year, Wang *et al*. disclosed a base catalyzed protocol for the synthesis of multifunctionalized pyrroles **14** with high efficiency. An array of 2,3,4-trisubstituted pyrroles are furnished from aurone analogues **12** and isocyanoacetates **13** via a [3+2] cyclisation reaction.[27] It is assumed that the reaction proceeds through a spiropyrroline intermediate **A** formation. Further, ring-opening of the benzofuran-3(2*H*)-one of the intermediate **A** followed by aromatization affords the desired product **14 (Scheme 1.5)**. The polysubstituted pyrroles synthesized by this operationally simple protocol bears a free hydroxyl group as well as an ester moiety, thus providing the possibility for further synthetic transformations.



Scheme 1.5. Base catalyzed synthesis of multifunctionalized pyrrole.

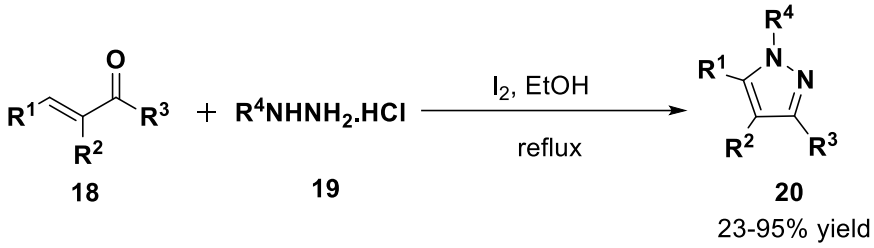
Recently in 2019, Zhang *et al*. reported the synthesis of pyrrolidine-2-carboxylates **17** utilising I_2/K_2CO_3 catalytic system. They have used readily available enone, chalcone **5** as a substrate for the reaction.[28] The authors could successfully demonstrate the diversity and generality of the multicomponent, one-pot operation with variously substituted chalcones **5** as well as aromatic aldehydes **15 (Scheme 1.6)**.



Scheme 1.6. I_2/K_2CO_3 catalyzed one-pot MCR for the synthesis of pyrrolidine-2-carboxylate.

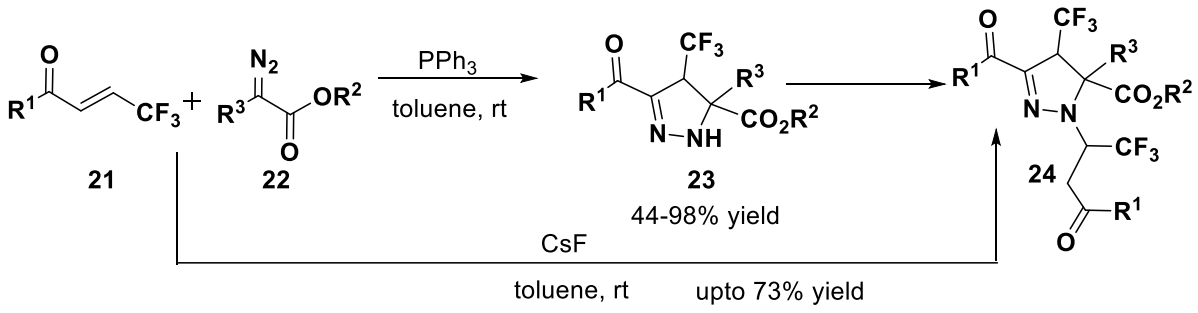
1.3.1.2. Pyrazole and its derivatives

Pyrazole, another five-membered nitrogen heterocycle, is a molecular scaffold of synthetic as well as biological significance. Zhang and co-workers disclosed a metal free approach for the synthesis of pyrazole in 2014. The reaction which affords di, tri and tetrasubstituted pyrazole derivatives **20**, proceeds with good regioselectivity.[29] The iodine mediated method utilises *α,β*-unsaturated ketones/aldehydes **18** and hydrazine salts **19** as the substrates **(Scheme 1.7)**. Unlike the usual methods, this one-pot strategy avoids the isolation of hydrazone intermediate.



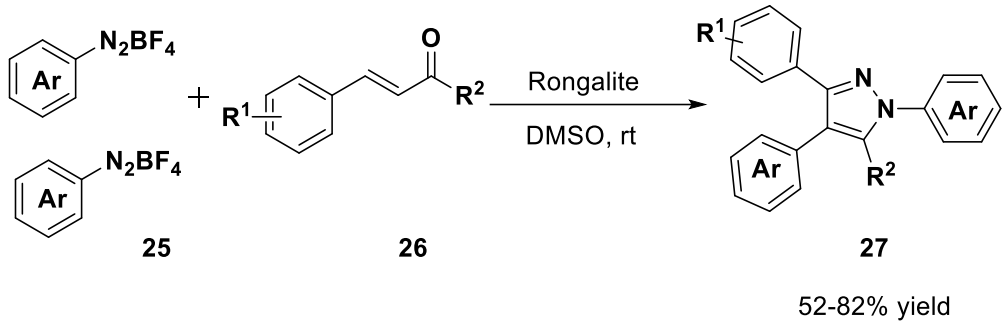
Scheme 1.7. Metal-free iodine mediated regioselective synthesis of substituted pyrazoles.

Later, a phosphine catalyzed [3+2] cycloaddition of *α*-diazoacetates **22** with *β*-trifluoromethyl enone **21** was established by Li *et al*. for the synthesis of pyrazolines **24 (Scheme 1.8)**.[30] Since they have used *β*-trifluoromethyl enone as the precursor, pyrazoline bears a trifluoromethyl group at the 4th position. Interestingly, it is the first report on phosphine being used as a catalyst for the [3+2] cycloaddition of alkenes with diazoacetates. The authors have also explored a cycloaddition/Michael addition strategy as well. This tandem process proceeds in the presence of CsF at room temperature, facilitating pyrazoline **24**. The formation of single diastereomer and broad substrate scope are the notable features of this procedure.



Scheme 1.8. Synthesis of pyrazolines via phosphine catalyzed [3+2] cycloaddition.

In 2019, Wang *et al*. devised a Rongalite mediated multicomponent reaction to synthesise fully substituted pyrazoles **27**.[31] It is a radical annulation of aryldiazonium salts **25** with unsaturated ketones or aldehydes **26** under mild conditions **(Scheme 1.9)**. Notably, this is the first protocol that has utilised aryldiazonium salt as dual synthons for a radical annulation reaction. In this reaction, Rongalite serves as a radical initiator as well as a reducing agent.

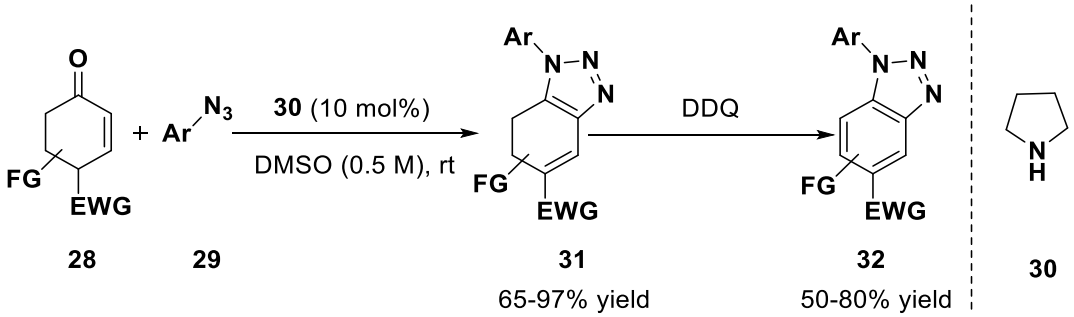


Scheme 1.9. Rongalite mediated synthesis of highly substituted pyrazoles.

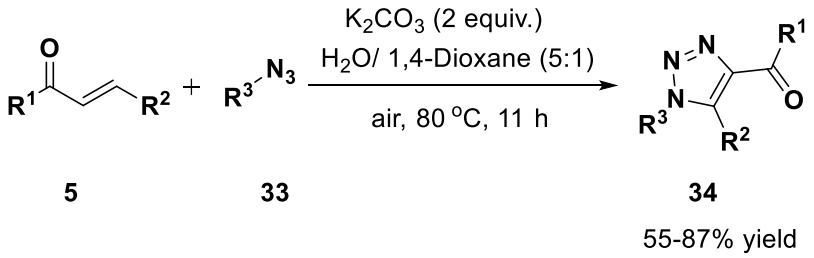
1.3.1.3 Triazoles

Triazoles are considered as an important structural entity: owing to their medicinal aspects, application in material science and utility as valuable building blocks in synthetic organic chemistry.[32] In 2013, Ramachary and co-workers devised an organocatalytic method for the construction of *N*-aryl-1,2,3- triazoles **31** and *N*-arylbenzotriazoles **32** from cyclic enones **28** and aryl azides **2**.[33] The *N*-arylbenzotriazole is synthesized by the oxidation of *N*-aryl-1,2,3-triazole **31** in the presence of DDQ. The reaction proceeds via a sequential [3+2] cycloaddition and oxidative aromatization in one pot. The cycloaddition of azide to the enone is catalyzed by Pyrrolidine **30** (**Scheme 1.10**).

In 2015 a transition metal-free cycloaddition of benzyl azide **33** across the double bond of chalcone **5** affording tri substituted triazole **34** was reported by Yang *et al*.[34] This 1,3-dipolar addition of the azide **29** is achieved in the presence of K_2CO_3 under air atmosphere in aqueous medium (**Scheme 1.11**).

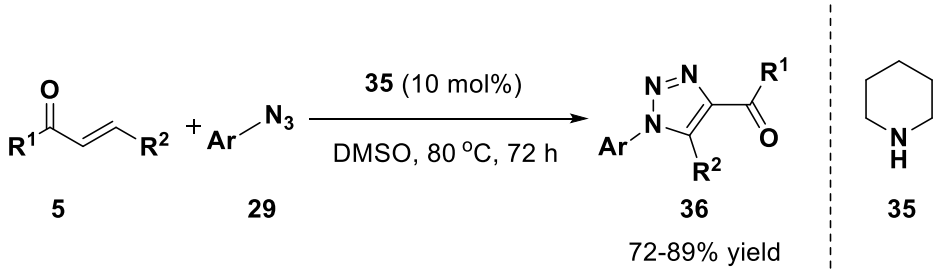


Scheme 1.10. Pyrrolidine catalyzed synthesis of *N*-aryl-1,2,3- triazoles and *N*-arylbenzotriazoles.

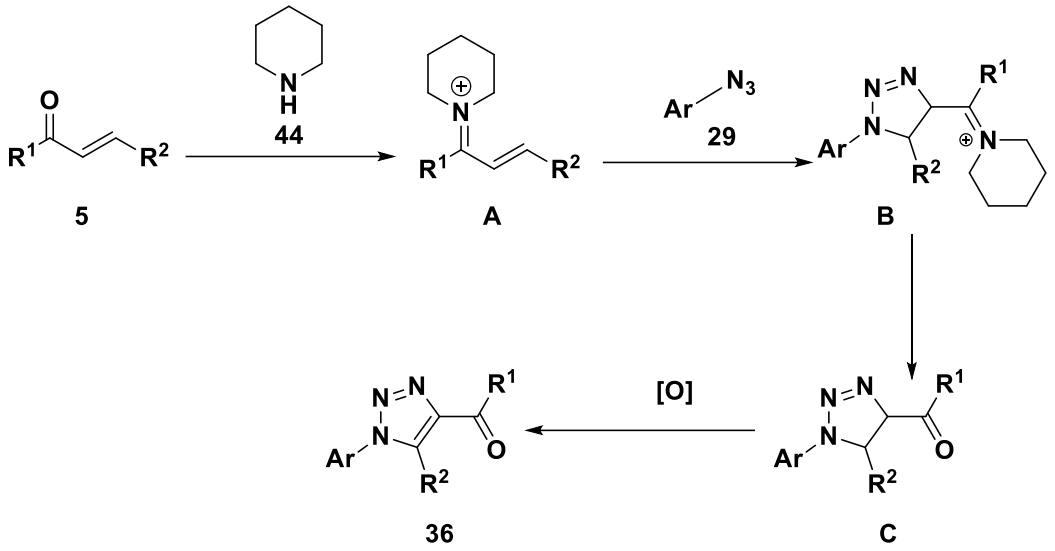


Scheme 1.11. Synthesis of 1,2,3-triazoles via K_2CO_3 mediated cycloaddition of azide.

Later, Li and co-workers illustrated piperidine **35** catalyzed highly regioselective 1,3-dipolar cycloaddition of aryl azide **29** to chalcone **5 (Scheme 1.12)**.[35] The reaction proceeds through an iminium intermediate **A** to which 1,3-dipolar addition of azide takes place affording **B** which releases the organocatalyst. The intermediate thus formed upon aerobic oxidation yields the 1,2,3-triazole **36** (**Scheme 1.13**). This protocol is compatible with alkyl azides as well. Readily available starting materials, cheap catalyst and high regioselectivity are the merits of this transition metal free protocol.

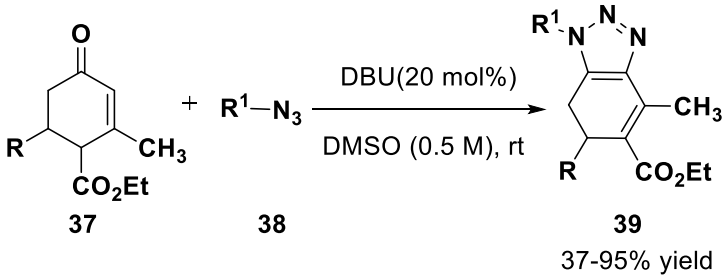


Scheme 1.12. Piperidine catalyzed synthesis of 1,2,3-triazoles.



Scheme 1.13. Proposed mechanism for the synthesis of 1,2,3-triazoles.

In 2020, Reddy *et al*. accomplished an atom economic method to synthesise C/N double vinyl and C-vinyl-1,2,3-triazoles **39** from enones **37 (Scheme 1.14)**.[36] They have extensively studied the reactivity of cyclic and acyclic enones **37** with comparatively less reactive vinyl, aryl and alkyl azides **38** under DBU catalysis. This protocol is based on the reactivity of enolates, which is much reactive than enamines towards less reactive azides at room temperature.



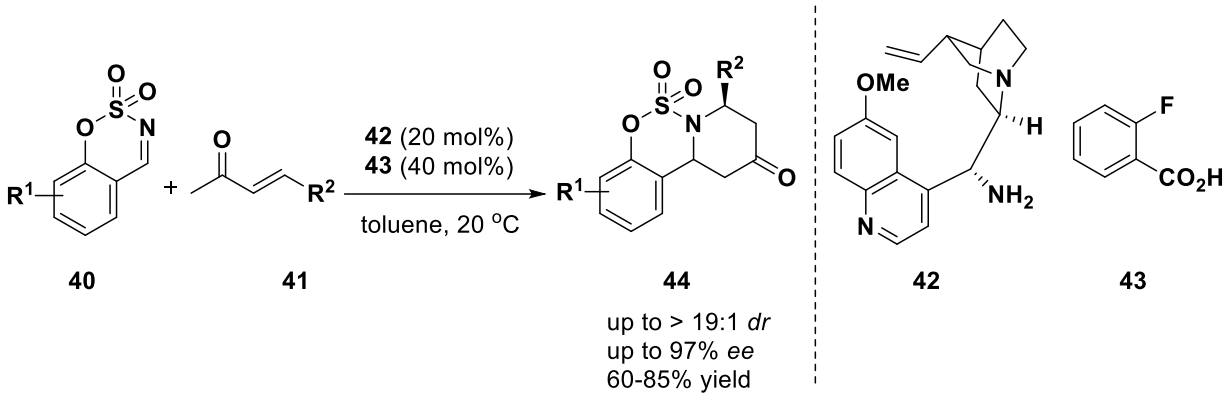
Scheme 1.14. DBU catalyzed synthesis of vinyl-1,2,3-triazoles.

1.3.2. Synthesis of six-membered nitrogen heterocycles

1.3.2.1. Piperidine

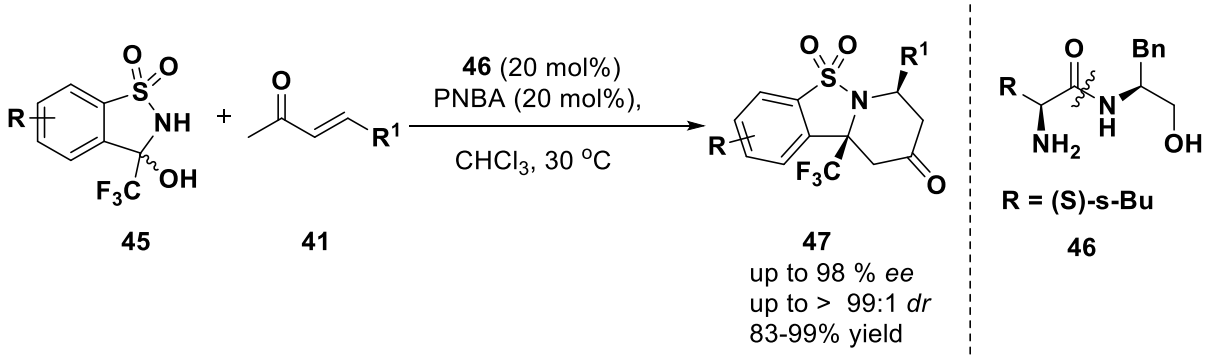
Like other nitrogen containing heterocycles piperidine is an interesting structural entity possessing vast biological properties and is found in many alkaloids.[37] In 2013, Liu *et al.*

reported a diastereo and enantioselective formal Aza-Diels- Alder reaction of cyclic *N*-sulfimines **40** with acyclic enones **41 (Scheme 1.15)**.[38] The reaction gives access to sulfamate-fused 2,6-disubstituted piperidin-4-ones **44** under mild conditions. A combination of chiral primary amine **42** and *o*-fluorobenzoic acid **43** catalyses the reaction affording the products in better yields.



Scheme 1.15. Synthesis of sulfamate-fused 2,6-disubstituted piperidin-4-ones via formal Aza-Diels-Alder reaction.

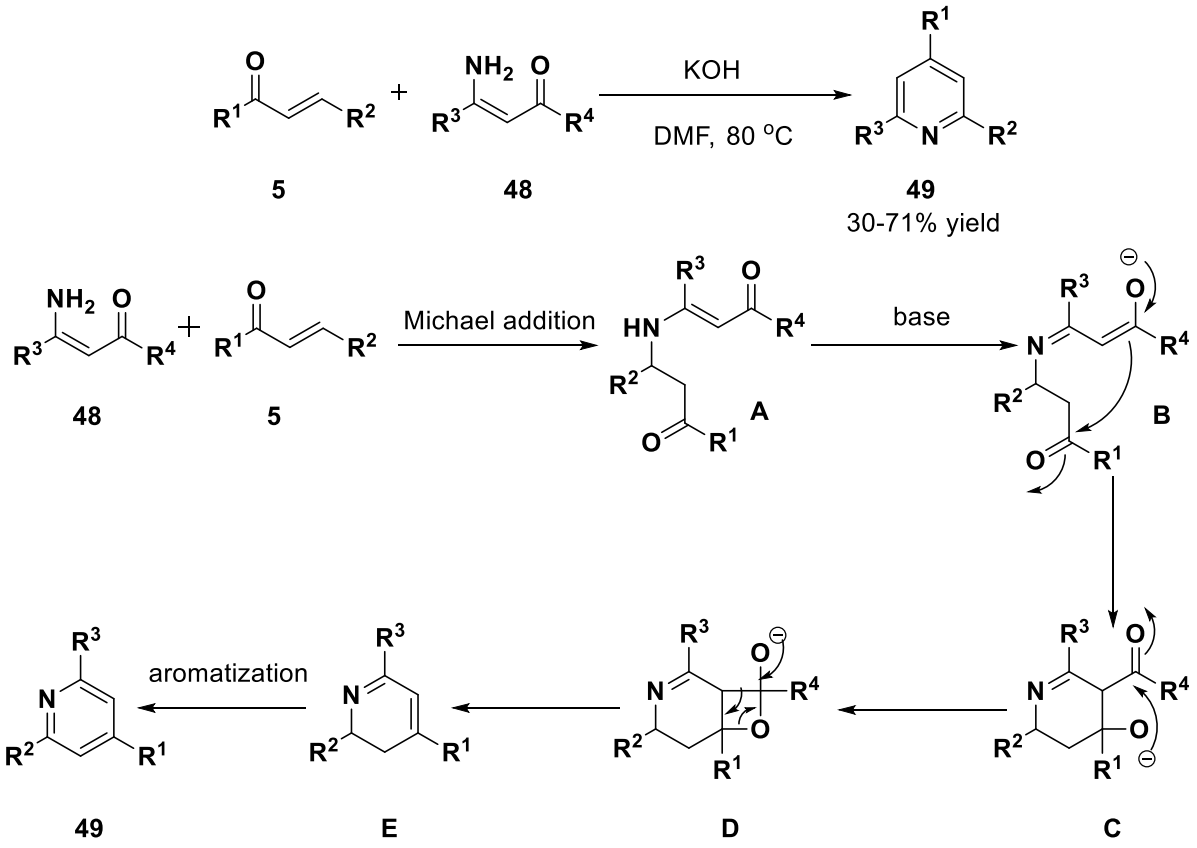
Based on the same concept, Zhang *et al*. established a metal-free method for the synthesis of trifluoromethyl substituted piperidines **47** from enones **41** and trifluoromethyl hemiaminals **45** under primary amine **46** catalysis.[39] They have used trifluoromethyl hemiaminal as the precursor of cyclic sulfimine. The utility of this method is demonstrated by the synthesis of biologically active 4-hydroxypiperidine in shortest routes **(Scheme 1.16).**



Scheme 1.16. Synthesis of trifluoromethyl substituted piperidine.

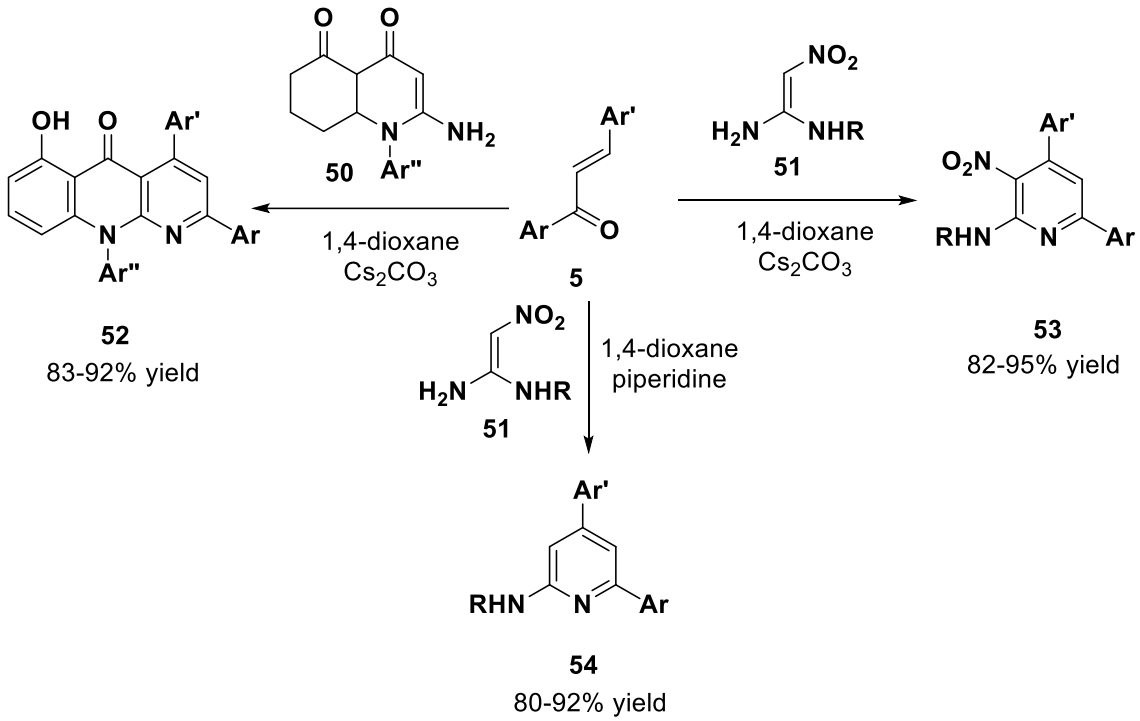
1.3.2.2. Pyridine

Pyridines are valuable heterocyclic scaffolds. These are important structural unit of various drugs as well as molecules of natural origin. Among different types of pyridine molecules 2,4,6-Triarylpyridines, which are known by the name of Krohnke pyridines have gained the attention of scientific community owing to its broad applications in multiple fileds.[40] In 2018, Zhang and co-workers accomplished a metal-free synthesis of 2,4,6-triaryl pyridines **49** from chalcones **5** and *N*-unsubstituted enaminones **48** (**Scheme 1.17**).[41] The reaction is promoted by KOH in DMF under air atmosphere. According to the proposed mechanism, initially Michael addition of enaminone **48** to the chalcone **5** occurs. Michael adduct **A** thus formed undergoes 1,5-hydrogen shift in the presence of base generating an iminoenolate intermediate **B**. The intermediate **B** upon intramolecular nucleophilic addition gives **C** which on subsequent nucleophilic addition, elimination of aryl formate and finally aromatization affords the triarylpyridine **49** (**Scheme 1.17**).



Scheme 1.17. Base mediated 2,4,6-triaryl pyridine synthesis.

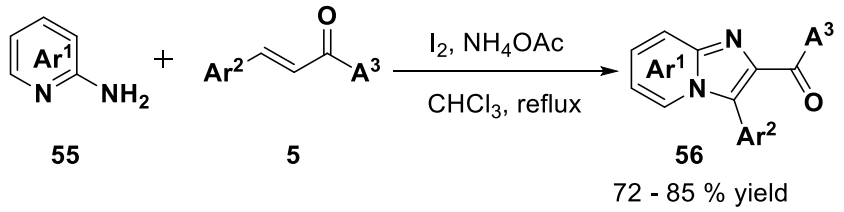
Recently Luo *et al*. unravelled a base mediated protocol which gives access to three types of 2-amino-4,6-diarylpyridine derivatives (**52-54**).[42] They accomplished the synthesis of pyridine from *α,β*-unsaturated ketones **5** and 1,1-enediamines (**51** and **52**). The reaction can be tuned by the proper choice of base and 1,1-enediamine to achieve the synthesis of any one of the 2-aminopyridines. The nitro functionality present in the 1,1-enediamine **51** acts as both activating group as well as orienting group. The metal-free methodology proceeds through a cascade of Michael addition, intramolecular cyclization, aromatization and/or loss of HNO_2 (**Scheme 1.18**).



Scheme 1.18. Base controlled one pot synthesis of 2-amino-4,6-diarylpyridine derivatives.

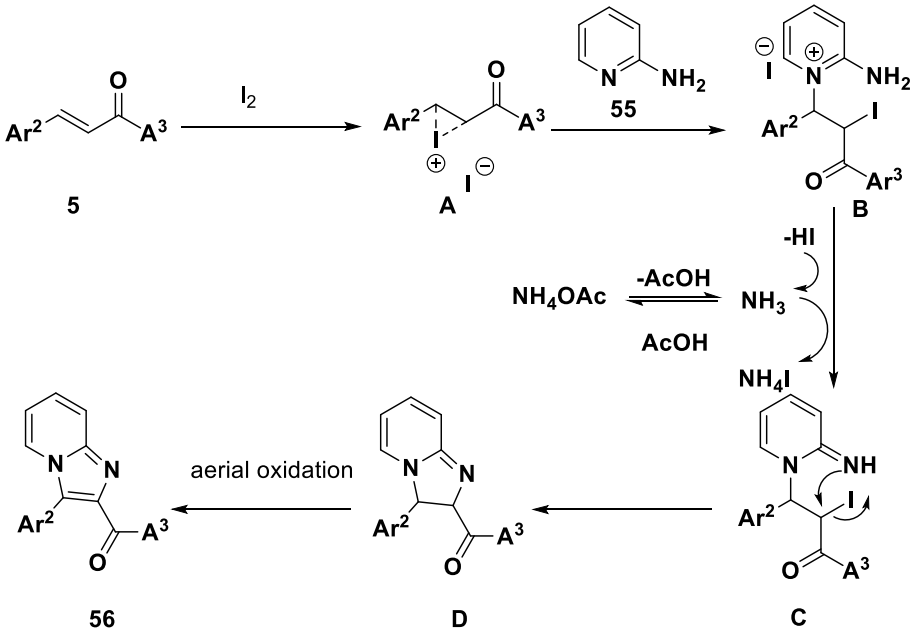
1.3.2.3. Imidazopyridine

Imidazopyridine is an integral structural unit of several drugs. It finds application in material science, organometallics and optoelectronics. In 2018 Kour *et al*. disclosed an I_2-NH_4OAc mediated regioselective synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridine **56 (Scheme 1.19)**. Chalcones **5** and 2-aminopyridines **55** are used as the precursors in this metal-free methodology.[43]



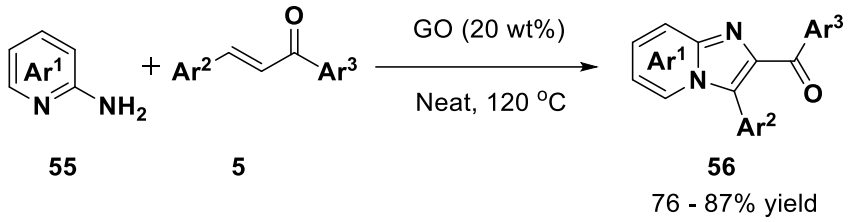
Scheme 1.19. I_2-NH_4OAc mediated regioselective synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridine.

Based on the mass spectrometric analysis of the reaction mixture at different time intervals, the authors proposed a plausible mechanistic pathway. According to which the reaction proceeds via an iodonium intermediate **A** which undergoes a nucleophilic addition by exocyclic *N*-atom of the 2-aminopyridine forming an Ortoleva-King type intermediate **B**. Subsequent intramolecular cyclization and aerial oxidation of **B** affords the 2-aroyl-3-arylimidazo[1,2-*a*]pyridine **56 (Scheme 1.20)**.



Scheme 1.20. Proposed mechanism of 2-aroyl-3-arylimidazo[1,2-*a*]pyridine formation.

Later, in 2020 a solvent free synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridine **56** under heterogeneous catalysis was reported by the same group **(Scheme 1.21)**.[44] The reaction is fast and operates under mild conditions. Graphene oxide is used as the heterogeneous catalyst in this environmentally benign method.

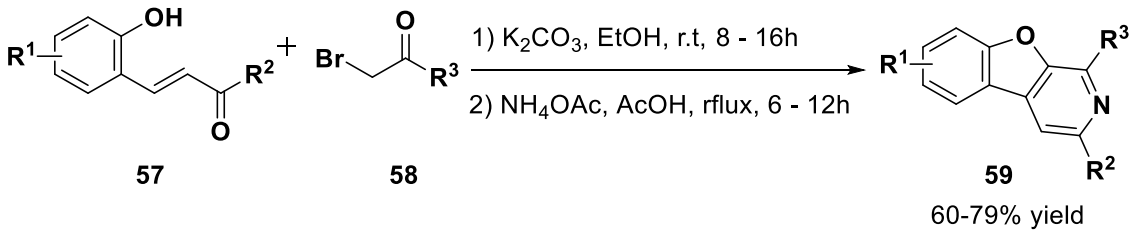


55 5 56

Scheme 1.21. Graphene oxide catalyzed synthesis of 2-aroyl-3-arylimidazo[1,2-*a*]pyridine.

1.3.2.4. Benzofuropyridine

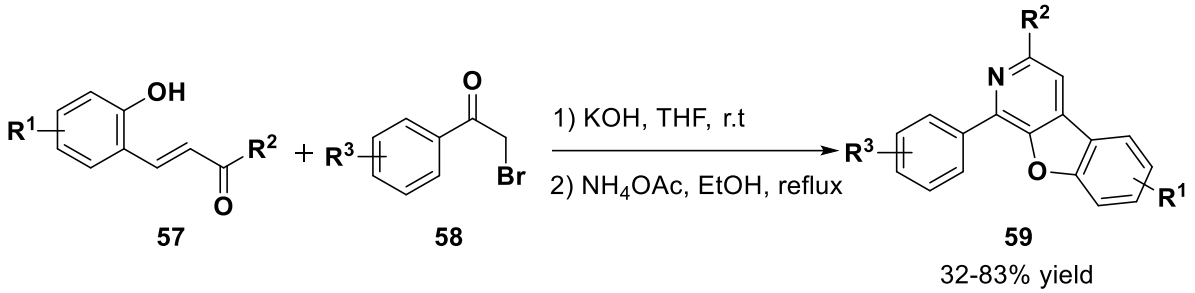
Benzofuropyridines, like other pyridine derivatives, are endowed with broad spectrum of biological properties. In 2014, Rao *et al.* devised a one pot domino reaction for the construction of benzofuro[2,3-*c*]pyridines from *o*-hydroxychalcones **57**, *α*-bromoketones **58** and ammonium acetate (**Scheme 1.22**).[45] The three component reaction involves formation of two ring systems in a single molecule **59**, namely furan and pyridine, in a one-pot metal-free operation. Moreover, column free purification makes this methodology more attractive.



57 58 59

Scheme 1.22. Base catalyzed synthesis of benzofuro[2,3-*c*]pyridines**.**

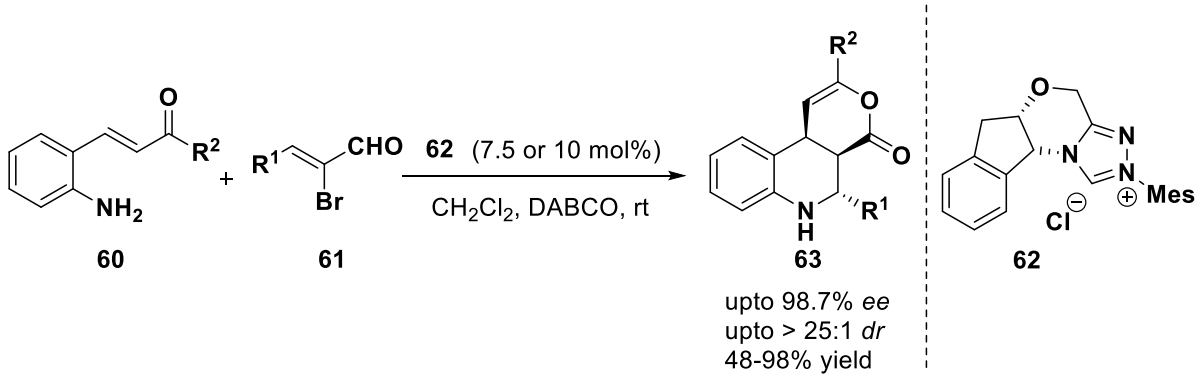
A similar reaction was reported by Hu and co-workers in the same year.[46] They have used hydroxyphenyl functionalized *α,β*-unsaturated ketones **57**, *α*-bromoketones **58** and ammonium acetate as substrates. In this protocol the initial *o*-alkylation step is performed using KOH in THF at room temperature (**Scheme 1.23**).



Scheme 1.23. One pot base mediated strategy for the synthesis of fused pyridines.

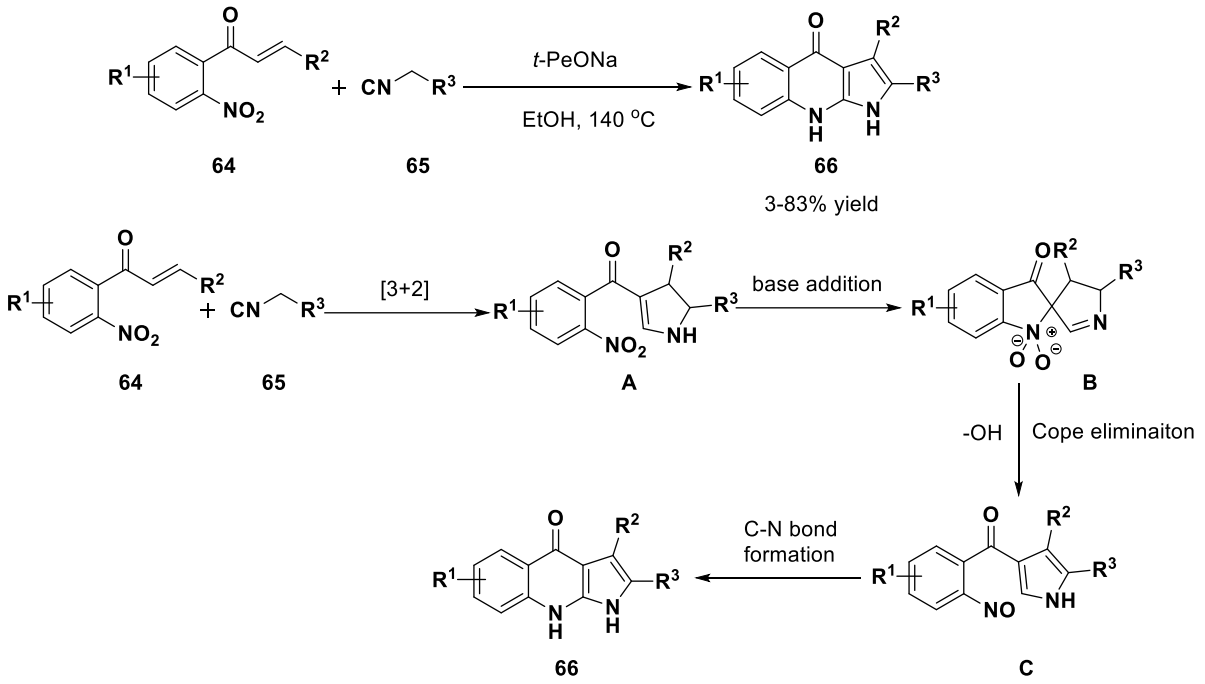
1.3.2.5. Quinoline

Quinolines are bicyclic compounds containing nitrogen as the hetero atom. These heterocyclic scaffolds are found in many natural products of biological significance.[47] In 2013, Zhang *et al.* reported an NHC **62** catalyzed reaction for the synthesis of chiral terahydroquinolines **63** with excellent enantioselectivity and diastereoselectivity.[48] It is an aza- Michael- Michael-lactonisation reaction of 2′-aminophenylenones **60** with 2-bromoenals **61** under mild conditions **(Scheme 1.24)**. Using this organocatalyzed reaction they have successfully showcased the synthesis of chiral tetrahydroquinoline derivatives **63** containing three consecutive stereogenic centers in high yield.



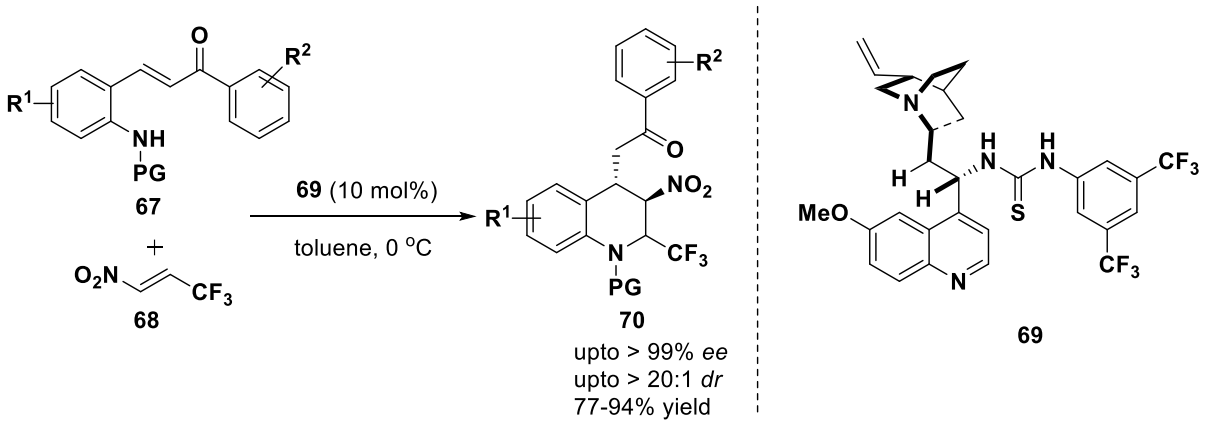
Scheme 1.24. NHC-catalyzed synthesis of chiral terahydroquinoline hybrids.

Later in 2017 Lin and co-workers accomplished a base mediated synthesis of pyrrolo[2,3-*b*] quinolones **66** from *o*-nitrochalcones **64** and activated methylene isocyanides **65 (Scheme 1.25)**.[49] From the control experiments they found that the reaction involves an in situ generation of dihydropyrroline **A** which further acts as an internal reductant to convert the nitro group into nitroso group. Then the subsequent intramolecular C-N bond formation furnishes the pyrrolo[2,3-*b*-]quinolone **66** (**Scheme 1.25**).



Scheme 1.25. Base mediated synthesis of pyrrolo[2,3-*b*] quinolones.

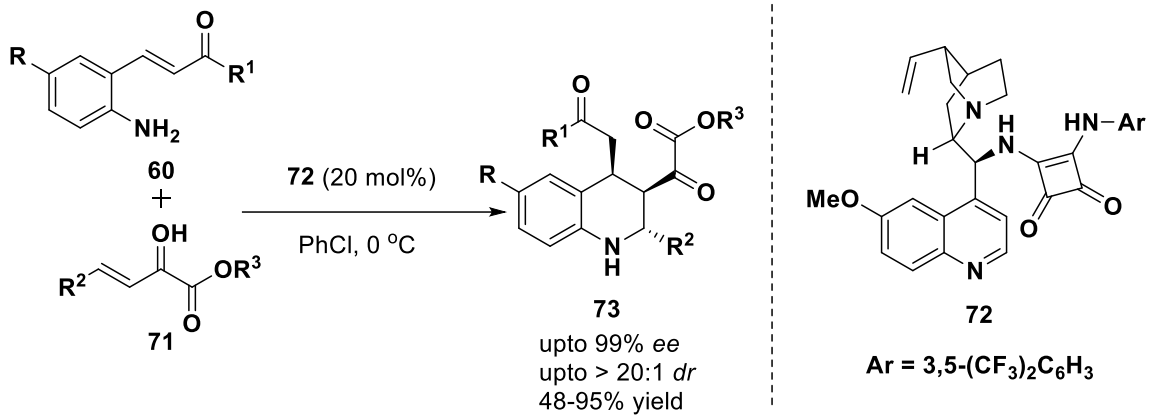
In the same year, Zhu *et al*. devised a thiourea **69** catalyzed enantioselective synthesis of CF_3-tetrahydroqinolines **70** from 2-aminochalcones **67** and β-CF_3 nitroalkenes **68**.[50] The protocol is found to be applicable to a wide range of aminochalcones and nitroalkenes including perfluoro substituted β-nitroalkene. According to the mechanistic proposal, the reaction proceeds through aza-Michael-Michael addition sequence **(Scheme 1.26)**.



Scheme 1.26. Enantioselective synthesis of CF_3 substituted tetrahydroqinoline

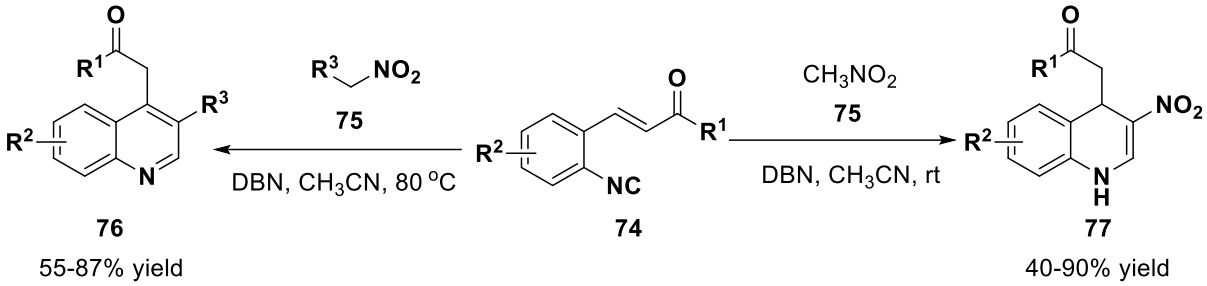
Later in 2018, a squaramide **72** catalyzed annulation reaction of 2-aminochalcones **60** with α,β-unsaturated α-ketoesters **71** towards the synthesis of tetrahydroquinolines **73** was

reported by Duan and co-workers.[51] They found that *β*-position of the *α,β*-unsaturated *α*-ketoester acts as a nucleophilic site in this annulation reaction **(Scheme 1.27)**.



Scheme 1.27. Organocatalyzed synthesis of tetrahydroquinolines.

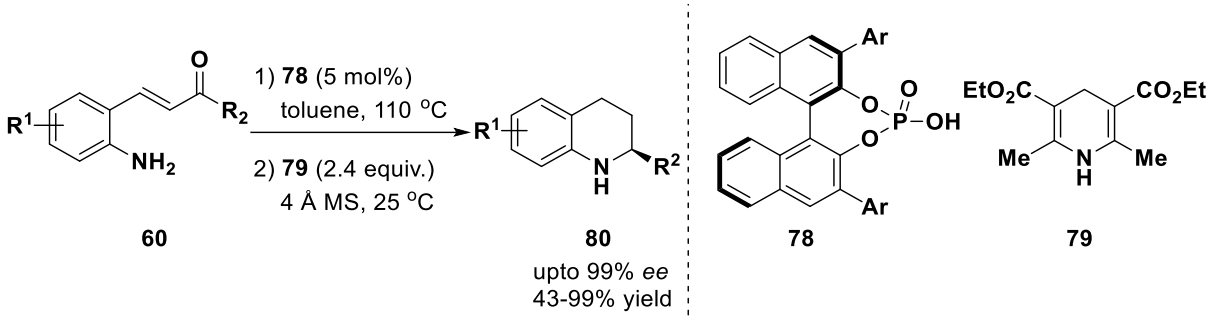
Bao *et al*. disclosed a base catalyzed [5+1] annulation reaction of 2-isocyanochalcones **74** with ntiro alkanes **75** for the synthesis of functionalised quinolines **76** and 3-nitrodihydroquinoline derivatives **77 (Scheme 1.28)**.[52] Quinoline **76** is formed by the selective elimination of the nitro group. While evaluating the scope of the reaction for various nitroalkanes they observed a complex reaction for nitromethane under the optimized reaction conditions. However, when the reaction was carried out at room temperature, instead of quinoline **76**, 3-nitro-1,4-dihydroquinoline **77** was formed. Thus, substrate dependent elimination or retention of nitro group is an attraction of this methodology.



Scheme 1.28. Base catalyzed synthesis of quinoline.

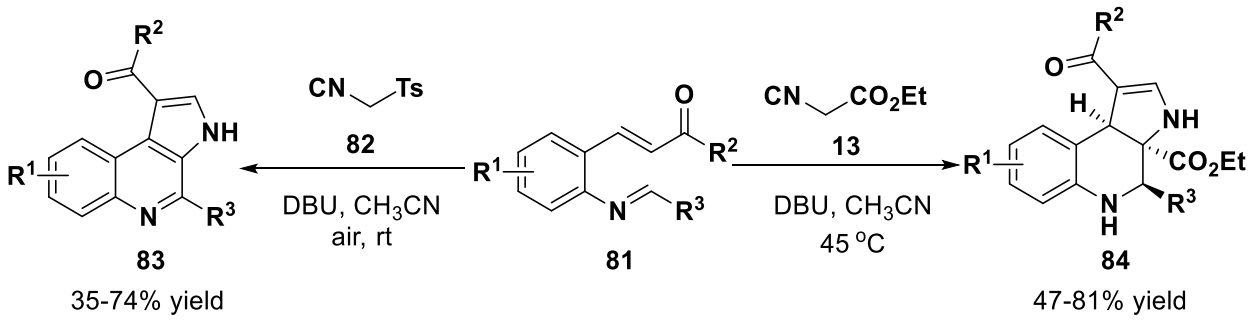
In the same year a chiral phosphoric acid **78** catalyzed two step one pot asymmetric synthesis of tetrahydroquinolines **80** was successfully achieved by Park *et al*. **(Scheme 1.29)**.[53] In this reaction, 2-aminochalcone **60** is initially transformed to quinoline derivative through chiral phosphoric acid catalyzed dehydrative cyclization. In the second step quinoline

derivative is reduced to the corresponding chiral tetrahydroquinoline in the presence of chiral phosphoric acid with Hantzsch ester **79**. This protocol affords optically active tetrahydroquinolines **78** in good yield and excellent enantioselectivity. Two consecutive reactions successfully performed using a single catalyst in one pot without the isolation of intermediate is the significant feature of this protocol.



Scheme 1.29. Chiral phosphoric acid catalyzed synthesis of tetrahydroquinolines.

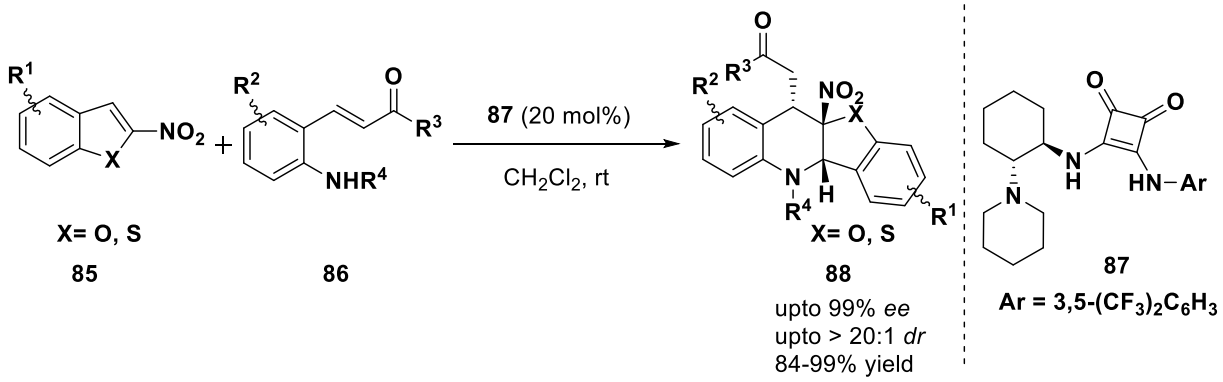
Later, Dong *et al*. reported a DBU mediated cyclization-annulation strategy for the synthesis of pyrrolo[2,3-*c*]quinolines **83** and tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolines **84.** They employed 2-methyleneaminochalcones **81** and *α*-acidic isocyanides (**82** and **13**) as the substrates to achieve the synthesis.[54] Both of the tricyclic pyrroloquinolines were synthesized via simultaneous assembly of quinoline and pyrrole rings **(Scheme 1.30)**.



Scheme 1.30. DBU mediated pyrrolo[2,3-*c*]quinolines and tetrahydro-3*H*-pyrrolo[2,3-*c*]quinolines.

In 2019 Zhou *et al*. devised an asymmetric synthesis of tetrahydrobenzofuro[2,3-*b*]quinolines and tetrahydrobenzo[4,5]thieno[3,2-*b*]quinolines **88** via an organocatalyzed dearomative aza-Michael/Michael addition of 2-nitrobenzofuran and 2-nitrobenzothiophene **85** with 2-aminochalcones **86 (Scheme 1.31).** The reaction was successful in synthesizing the

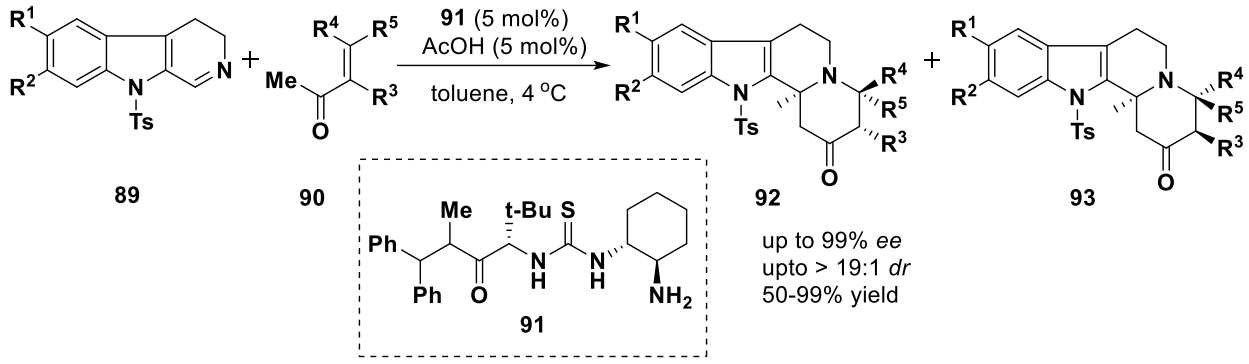
chiral quinoline derivatives **88** containing multiple stereocenters with good enantioselectivity.[55] It is the first report on the asymmetric dearomative reaction of 2-nitrobenzofurans initiated by aza-Michael addition.



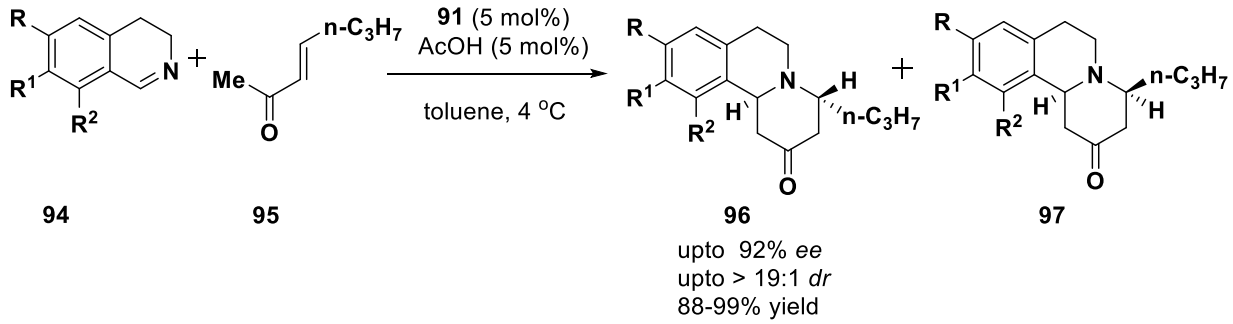
Scheme 1.31. Asymmetric synthesis of tetrahydrobenzofuro[2,3-*b*]quinolines and tetrahydrobenzo[4,5]thieno[3,2-*b*]quinolines via an organocatalyzed dearomative aza-Michael/Michael addition.

1.3.3. Indole fused Heterocycles

Indole and indole fused heterocyclic compounds have always attracted the attention of synthetic as well as medicinal chemists across the academia and industries.[56,57] Owing to the significance as synthetic building block and biologically important structural motif, numerous methods have been devoted towards the synthesis of indole and indole appended analogues.[58] In 2013 Lalonde and co-workers disclosed a formal aza-Diels-Alder reaction of enones **89** with cyclic imines **90** for the enantioselective construction of indoloquinolizidines (**92** and **93**).[59] The reaction is catalyzed by a primary aminothiourea **91** in combination with acetic acid **(Scheme 1.32).** The reaction requires carboxylic acid for the activation of imine as well as the condensation or hydrolysis involved in the catalytic cycle. The primary aminothiourea plays an important role as dual activator. It activates both enone and imine. This protocol is also applicable for the synthesis of benzoquinolizidines (**96** and **97**) as well. In both the cases formation of exo and endo products are observed **(Scheme 1.33)**.

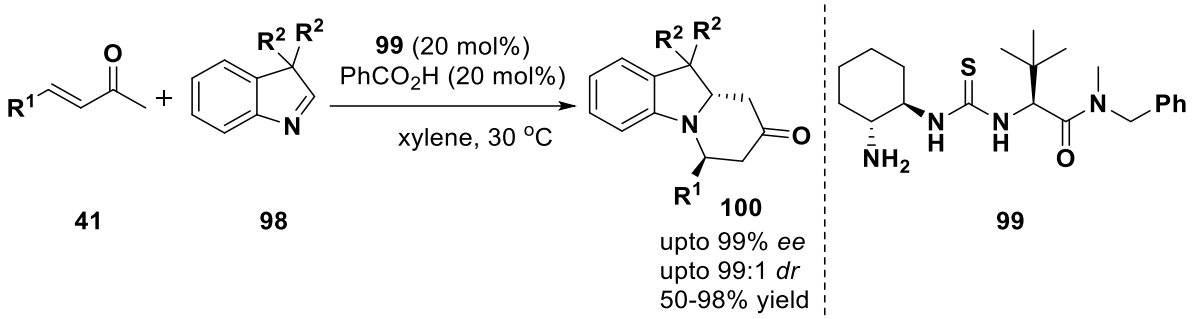


Scheme 1.32. Enantioselective synthesis of indoloquinolizidines via formal aza-Diels-Alder reaction.

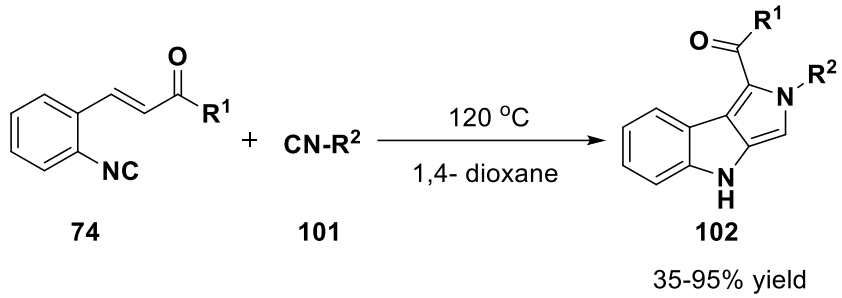


Scheme 1.33. Enantioselective synthesis of benzoquinolizidines via formal aza-Diels-Alder reaction.

Later in 2015, Hu *et al*. unravelled an organocatalyzed asymmetric synthesis of hexahydropyrido[1,2-*a*]indole-2-ones **100** from *α,β*-unsaturated ketones **41** and 3*H*-indoles **98**.[60] They have used a primary amine thiourea bifunctional catalyst **99** to promote the formal aza-Diels-Alder reaction of *α,β*-unsaturated ketone under mild conditions **(Scheme 1.34)**. As mentioned in the earlier report, the catalyst acts as an activator of both the substrates. The primary amine part of the catalyst activates the enone, while the thiourea component through hydrogen bonding binds with the imine. This methodology is very useful for the enantioselective construction of chiral hexahydropyrido[1,2-*a*]indole-2-ones **100**. In 2016, a cross cycloaddition between isocyanides **101** and 2-isocyanochalcones **74** for the synthesis of pyrrolo[3,4-*b*]indoles **102** was documented.[61] The reaction proceeds through a heterodimerization of isocyanides under thermal conditions **(Scheme 1.35)**.

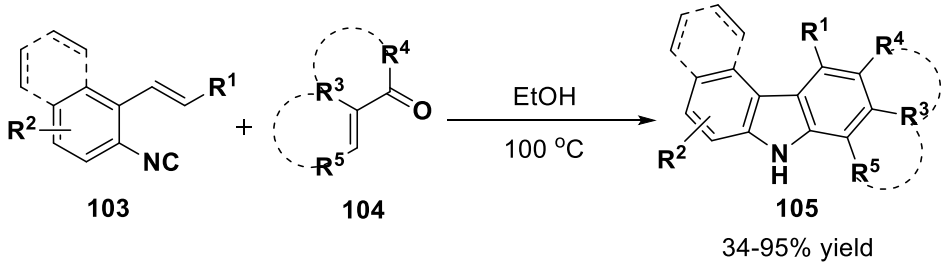


Scheme 1.34. Organocatalyzed asymmetric synthesis of hexahydropyrido[1,2-*a*]indole-2-ones.



Scheme 1.35. Organocatalyzed synthesis of pyrrolo[3,4-*b*]indoles.

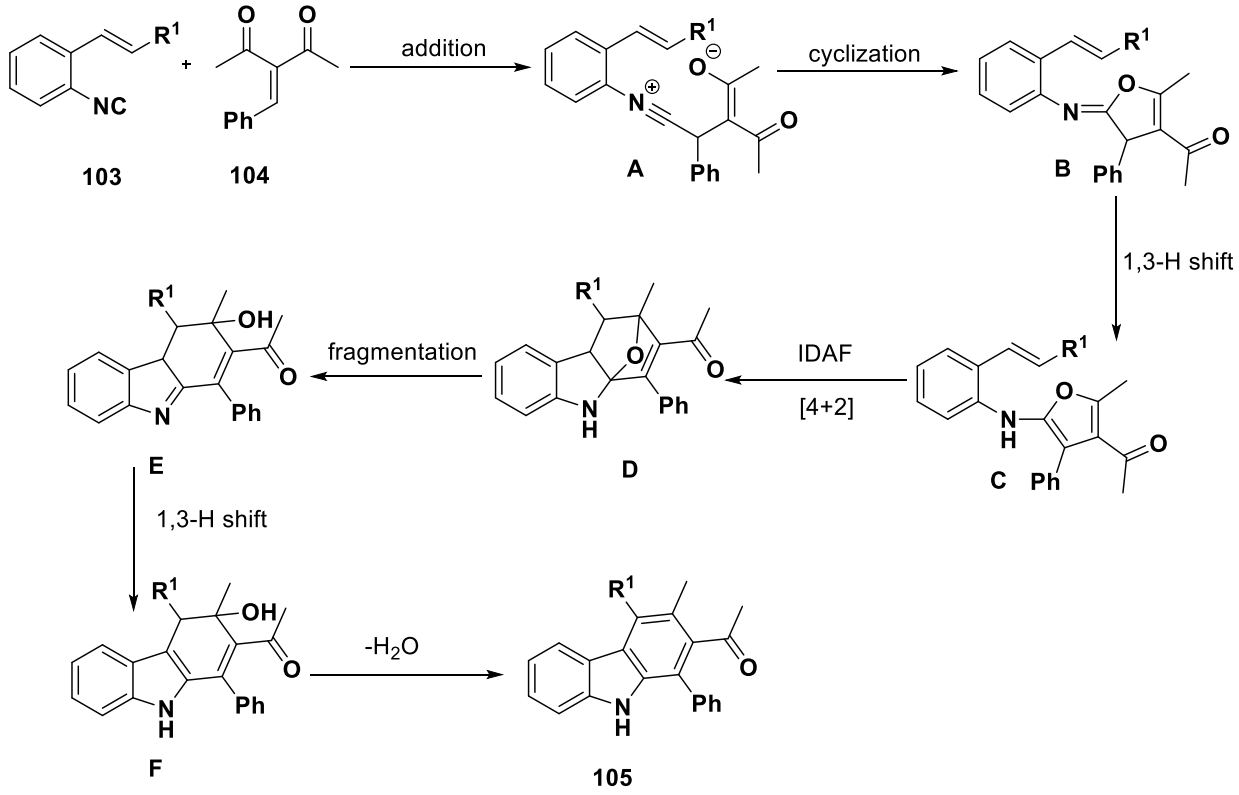
In 2018, Men *et al*. developed a metal-free protocol for the efficient synthesis of carbazoles **105**. It is a [1+2+3] annulation strategy which uses alkenyl arylisocyanides **103** and *α,β*-unsaturated ketones **104** as the substrates **(Scheme 1.36)**.[62] This environmentally benign protocol features the construction of two rings and three bonds in one pot.



Scheme 1.36. Facile synthesis of carbazoles via [1+2+3] annulation strategy.

The reaction involves following steps in the formation of the carbazole **105**. Initially, nucleophilic addition of the isocyanide **103** to enone **104** occurs generating the zwitter ionic intermediate **A**. Subsequent cyclization of **A** followed by 1,3-hydrogen shift affords

aminofuran **C**. Intramolecular Diels-Alder reaction of aminofuran produces a bridged intermediate **D** which on further C-O fragmentation and 1,3-hydrogen shift yields **F**. Finally, loss of water from **F** affords the carbazole **105** (**Scheme 1.37**).



Scheme 1.37. Proposed mechanism for the synthesis of carbazoles.

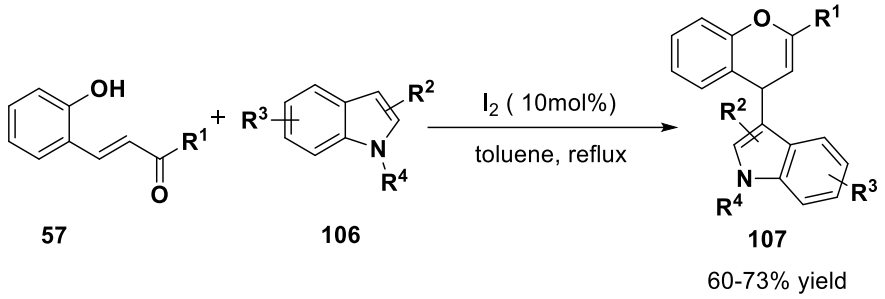
1.4. Synthesis of oxygen containing heterocycles

Similar to the nitrogen heterocycles, oxygen bearing molecules are important class of heterocyclic compounds which are widely distributed in the nature. These structural scaffolds constitute an integral part of various pharmaceuticals and biologically active compounds.[63] Various synthetic protocols developed for the synthesis of oxygen containing heterocycles are discussed in the following sections.

1.4.1 Chroman derivatives

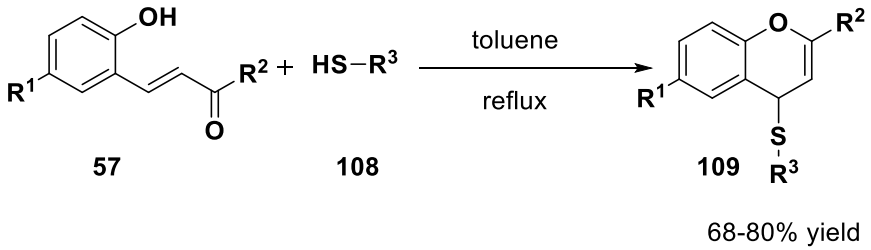
Chroman and chromene are important oxygen bearing structural units. These unique heterocyclic scaffolds are endowed with broad spectrum of biological properties and are widely distributed in the nature. Chroman derivatives are used as key intermediates in the

synthesis of various natural products.[64] In 2012 Yin *et al*. developed an iodine mediated multicomponent method for the synthesis of indolyl chromenes **107** from *o*-hydroxychalcones **57** and indoles **106 (Scheme 1.38)**.[65] The one pot reaction involves Michael addition of indole **106** to *o*-hydroxychalcone **57** followed by intramolecular cyclisation and loss water **(Scheme 1.38)**.



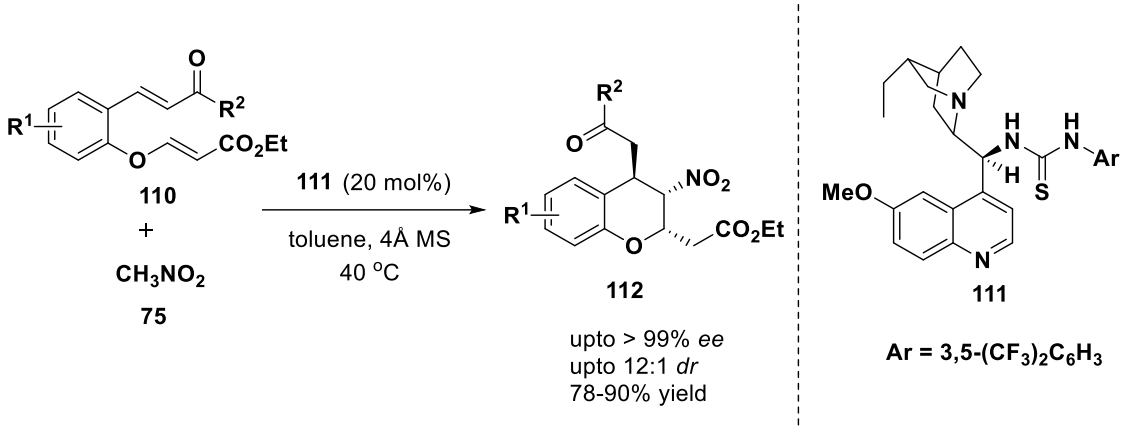
Scheme 1.38. Iodine mediated multicomponent synthesis of indolyl chromene.

Later in 2013, a metal-free protocol for the synthesis of thio-substituted chromenes was reported by Yin *et al*.[66] The protocol furnishes 4-thio-substituted-2-aryl-4*H*-chromenes **109** from 2-hydroxychalcones **57** under catalyst free conditions **(Scheme 1.39)**. The reaction is found to be compatible with aryl as well as aliphatic thiols.



Scheme 1.39. Synthesis of thio-substituted chromenes via intramolecular cyclization sequence.

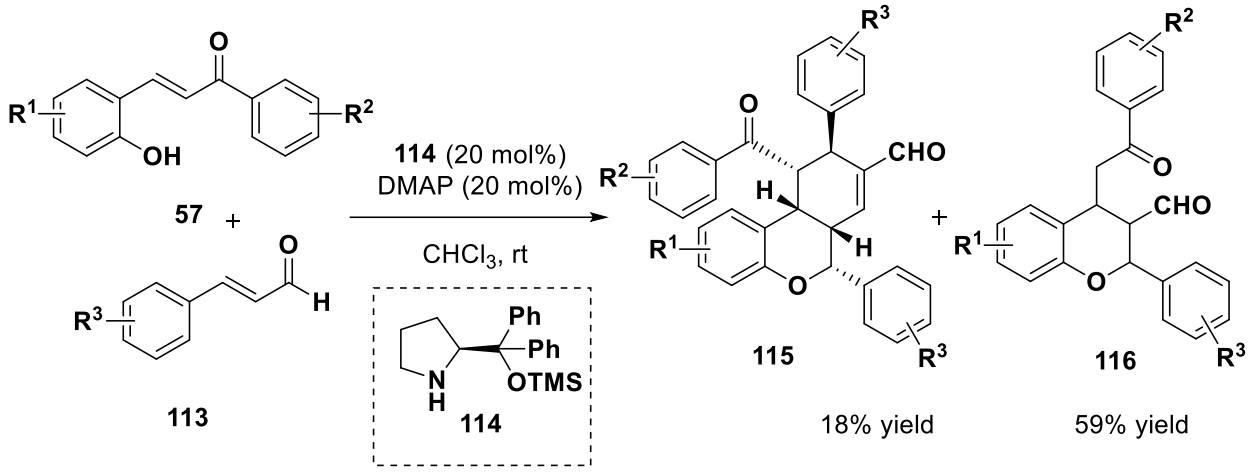
A bifunctional thiourea **111** catalyzed approach towards chiral chromans **112** was devised by Jia *et al.* in the same year.[67] They have used chalcone enolates **110** and nitromethane **75** as the reaction partners **(Scheme 1.40)**. The asymmetric synthesis proceeds via a cascade of double Michael addition reactions. Successful formation of chiral chromans endowed with three consecutive stereocenters under mild conditions is the attraction of this protocol.



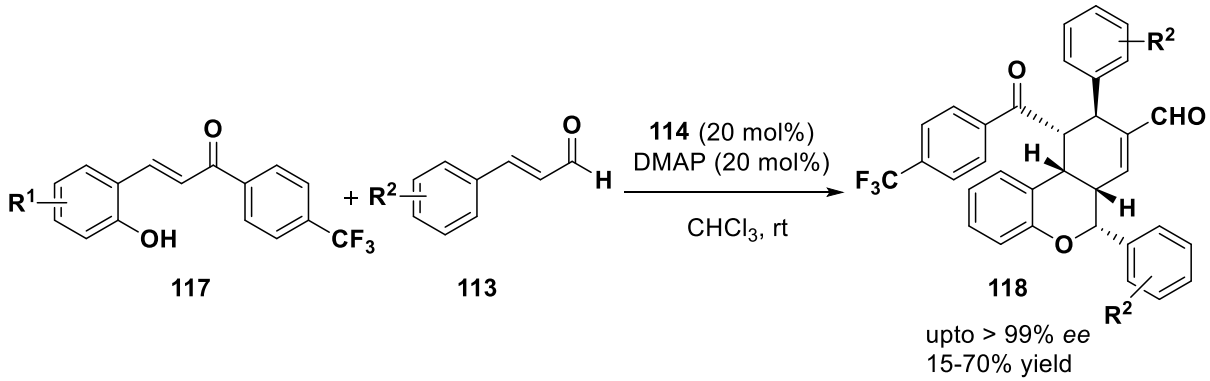
Scheme 1.40. Bifunctional thiourea catalyzed approach towards chiral chromans.

While Liu *et al*. reported an asymmetric synthesis of chiral chromene derivatives **115** bearing five stereocenters from *o*-hydroxychalcones **57** and cinnamaldehydes **113 (Scheme 1.41)**.[68] It is achieved through an organocatalyzed quadrupole reaction. Interestingly, under the optimized reaction conditions formation of product **116** is also observed. But when the reaction is carried out with 2-hydroxy-4'-(trifluoromethyl)chalcones **117** chiral chromene derivative **118** is obtained as the sole product **(Scheme 1.42)**. The reaction has a limited substrate scope. The yield of the reaction is highly influenced by the steric and electronic nature of the substituent present on the *o*-hydroxychalcone. This one pot protocol proceeds through a cascade of oxa-Michael-Michael-Michael-aldol quadrupole reaction sequence.

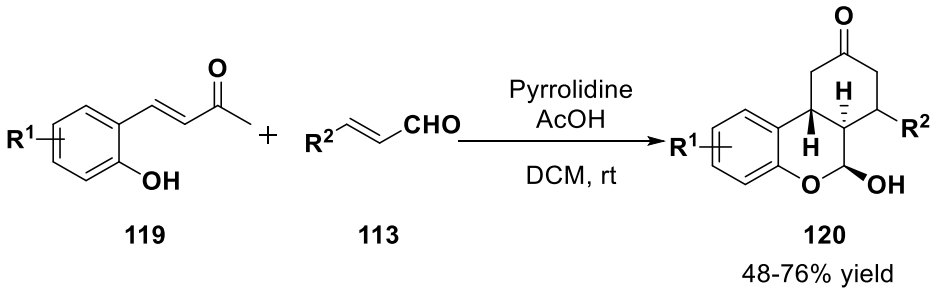
Using variously substituted cinnamaldehydes **113** and 4-(2-hydroxyphenyl)but-3-en-2-ones **119** as the substrate, Liu *et al*. devised a pyrrolidine promoted diastereoselective approach towards polycyclic chromen-9-one derivatives **120 (Scheme 1.43)**.[69] In this reaction pyrrolidine plays an important role as dual activator for both enone and enal in the presence of acetic acid. Interestingly, 2-thiofuran core is also found to be compatible under the optimized reaction conditions.



Scheme 1.41. Asymmetric synthesis of chiral chromene derivatives.



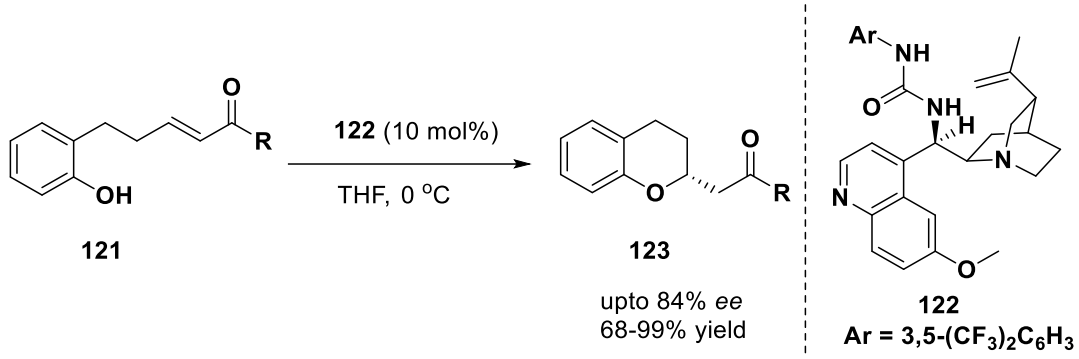
Scheme 1.42. Synthesis of chiral chromene derivatives.



Scheme 1.43. Pyrrolidine promoted synthesis of polycyclic chromen-9-one derivatives.

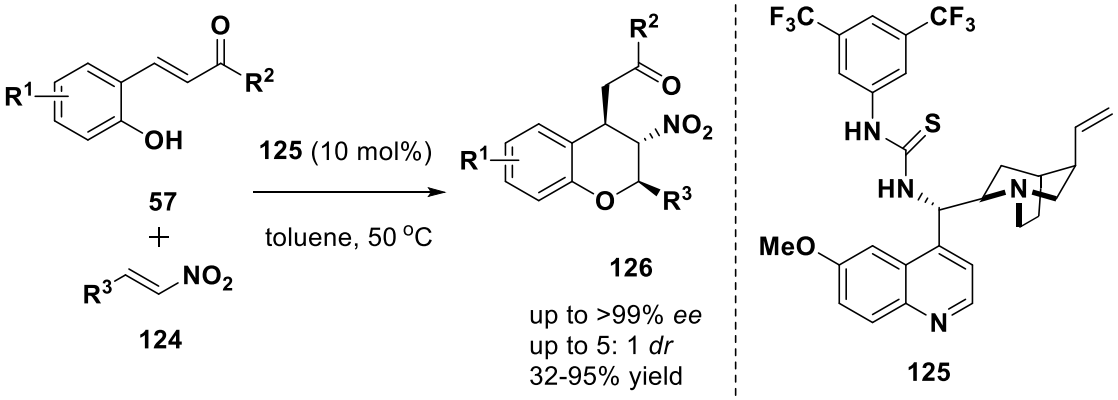
Based on the concept of intramolecular oxa-Michael addition, Miyaji *et al*. documented an asymmetric synthesis of 2-substituted chromans **123 (Scheme 1.44)**.[70] The reaction utilizes

phenol bearing *α,β*-unsaturated ketones **121** as the substrate. The oxa-Michael addition is promoted by cinchona-alkaloid-urea based bifunctional catalyst **122**.



Scheme 1.44. Asymmetric synthesis of 2-substituted chromans.

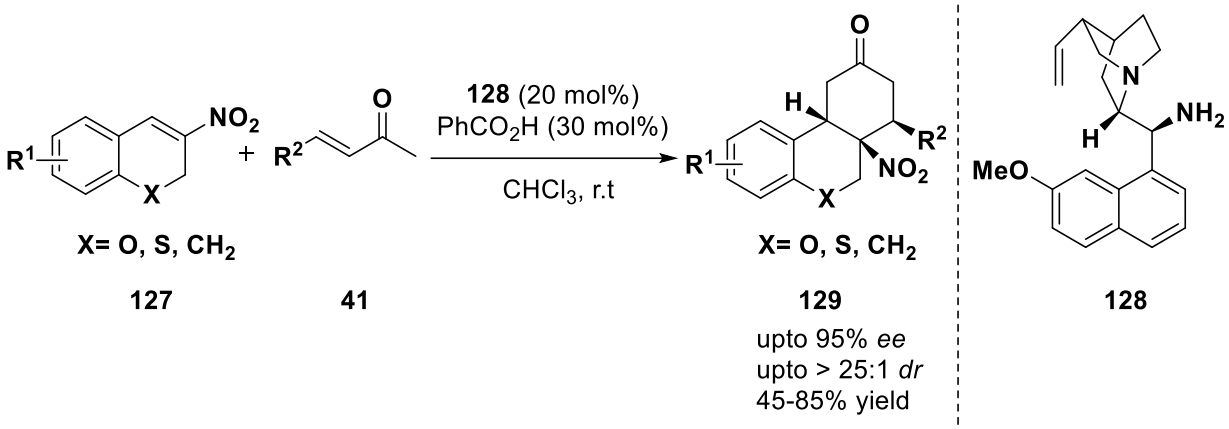
In 2015, Saha *et al*. demonstrated an Oxa-Michael-Michael reaction sequence for the synthesis of highly substituted chiral chroman derivatives **126**.[71] The protocol used *o*-hydroxychalcones **57** and *trans* nitroalkenes **124** as the substrates and bifunctional thiourea **125** as the catalyst **(Scheme 1.45)**. The excellent enantioselectivity (>99%) and diastereoselectivity (5:1) are notable features of the asymmetric synthesis. The optically active chroman derivatives obtained bears three contiguous stereocenters.



Scheme 1.45. Bifunctional thiourea catalyzed synthesis of highly substituted chiral chroman derivatives.

In the same year a double Michael addition reaction towards the enantioselective synthesis of tricyclic chorman derivatives **129** was developed by Li *et al*.[72] The reaction occurs between 3-nitro-2*H*-chromenes **127** and its derivatives with enones **41** in the presence of a

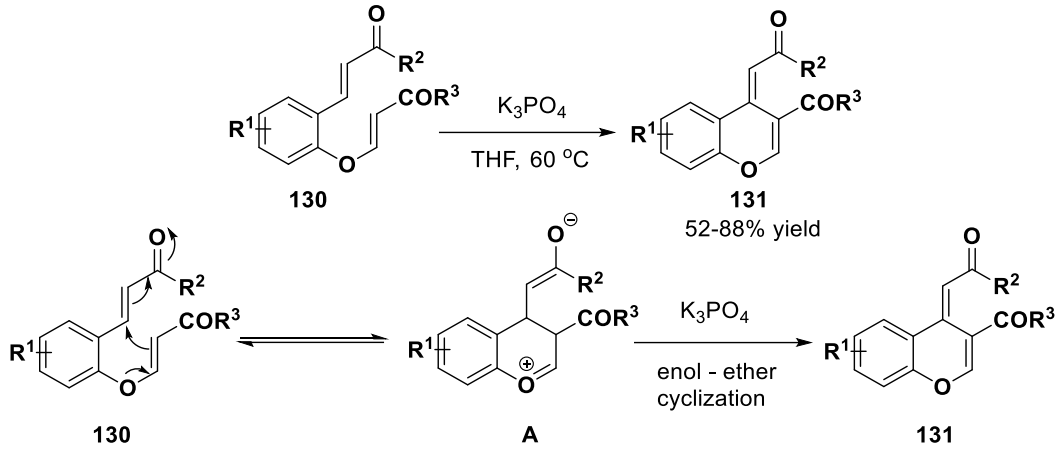
primary amine catalyst **128** and benzoic acid **(Scheme 1.46)**. In addition to the synthesis of tetrahydro-6*H*-benzo[*c*]chromene, this protocol gives access to tetrahydro-6*H*-benzo[*c*]thiochromene and hexahydrophenanthrene as well.



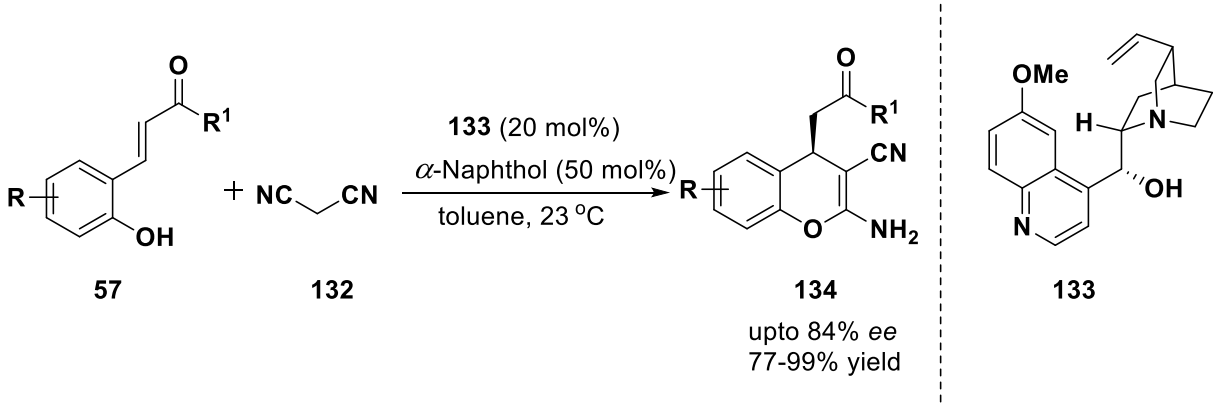
Scheme 1.46. Enantioselective synthesis of tricyclic chroman derivatives.

An inorganic base mediated intramolecular Rauhut-Currier type reaction was reported by Bhunia *et al*. in 2016 for the synthesis of functionalized 4*H*-chromenes **131** from enon-enoate **130 (Scheme 1.47)**.[73] This reaction is compatible with bis(enone) as well and affords 4*H*-chromene bearing 1,5-diketone. The reaction proceeds through an intramolecular cyclization of enone-enoate **129** affording oxonium enolate **A**, which in the presence of stoichiometric amounts of K_3PO_4 yields 4*H*-chromene derivative **131**. The synthetic potential of the methodology was successfully showcased by carrying out various synthetic transformations on the 4*H*-chromene derivatives.

Zheng *et al*. in 2016, developed a cinchona alkaloid **133** catalyzed enantioselective synthesis of amino and nitrile group substituted chromene derivatives **134 (Scheme 1.48)**.[74] The reaction proceeds via Michael addition between *o*-hydroxychalcones **57** and malononitrile **132** followed by intramolecular cyclization. Moreover, a combination of quinine and α-naphthol is found to have a pronounced effect on the enantioselectivity of the reaction. Solvent polarity also has prominent influence on the enantioselective formation of 3-amino-2-nitrile chromenes **134**.

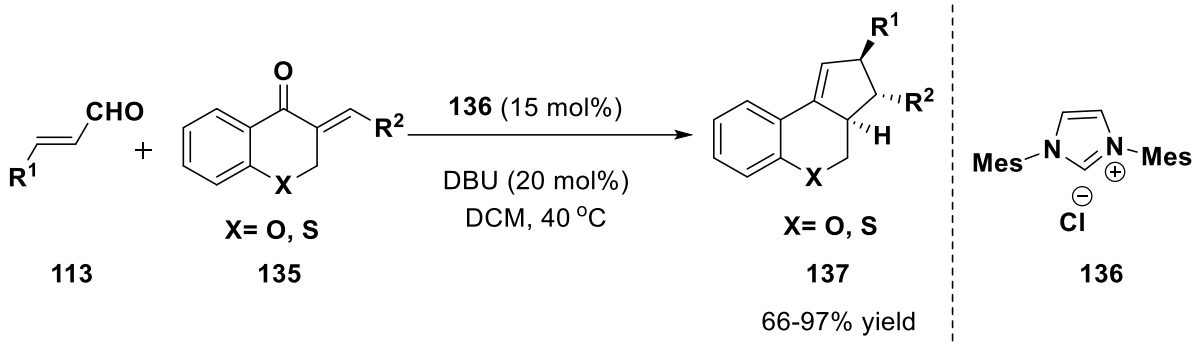


Scheme 1.47. Synthesis of functionalised 4*H*-chromene via base mediated intramolecular Rauhut-Currier type reaction.



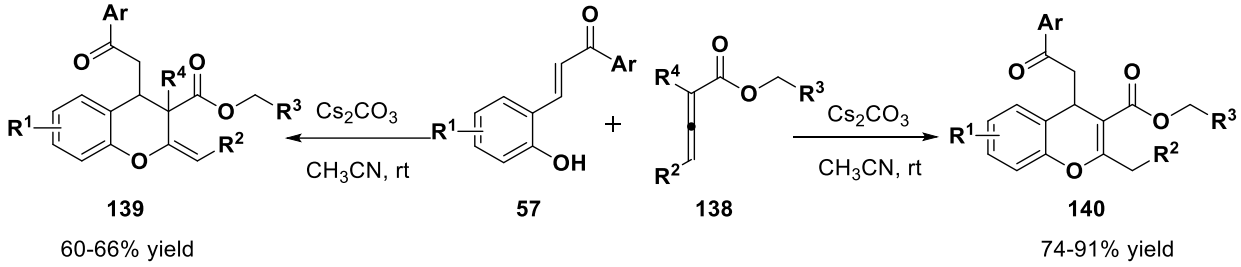
Scheme 1.48. Cinchona alkaloid catalyzed enantioselective synthesis of amino and nitrile group substituted chromene derivatives.

Later, Krishnan *et al*. reported a homoenolate annulation reaction of enones **135** with enals **113** under mild conditions.[75] The reaction affords substituted tetrahydrocyclopentachormenes and tetrahydrocyclopentathiochromenes **137** with high yields **(Scheme 1.49)**.



Scheme 1.49. DBU mediated facile synthesis of tetrahydrocyclopentachormenes and tetrahydrocyclopentathiochromenes.

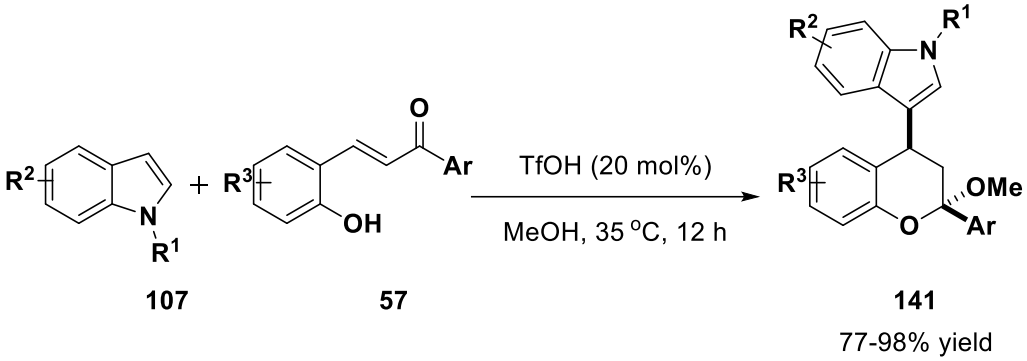
In 2018, Rouh *et al*. reported a substrate controlled approach towards chromene **140** and chroman **139** derivatives via a [4+2] annulation reaction of *o*-hydroxychalcones **57** **(Scheme 1.50)**.[76] The reaction involves annulation of hydroxychalcone **57** with allenoate **138** to produce chromene derivatives **140** in the presence of Cs_2CO_3 under ambient temperature. But α substituted allenoate furnishes chroman derivates **139** under identical reaction conditions.



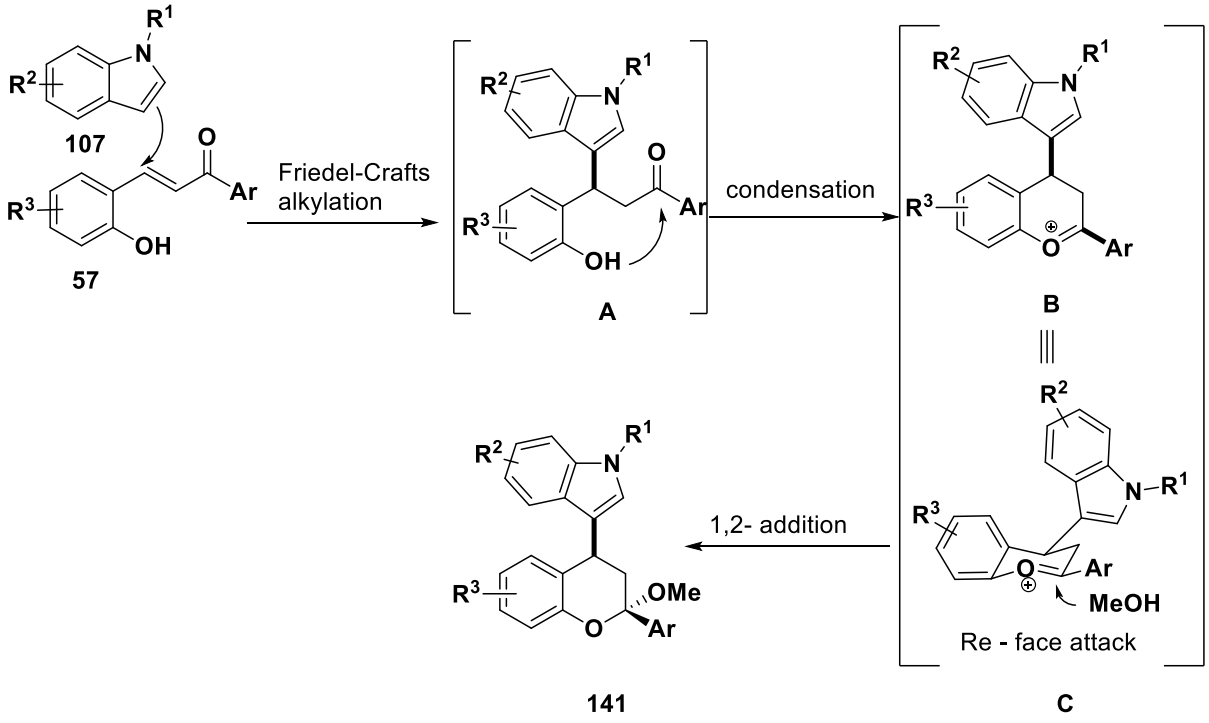
Scheme 1.50. Cs_2CO_3 mediated synthesis of chromenes and chromans.

Guo *et al*. proposed a TfOH catalyzed three component reaction which gives easy access to indole substituted chromans **141** from readily available substrates (**Scheme 1.51**).[77] It is the first literature report on the TfOH catalyzed Friedel Crafts alkylation/ ketalization sequence of alcohols, indoles **107**, and *o*-hydroxychalcones **57**. The multicomponent reaction involves Friedel Crafts reaction between indole and *o*-hydroxychalcone furnishing the intermediate **A**. The intramolecular condensation of **A** leads to the formation of oxocarbenium ion **B**. The nucleophilic attack of the alcohol from the re-face of the oxocarbenium ion delivers the final product **141** (**Scheme 1.52**). To highlight the synthetic potential of this protocol author

has successfully performed various synthetic transformations on the 2-indole substituted chromans. High yield, selective formation of a single diastereomer, column free purification of the products and mild reaction conditions are the attraction of this protocol.



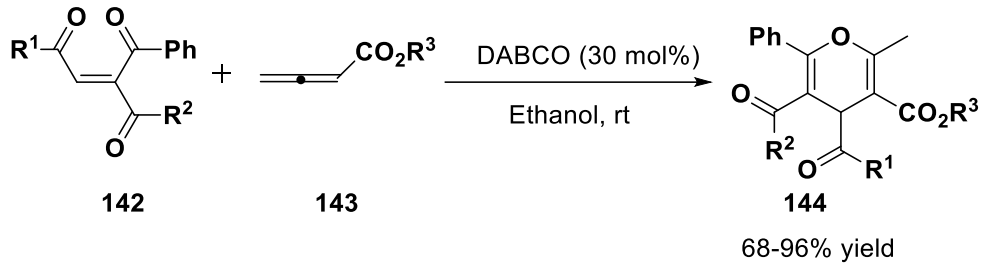
Scheme 1.51. A multicomponent Friedal Crafts reaction for the synthesis of 2-indole substituted chromans.



Scheme 1.52. Mechanism proposed for the synthesis of indole substituted chromans.

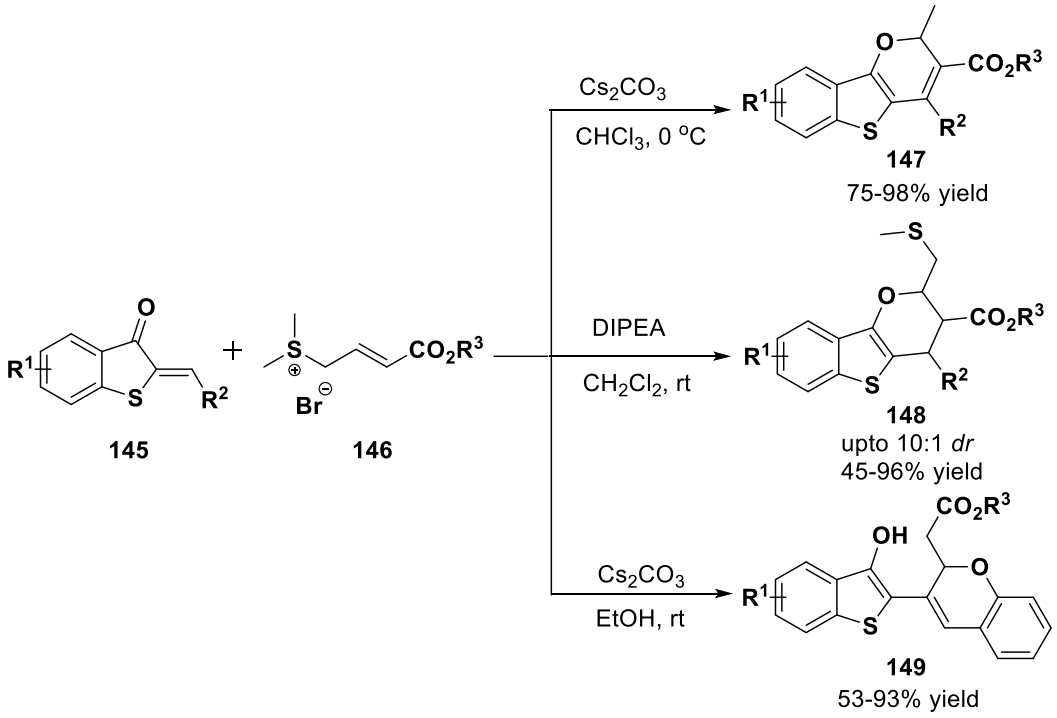
1.4.2. Pyran and its derivatives

Pyran and its derivatives are widely found in various biologically active natural products. Dihydropyrans are used as key intermediates in the synthesis of carbohydrates.[78] In 2016 Meng and co-workers demonstrated synthesis of dihydropyans **144** utilising the reactivity of allenoates **143** as 1,2-dipole in a formal [4+2] cycloaddition reaction **(Scheme 1.53)**.[79] 1,4-enedione **142** is used as the competent reaction partner in this protocol. It is a DABCO catalyzed highly regioselective reaction and affords multisubstituted dihydropyrans under mild reaction conditions.



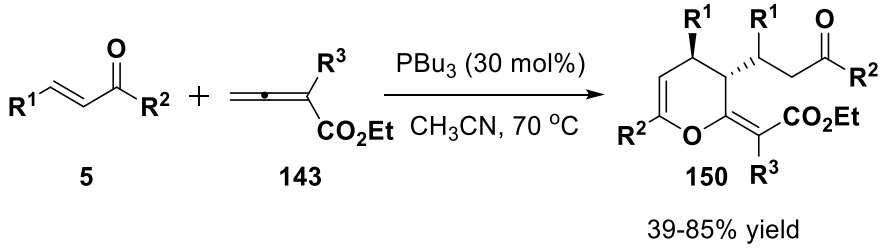
Scheme 1.53. DABCO catalyzed regioselective synthesis of multisubstituted dihydropyrans.

Later, Ding *et al*. unravelled a base mediated [4+2] annulation reaction of crotonate derived sulphur ylides **146** with thioaurone analogues **145** for the construction of benzothiophene fused pyran derivatives (**147** and **148**).[80] The reaction marks the first ever report on crotonate derived sulphur ylide being used as a two carbon synthon **(Scheme 1.54)**. It is a substrate controlled divergent synthetic protocol which gives access to pyran derivatives (**147** and **148**) as well as chromene derivatives **149** under mild reaction conditions. The reaction furnishes benzothiophene fused pyran when thioaurone analogues bearing acyl or ester group is used as the substrate in the presence of Cs_2CO_3. While arylidene thioaurone affords pyran incorporated with sulphide unit **148** in the presence of DIPEA as the base. Interestingly when a hydroxyl group is introduced on the aryl ring of the arylidene thioaurone, formation of 3-benzothiophene substituted chromene **149** is observed **(Scheme 1.54)**.

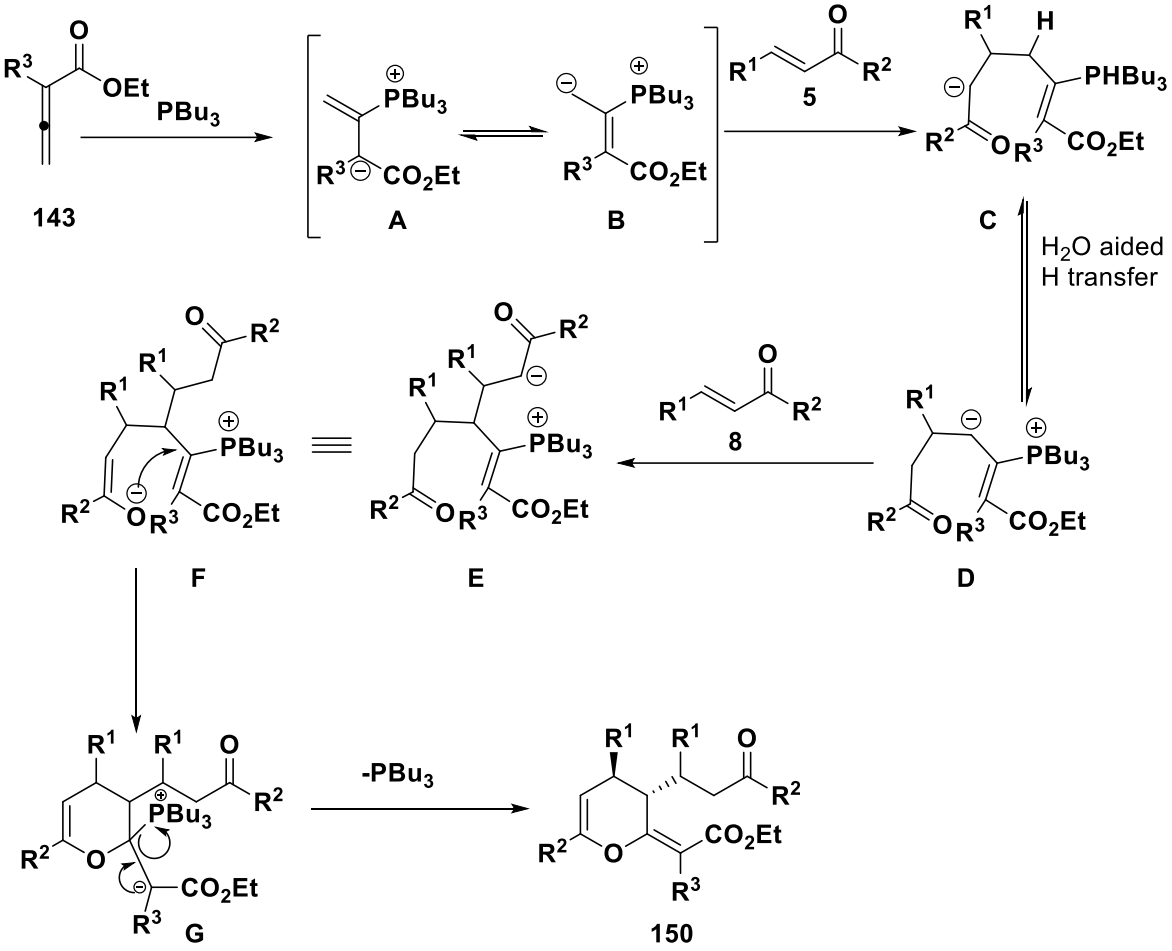


Scheme 1.54. Base mediated construction of benzothiophene fused pyran derivatives.

Li and co-workers in 2018 established a domino reaction between allenoates **143** and *α,β*-unsaturated ketones **5** to access polysubstituted dihydro-2*H*-pyrans **150** under phosphine catalysis.[81] The reaction utilizes two molecules of the enone to afford highly substituted dihydropyran core with excellent stereoselectivity **(Scheme 1.55)**. According to the proposed mechanism the reaction is triggered by the formation of a zwitter ionic intermediate **A** by the attack of the phosphine catalyst to the allenoate. The zwitter ion then undergoes Michael addition with the *α,β*-unsaturated ketone **5**. Subsequent water aided hydrogen transfer generates the intermediate **D** from the Michael adduct **C**. Michael addition of **D** with the second molecule of *α,β*-unsaturated ketone followed by intramolecular cyclization and elimination of the phosphine catalyst delivers the final product **(Scheme 1.56)**.

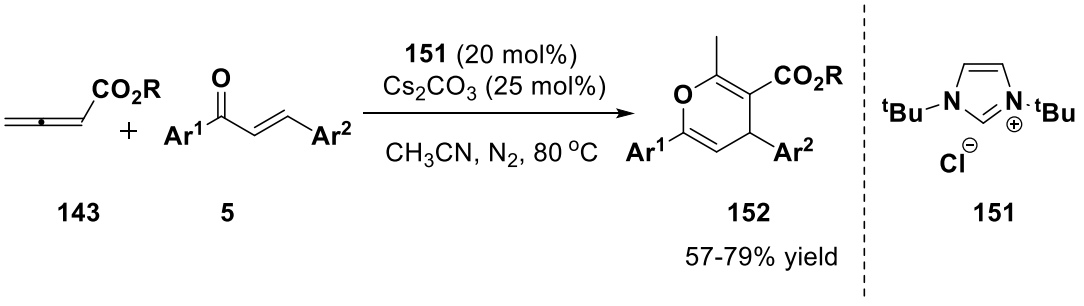


Scheme 1.55. Stereoselective synthesis of polysubstituted dihydro-2*H*-pyrans.



Scheme 1.56. Proposed mechanism for the formation of dihydro-2*H*-pyrans.

In the same year Hu *et al*. demonstrated the synthesis of multisubstituted pyranyl carboxylates **152** from allenoates **143** and chalcones **5 (Scheme 1.57)**.[82] It is a [4+2] annulation reaction of allenoate with chalcone in the presence of imidazolium catalyst **151** and Cs_2CO_3. This atom economic reaction requires only mild conditions to operate.



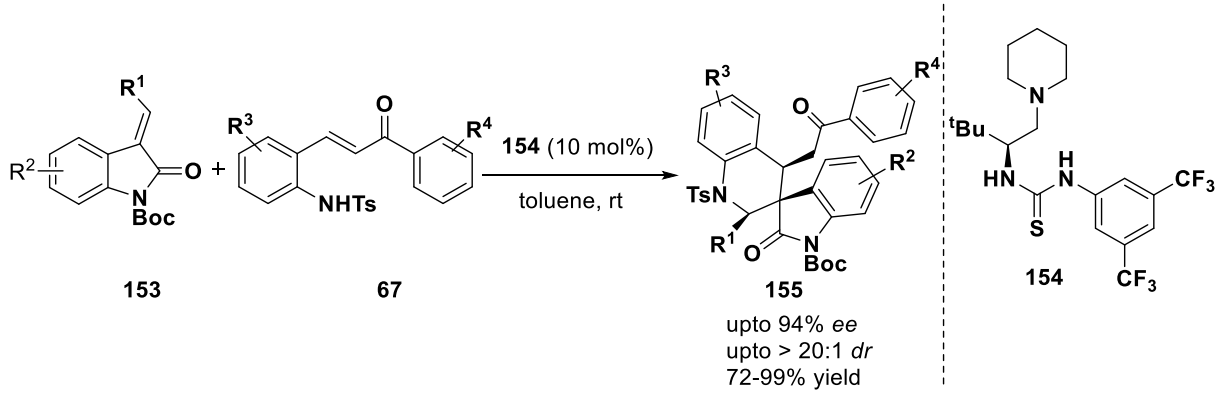
Scheme 1.57. NHC catalyzed synthesis of multisubstituted pyranyl carboxylates.

1.5. Synthesis of Spiroheterocycles

Spiro heterocyclic skeletons are found in numerous natural alkaloids and pharmaceuticals. These structural motifs are endowed with wide spectrum of biological activities.[83] Hence numerous protocols have been established till now for accessing various spiro molecules of structural complexity.

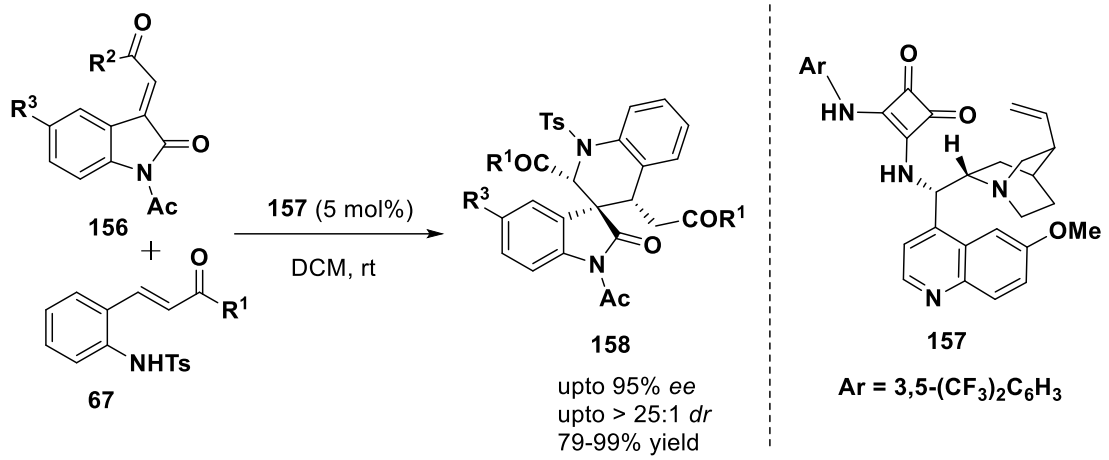
1.5.1. Spirooxindole

Among various spiroheterocyclic compounds spirooxindoles, especially those bearing five or six membered carbo or heterocycles are found in numerous alkaloids of biological significance. They have attained growing interest among synthetic organic chemists owing to its importance as emerging drug candidates. Huang *et al*. in 2013, reported an amino acid derived tertiary amine thiourea **154** catalyzed enantioselective synthesis of polysubstituted spirooxindole-tetrahydroquinolines **155** (**Scheme 1.58**).[84] The reaction involves aza-Michael-Michael addition reaction of 2-tosylaminochalcones **67** with methyleneindolinones **153** under mild reaction conditions.



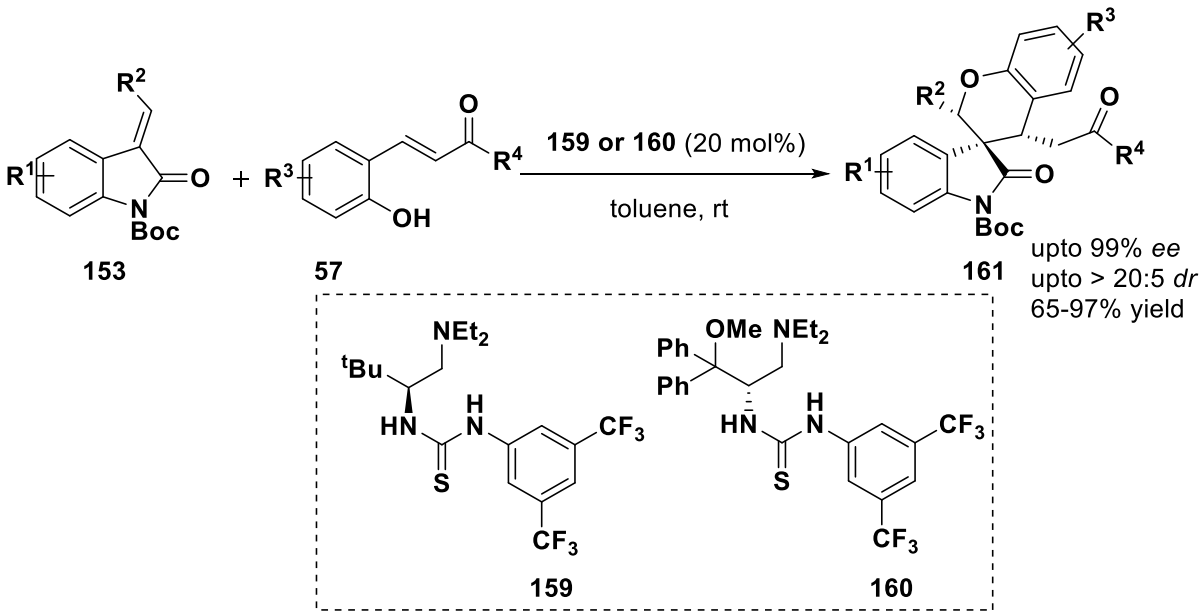
Scheme 1.58. Organocatalyzed asymmetric synthesis of polysubstituted spirooxindole-tetrahydroquinolines.

In the same year a similar reaction was reported by Yang and co-workers. The have used a squaramide catalyst **157** in the reaction to achieve the synthesis of tetrahydroquinoline fused spirooxindoles **158** (**Scheme 1.59**).[85] Additionally, the protocol is compatible with *β*-ester group substituted 3-ylideneoxindoles as well.



Scheme 1.59. Enantioselective synthesis of spirooxindole-tetrahydroquinolines.

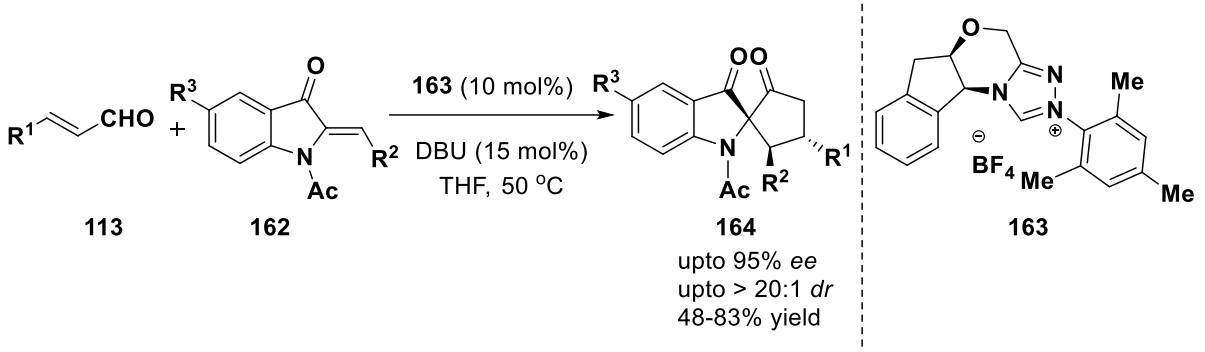
Later Huang and co-workers reported an asymmetric synthesis of spirooxindole-chroman derivatives **161** from *o*-hydroxychalcones **57** and methyleneindolinones **153** **(Scheme 1.60)**.[86] Interestingly two types of tertiary amine catalysts **159** and **160** are found to be suitable for the reaction. The reaction proceeds through an Oxa-Michael-Michael addition cascade.



Scheme 1.60. Asymmetric synthesis of spirooxindole-chroman derivatives.

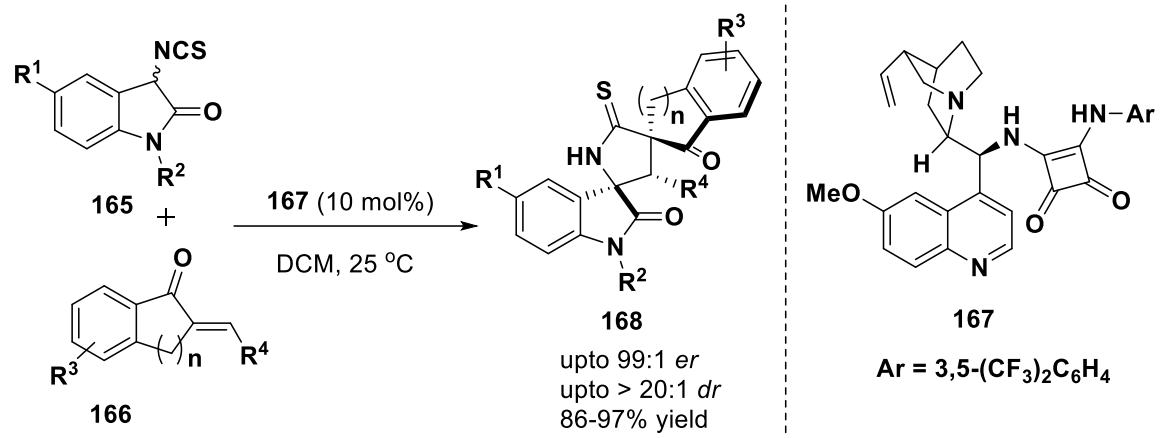
An NHC catalyzed enantioselective protocol towards spiro-pseudoindoxyl moieties **164** was reported by Glorius group.[87] The reaction proceeds through a [3+2] annulation

reaction of enals **113** with aurone/azaaurones **162 (Scheme 1.61)**. The desired products are obtained with excellent enantioselectivity in the presence of azolium catalyst **163** and DBU in THF at ambient temperature.



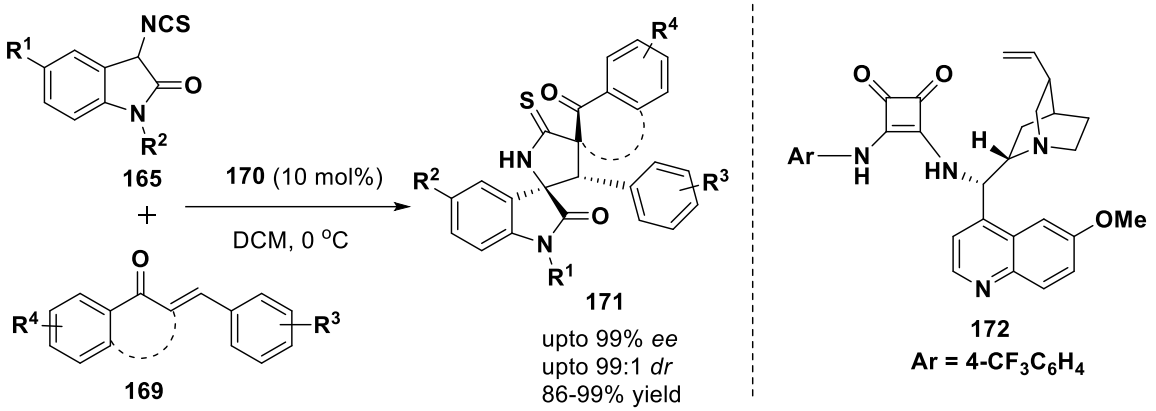
Scheme 1.61. NHC catalyzed enantioselective protocol towards spiro-pseudoindoxyl moieties.

In 2016, Kayal *et al*. devised a straight forward synthetic route to 3,2'-pyrrolidinyl bispirooxindoles **168** from 3-isothiocyanato oxindoles **165** and exocyclic *α,β*-unsaturated ketones **166 (Scheme 1.62)**.[88] It is a tertiary amino squaramide **167** catalyzed Michael addition-cyclization strategy. The reaction successfully delivered the spirocycles, which contains three adjacent stereocenters and two all carbon quaternary centers, in a single operation with excellent diastereoselectivity.



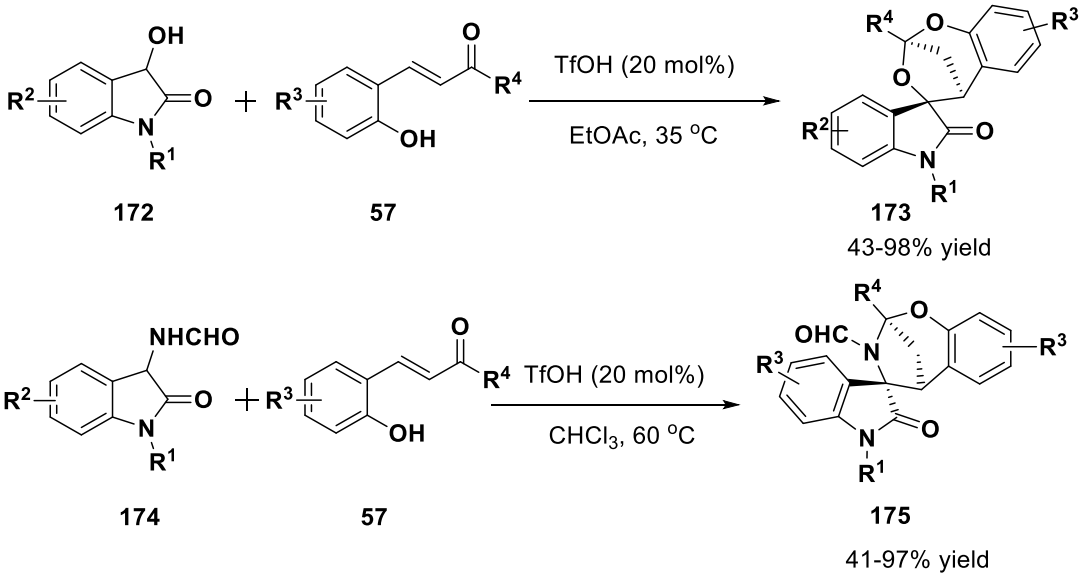
Scheme 1.62. Tertiary amino squaramide catalyzed synthesis of pyrrolidinyl bispirooxindoles.

A similar reaction of 3-isothiocyanato oxindoles **165** with enones **169** was reported by Lin and co-workers in 2017.[89] The reaction utilises a bifunctional cinchona derived squaramide **170** as the catalyst to achieve the synthesis of chiral 3,2'-pyrrolidinyl spiroxindoles **171** with excellent diasteroselectivity and enantioselectivity **(Scheme 1.63)**.



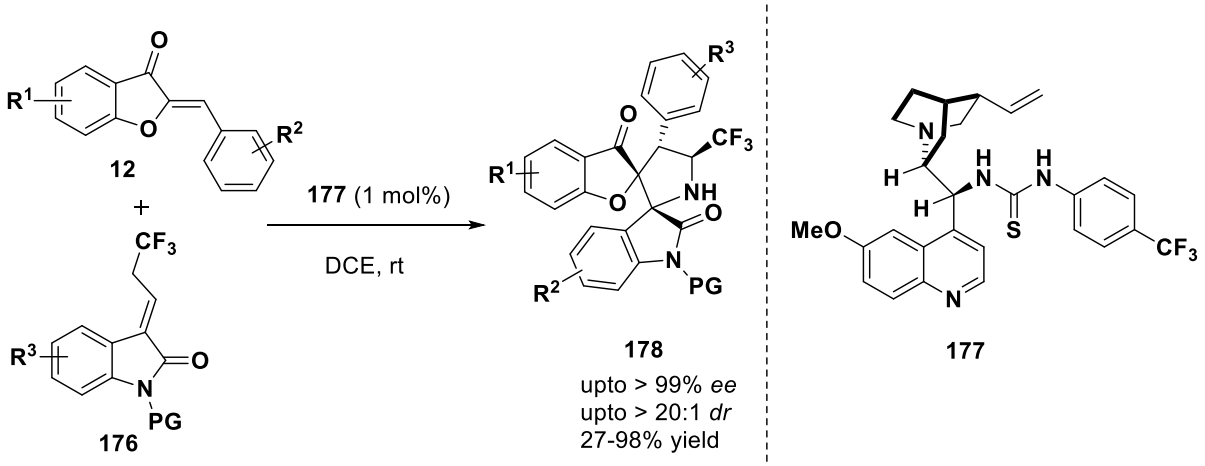
Scheme 1.63. Organocatalyzed synthesis of pyrrolidinyl bispirooxindoles.

Later Zhu *et al*. introduced a TfOH catalyzed straight forward synthesis of bridged ketal spirooxindoles **173**.[90] They have used 3-hydroxyoxindoles **172** and *o*-hydroxychalcones **57** as the substrates for the reaction **(Scheme 1.64)**. The reaction proceeds through Michael addition, ketalization sequence. They have successfully extended the protocol to accomplish the synthesis of spirooxindoles **175** bearing bridged cyclic *N*,*O*-ketals.[95] The reaction is carried out between *o*-hydroxychalcones **57** and 3-aminooxindoles **174 (Scheme 1.64)**.



Scheme 1.64. TfOH catalyzed diverse synthesis of spiroheterocycles.

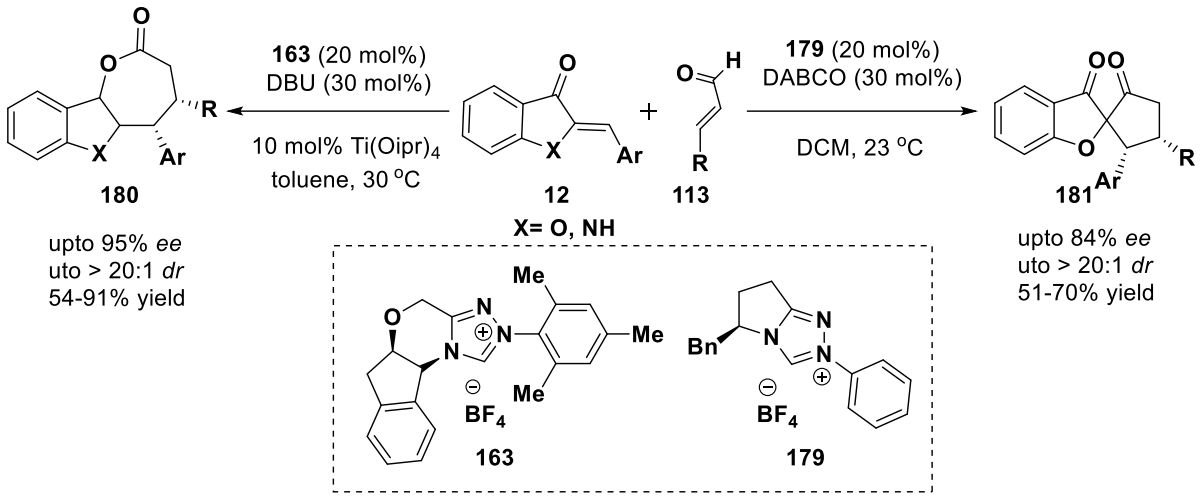
Recently in 2019 Li *et al*. devised an enantioselective organocatalyzed 1,3-dipolar cycloaddition reaction of *N*-2,2,2-trifluoroethylisatin ketimines **176** with aurones **12** for the construction of bispiro[benzofuran-oxindole-pyrrolidine] derivatives **178 (Scheme 1.65)**.[91] In this reaction *N*-2,2,2-trifluoroethylisatin ketimine **176** act as the precursor of azomethine ylide. The reaction involves the initial Michael addition of the in situ generated azomethine ylide to aurone **12** and intramolecular Mannich reaction to furnish the bispiro[benzofuran-oxindole-pyrrolidine] **178**.



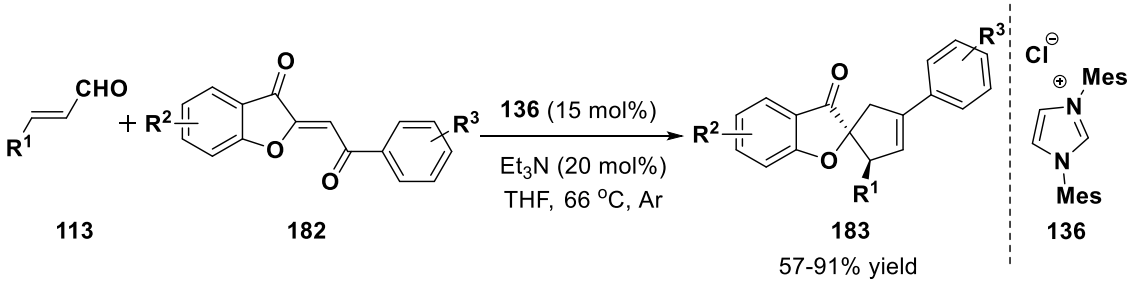
Scheme 1.65. Enantioselective organocatalyzed synthesis of bispiro[benzofuran-oxindole-pyrrolidine] derivatives.

1.5.2. Other Spiroheterocycles

In 2014 Wang *et al.* devised an NHC catalyzed divergent synthetic protocol for the construction of spiroheterocycle **181** as well as benzofuran or indole fused *ε*-lactone **180** from *α,β*-unsaturated aldehydes **113** and heterocyclic enones **12 (Scheme 1.66)**.[92] The reaction affords the spirocycle **181** in the presence of the catalyst **179** and DABCO in DCM, while the formation of the benzofuran or indole fused *ε*-lactone **180** is observed when the catalyst **163** is used along with DBU and a metal based Lewis acid. This catalyst controlled divergent reaction proceeds through a [3+2] annulation reaction of enal and enone to deliver spiroheterocycles. On the other hand *ε*-lactone is formed via a [3+4] annulation reaction. In the same year Lakshmi *et al*. reported the synthesis of cyclopentane fused spirobenzofuran-3-ones **183** via NHC catalyzed annulation reaction of enals **113** with aurone analogues **182 (Scheme 1.67)**.[93]

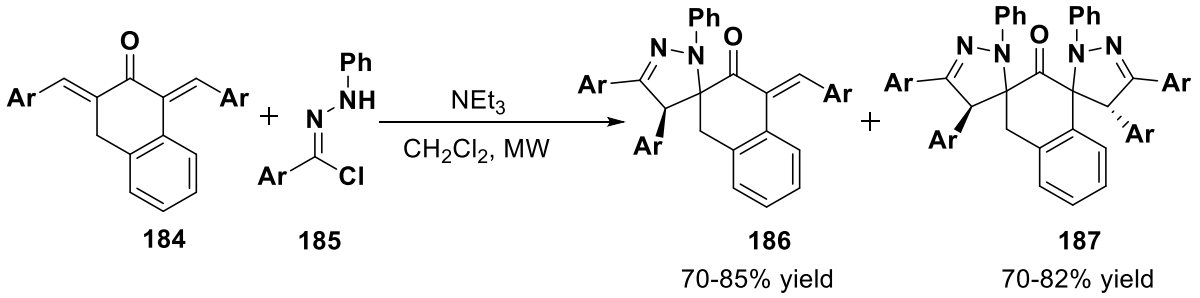


Scheme 1.66. NHC catalyzed divergent synthesis of spiroheterocycles.



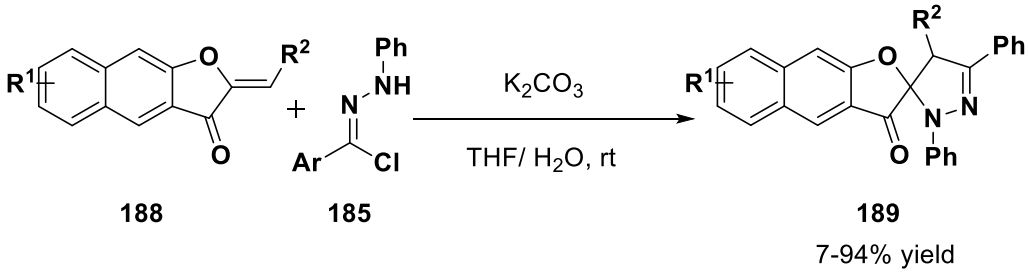
Scheme 1.67. NHC catalyzed annulation leading to cyclopentane fused spirobenzofuran-3-one.

Later Gazzeh and co-workers accomplished a Microwave assisted synthesis of mono and dispiropyrazolines (**186** and **187)**.[94] It is a 1,3-dipolar cycloaddition reaction of in situ generated nitrilimines with exocyclic dienones **184 (Scheme 1.68)**. The outcome of the reaction is highly controlled by the stoichiometry of the hydrazonoyl chloride **185**, which is the precursor of nitrilimine. When the reaction is performed with 1.5 equivalents of hydrazonoyl chloride, the mono spiropyrazoline **186** is formed as the major product, while 3 equivalents of hydrazonoyl chloride affords dispiropyrazoline **187** as the major product. Excellent yield, high regio, chemo and diastereoselectivity are the attraction of this protocol.



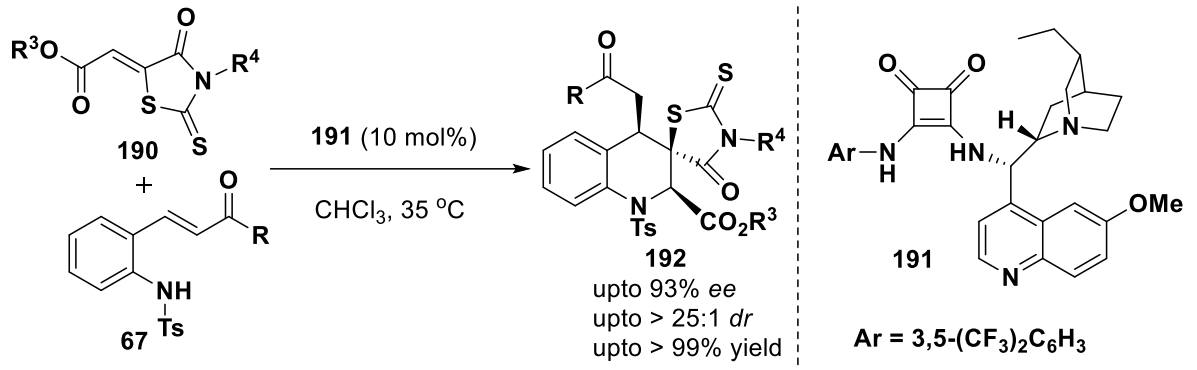
Scheme 1.68. Synthesis of mono and dispiropyrazolines.

Based on the same concept of 1,3 dipolar cycloaddition reaction of in situ generated nitrilimine with enone, Su and co-workers demonstrated an efficient synthesis of spiro naphthofuranone-pyrazolines **189 (Scheme 1.69)**.[95] They have utilized aurone analogues **188** as the competent reaction partner in this catalyst free protocol. It enables the construction of the spiroheterocycle with high regioselectivity under mild conditions.



Scheme 1.69. Synthesis of spiro naphthofuranone-pyrazoline.

In 2018, Song *et al*. disclosed a squaramide **191** catalyzed straight forward synthesis of spirothiazolidinone tetrahydroquinolines **192** from unsaturated thiazolidinones **190** and 2-tosylaminochalcones **67 (Scheme 1.70)**.[96] It is the first report on the organocatalyzed synthesis of chiral spirothiazolidinone tetrahydroquinoline from simple starting materials. This protocol proceeds through a cascade of aza-Michael-Michael addition sequence and affords the spirothiazolidinone tetrahydroquinoline derivatives in a highly diastereo and enantioselective fashion.



Scheme 1.70. Squaramide catalyzed facile synthesis of spirothiazolidinone tetrahydroquinolines.

1.6. Summary and Outline of the Thesis

Heterocycles are ubiquitous structural entities which finds extensive application in our daily life. Hence developement of novel protocols which gives easy access to various heterocyclic scaffolds are of atmost importance. Over these years endless synthetic strategies have been devised and among them transition metal catalyzed reactions are of greater significance. However, nowadays transition metal free protocols are gaining considerable attention in organic synthesis. From the Green Chemistry point of view the iodine catalyzed reactions are appealing owing to low toxicity effects of iodine compared to transition metal catalysts. Iodine or hypervalent iodine reagents are efficient alternative to transition metal catalysts. Bronsted acid and Lewis acid mediated protocols are also promising tools for the successful sunthesis of various heterocyclic molecules of structural complexity. On the other hand *N*-heterocyclic carbene catalysis has tremendously contributed to the synthesis of numerous heterocyclic motifs, especially the asymmetric synthesis. Amine based organocatalysts are also promising candidates in the asymmetric synthesis of heterocyclic entities.

On the other hand *α,β*-unsturated ketones are versatile synthons in organic synthesis. It consists of multiple reaction sites, owing to which, these class of molecules can undergo various reactions and are easily transformable into diverse heterocycles and valuable building blocks. Overall, metal-free and operationally simple methodologies using easily accessible substrates which give access to valuable heterocyclic cores of medicinal as well as industrial relevance are always desirable. In this context, we have explored the chemical reactivity of

α,β-unsturated ketones under metal-free condition towards the synthesis of heterocyclic entities of structural complexity and medicinal relevance.

We have developed a one-pot annulation reaction of arylidenones, alkynes and nitriles for the construction of chromeno/thiochromeno and pyrano/thiopyrano fused *N*-substituted pyridine derivatives in the presence of $BF_3 \cdot OEt_2$ under mild conditions. The details of the reaction are the subject matter of second chapter. Synthesis of spiroaziridine from *α,β*-unsturated ketone and amine in the presence of moleculalr iodine is the highlight of the third chapter. The fourth chapter deals with the one pot synthesis of benzo[*d*]imidazo[1,2-*b*]thiazole tethered with an indole unit under metal-free conditions. The reaction involves an 1,2-indole migration along with a C_α-C_β bond cleavage.

1.7. References

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BF_3·OEt_2 Mediated Cascade Annulation Strategy for the Synthesis of Functionalized Chromeno and Pyrano Fused Pyridines

2.1. Abstract

A simple and efficient one-pot annulation of arylidenones, alkynes and nitriles in the presence of BF_3·OEt_2 is described. A highly functionalized variety of chromeno/pyrano fused *N*-substituted pyridine derivatives were obtained with satisfactory yields under mild reaction conditions. The method was proven to be valid for the synthesis of a diverse library of chromeno[3,4-*c*]pyridines, thiochromeno[3,4-*c*]pyridines, pyrano[3,4-*c*]pyridines and thiopyrano[3,4-*c*]pyridine derivatives from readily accessible substrates. This experimentally simple protocol provides structurally complex, biologically relevant heterocycles in a one-pot operation.

2.2. Introduction

Chromenes are important structural scaffolds belonging to the family of oxygen heterocycles. Chromene and its derivatives are widely found in various natural products. These are core structural units of flavonoids, alkaloids, tocopherols and anthocyanins.[1,2] On account of broad spectrum of biological properties, chromenes have attracted the attention of synthetic as well as medicinal chemists. Numerous derivatives of chromenes, including natural products as well as compounds of synthetic origin, are known to possess biological activities such as anticancer, antitumor, antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory, anticoagulant, anticonvulsant, antivascular and analgesic activity.[3-7] Consequently, molecules with chromene backbone are anticipated to be potent drug candidates.[8] Moreover, some of the molecules are used as drugs for the treatment of various diseases. For example, Amlexanox which is marketed under the trade name Aphthasol (**I**) is an antiallergic and anti- inflammatory drug and Pranoprofen (**II**) is a non-steroidal anti-inflammatory agent (**Figure 2.1**).[9] In addition to this, chromenes are associated with photochemical properties. They are used in

electroluminescent and electrophotographic devices.[10] On the other hand, pyridine as a privileged *N*-heterocycle is a structural component of various natural products and pharmaceuticals.[11] Pyridine and its derivatives are endowed with wide array of biological properties.[12] Moreover, polar nature, water solubility and hydrogen bond forming ability make pyridine attractive scaffold in drug discovery.[13] Interestingly, more than 100 currently marketed drugs contain this core.[14]

The medicinal properties of these compounds are associated with their bi- and tricyclic molecular hybrids. Moreover, merging these two units is beneficial as it can lead to the emergence of new bioactive compounds. Consequently, a variety of chimeric structures of chromenes and pyridines have been prepared and evaluated for therapeutic applications.[15] Similarly, a fusion of pyrans and pyridines are an interesting area of investigation among the organic chemists. Like chromene, pyran and its derivatives are widely found in nature. It is one of the important classes of oxygen heterocycle.[16] Moreover, pyranopyridines have already been explored for their antibacterial activity.[17]

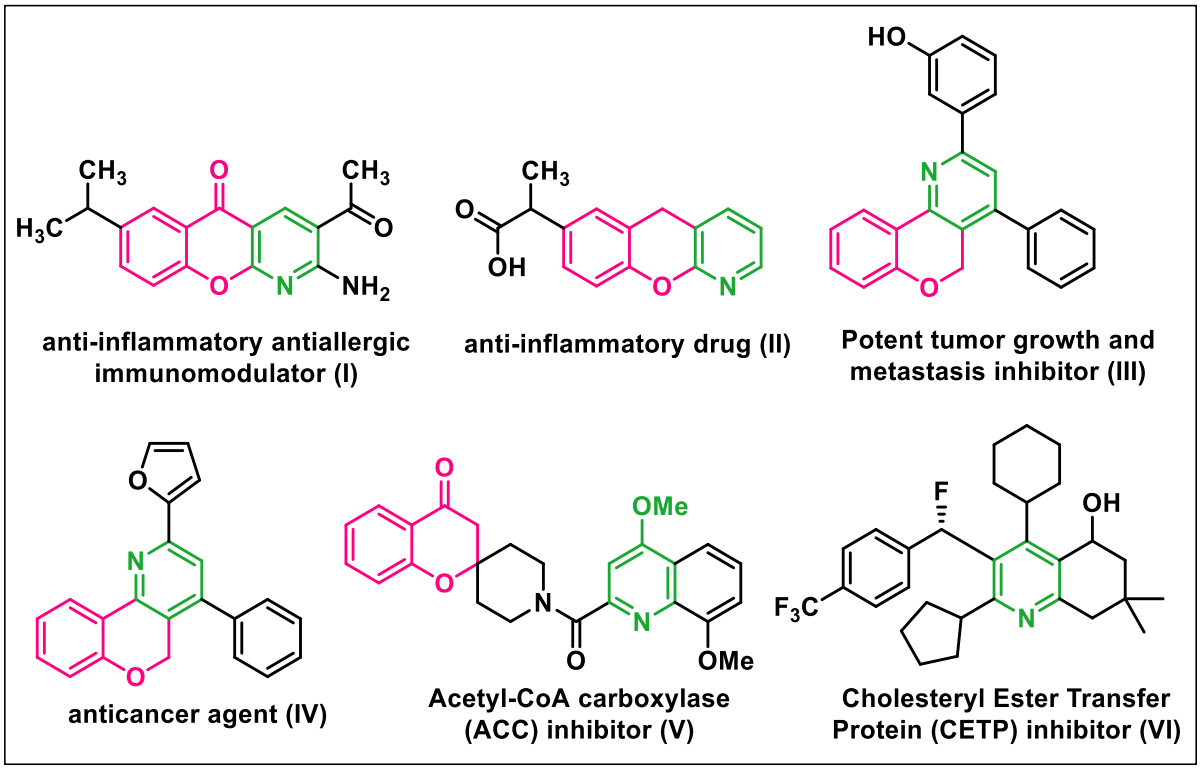
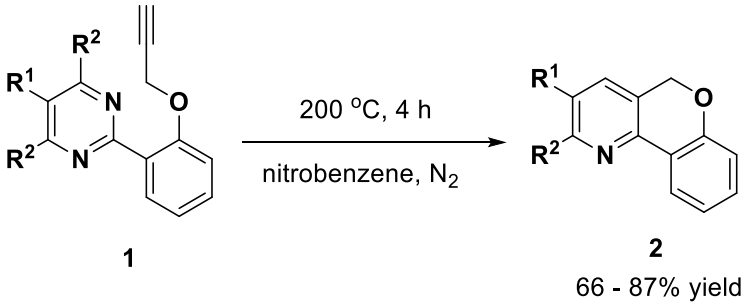


Figure 2.1. Medicinally relevant scaffolds with pyridine core.

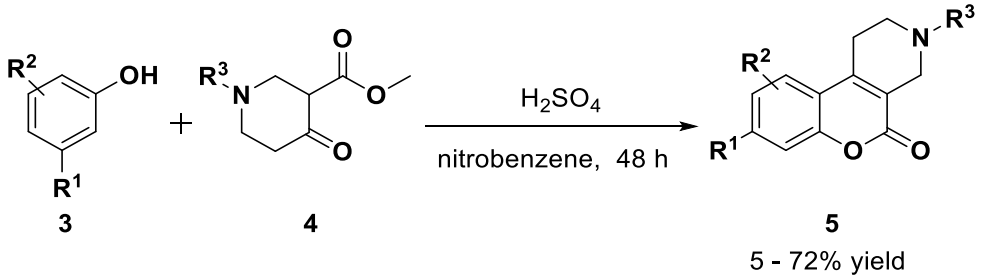
2.2.1. Synthetic approaches towards chromenopyridine and its derivatives

On account of biological as well as photochemical properties of chromenopyridines, various synthetic strategies have been developed for its synthesis. In 1992 Stolle *et al.* reported an intramolecular Diels-Alder reaction followed by retro Diels-Alder reaction to synthesise chromenopyridines **2** from the pyrimidine derivative **1** (**Scheme 2.1**). The reaction proceeds through an intermediate formed via the intra molecular Diels-Alder reaction of **1**, which subsequently undergoes retro Diels-Alder reaction to furnish the chromenopyridine **2**. This protocol requires a higher temperature of 200 ^oC to accomplish the synthesis of the desired pyridine.[18]



Scheme 2.1. Synthesis of chromenopyridine via combination of intramolecular Diels-Alder and retro Diels-Alder reaction.

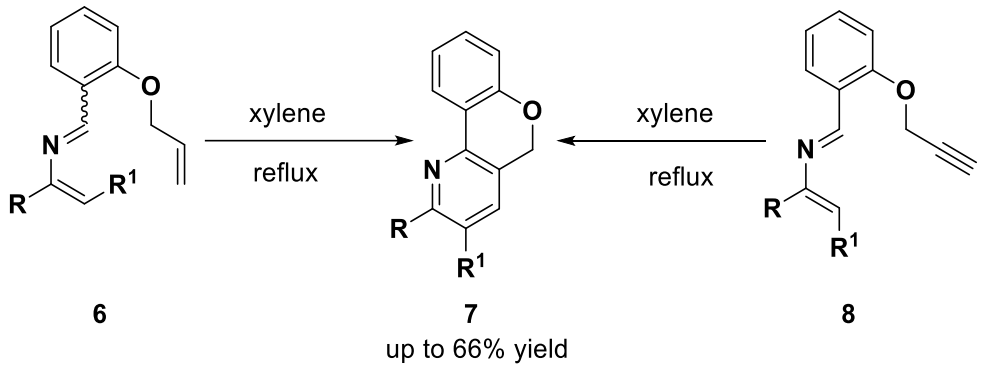
Later in 1997, Unangst *et al*. synthesized chromeno[3,4-*c*]pyridin-5-ones **5** by cyclocondensation reaction under strongly acidic conditions. The reaction is carried out with phenol **3** and a piperidone ester **4** (**Scheme 2.2**).[19]



Scheme 2.2. Cyclocondensation reaction for the synthesis of chromeno[3,4-*c*]pyridin-5-ones.

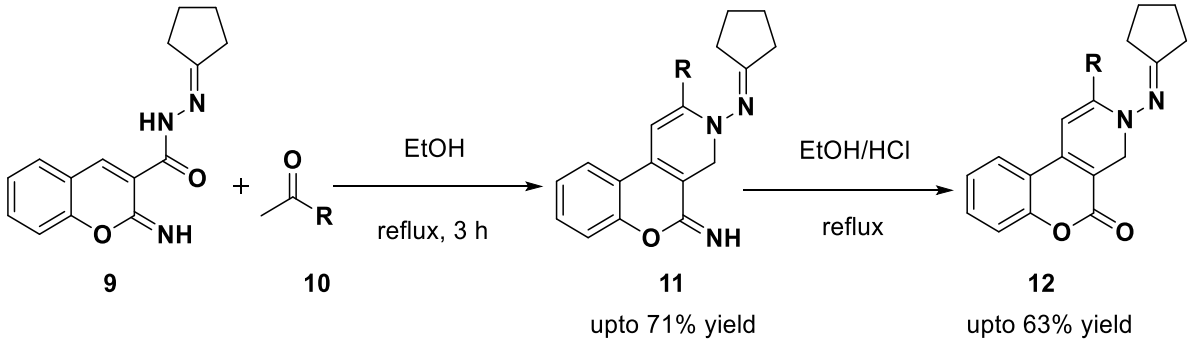
Palacios *et al*. in 2001 explored an intramolecular aza-Diels-Alder reaction for the synthesis of polynuclear heterocycles. The reaction is compatible for the synthesis of 5*H*-

chromeno[4,3-*b*]pyridine **7**, when azadiene **6** is used as the starting material. They have successfully explored the reaction for an azadiene **8** tethered with terminal alkyne, which also afforded the desired product **7** (**Scheme 2.3**).[20]



Scheme 2.3. Intramolecular aza-Diels-Alder reaction for the synthesis of 5*H*-chromeno[4,3-*b*]pyridine.

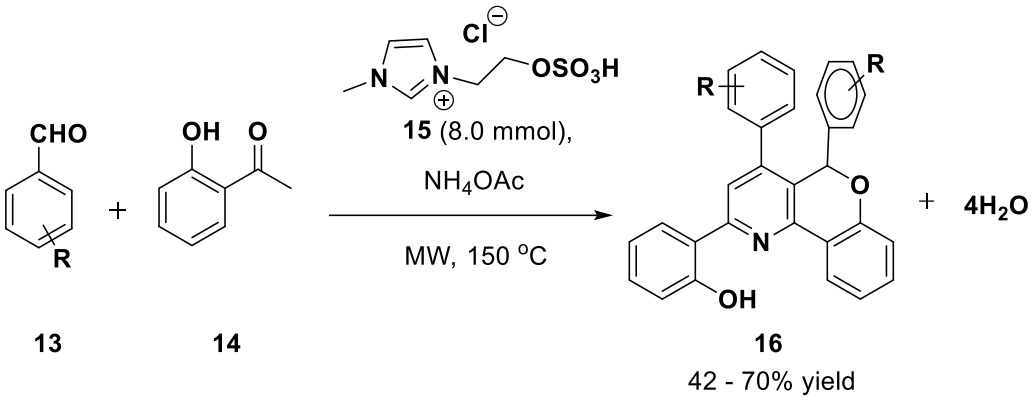
In 2004, a reaction of coumarin imine **9** with an appropriate ketone **10** was reported for the synthesis of chromeno[3,4-*c*]pyridine derivative **12** (**Scheme 2.4**). The reaction is carried out by refluxing the substrates **9** and **10** in anhydrous ethanol for 3 hours. The compound **11** is then hydrolyzed into corresponding ketone **12** by refluxing in ethanol/HCl mixture.[21]



Scheme 2.4. Chromeno[3,4-*c*]pyridine synthesis using coumarin imine as the substrate.

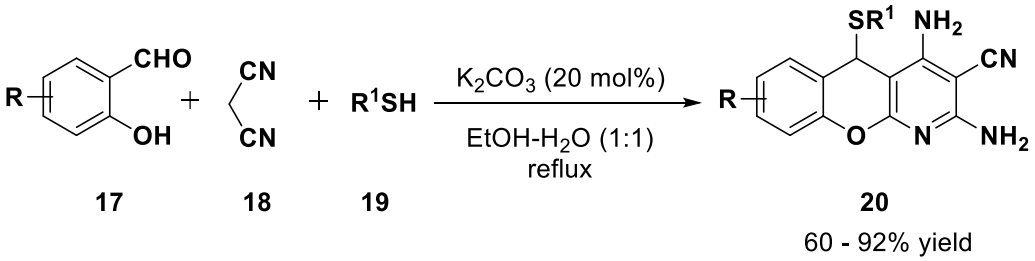
Later in 2009, Wu *et al*. disclosed a one pot three component protocol to access triaryl 5*H*-chromeno[4,3-*b*]pyridines **16**. It is a microwave assisted reaction of aromatic aldehyde **13** with 2′-hydroxyacetophenone **14** and ammonium acetate. In order to achieve good selectivity, they used 2-1'-methylimidazolium-3-yl-1-ethyl sulfate **15** as the catalyst. Even though the

reaction affords the product in moderate yields, it is an environment friendly method as it generates water as the sole by product (**Scheme 2.5**).[22]



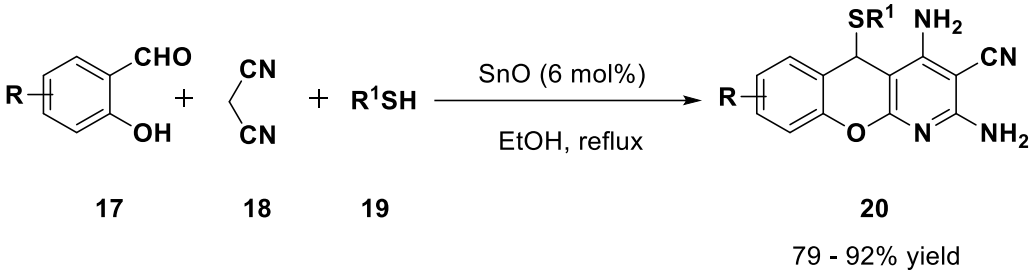
Scheme 2.5. Microwave assisted synthesis of triaryl 5*H*-chromeno[4,3-*b*]pyridine.

Mishra *et al*. reported a K_2CO_3 catalyzed reaction of salicylaldehyde or its analogue **17** with thiophenol **19** and malononitrile **18** in one pot fashion. The reaction afforded multi functionalized chromeno[2,3-*b*]pyridines **20** in excellent yield.[23] Gan *et al*. also explored the same multicomponent reaction in the presence of various organic bases. They have done a detailed study of dependence of multicomponent reaction (MCR) on the temperature and found out that MCR adopts different pathways with varying temperatures under the catalysis of different organic bases (**Scheme 2.6**).[24]



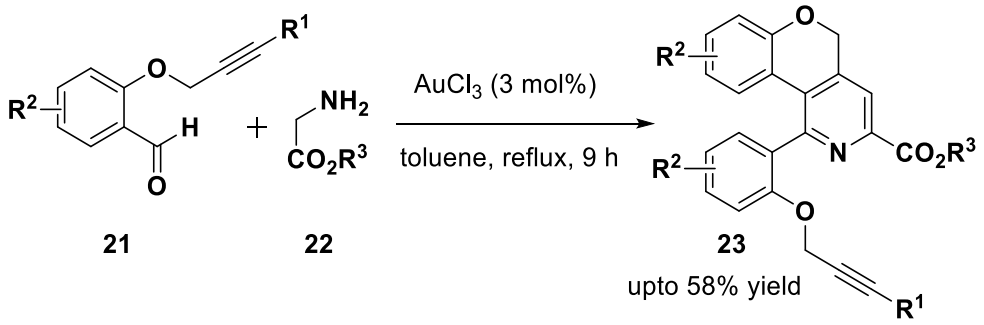
Scheme 2.6. Synthesis of chromenopyridine via multicomponent reaction.

SnO nanoparticle catalyzed condensation of salicylaldehyde with malononitrile and thiol was established by Ghomi *et al.* for the straightforward synthesis of chromeno[2,3-*b*]pyridines **20**. This protocol enables a cleaner construction of chromenopyridines in excellent yield within a shorter reaction time (**Scheme 2.7**).[25]



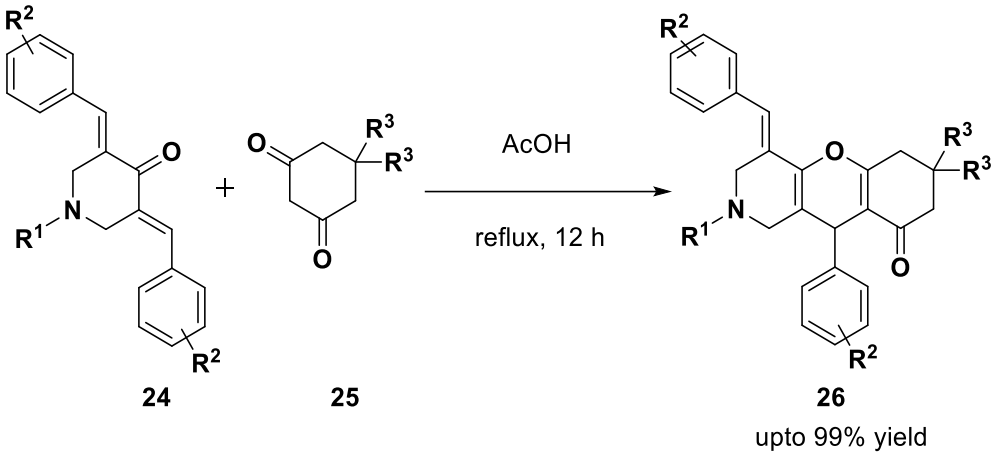
Scheme 2.7. SnO nanoparticle catalyzed synthesis of chromeno[2,3-*b*]pyridine.

In 2013, a [3+2+1] cycloaddition catalyzed by $AuCl_3$ was reported for the synthesis of 5*H*-benzopyrano[4,3-*c*]pyridine **23**. The annulation reaction occurs between an aldehyde **21**, glycine ester **22** and a terminal alkyne. The protocol has successfully utilized aldehyde as an alternative for CO, as a single carbon synthon in the triple C-C coupling reaction (**Scheme 2.8**).[26]



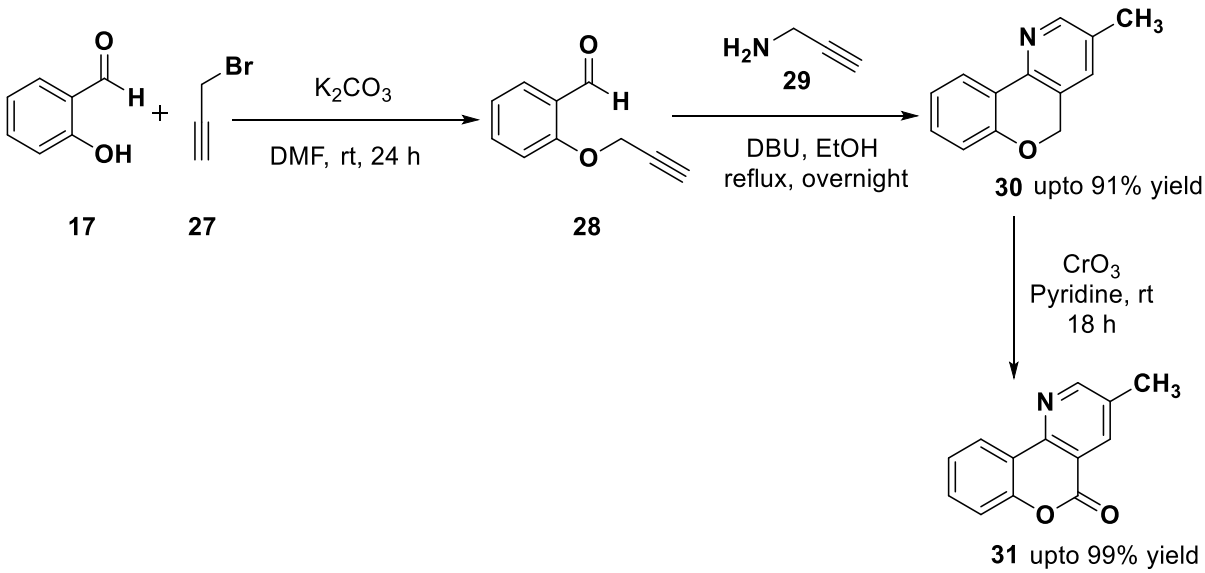
Scheme 2.8. $AuCl_3$ catalyzed cycloaddition reaction for the synthesis of 5*H*-benzopyrano[4,3-*c*]pyridine.

In 2015, Sumesh *et al*. established a tandem reaction of cyclic 1,3-diketones **25** with 3,5-((*E*)-arylidene)-1-methylpiperidin-4-ones **24** for the efficient synthesis of chromeno[3,2-*c*]pyridines **26.** The reaction is carried out in acetic acid under refluxing condition. It involves Michael addition of 1,3-diketone to 3,5-((*E*)-arylidene)-1-methylpiperidin-4-one followed by intramolecular *O*-cyclization and elimination of water molecule in a single operation (**Scheme 2.9**).[27]



Scheme 2.9. Tandem reaction of 1,3-diketones to furnish chromenopyridines.

In the same year Keskin *et al*. unravelled a two-step protocol for the synthesis of 5*H*-chromeno[4,3-*b*]pyridine **30**. They started the reaction with *O*-propargylation of salicylaldehyde by treating it with propargyl bromide in the presence of K_2CO_3. In the second step, compound **28** is treated with propargylamine in the presence of DBU. This step involves an alkyne cyclization which is the key step in the synthesis of the chromenopyridine **30**. Moreover, the synthesized 5*H*-chromeno[4,3-*b*]pyridine can be oxidized into 5*H*-chromeno[4,3-*b*]pyridine-5-one **31** by treating it with CrO_3 in pyridine/DCM at room temperature (**Scheme 2.10**).[28]

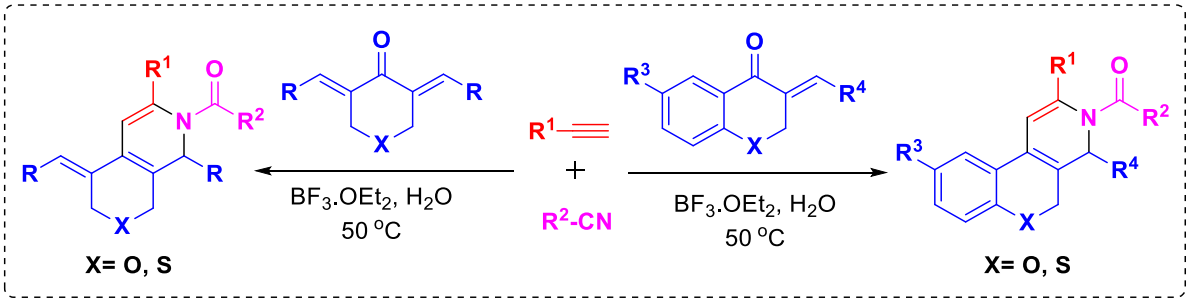


Scheme 2.10. Two step synthesis of 5*H*-chromeno[4,3-*b*]pyridine.

2.3. Background to the present work

Chromenopyridines and pyranopyridines possess significant biological properties. Therefore, generation of such hybrid pharmacophore through the fusion of medicinally active chromenes/pyrans and pyridines will undoubtedly enrich the structural template. Despite the medicinal relevance of chromenopyridines, only few methods are reported for the synthesis of these moieties. The highlighted methods in the above section mainly possess drawbacks such as unavailability of starting substrates, harsh reaction conditions and multistep synthesis. One of the important methods used for the synthesis of these fused heterocycles are multicomponent reactions (MCRs), which enables the formation of multiple bonds in a single operation. The significance of applications of MCRs in the drug discovery process, total synthesis and the development of various strategies for the construction of new chemical entities is quite evident.[29,30]

Owing to the biological importance of pyridine, related hybrids and our interest in the design and development of medicinally essential heterocycles, in 2016 we have unravelled a one-pot multicomponent cascade synthesis of pyridine appended carbocycles from the readily accessible arylidenones, alkynes and nitriles.[31] Therefore, herein we attempted the feasibility of this Lewis acid mediated reaction for the synthesis of chromenopyridines. Delightfully, we were able to accomplish the construction of chromeno[3,4-*c*]pyridines under transition metal free conditions. Moreover, we have synthesized a diverse library of thiochromeno[3,4-*c*]pyridines, pyrano[3,4-*c*]pyridines and thiopyrano[3,4-*c*]pyridines as well (**Scheme 2.11**).



Scheme 2.11. Lewis acid mediated synthesis of fused pyridines.

2.4. Results and discussion

In sharp contrast to the well documented approaches to access either chromeno[4,3-*b*]pyridines or chromeno[3,2-*c*]pyridines, we developed a one-pot, multicomponent cascade annulation for the construction of chromeno[3,4-*c*]pyridines. As an extension of our previous work, feasibility of this annulation reaction was first tested using 1 equiv of (*E*)-3-benzylidenechroman-4-one (**32a**), phenylacetylene (**33a**) and acetonitrile in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ at 50 °C, which presumably afforded 1-(2,4-diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (**34a**) in 22% of yield (**Table 2.1**, entry 2). The structure of the product was confirmed through various spectroscopic analyses such as ^{1}H NMR, ^{13}C NMR and mass spectrometry. In the ^{1}H NMR, a three proton singlet at δ 1.70 indicated the presence of acetyl CH_3 (**Figure 2.2**). It is further confirmed by the peak at δ 24.6 in the ^{13}C NMR spectrum. Moreover, the peak appeared at δ 171.9 in ^{13}C NMR corresponds to the carbonyl carbon of amide group present in the molecule (**Figure 2.3**). It was further confirmed from the IR absorption value of 1661 cm^{-1}. Additionally, the proton at the stereogenic carbon was found to resonate at δ 6.52 in the ^{1}H NMR spectrum. The doublets appeared at δ 4.90 and δ 4.77 are attributed to the methylene protons present in the chromene ring. The mass spectrometric data was also in good agreement with the exact mass of the product.

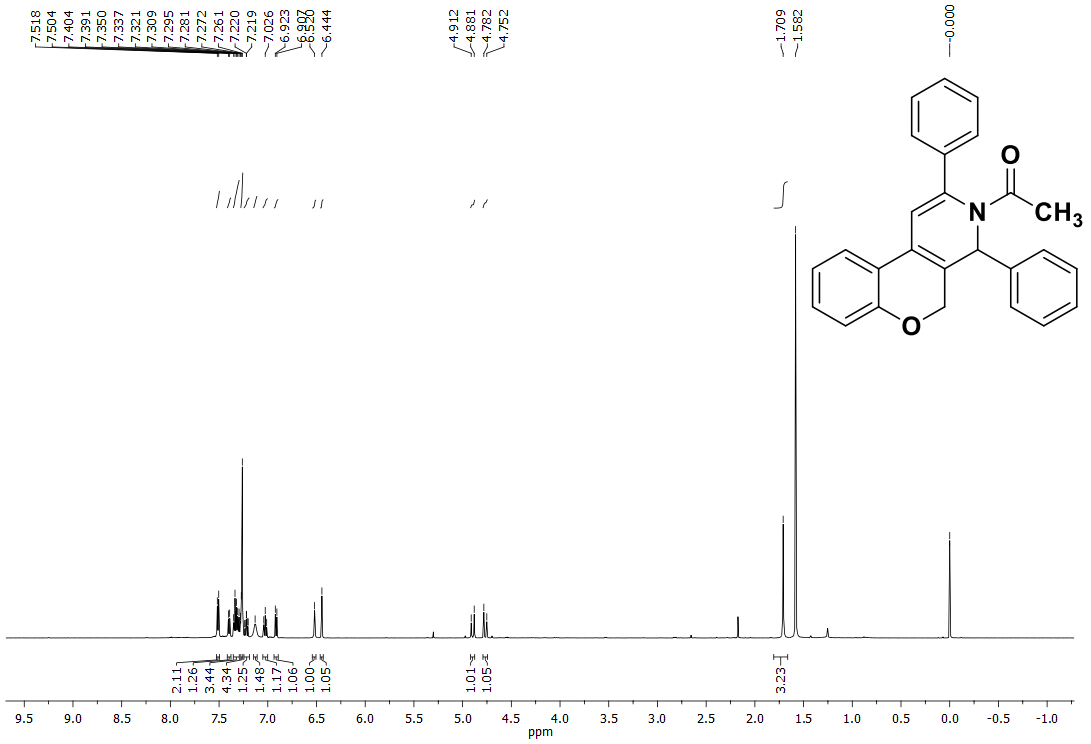


Figure 2.2. ^{1}H NMR of **34a**

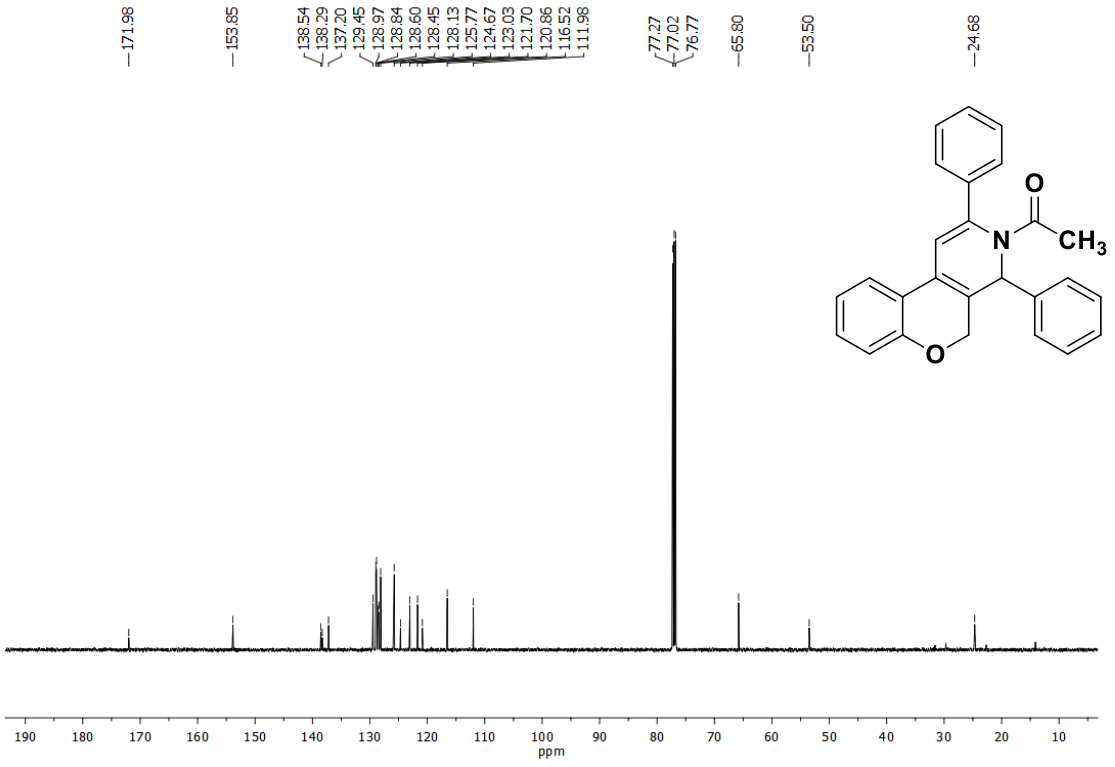
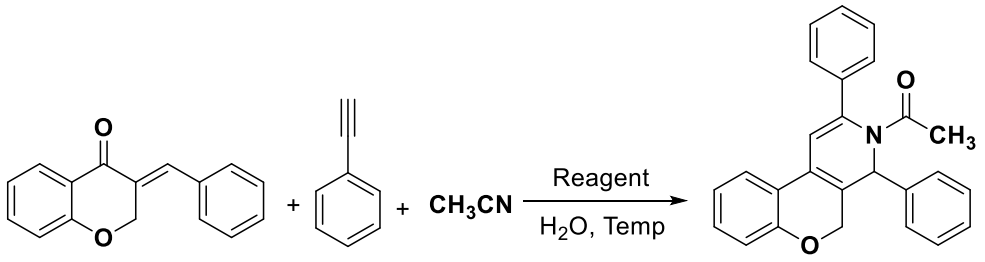


Figure 2.3. ^{13}C NMR of **34a**

After confirming the structure of the product, we screened various reaction parameters to obtain optimized conditions for the reaction. From our previous work it was evident that acetonitrile (CH_3CN) and water are essential for the reaction to proceed. Hence we have evaluated combination of 2 equiv of CH_3CN with other solvents like toluene, DCE, DCM, THF and DMF (Table 2.1, entry 3-7). These combinations were found to have a detrimental effect on the reaction yield. Then we evaluated various Lewis acids like $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $La(OTf)_3$, etc. (entry 8 – 14). All of them failed to furnish the product even in trace quantities. Next, various Bronsted acids like TFA, PTSA and phenylboronic acid were screened, which also had a negative impact on the reaction yield (entry 14 – 16). These results indicate that the reaction proceeds only in the presence of $BF_3.OEt_2$. When we tried to optimize the reaction with carbophilic Lewis acids, such as $Cu(OAc)_2$, $AuCl_3$, $AuCl_3.H_2O$, $AuPPh_3$ and I_2 as additives along with $BF_3.OEt_2$, we could not find any marked improvement in the reaction yield (entry 17 – 21). A low yield of about 12% was obtained when the reaction was performed at room temperature. On increasing the temperature from 50 °C, the reaction started to produce some byproducts which apparently resulted in poor yields. Moreover, we varied equivalents of both alkyne as well as $BF_3.OEt_2$ (**Table 2.2**). Finally we obtained a maximum yield of 66% for the targeted 1-(2,4-diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone, when 3 equiv of $BF_3.OEt_2$ was added to 1 equiv of (*E*)-3-benzylidenechroman-4-one , 2 equiv of H_2O and 3 equiv of alkyne in 2 mL of CH_3CN at 50 ^oC (**Table 2.2**, entry 4).

Table 2.1. Optimization of reaction conditions [a]



32a **33a** **34a**

Entry	Reagent	Solvent	Temperature [°C]	Yield [%][b]
1	$BF_3.OEt_2$	CH_3CN	50	22
2	$BF_3.OEt_2$	CH_3CN	rt	12
3	$BF_3.OEt_2$	Toluene + CH_3CN (2 equiv)	50	Trace
4	$BF_3.OEt_2$	DCE + CH_3CN (2 equiv)	50	Trace
5	$BF_3.OEt_2$	DCM + CH_3CN (2 equiv)	50	Trace
6	$BF_3.OEt_2$	THF + CH_3CN (2 equiv)	50	ND
7	$BF_3.OEt_2$	DMF + CH_3CN (2 equiv)	50	ND
8	$Sc(OTf)_3$	CH_3CN	50	ND
9	$Zn(OTf)_3$	CH_3CN	50	ND
10	$Cu(OTf)_3$	CH_3CN	50	ND
11	$ZnCl_2$	CH_3CN	50	ND
12	$AlCl_3$	CH_3CN	50	ND
13	I_2	CH_3CN	50	ND
14	$PhB(OH)_2$	CH_3CN	50	ND
15	PTSA	CH_3CN	50	ND
16	CF_3COOH	CH_3CN	50	ND
17	$BF_3.OEt_2$ + $Cu(OAc)_2$	CH_3CN	50	ND
18	$BF_3.OEt_2$ + $AuCl_3$	CH_3CN	50	23
19	$BF_3.OEt_2$ + $AuCl_3.H_2O$	CH_3CN	50	21
20	$BF_3.OEt_2$ + $AuPPh_3$	CH_3CN	50	20
21	$BF_3.OEt$ + I_2	CH_3CN	50	ND

Reaction conditions: [a] **32a** (0.12 mmol), **33a** (0.12 mmol), H_2O (0.24 mmol), Solvent (2 mL). [b] Yield of the isolated product.

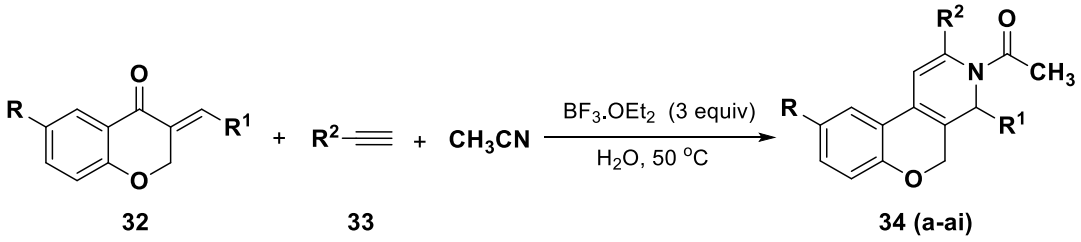
Table 2.2. Optimization of equivalents [a]

Entry	33a (equiv)	BF_3.OEt (equiv)	Yield [%][b]
1	2	1	30
2	3	1	42
3	3	2	56
4	3	3	66

Reaction conditions: [a] **32a** (0.12 mmol), H_2O (0.24 mmol), Solvent (2 mL). All the reactions were carried out at 50 ^oC. [b] Yield of the isolated product.

With the optimized reaction conditions in hand, the generality of this three component annulation was well explored for (*E*)-3-arylidenechroman-4-one and aromatic acetylenes. Delightfully, all the targeted products were formed under the optimal conditions for both the substrates bearing a series of electron-withdrawing and electron-donating substituents (**Table 2.3**, **34a – 34u**). The reactivity of acetylenes as well as (*E*)-3- arylidenechroman-4-one bearing the heteroaryl ring, thiophene was also investigated. Satisfyingly these substrates were found to be compatible with the reaction conditions and the desired products were obtained in moderate yields (**34v** – **34z**). Moreover, 6-Fluoroarylidenechromanones were also subjected to react with the variety of alkynes in the presence of acetonitrile. These substrates also reacted efficiently under the optimized conditions to afford the corresponding chromeno[3,4-*c*] pyridines in acceptable yields (**34aa – 34ai**).

Table 2.3. Scope of the reaction for chromeno[3,4-*c*]pyridines



32 **33** **34 (a-ai)**

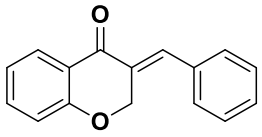
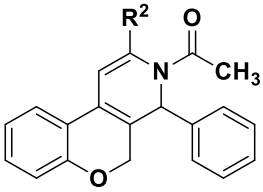
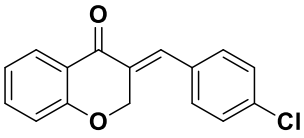
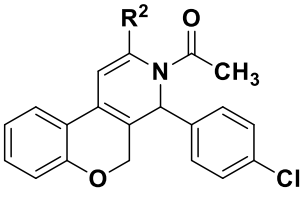
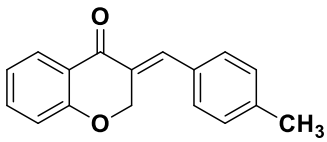
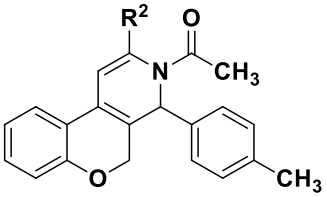
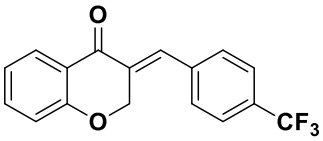
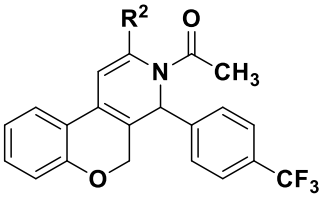
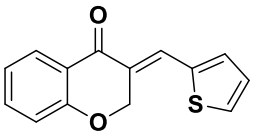
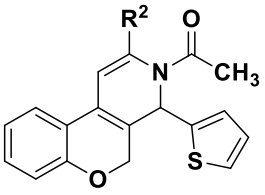
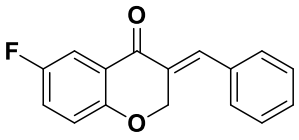
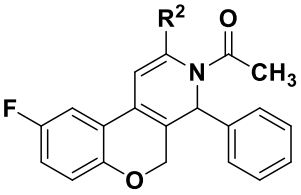
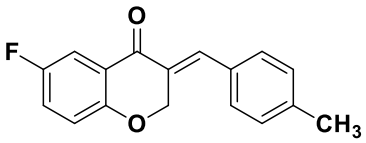
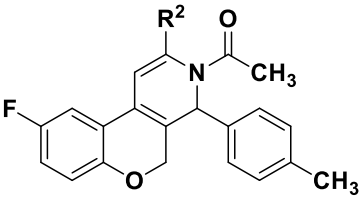
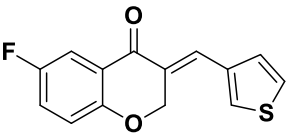
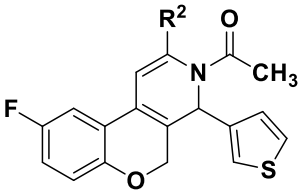
Entry	Arylidenechroman-4-one	Product	Yield [%]
1.	 **32a**	 **34 (a-e)**	**34a**; R^2= Ph, 66% **34b**; R^2= 4-CH_3-Ph, 56% **34c**; R^2= 4-Br-Ph, 52% **34d**; R^2= 4-F-Ph, 42% **34e**; R^2= 4-propyl-Ph, 43%
2.	 **32b**	 **34 (f-k)**	**34f**; R^2= Ph, 39% **34g**; R^2= 4-CH_3-Ph, 63% **34h**; R^2= 4-Br-Ph, 49% **34i**; R^2= 4-F-Ph, 48% **34j**; R^2= 4-propyl-Ph, 55% **34k**; R^2= 3-thiophen, 60%
3.	 **32c**	 **34 (l-q)**	**34l**; R^2= Ph, 74% **34m**; R^2= 4-CH_3-Ph, 77% **34n**; R^2= 4-Br-Ph, 61% **34o**; R^2= 4-F-Ph, 62% **34p**; R^2= 4-propyl-Ph, 74% **34q;** R^2= 3-thiophen, 77%
4.	 **32d**	 **34 (r-u)**	**34r**; R^2= Ph, 36% **34s**; R^2= 4-CH_3-Ph, 54% **34t**; R^2= 4-F-Ph, 32% **34u**; R^2= 4-propyl-Ph, 47%
5.	 **32e**	 **34 (v-z)**	**34v**; R^2= Ph, 50% **34w**; R^2= 4-CH_3-Ph, 74% **34x**; R^2= 4-Br-Ph, 38% **34y**; R^2= 4-F-Ph, 24% **34z;** R^2= 4-propyl-Ph, 47%

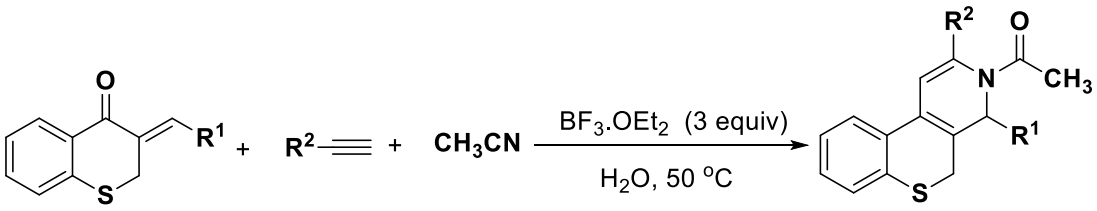
Table 2.3. continues…….

Entry	Arylidenechroman-4-one	Product	Yield [%]
6.	 **32f**	 **34 (aa-af)**	**34aa**; R^2= Ph, 63% **34ab**; R^2= 4-CH_3-Ph, 67% **34ac**; R^2= 4-Br-Ph, 39% **34ad**; R^2= 4-F-Ph, 51% **34ae**; R^2= 4-propyl-Ph, 50% **34af**; R^2= 3-thiophen, 33%
7.	 **32g**	 **34ag**	**34ag**; R^2= 4-Br-Ph, 36%
8.	 **32h**	 **34 (ah-ai)**	**34ah**; R^2= Ph, 64% **34ai**; R^2= 4-CH_3-Ph, 41%

Reaction conditions: **32** (0.12 mmol), **33** (0.36 mmol), $BF_3.OEt_2$ (0.36 mmol), H_2O (0.24 mmol) in 2 mL of CH_3CN at 50 °C. Yields of isolated product.

Next, we turned our attention to assess the scope of this annulation reaction with arylidene thiochromanone and alkynes bearing a series of electron-withdrawing and electron-donating substituents (**Table 2.4**). In all cases, the methodology worked well to afford the targeted thiochromeno[3,4-*c*]pyridines (**36a** – **36f**) in moderate to good yields. From our observations, we found that the yields of the thiochromeno[3,4-*c*]pyridines are lower than those of the chromeno[3,4-*c*]pyridines. It may be attributed to the basicity of heteroatom sulfur as compared to that of oxygen.

Table 2.4. Scope of the reaction for thiochromeno[3,4-*c*]pyridines



35 33 36a-36f

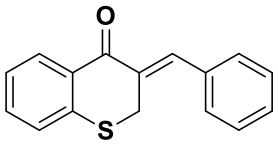
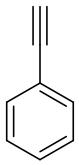
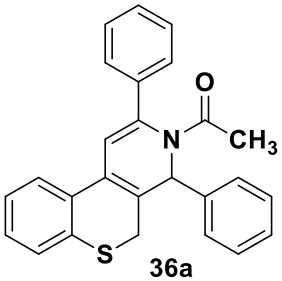
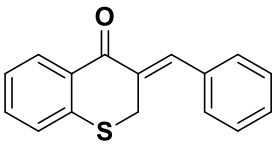
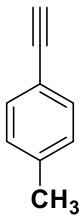
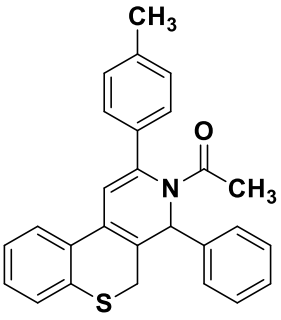
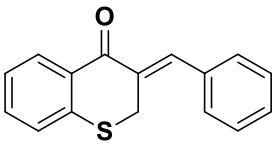
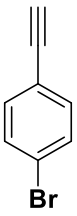
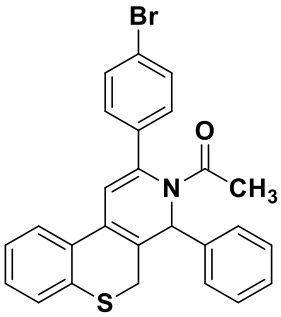
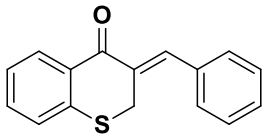
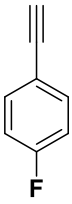
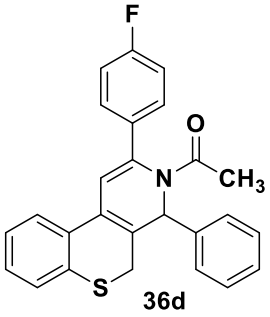
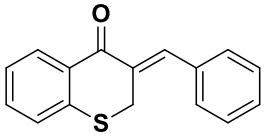
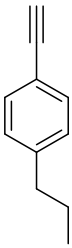
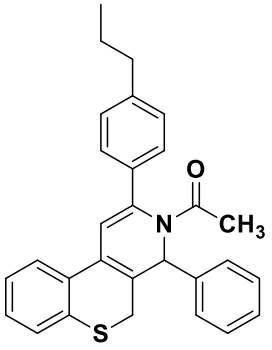
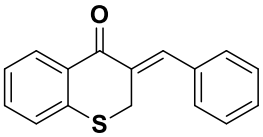
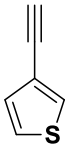
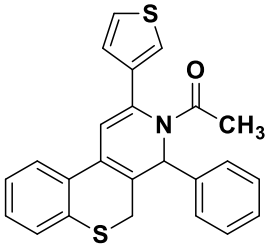
Entry	Arylidenethiochroman-4-one	Alkyne	Product	Yield [%]
1.	 35a	 33a	 36a	46
2.	 35a	 33b	 36b	26
3.	 35a	 33c	 36c	31

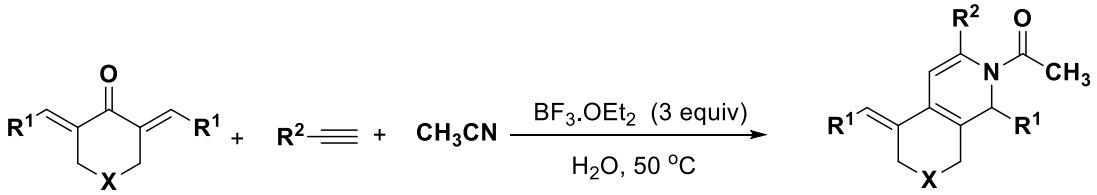
Table 2.4. continues…….

Entry	Arylidenethiochroman-4-one	Alkyne	Product	Yield [%]
4.	 **35a**	 **33d**	 **36d**	40
5.	 **35a**	 **33e**	 **36e**	23
6.	 **35a**	 **33f**	 **36f**	39

Reaction conditions: **35a** (0.12 mmol), **33** (0.36 mmol), $BF_3.OEt_2$ (0.36 mmol), H_2O (0.24 mmol) in 2 mL of CH_3CN at 50 °C. Yields of isolated product.

The successful formation of chromeno[3,4-*c*]pyridines and thiochromeno[3,4-*c*]pyridines led us to examine the reactivity of (3*E*,5*E*)-3,5-diarylidenedihydro-2*H*-pyran-4(3*H*)-one and (3*Z*,5*Z*)-3,5-diarylidenedihydro-2*H*-thiopyran-4(3*H*)-one with various substituted alkynes and acetonitrile under the same optimized conditions (**Table 2.5**). Pyranone and thiopyranone diarylidenes bearing phenyl and thiophene ring were utilized for the three-component cascade annulation. To our delight, we obtained a new molecular templates of pyrano[3,4-*c*]pyridines and thiopyrano[3,4-*c*]pyridines in acceptable yields (**38a** – **38f**).

Table 2.5. Generality of pyrano and thiopyrano[3,4-*c*]pyridine synthesis



37 **33** **38a-38f**

X= O, S **X= O, S**

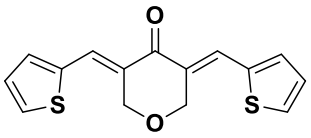
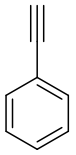
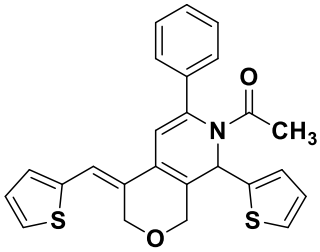
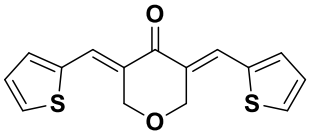
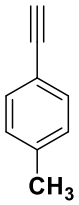
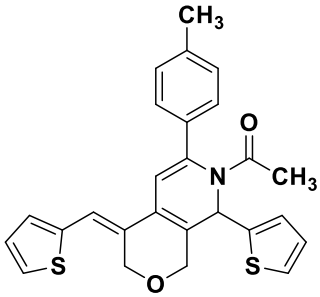
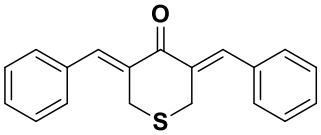
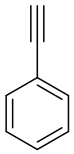
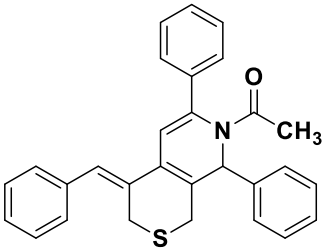
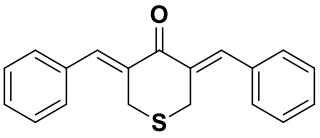
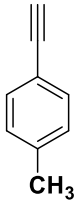
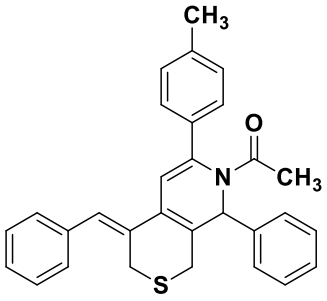
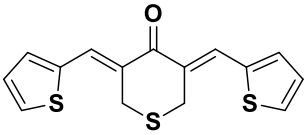
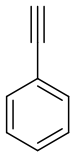
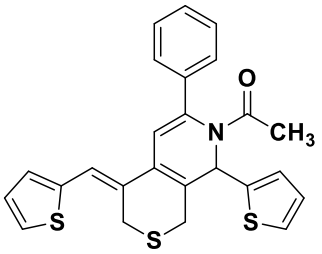
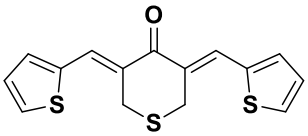
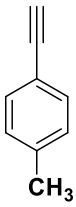
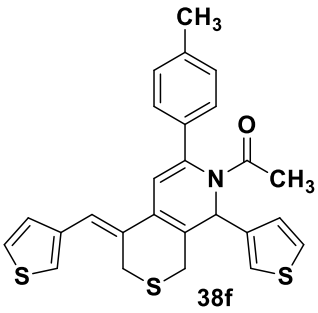
Entry	Diarylidenedihydro pyran/thiopyran-4-one	Alkyne	Product	Yield [%]
1.	 **37a**	 **33a**	 **38a**	77
2.	 **37a**	 **33b**	 **38b**	40
3.	 **37b**	 **33a**	 **38c**	33

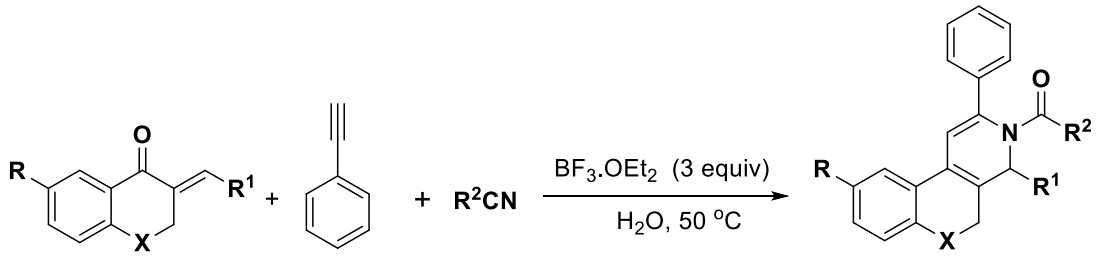
Table 2.5. continues…….

Entry	Diarylidenedihydro pyran/thiopyran-4-one	Alkyne	Product	Yield [%]
4.	 **37b**	 **33b**	 **38d**	17
5.	 **37c**	 **33a**	 **38e**	61
6.	 **37c**	 **33b**	 **38f**	41

Reaction conditions: **37** (0.12 mmol), **33** (0.36 mmol), $BF_3.OEt_2$ (0.36 mmol), H_2O (0.24 mmol) in 2 mL of CH_3CN at 50 °C. Yields of isolated product.

Delighted with the success of the broad diversity of arylidenones and alkynes, we further explored the compatibility of other nitrile sources such as benzonitrile and acrylonitrile (**Table 2.6**). As targeted, we successfully obtained *N*-substituted chromeno- and thiochromeno-fused pyridines under mild and straightforward reaction conditions in acceptable yields (**40a** – **40h**).

Table 2.6. Scope of nitriles for chromeno and thiochromeno[3,4-*c*]pyridine synthesis



32 or 35 (X=O, S) | 33a | 39 | 40a-40h (X=O, S)

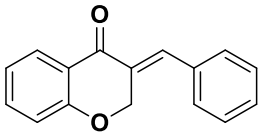
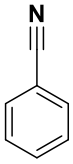
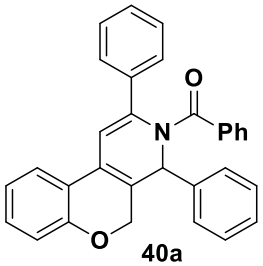
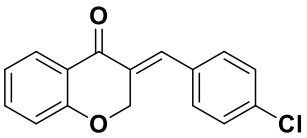
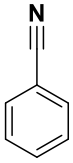
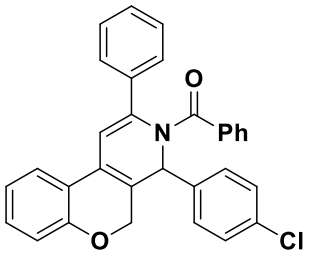
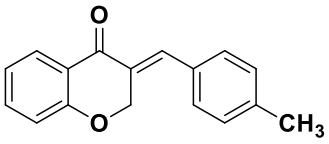
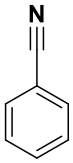
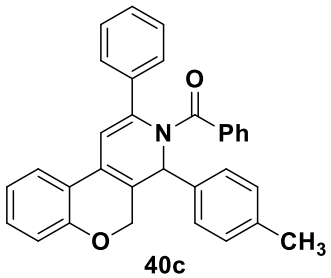
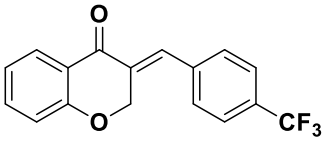
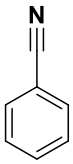
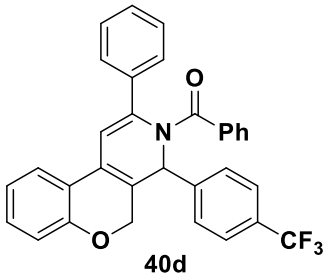
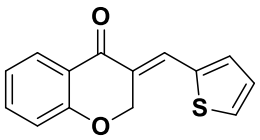
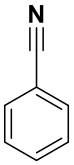
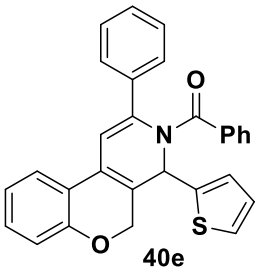
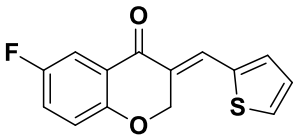
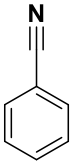
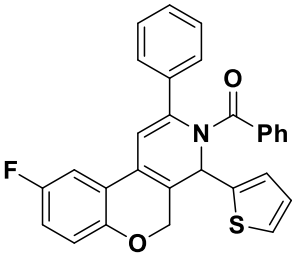
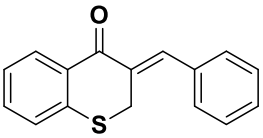
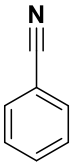
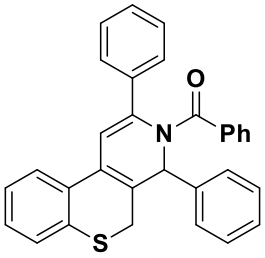
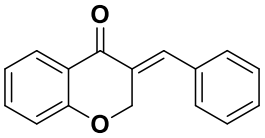
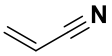
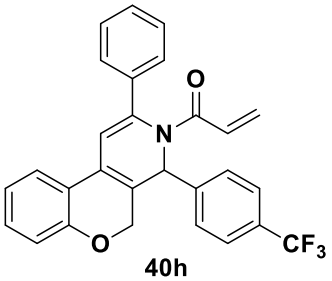
Entry	Arylidenechroman/ thiochroman-4-one	Nitrile	Product	Yield [%]
1.	 32a	 39a	 40a	51
2.	 32b	 39a	 40b	47
3.	 32c	 39a	 40c	47
4.	 32d	 39a	 40d	27

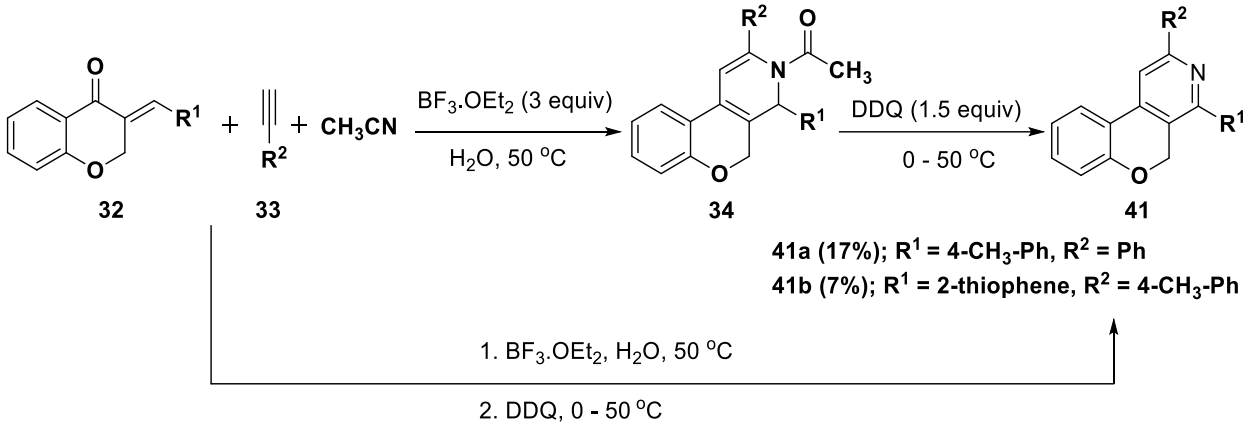
Table 2.6. continues…….

Entry	Arylidenechroman/ thiochroman-4-one	Nitrile	Product	Yield [%]
5.	 **32e**	 **39a**	 **40e**	34
6.	 **32h**	 **39a**	 **40f**	29
7.	 **35a**	 **39a**	 **40g**	40
8.	 **32a**	 **39b**	 **40h**	28

Reaction conditions: **32/35** (0.12 mmol), **33** (0.36 mmol), $BF_3.OEt_2$ (0.36 mmol), **39** (2 mL), H_2O (0.24 mmol) at 50 ^oC. Yields of isolated product.

Finally, in order to showcase the synthetic utility of the molecule we have performed an aromatization reaction (**Scheme 2.12**). Under DDQ oxidation conditions, product **34** was successfully transformed into corresponding 5*H*-chromeno[3,4-*c*]- pyridines (**41a** and **41b**) of

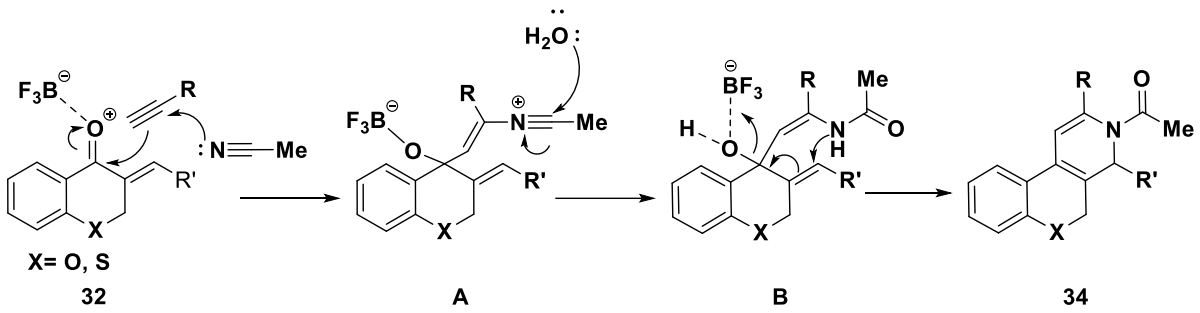
biological relevance. This synthetic transformation can also be carried out without the isolation of **34** as a two-step, one-pot reaction.



Scheme 2.12. One-pot synthesis of 5*H*-chromeno[3,4-*c*]pyridines.

2.5. Plausible Mechanism

Based on our previous work and aforementioned experimental results, a plausible mechanistic pathway is outlined in **Scheme 2.13**.[31] Being oxophilic in nature, $BF_3{\cdot}OEt_2$ activates carbonyl carbon of arylidene ketone **32** by coordinating with the oxygen. This will favor the carbonyl group to undergo 1,2-addition by phenylacetylene and which in turn is followed by the attack of nitrogen atom of acetonitrile to phenylacetylene leading to the formation of intermediate **A**. Subsequent hydrolysis of nitrile group of intermediate **A** under acidic conditions leads to the formation of intermediate **B** which on intramolecular cyclization affords the product **34**.



Scheme 2.13. Plausible mechanism

2.6. Conclusion

In conclusion, a simple and efficient BF_3·OEt_2 mediated cascade annulation of arylidenones, alkynes and nitriles have been developed. This reaction affords a highly generalized and straightforward way to construct *N*-substituted chromeno, thiochromeno, pyrano, and thiopyrano[3,4-*c*]pyridines under mild conditions and tolerates a wide range of functional groups. In addition, a one-pot synthesis of 5*H*-chromeno[3,4-*c*]pyridines was successfully achieved. Notably, the reaction is process friendly, with easily accessible substrates and proceeds without any inert conditions. Our protocol will aid in the generation of a diverse library of fused pyridine hybrids with potential biological significance.

2.7. General experimental methods

All the reactions were performed with commercially available best grade chemicals without further purification. All the solvents used were reagent-grade and commercially available. Column chromatography was performed using 100−200 mesh silica gel, and mixtures of hexane−ethyl acetate were used for elution of the products. Proton nuclear magnetic resonance spectra (^{1} H NMR) were recorded on a Bruker AMX 500 spectrometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities are given as s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet); m (multiplet). Coupling constants are reported as *J* values in Hz. Carbon Nuclear Magnetic Resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). HRMS analysis was recorded on a Thermo Scientific Exactive-LCMS instrument by electron spray ionization method with ions given in m/z using Orbitrap analyzer. IR spectra were recorded on a Bruker FT-IR spectrometer.

2.8. General procedure for the synthesis of arylidenechroman-4-ones/ arylidenethiochroman-4-ones (1).

To a solution of chroman-4-one/thiochroma-4-one (4.0 mmol) in ethanol, aryl or hetero aryl aldehyde (4.40 mmol) was added at 0 °C. An aqueous solution of NaOH (10%, 10 mL) was added dropwise to this reaction mixture. The solid precipitate formed was collected by filtration and washed with water and hexane. It was dried and used for further reaction.

2.9. General procedure for the synthesis of (3*E*,5*E*)-3,5-diarylidenedihydro-2*H*-pyran-4(3*H*)-one/(3*Z*,5*Z*)-3,5-diarylidenedihydro-2*H*-thiopyran-4(3*H*)-one (2).

To a solution of dihydro-2*H*pyran-4(3*H*)-one/dihydro-2*H*-thiopyran-4(3*H*)-one (2.00 mmol) in ethanol, aryl or hetero aryl aldehyde (2.20 mmol) was added at 0 °C. An aqueous solution of NaOH (10%, 10 mL) was added dropwise to this reaction mixture. The solid precipitate formed was collected by filtration and washed with water and hexane. It was dried and used for further reaction.

2.10. General procedure for $BF_3{\cdot}OEt_2$-mediated one-pot synthesis of *N*-acetylated chromeno[3,4-*c*]pyridines/thiochromeno[3,4-*c*]-pyridines (3).

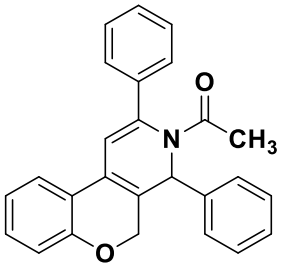
To a mixture of 1 equiv of substituted arylidenechroman-4-one/thiochroman-4-one (0.12 mmol), 3 equiv of aryl/heteroarylalkyne (0.36 mmol) and 2 equiv of water in acetonitrile (2 mL) at 50 °C, 3 equiv of $BF_3{\cdot}OEt_2$ (0.36 mmol) was added. The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The solvent was evaporated in *vacuo* and the residue on silica gel (100−200 mesh) column chromatography using a mixture of ethyl acetate - hexane as the eluent afforded the corresponding *N*-acetylated fused pyridines.

2.11. Characterization data of compounds

1-(2,4-Diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)-ethanone (34a)

The compound **34a** was synthesized following the procedure 3, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O

(4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34a** as colourless foam in 66% (30 mg) yield.



IR (neat) ν_{max}: 3062, 1661, 1601, 1036 cm^{-1}.

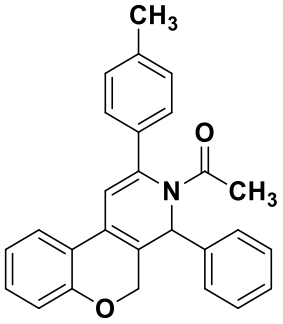
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.35−7.29 (m, 3H), 7.28−7.26 (m, 4H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.13 (s, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 6.44 (s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 153.9, 138.5, 138.3, 137.2, 129.5, 129.0, 128.8, 128.6, 128.5, 128.1, 125.8, 124.7, 123.0, 121.7, 120.9, 116.5, 112.0, 65.8, 53.5, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{21}NO_2Na$, $[M+Na]^+$: 402.1470; Found: 402.1461.

(4-Phenyl-2-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin3-yl)ethanone (34b)

The compound 3**4b** was synthesized following the procedure 3, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), 4-ethynyltoluene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34b** as colourless foam in 56% (26 mg) yield.



IR (neat) ν_{max}: 3061, 1666, 1604, 1116 cm^{-1}.

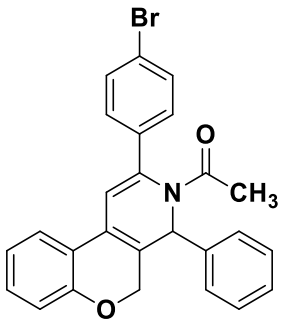
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.49 (m, 2H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.34−7.27 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 3H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 2.30 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.9, 138.8, 138.3, 137.2, 135.7, 133.2, 129.7, 129.4, 128.8, 128.6, 128.4, 128.3, 128.1, 125.7, 125.5, 124.7, 123.1, 121.7, 121.0, 116.5, 111.3, 65.8, 53.5, 24.8, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{23}NO_2Na$, $[M+Na]^+$: 416.1626; Found: 416.1620.

1-(2-(4-Bromophenyl)-4-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34c)

The compound **34c** was synthesized following the procedure 3, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34c** as colourless foam in 52% (29 mg) yield.



IR (neat) ν_{max}: 3062, 1669, 1586, 1072, 1040 cm^{-1}.

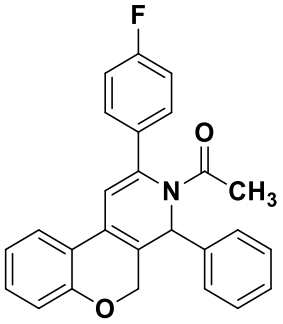
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.46 (m, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.34-7.29 (m, 3H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.50 (s, 1H), 6.44 (s, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 137.5, 137.2, 137.0, 132.2, 129.6, 128.9, 128.6, 128.0, 127.2, 126.4, 124.7, 123.0, 122.7, 121.7, 120.7, 116.6, 112.6, 65.7, 53.5, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}BrNO_2Na$ $[M+Na]^+$: 480.0575; Found: 480.0580.

1-(2-(4-fluorophenyl)-4-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34d)

The compound **34d** was synthesized following the procedure 3, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), 1-ethynyl-4-fluorobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34d** as colourless foam in 42% (20 mg) yield.



IR (neat) ν_{max}: 3065, 1667, 1599, 1098 cm^{-1}.

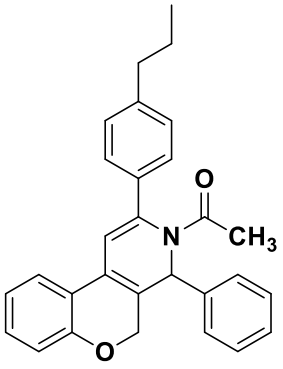
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50−7.49 (m, 2H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.35−7.29 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.09 (s, 2H), 7.02 (td, *J* = 7.5, 1 Hz, 1H), 6.96 (t, *J* = 9.0 Hz, 2H), 6.91 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.51 (s, 1H), 6.39 (s, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 153.8, 137.2, 137.1, 134.7, 134.7, 133.7, 131.6, 129.5, 128.9, 128.6, 128.1, 127.5, 127.4, 125.8, 124.7, 123.0, 121.7, 120.8, 116.6, 116.2, 116.0, 112.0, 65.7, 53.5, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}FNO_2Na$, $[M+Na]^+$: 420.1376; Found: 420.1376.

1-(4-Phenyl-2-(4-propylphenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34e)

The compound **34e** was synthesized following the procedure 3, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34e** as colourless foam in 43% (22 mg) yield.



IR (neat) ν_{max}: 3062, 1666, 1606, 1040 cm^{-1}.

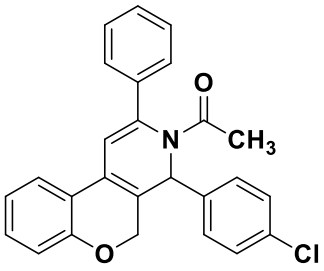
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.34−7.28 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.08−7.00 (m, 5H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.5 Hz, 1H), 2.54−2.51 (m, 2H), 1.71 (s, 3H), 1.60−1.56 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.9, 143.5, 138.4, 137.3, 135.9, 129.4, 129.1, 128.8, 128.4, 128.1, 125.7, 125.4, 124.7, 123.1, 121.7, 121.0, 116.5, 111.2, 65.8, 53.5, 37.7, 24.7, 24.4, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{27}NO_2Na$, $[M+Na]^+$: 444.1939; Found: 444.1943.

1-(4-(4-Chlorophenyl)-2-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34f)

The compound **34f** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34f** as colourless foam in 39% (20 mg) yield.



IR (neat) ν_{max}: 3063, 1666, 1593, 1091 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.40 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.31−7.28 (m, 5H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (s, 2H), 7.03 (td, *J* = 7.5, 1 Hz, 1H), 6.92 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.8, 138.3, 138.3, 135.8, 134.4, 129.6, 129.1, 129.1, 128.8, 125.7, 125.1, 125.0, 123.1, 121.8, 120.7, 116.6, 111.8, 65.6, 52.8, 24.7.

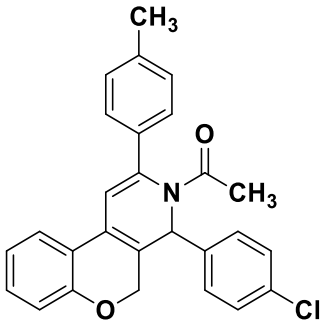
HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}ClNO_2Na$, $[M+Na]^+$: 436.1080; Found: 436.1089.

1-(4-(4-Chlorophenyl)-2-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-c]pyridin-3-yl)ethanone (34g)

The compound **34g** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34g** as colourless foam in 63% (32 mg) yield.

IR (neat) ν_{max}: 3035, 1667, 1588, 1091 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 3H), 6.91 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.46 (s,



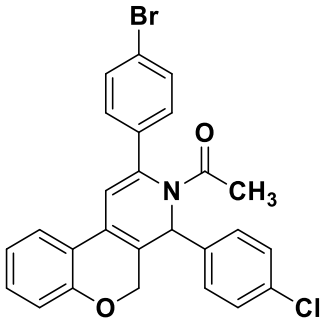
1H), 6.40 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.9, 139.0, 138.3, 135.8, 135.5, 134.3, 129.8, 129.6, 129.6, 129.0, 125.6, 125.0, 124.8, 123.1, 121.8, 120.8, 116.6, 111.2, 65.6, 52.8, 24.7, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{22}ClNO_2Na$, $[M+Na]^+$: 450.1237; Found: 450.1233.

1-(2-(4-Bromophenyl)-4-(4-chlorophenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34h)

The compound **34h** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34h** as colourless foam in 49% (29 mg) yield.



IR (neat) ν_{max}: 2928, 1666, 1588, 1269, 1091 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.5, 2.0 Hz, 4H), 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 6.44 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.70 (d, *J* = 15.0 Hz, 1H), 1.72 (s, 3H).

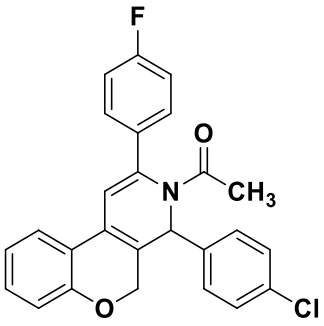
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 153.8, 137.2, 137.1, 135.6, 134.5, 133.6, 132.3, 131.6, 129.8, 129.5, 129.2, 127.1, 125.6, 124.9, 123.1, 122.9, 121.8, 120.6, 116.6, 112.4, 65.5, 52.8, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{19}BrClNO_2Na$, $[M+Na]^+$: 514.0185; Found: 514.0177.

1-(4-(4-Chlorophenyl)-2-(4-fluorophenyl)-4,5-dihydro-3H-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34i)

The compound **34i** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), 1-ethynyl-4-fluorobenzene (43 mg,

0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 °C. The reaction afforded **34i** as colourless foam in 48% (25 mg) yield.



IR (neat) ν_{max}: 3068, 1669, 1600, 1092 cm^{-1}.

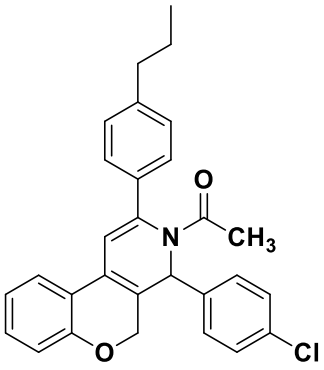
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.09 (s, 2H), 7.04−6.97 (m, 3H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 6.39 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.71 (d, *J* = 15.0 Hz, 1H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 163.9, 161.9, 153.8, 137.1, 135.7, 134.5, 129.7, 129.5, 129.1, 127.5, 127.4, 124.9, 123.1, 121.8, 120.6, 116.6, 116.3, 116.1, 111.8, 65.6, 52.9, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{19}ClFNO_2Na$, $[M+Na]^+$: 454.0986; Found: 454.0995.

1-(4-(4-Chlorophenyl)-2-(4-propylphenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34j)

The compound **34j** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 °C. The reaction afforded **34*J*** as colourless foam in 55% (30 mg) yield.



IR (neat) ν_{max}: 3062, 1668, 1588, 1091 cm^{-1}.

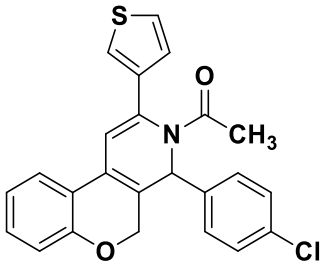
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 5.5 Hz, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.12 (s, 5H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.93−6.89 (m, 2H), 6.65 (s, 1H), 6.41 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.84 (d, *J* = 15.5 Hz, 1H), 2.57−2.54 (m, 2H), 1.70 (s, 3H), 1.63−1.58 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 143.6, 140.4, 138.2, 135.9, 129.5, 129.1, 126.8, 126.8, 126.5, 125.9, 125.2, 124.2, 123.2, 121.7, 120.8, 116.5, 110.7, 65.6, 49.7, 37.7, 24.8, 24.4, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{26}ClNO_2Na$, $[M+Na]^+$: 478.1550; Found: 478.1553.

1-(4-(4-Chlorophenyl)-2-(thiophene-3-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34k)

The compound **34k** was synthesized following the procedure 3, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (33 mg, 0.12 mmol), 3-ethynylthiophene (39 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34k** as colourless foam in 60% (30 mg) yield.



IR (neat) ν_{max}: 3106, 1666, 1596, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29−7.27 (m, 3H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.03−7.00 (m, 2H), 6.92−6.90 (m, 2H), 6.42 (s, 2H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.8, 140.1, 135.9, 134.3, 133.6, 130.9, 129.6, 129.5, 129.4, 129.0, 127.2, 125.3, 125.0, 125.0, 123.1, 122.0, 121.8, 120.7, 65.7, 52.7, 24.1.

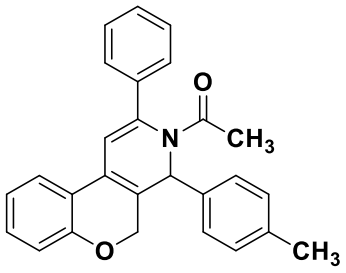
HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}ClNO_2SNa$, $[M+Na]^+$: 442.0644; Found: 442.0636.

1-(2-Phenyl-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridine-3-yl)ethanone (34l)

The compound **34l** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34l** as colourless foam in 74% (35 mg) yield.

IR (neat) ν_{max}: 3060, 1666, 1596, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 3H), 7.27−7.25 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 4H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 4.88 (d, *J* = 15.5



Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 2.30 (s, 3H), 1.70 (s, 3H).

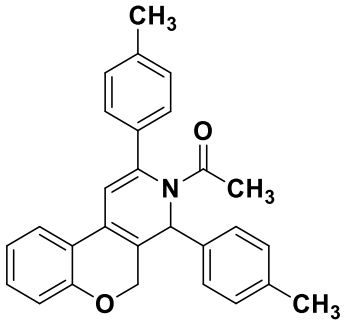
^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 153.8, 138.6, 138.3, 138.2, 134.2, 129.5, 129.4, 129.0, 128.6, 128.1, 126.1, 125.8, 124.5, 123.0, 121.7, 121.0, 116.5, 111.9, 65.8, 53.3, 24.7, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{23}NO_2Na$, $[M+Na]^+$: 416.1626; Found: 416.1637.

1-(2,4-Di-*p*-tolyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)-ethanone (34m)

The compound **34m** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34m** as colourless foam in 77% (38 mg) yield.

IR (neat) ν_{max}: 3031, 1666, 1606, 1041 cm^{-1}.



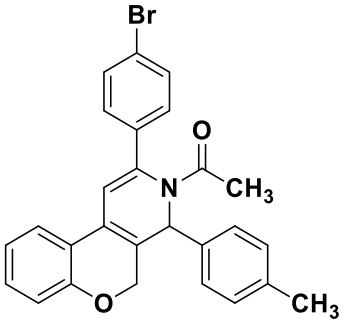
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.37 (m, 3H), 7.20 (td, *J* = 7.5, 1.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.04−6.99 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 6.39 (s, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.75 (d, *J* = 15.0 Hz, 1H), 2.30 (s, 6H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.8, 138.7, 138.2, 138.1, 135.8, 134.1, 129.9, 129.7, 129.5, 129.4, 128.0, 125.7, 124.5, 123.0, 121.7, 121.0, 116.5, 111.2, 65.8, 53.2, 24.8, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{28}H_{25}NO_2Na$, $[M+Na]^+$: 430.1783; Found: 430.1761.

1-(2-(4-Bromophenyl)-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34n)

The compound **34n** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34n** as colourless foam in 61% (35 mg) yield.



IR (neat) ν_{max}: 3063, 1666, 1587, 1072 cm^{-1}.

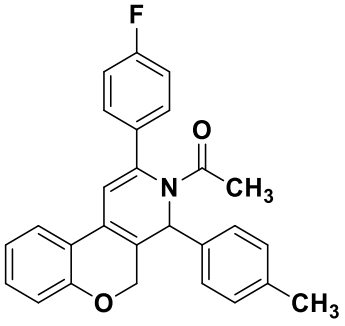
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.37−7.34 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 3H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.46 (s, 1H), 6.43 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.74 (d, *J* = 15.5 Hz, 1H), 2.31 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 138.4, 137.5, 137.1, 133.9, 132.2, 129.6, 129.5, 128.0, 127.2, 126.7, 124.5, 123.0, 122.6, 121.7, 120.7, 116.6, 112.5, 65.8, 53.3, 24.8, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{22}BrNO_2Na$, $[M+Na]^+$: 494.0732; Found: 494.0721.

1-(2-(4-Fluorophenyl)-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34o)

The compound **34o** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), 1-ethynyl-4-flourobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34o** as colourless foam in 62% (31 mg) yield.



IR (neat) ν_{max}: 3063, 1667, 1600, 1042 cm^{-1}.

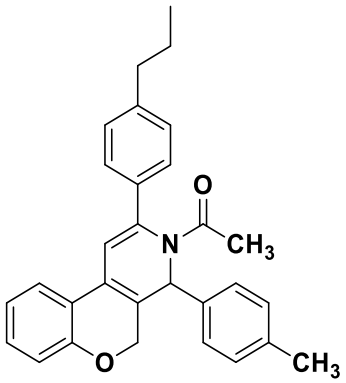
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.5 Hz, 3H), 7.21 (td, *J* = 8.0, 2.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 4H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.97 (t, *J* = 9.0 Hz, 2H), 6. 91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 2.31 (s, 3H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 163.8, 161.8, 153.8, 138.3, 137.2, 134.8, 134.1, 129.6, 129.5, 128.0, 127.5, 127.5, 126.1, 124.5, 123.0, 121.7, 120.8, 116.5, 116.2, 116.0, 111.9, 65.8, 53.3, 24.7, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{22}FNO_2Na$, $[M+Na]^+$: 434.1532; Found: 434.1530.

1-(2-(4-Propylphenyl)-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34p)

The compound **34p** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34p** as colourless foam in 74% (39 mg) yield.



IR (neat) ν_{max}: 2958, 1666, 1588, 1228 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.0 Hz, 3H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.08− 7.07 (m, 4H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 6.40 (s, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 2.55−2.52 (m, 2H), 2.30 (s, 3H), 1.70 (s, 3H), 1.61−1.56 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.9, 143.5, 138.4, 138.1, 136.0, 134.3, 129.5, 129.3, 129.0, 128.0, 125.7, 124.5, 123.0, 121.6, 121.0, 116.5, 111.1, 65.9, 53.3, 37.7, 24.7, 24.3, 21.2, 13.8.

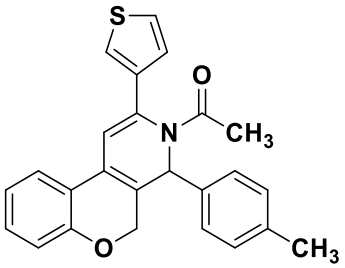
HRMS (ESI) (m/z): Calcd for $C_{30}H_{29}NO_2Na$, $[M+Na]^+$: 458.2096; Found: 458.2086.

1-(2-(Thiophene-3-yl)-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34q)

The compound **34q** was synthesized following the procedure 3, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), 3-ethynylthiophene (39 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34q** as colourless foam in 77% (37 mg) yield.

IR (neat) ν_{max}: 3103, 1663, 1587, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.34 (m, 3H), 7.25 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.02−6.99 (m, 2H), 6.94 (dd, *J* = 5.0,



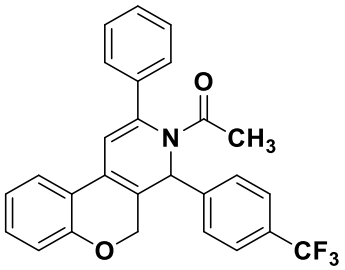
1.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 4.5 Hz, 2H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.76 (d, *J* = 15.5 Hz, 1H), 2.29 (s, 3H), 1.80 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.8, 140.4, 138.1, 134.3, 133.6, 129.5, 129.4, 127.8, 127.0, 126.1, 125.5, 124.5, 123.0, 122.0, 121.7, 120.9, 116.5, 110.7, 65.9, 53.1, 24.2, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{21}NO_2SNa$, $[M+Na]^+$: 422.1191; Found: 422.1196.

1-(2-Phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34r)

The compound **34r** was synthesized following the procedure 3, using (*E*)-3-(4-(trifluoromethyl)benzylidene)chroman-4-one (37 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34r** as colourless foam in 19% (36 mg) yield.



IR (neat) ν_{max}: 3064, 1665, 1609, 1067 cm^{-1}.

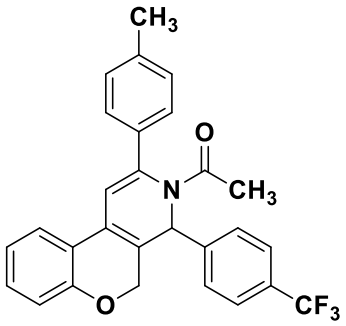
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.41 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.31−7.29 (m, 3H), 7.23 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.13 (s, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.55 (s, 1H), 6.45 (s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.9, 141.4, 138.4, 138.1, 129.8, 129.1, 128.9, 128.6, 125.9, 125.8, 125.7, 125.3, 124.5, 123.2, 121.9, 120.7, 116.6, 111.8, 65.6, 53.0, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{20}F_3NO_2Na$, $[M+Na]^+$: 470.1344; Found: 470.1335.

1-(2-(*p*-Tolyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34s)

The compound **34s** was synthesized following the procedure 3, using (*E*)-3-(4-(trifluoromethyl)benzylidene)chroman-4-one (37 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34s** as colourless foam in 54% (31 mg) yield.



IR (neat) ν_{max}: 3066, 1663, 1166, 1067 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.41 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.05−7.02 (m, 3H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 2.31 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 153.9, 141.4, 139.1, 138.4, 135.3, 129.8, 129.7, 128.6, 125.8, 125.8, 125.6, 125.3, 124.2, 123.2, 121.8, 120.7, 116.6, 111.0, 65.6, 53.0, 24.7, 21.2.

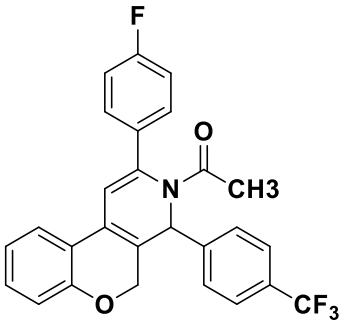
HRMS (ESI) (m/z): Calcd for $C_{28}H_{22}F_3NO_2Na$ $[M+Na]^+$: 484.1500; Found: 484.1487.

1-(2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanon (34t)

The compound **34t** was synthesized following the procedure 3, using (*E*)-3-(4-(trifluoromethyl)benzylidene)chroman-4-one (37 mg, 0.12 mmol), 1-ethynyl-4-fluorobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34t** as colourless foam in 32% (18 mg) yield.

IR (neat) ν_{max}: 3073, 1666, 1601, 1067 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (q, *J* = 8.5 Hz, 4H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.10 (s, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.02−6.98 (m, 2H), 6.93 (d, *J*



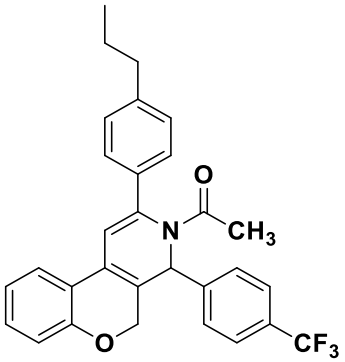
= 8.0 Hz, 1H), 6.54 (s, 1H), 6.41 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.5 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 164.0, 162.0, 153.9, 141.3, 137.3, 134.3, 129.8, 128.5, 127.5, 127.4, 125.9, 125.9, 125.3, 124.6, 123.1, 121.9, 120.6, 116.7, 116.4, 116.2, 111.7, 65.5, 53.0, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{19}F_4NO_2Na$, $[M+Na]^+$: 488.1250; Found: 488.1256.

1-(2-(4-Propylphenyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34u)

The compound **34u** was synthesized following the procedure 3, using (*E*)-3-(4-(trifluoromethyl)benzylidene)chroman-4-one (37 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34u** as colourless foam in 47% (28 mg) yield.



IR (neat) ν_{max}: 3056, 1666, 1606, 1065 cm^{-1}.

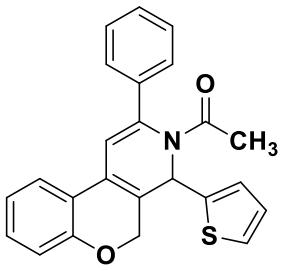
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.25−7.21 (m, 1H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.04 (td, *J* = 7.5, 1.5 Hz, 3H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 2.56−2.53 (m, 2H), 1.73 (s, 3H), 1.62−1.57 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 153.9, 143.9, 141.5, 138.5, 135.5, 129.7, 129.2, 128.6, 125.8, 125.8, 125.7, 125.3, 124.2, 123.2, 121.8, 120.8, 116.6, 111.0, 65.6, 53.0, 37.7, 24.7, 24.3, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{30}H_{26}F_3NO_2Na$, $[M+Na]^+$: 512.1813; Found: 512.1823.

1-(2-Phenyl-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34v)

The compound **34v** was synthesized following the procedure 3, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), 1-ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34v** as colourless foam in 50% (23 mg) yield.



IR (neat) ν_{max}: 2922, 1648, 1605, 1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.31−7.28 (m, 3H), 7.27 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.22−7.18 (m, 3H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.01 (td, *J* = 7.5, 1.5 Hz, 1H), 6.93 (dd, *J* = 5.5, 4.0 Hz 1H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.66 (s, 1H), 6.45 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 153.9, 140.3, 138.5, 138.1, 129.6, 129.0, 128.8, 128.7, 126.8, 126.8, 126.6, 126.0, 125.6, 124.2, 123.2, 121.7, 120.7, 116.6, 111.5, 65.6, 49.7, 33.6, 24.8.

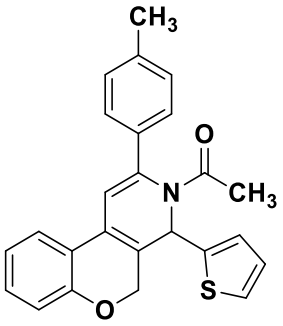
HRMS (ESI) (m/z): Calcd for $C_{24}H_{19}NO_2SNa$, $[M+Na]^+$: 408.1034; Found: 408.1028.

1-(4-(Thiophene-2-yl)-2-(*p*-tolyl)-4,5-dihydro-3-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34w)

The compound **34w** was synthesized following the procedure 3, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34w** as colourless foam in 74% (35 mg) yield.

IR (neat) ν_{max}: 3069, 1665, 1606, 1040 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.25 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 1H), 7.16 (s, 5H), 7.01 (td, *J* = 7.5, 1.5 Hz, 1H), 6.92 (dd, *J* = 5.5, 1.5 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.65 (s,



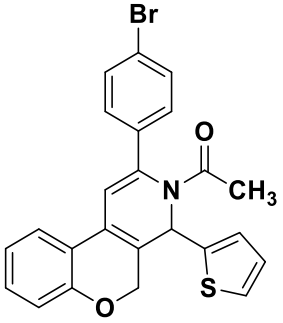
1H), 6.41 (s, 1H), 4.88 (d, *J* = 15.5 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 2.32 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 140.3, 138.9, 138.1, 135.7, 129.7, 129.5, 126.8, 126.7, 126.5, 125.9, 125.3, 124.2, 123.2, 121.7, 120.8, 116.5, 110.8, 65.6, 49.7, 24.8, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{21}NO_2SNa$, $[M+Na]^+$: 422.1191; Found: 422.1188.

1-(2-(4-Bromophenyl)-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34x)

The compound **34x** was synthesized following the procedure 3, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34x** as colourless foam in 38% (21 mg) yield.



IR (neat) ν_{max}: 3063, 1670, 1586, 1072 cm^{-1}.

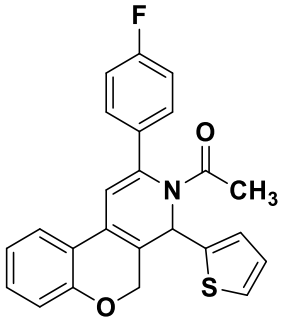
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.37 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.27 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.09 (d, *J* = 6.0 Hz, 2H), 7.01 (td, *J* = 7.5, 1.1 Hz, 1H), 6.93 (dd, *J* = 5.10, 3.5 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.65 (s, 1H), 6.45 (s, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 153.8, 140.0, 137.4, 137.0, 132.3, 129.7, 127.4, 126.9, 126.7, 126.1, 124.1, 123.2, 122.8, 121.8, 120.6, 116.6, 112.1, 65.5, 49.6, 24.8.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}BrNO_2SNa$, $[M+Na]^+$: 486.0139; Found: 486.0132.

1-(2-(4-Fluorophenyl)-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34y)

The compound **34y** was synthesized following the procedure 3, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), 1-ethynyl-4-fluorobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34y** as colourless foam in 24% (12 mg) yield.



IR (neat) ν_{max}: 3072, 1670, 1599, 1229 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.28 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.23−7.19 (m, 3H), 7.13 (d, *J* = 3.5, Hz, 1H), 7.06−6.99 (m, 3H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.65 (s, 1H), 6.40 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 1.70 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 163.9, 161.9, 153.8, 140.2, 137.0, 134.7, 129.6, 127.8, 127.7, 126.9, 126.6, 125.6, 124.2, 123.1, 121.7, 120.6, 116.6, 116.2, 116.1, 111.5, 65.5, 49.7, 24.8.

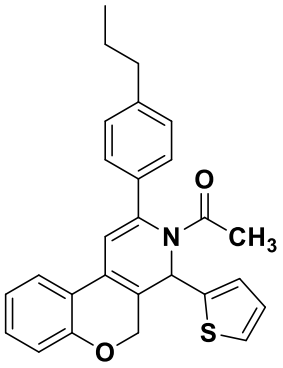
HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}FNO_2SNa$, $[M+Na]^+$: 426.0940; Found: 426.0930.

1-(2-(4-Propylphenyl)-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34z)

The compound **34z** was synthesized following the procedure 3, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34z** as colourless foam in 47% (24 mg) yield.

IR (neat) ν_{max}: 3070, 1667, 1606, 1040 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 1H), 7.26−7.25 (m, 1H), 7.20 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (s, 5H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.65 (s, 1H), 6.42 (s, 1H), 4.89 (d, *J* = 15.0 Hz, 1H), 4.84 (d, *J* = 15.0 Hz, 1H), 2.55 (t, *J* = 7.5



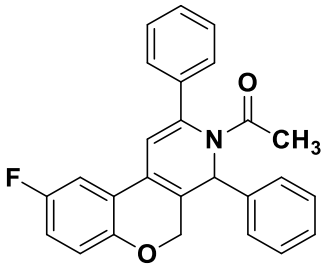
Hz, 2H), 1.70 (s, 3H), 1.63−1.57 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 143.6, 140.4, 138.2, 135.9, 129.5, 129.1, 126.8, 126.8, 126.5, 125.9, 125.2, 124.2, 123.2, 121.7, 120.8, 116.5, 110.7, 65.6, 49.7, 37.7, 26.9, 24.8, 24.4, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{25}NO_2SNa$, $[M+Na]^+$: 450.1504; Found: 450.1512.

1-(9-Fluoro-2,4-diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]-pyridin-3-yl)ethanone (34aa)

The compound **34aa** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34aa** as colourless foam in 63% (30 mg) yield.



IR (neat) ν_{max}: 3063, 1665, 1591, 1074 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.0 Hz, 2H), 7.36−7.30 (m, 3H), 7.28−7.27 (m, 3H), 7.13 (s, 2H), 7.09 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.92−6.88 (m, 1H), 6.86 (dd, *J* = 9.0, 5.5 Hz, 1H), 6.53 (s, 1H), 6.34 (s, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.74 (d, *J* = 15.5 Hz, 1H), 1.70 (s, 3H).

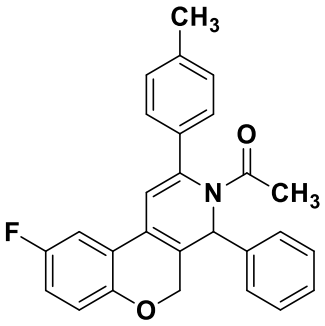
^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 158.8, 156.9, 149.7, 138.7, 138.3, 137.0, 129.0, 128.9, 128.8, 128.6, 128.1, 127.0, 125.8, 124.2, 122.1, 117.4, 117.3, 115.5, 115.3, 111.4, 109.8, 109.6, 65.8, 53.4, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}FNO_2Na$, $[M+Na]^+$: 420.1376: Found: 420.1368.

1-(9-Fluoro-4-phenyl-2-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ab)

The compound **34ab** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol),1-ethynyl-4-methylbenzene (42 mg, 0.36

mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ab** as colourless foam in 67% (33 mg) yield.



IR (neat) ν_{max}: 3060, 1667, 1589, 1025 cm^{-1}.

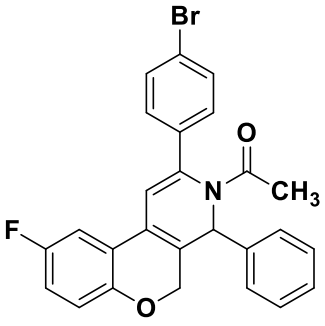
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.0 Hz, 2H), 7.34−7.27 (m, 3H), 7.10−7.07 (m, 3H), 7.02 (s, 2H), 6.89 (td, *J* = 8.5, 3.0 Hz, 1H), 6.85 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.52 (s, 1H), 6.30 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 15.5 Hz, 1H), 2.30 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 139.0, 138.8, 137.0, 135.5, 129.7, 128.9, 128.5, 128.1, 125.7, 124.4, 122.2, 122.1, 117.4, 117.3, 115.4, 115.3, 110.7, 109.8, 109.6, 65.9, 53.4, 24.8, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{22}FNO_2Na$, $[M+Na]^+$: 434.1532; Found: 434.1522.

1-(2-(4-Bromophenyl)-9-fluoro-4-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ac)

The compound **34ac** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol),1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ac** as colourless foam in 39% (22 mg) yield.



IR (neat) ν_{max}: 3062, 1669, 1489, 1073, 1032 cm^{-1}.

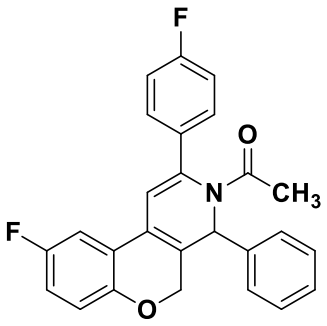
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.0 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.35− 7.30 (m, 3H), 7.07 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.99 (d, *J* = 7.0 Hz, 2H), 6.91 (td, *J* = 8.5, 3.0 Hz, 1H), 6.86 (dd, *J* = 9.0, 5.5 Hz, 1H), 6.52 (s, 1H), 6.35 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 15.5 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 158.8, 156.9, 149.7, 137.6, 137.2, 136.8, 132.3, 129.0, 128.7, 128.0, 127.2, 124.3, 122.9, 117.4, 117.4, 115.6, 115.5, 112.0, 109.8, 109.6, 65.8, 53.4, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{19}BrFNO_2Na$, $[M+ Na]^+$: 498.0481; Found: 498.0472.

1-(9-Fluoro-2-(4-fluorophenyl)-4-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ad)

The compound **34ad** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol),1-ethynyl-4-fluorobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ad** as colourless foam in 51% (25 mg) yield.



IR (neat) ν_{max}: 3064, 1669, 1597, 1099, 1024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl^3$): δ 7.48 (d, *J* = 7.0 Hz, 2H), 7.36−7.29 (m, 3H), 7.09−7.06 (m, 3H), 6.98 (t, *J* = 9.0 Hz, 2H), 6.90 (td, *J* = 9.0, 3.0 Hz, 1H), 6.86 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.52 (s, 1H), 6.29 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.73 (d, *J* = 15.5 Hz, 1H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 163.9, 161.9, 158.8, 156.9, 149.7, 137.6, 136.9, 129.0, 128.7, 128.0, 127.5, 127.4, 127.1, 117.4, 117.3, 116.3, 116.1, 115.6, 115.4, 111.4, 109.8, 109.6, 65.8, 53.4, 24.7.

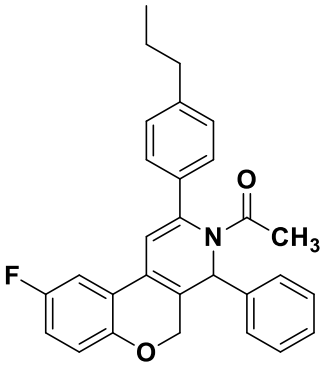
HRMS (ESI) (m/z): calcd for $C_{26}H_{19}F_2NO_2Na$, $[M+Na]^+$: 438.1282; Found: 438.1265.

1-(9-Fluoro-4-phenyl-2-(4-propylphenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ae)

The compound **34ae** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol),1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ae** as colourless foam in 50% (26 mg) yield.

IR (neat) ν_{max}: 3063, 1669, 1591, 1549, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.0 Hz, 2H), 7.35−7.29 (m, 3H), 7.08 (d, *J* = 6.5 Hz, 3H), 7.04 (s, 2H), 6.90 (t, *J* = 8.5 Hz, 1H), 6.87−6.83 (m, 1H), 6.52 (s, 1H), 6.31 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.74 (d, *J* = 15.5 Hz,



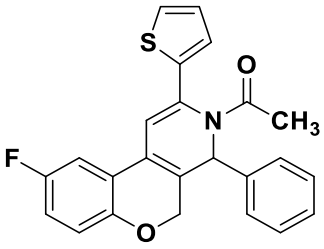
1H), 2.54 (t, *J* = 8.0 Hz, 2H), 1.71 (s, 3H), 1.61−1.56 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 143.7, 138.8, 137.1, 135.7, 129.1, 128.9, 128.5, 128.1, 126.7, 125.7, 124.4, 122.1, 117.4, 117.3, 115.4, 115.2, 110.6, 109.8, 109.6, 65.9, 53.4, 37.7, 24.8, 24.4, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{26}FNO_2Na$, $[M+Na]^+$: 462.1845; Found: 462.1848.

1-(9-Fluoro-4-phenyl-2-(thiophene-3-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34af)

The compound **34af** was synthesized following the procedure 3, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol), ethynylthiophene (39 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34af** as colourless foam in 33% (16 mg) yield.



IR (neat) ν_{max}: 3066, 1664, 1490, 1079 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.34−7.26 (m, 4H), 7.05 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.93 (d, *J* = 5.5 Hz, 1H), 6.89 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.86 (dd, *J* = 8.5, 5.0 Hz, 1H), 6.48 (s, 1H), 6.32 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.75 (d, *J* = 15.5 Hz, 1H), 1.81 (s, 3H).

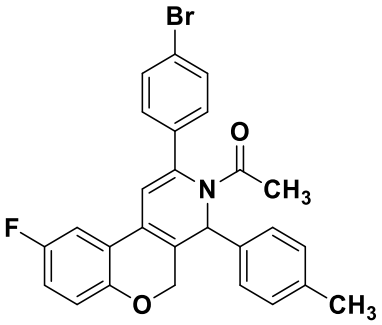
^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 140.1, 137.2, 134.1, 128.9, 128.5, 127.8, 127.1, 125.4, 124.3, 122.2, 117.4, 117.3, 115.5, 115. 3, 110.2, 109.8, 109.6, 65.9, 53.3, 24.2.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}FNO_2SNa$, $[M+Na]^+$: 426.0940; Found: 426.0929.

1-(2-(4-Bromophenyl)-9-fluoro-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ag)

The compound **34ag** was synthesized following the procedure 3, using (*E*)-6-fluoro-3-(4-methylbenzylidene)chroman-4-one (32 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65

mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ah** as colourless foam in 36% (21 mg) yield.



IR (neat) ν_{max}: 3058, 1666, 1589, 1073 cm^{-1}.

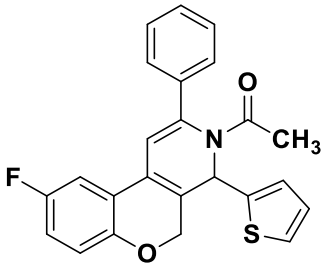
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 5.0 Hz, 1H), 6.91−6.83 (m, 2H), 6.48 (s, 1H), 6.34 (s, 1H), 4.84 (d, *J* = 15.0 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 2.32 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 158.8, 156.8, 149.7, 138.5, 137.5, 137.3, 133.7, 132.3, 129.7, 127.9, 127.2, 124.1, 122.8, 121.9, 121.9, 117.4, 117.3, 115.6, 115.4, 112.0, 109.8, 109.6, 65.8, 53.2, 24.7, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{21}BrFNO_2Na$, $[M+Na]^+$: 512.0637; Found: 512.0627.

1-(9-Fluoro-2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ah)

The compound **34ah** was synthesized following the procedure 3, using (*E*)-6-fluoro-3-(thiophen-2-ylmethylene)chroman-4-one (31 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ah** as colourless foam in 64% (31 mg) yield.



IR (neat) ν_{max}: 3070, 1666, 1590, 1177 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 3H), 7.28 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.22 (s, 2H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.90 (td, *J* = 9.0, 3.0 Hz, 1H), 6.85 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.68 (s, 1H), 6.35 (s, 1H), 4.86 (d, *J* = 15.5 Hz, 1H), 4.81 (d, *J* = 15.0 Hz, 1H) 1.70 (s, 3H).

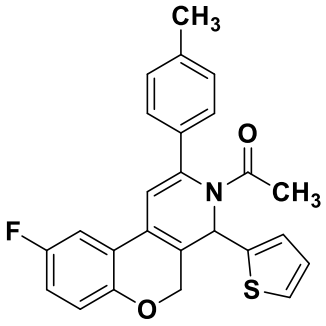
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 158.8, 156.9, 149.71, 140.0, 138.5, 138.3, 129.1, 126.9, 126.7, 126.0,

123.8, 121.9, 121.9, 117.4, 117.4, 115.7, 115.5, 110.9, 109.9, 109.8, 65.6, 49.6, 24.8.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}FNO_2SNa$, $[M+Na]^+$: 426.0940; Found: 426.0940.

1-(9-Fluoro-4-(thiophene-2-yl)-2-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (34ai)

The compound **34ai** was synthesized following the procedure 3, using (*E*)-6-fluoro-3-(thiophen-2-ylmethylene)chroman-4-one (31 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **34ai** as colourless foam in 41% (21 mg) yield.



IR (neat) ν_{max}: 3071, 1670, 1492, 1031 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26−7.25 (m, 1H), 7.12−7.11 (m, 5H), 7.08 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.90−6.86 (m, 1H), 6.84 (dd, *J* = 9.0, 5.0 Hz,1H) 6.67 (s, 1H), 6.32 (s, 1H), 4.85 (d, *J* = 15.5 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H), 2.33 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 158.8, 156.9, 149.7, 149.7, 140.0, 139.1, 138.6, 135.5, 129.8, 126.8, 126.6, 126.5, 125.9, 117.4, 117.3, 115.6, 115.4, 110.2, 110.0, 109.8, 65.7, 49.6, 24.8, 21.2.

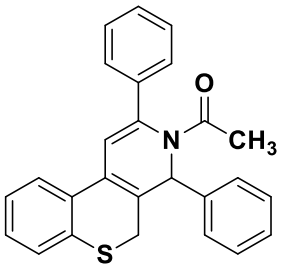
HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}FNO_2SNa$, $[M+Na]^+$: 440.1096; Found: 440.1087.

1-(2,4-Diphenyl-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)ethanone (36a)

The compound **36a** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **36a** as colourless foam in 46% (22 mg) yield.

IR (neat) ν_{max}: 3059, 1667, 1596, 1032 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.36−7.33 (m, 3H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.26−7.24 (m, 4H), 7.22 (dd, *J* = 3.0, 2.0



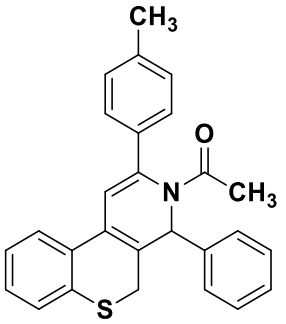
Hz, 1H), 7.20 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.13 (s, 1H), 6.62 (s, 1H), 6.40 (s, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 1.72 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 138.4, 137.7, 137.3, 133.6, 132.6, 132.2, 131.6, 129.2, 128.9, 128.7, 128.5, 128.4, 128.1, 127.8, 127.5, 126.1, 125.8, 125.1, 115.1, 57.0, 27.3, 24.6.

HRMS (ESI) (m/z): calcd for $C_{26}H_{21}NOSNa$, $[M+Na]^+$: 418.1242; Found: 418.1232.

1-(4-Phenyl-2-(*p*-tolyl)-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]-pyridin-3-yl)ethanone (36b)

The compound **36b** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **36b** as colourless foam in 26% (13 mg) yield.



IR (neat) ν_{max}: 2925, 1663, 1371, 1039 cm^{-1}.

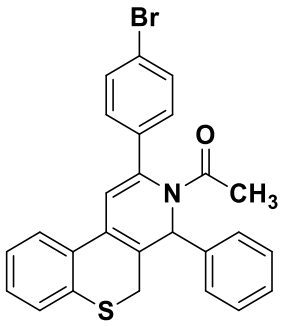
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.0 Hz, 2H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.36−7.32 (m, 3H), 7.29 (d, *J* = 7 Hz, 1H), 7.23−7.21 (m, 1H), 7.19 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 7.0 Hz, 2H), 6.61 (s, 1H), 6.36 (s, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 2.29 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 138.6, 137.7, 137.3, 135.5, 133.6, 132.6, 132.3, 131.6, 129.6, 129.2, 128.7, 128.4, 128.4, 128.0, 127.8, 127.2, 126.1, 125.7, 125.1, 114.4, 57.0, 27.3, 24.6, 21.1.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{23}NOSNa$, $[M+Na]^+$: 432.1398; Found: 432.1406.

1-(2-(4-Bromophenyl)-4-phenyl-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)ethanone (36c)

The compound **36c** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), 1-bromo-4-ethynylbenzene (65 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **36c** as colourless foam in 31% (18 mg) yield.



IR (neat) ν_{max}: 3059, 1668, 1584, 1072, 1035 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.0 Hz, 2H), 7.48 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.37−7.34 (m, 2H), 7.33−7.30 (m, 2H), 7.23 (dd, *J* = 7.5, 2.0 Hz 1H), 7.20 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.61 (s, 1H), 6.40 (s, 1H), 3.82 (d, *J* = 15.5 Hz, 1H), 3.14 (d, *J* = 15.5 Hz, 1H), 1.74 (s, 3H).

^{13}CNMR (125 MHz, $CDCl_3$): δ 171.7, 137.3, 137.1, 136.6, 132.6, 132.2, 132.1, 129.1, 128.8, 128.6, 128.3, 128.2, 128.1, 127.9, 127.1, 126.1, 125.1, 122.6, 115.7, 56.9, 27.3, 24.6.

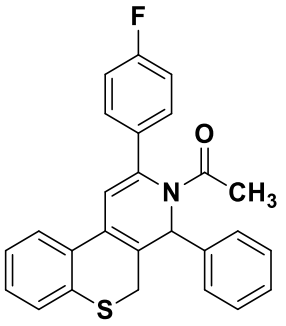
HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}BrNOSNa$, $[M+Na]^+$: 496.0347; Found: 496.0346.

1-(2-(4-Fluorophenyl)-4-phenyl-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)ethanone (36d)

The compound **36d** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), 1-ethynyl-4-fluorobenzene (43 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **36d** as colourless foam in 40% (20 mg) yield.

IR (neat) ν_{max}: 3061, 1668, 1598, 1077, 1034 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.0 Hz, 2H), 7.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 3H), 7.32 (d, *J* = 7.0 Hz, 1H), 7.23 (td, *J* = 8.0, 2.0 Hz, 2H), 7.09 (s, 2H), 6.96 (t, *J* = 8.5 Hz, 2H), 6.61 (s, 1H), 6.35 (s, 1H), 3.83 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 1.72 (s, 3H).

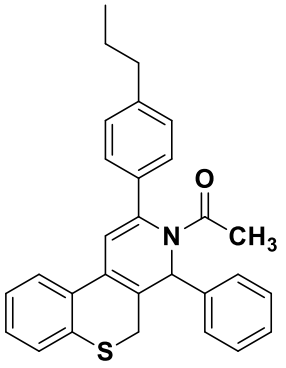


^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 163.8, 161.8, 137.2, 132.6, 132.2, 129.1, 128.8, 128.5, 128.3, 128.1, 127.9, 127.5, 127.4, 126.1, 125.1, 116.1, 116.0, 115.1, 57.0, 27.3, 24.6.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}FNOSNa$, $[M+Na]^+$: 436.1147; Found: 436.1149.

1-(4-Phenyl-2-(4-propylphenyl)-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)ethanone (36e)

The compound **36e** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), 1-ethynyl-4-propylbenzene (52 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **36e** as colourless foam in 23% (12 mg) yield.



IR (neat) ν_{max}: 3058, 1668, 1605, 1035 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.36−7.33 (m, 3H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.23−7.18 (m, 2H), 7.07−7.03 (m, 4H), 6.61 (s, 1H), 6.36 (s, 1H), 3.83 (d, *J* = 15.5 Hz, 1H), 3.15 (d, *J* =16.0 Hz, 1H), 2.54−2.51 (m, 2H), 1.72 (s, 3H), 1.60−1.56 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H).

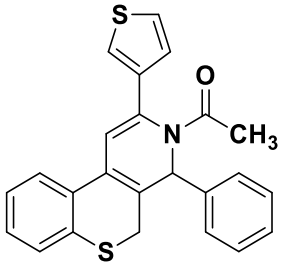
^{13}C NMR (125 MHz, CDCl3): δ 172.1, 143.4, 137.8, 137.4, 135.8, 132.6, 132.3, 129.0, 128.7, 128.4, 128.3, 128.0, 127.8, 127.1, 126.1, 125.7, 125.1, 114.3, 57.0, 37.7, 27.4, 24.6, 24.4, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{28}NOS$, $[M+H]^+$: 438.1891; Found: 438.1894.

1-(4-Phenyl-2-(thiophene-3-yl)-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)ethanone (36f)

The compound **36f** was synthesized following the procedure 3, using (*Z*)-3-benzylidenethiochroman-4-one (31 mg, 0.12 mmol), ethynylthiophene (39 mg, 0.36 mmol),

H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 °C. The reaction afforded **36f** as colourless foam in 39% (18 mg) yield.



IR (neat) ν_{max}: 3103, 1670, 1588, 1230 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.0 Hz, 2H), 7.47−7.45 (m, 1H), 7.36 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.25−7.24 (m, 1H), 7.23−7.20 (m, 2H), 7.02 (d, *J* = 1.5 Hz, 1H), 6.92 (dd, *J* = 5.0, 1.0 Hz, 1H), 6.56 (s, 1H), 6.37 (s, 1H), 3.83 (d, *J* = 15.5 Hz, 1H), 3.15 (d, *J* = 16.0 Hz, 1H), 1.83 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 140.2, 137.5, 132.6, 132.2, 129.1, 128.7, 128.3, 128.1, 128.1, 127.8, 127.4, 126.9, 126.1, 125.5, 125.1, 121.8, 113.9, 56.9, 27.5, 24.0.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{19}NOS_2Na$, $[M+Na]^+$: 424.0806; Found: 424.0803.

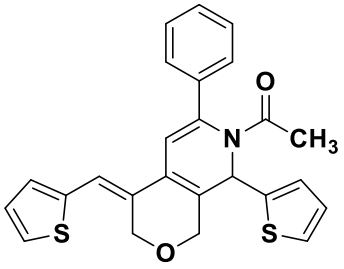
2.12. General procedure for BF_3·OEt_2-mediated synthesis of *N*-acetylated pyrano /thiopyranopyridines (4)

To a mixture of 1 equiv of (3*E*,5*E*)-3,5-diarylidenedihydro-2*H*-pyran-4(3*H*)-one/ (3*Z*,5*Z*)-3,5-diarylidenedihydro-2*H*-thiopyran-4(3*H*)-one (0.12 mmol), 3 equiv of aryl- or heteroarylalkyne (0.36 mmol) and 2 equiv of water in CH_3CN (2 mL) at 50 °C, 3 equiv of BF_3·OEt_2 (0.36 mmol) was added. The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The solvent was evaporated in *vacuo* and the residue on silica gel (100 – 200 mesh) column chromatography using a mixture of ethyl acetate – hexane afforded the *N*-acetylated fused pyridines.

(*Z*)-1-(6-Phenyl-8-(thiophene-2-yl)-4-(thiophene-2-ylmethylene)-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38a)

The compound **38a** was synthesized following the procedure 4, using (3*E*,5*E*)-3,5-bis(thiophen-2-ylmethylene)tetrahydro-4*H*-pyran-4-one (35 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36

mmol) in CH_3CN (2 mL) at 50 °C. The reaction afforded **38a** as colourless foam in 77% (40 mg) yield.



IR (neat) ν_{max}: 3063, 1668, 1587, 1097, 1040 cm^{-1}.

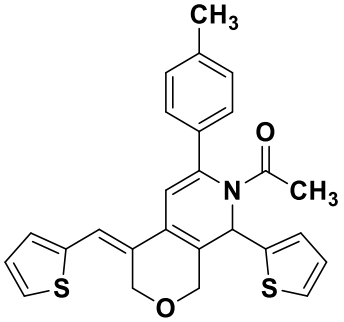
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J* = 5.0, Hz, 1H), 7.31 (d, *J* = 6.5 Hz, 3H), 7.26−7.25 (m, 1H), 7.20 (d, *J* = 4.0 Hz, 2H), 7.09−7.06 (m, 2H), 7.04 (d, *J* = 3.5 Hz, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.89 (s,1H), 6.61 (s,1H), 6.43 (s, 1H), 4.95 (dd, *J* = 14.5, 1.5 Hz, 1H), 4.71 (dd, *J* = 14.5, 1.5 Hz, 1H), 4.36 (s, 2H), 1.68 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 140.3, 139.4, 138.5, 137.2, 133.1, 132.9, 129.0, 128.7, 128.6, 128.4, 127.6, 126.8, 126.6, 126.4, 126.1, 115.6, 111.9, 66.1, 65.9, 50.0, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{21}NO_2S_2Na$, $[M+Na]^+$: 454.0911; Found: 454.0911.

(Z)-1-(8-(Thiophene-2-yl)-4-(thiophene-2-ylmethylene)-6-(*p*-tolyl)-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38b)

The compound **38b** was synthesized following the procedure 4, using (3*E*,5*E*)-3,5-bis(thiophen-2-ylmethylene)tetrahydro-4*H*-pyran-4-one (35 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 °C. The reaction afforded **38b** as colourless foam in 40% (21 mg) yield.



IR (neat) ν_{max}: 3063, 1669, 1587, 1183 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 5.5, 1.0 Hz, 1H), 7.24 (dd, *J* = 5.0 Hz, 1.0 Hz, 1H), 7.10 (s, 3H), 7.08 (dd, *J* = 5.0, 4.0 Hz, 2H), 7.06−7.02 (m, 2H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.88 (s, 1H), 6.60 (s, 1H), 6.39 (s, 1H), 4.94 (dd, *J* = 14.5, 1.5 Hz, 1H), 4.71 (dd, *J* = 14.5, 2.0 Hz, 1H), 4.36 (s, 2H), 2.32 (s, 3H), 1.69 (s, 3H).

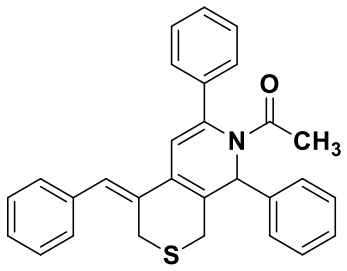
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 140.3, 139.4, 138.8, 137.2, 135.7, 132.7, 129.7, 129.1, 128.4, 127.6, 126.7,

126.7, 126.6, 126.3, 125.9, 125.8, 115.5, 112.4, 111.1, 66.13, 65.9, 50.0, 24.7, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{23}NO_2S_2Na$, $[M+Na]^+$: 468.1068; Found: 468.1074.

(Z)-1-(4-Benzylidene-6,8-diphenyl-3,4-dihydro-1*H*-thiopyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38c)

The compound **38c** was synthesized following the procedure 4, using 3,5-di((*Z*)-benzylidene)tetrahydro-4*H*-thiopyran-4-one (35 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **38c** as colourless foam in 33% (17 mg) yield.



IR (neat) ν_{max}: 3058, 1665, 1599, 1054, 1030 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.34−7.28 (m, 7H), 7.24−7.23 (m, 2H), 7.08 (s, 2H), 6.96 (s, 1H), 6.48 (s, 1H), 6.41 (s, 1H), 3.74 (d, *J* = 14.5 Hz, 1H), 3.69 (d, *J* = 14.5 Hz, 1H) 3.50 (d, *J* = 18.5 Hz, 1H), 3.36 (d, *J* = 18.5 Hz, 1H), 1.70 (s, 3H).

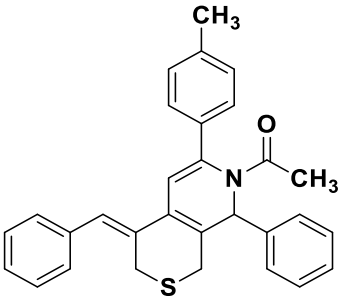
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 138.4, 137.3, 136.8, 136.5, 131.5, 131.4, 129.6, 129.3, 128.9, 128.8, 128.5, 128.3, 128.2, 127.3, 125.8, 125.6, 115.0, 57.7, 29.2, 27.1, 24.5.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{25}NOSNa$, $[M+Na]^+$: 458.1555; Found: 458.1560.

(Z)-1-(4-Benzylidene-8-phenyl-6-(*p*-tolyl)-3,4-dihydro-1*H*-thiopyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38d)

The compound **38d** was synthesized following the procedure 4, using 3,5-di((*Z*)-benzylidene)tetrahydro-4*H*-thiopyran-4-one (35 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **38d** as colourless foam in 17% (9 mg) yield.

IR (neat) ν_{max}: 3028, 1665, 1607, 1033 cm^{-1}.



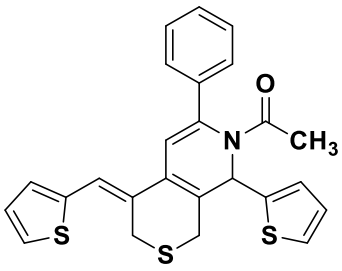
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.5 Hz, 3H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 5H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 7.0 Hz, 2H), 6.95 (s, 1H), 6.47 (s, 1H), 6.37 (s, 1H), 3.73 (d, *J* = 14.5 Hz, 1H), 3.69 (d, *J* = 14.5 Hz, 1H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.37 (d, *J* = 18.5 Hz, 1H), 2.29 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 138.6, 137.3, 136.8, 136.5, 135.5, 131.4, 131.2, 129.7, 129.6, 129.3, 128.7, 128.5, 128.2, 127.2, 125.7, 125.5, 114.3, 57.6, 29.2, 27.1, 24.6, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{30}H_{27}NOSNa$, $[M+Na]^+$: 472.1711; Found: 472.1710.

(*Z*)-1-(6-Phenyl-8-(thiophene-2-yl)-4-(thiophene-2-ylmethylene)-3,4-dihydro-1*H*-thiopyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38e)

The compound **38e** was synthesized following the procedure 4, using (3*Z*,5*Z*)-3,5-bis(thiophen-2-ylmethylene)tetrahydro-4*H*-thiopyran-4-one (37 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **38e** as colourless foam in 61% (33 mg) yield.



IR (neat) ν_{max}: 3069, 1666, 1592, 1036 cm^{-1}.

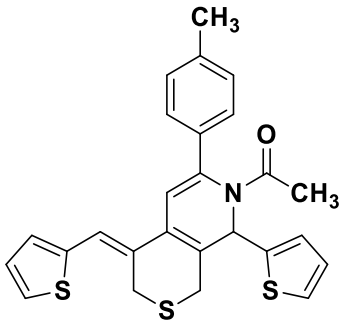
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.30− 7.29 (m, 3H), 7.26 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.20 (d, *J* = 6.0 Hz, 2H), 7.14 (d, *J* = 3.5 Hz, 1H), 7.10−7.07 (m, 2H), 7.00 (s, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.62 (s, 1H), 6.38 (s, 1H), 3.86 (s, 2H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.41 (d, *J* = 18.0 Hz, 1H), 1.68 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 140.2, 139.5, 138.3, 136.6, 132.2, 129.5, 129.1, 129.0, 129.0, 128.6, 127.4, 126.9, 126.7, 126.6, 126.4, 126.1, 118.7, 114.5, 53.9, 28.6, 27.6, 24.6.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{21}NOS_3Na$, $[M+Na]^+$: 470.0683; Fou: 470.0683.

(*Z*)-1-(8-(Thiophene-2-yl)-4-(thiophene-2-ylmethylene)-6-(*p*-tolyl)-3,4-dihydro-1*H*-thiopyrano[3,4-*c*]pyridin-7(8*H*)-yl)ethanone (38f)

The compound **38f** was synthesized following the procedure 4, using (3*Z*,5*Z*)-3,5-bis(thiophen-2-ylmethylene)tetrahydro-4*H*-thiopyran-4-one (37 mg, 0.12 mmol), 1-ethynyl-4-methylbenzene (42 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) at 50 ^oC. The reaction afforded **38f** as colourless foam in 43% (24 mg) yield.



IR (neat) ν_{max}: 3026, 1667, 1510, 1038 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 5.0, 1 Hz, 1H), 7.24 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.10−7.06 (m, 6H), 6.99 (s, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.61 (s, 1H), 6.34 (s, 1H), 3.86 (s, 2H), 3.48 (d, *J* = 18.5 Hz, 1H), 3.41(d, *J* = 18.0 Hz, 1H), 2.32 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 140.3, 139.6, 138.7, 136.6, 135.5, 132.0, 129.6, 129.2, 128.9, 127.4, 126.9, 126.7, 126.5, 126.3, 126.0, 118.7, 113.8, 53.9, 31.6, 28.6, 27.6, 24.6, 21.2.

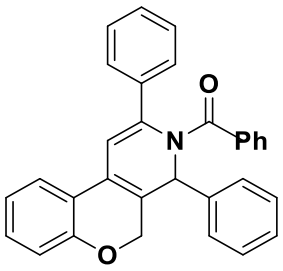
HRMS (ESI) (m/z): Calcd for $C_{26}H_{23}NOS_3Na$, $[M+Na]^+$: 484.0839; Found: 484.0834.

2.13. General procedure for $BF_3{\cdot}OEt_2$-mediated synthesis of *N*-substituted chromeno/thiochromenopyridines (5).

To a mixture of 1 equiv of substituted arylidenechroman-4-one/thiochroman-4-one (0.12 mmol) 3 equiv of aryl or heteroarylalkyne (0.36 mmol) and 2 equiv of water in the respective nitrile (2 mL) at 50 °C, 3 equiv of $BF_3{\cdot}OEt_2$ (0.36 mmol) was added. The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The solvent was evaporated in *vacuo* and the residue on silica gel (100 – 200 mesh) column chromatography using a mixture of ethyl acetate – hexane afforded the products.

(2,4-Diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)-(phenyl)methanone (40a)

The compound **40a** was synthesized following the procedure 5, using (*E*)-3-benzylidenechroman-4-one (28 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 ^oC. The reaction afforded **40a** as colourless foam in 51% (27 mg) yield.



IR (neat) ν_{max}: 3062, 1675, 1485, 1028 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.46 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 3H), 6.96− 6.91 (m, 4H), 6.77 (d, *J* = 6.5 Hz, 2H), 6.39 (s, 1H), 6.32 (s, 1H), 5.00 (d, *J* = 15.5 Hz, 1H), 4.84 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 153.9, 139.8, 138.4, 137.2, 136.7, 130.3, 129.5, 128.9, 128.6, 128.4, 128.2, 128.0, 127.8, 127.7, 126.1, 124.7, 124.6, 123.1, 121.7, 120.9, 116.6, 109.7, 65.9, 55.6.

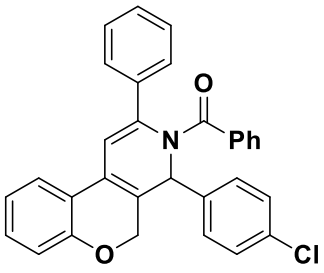
HRMS (ESI) (m/z): Calcd for $C_{31}H_{23}NO_2Na$, $[M+Na]^+$: 464.1626; Found: 464.1629.

(4-(4-Chlorophenyl)-2-phenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]-pyridin-3-yl)(phenyl)methanone (40b)

The compound **40b** was synthesized following the procedure 5, using (*E*)-3-(4-chlorobenzylidene)chroman-4-one (32 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 ^oC. The reaction afforded **40b** as colourless foam in 47% (27 mg) yield.

IR (neat) ν_{max}: 3059, 1651, 1599, 1091, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 6.5, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.27−7.25 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.07−7.04 (m, 3H), 6.95 (t, *J* = 7.0 Hz, 4H), 6.76 (d, *J* = 6.0 Hz, 2H), 6.34 (s, 1H),



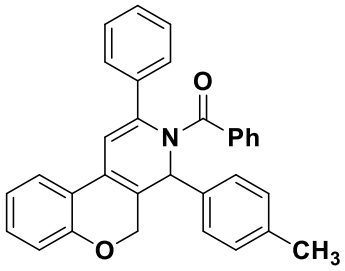
6.31 (s, 1H), 4.98 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.5 Hz, 1H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 171.3, 153.9, 139.7, 138.2, 136.5, 135.7, 134.5, 130.5, 129.9, 129.7, 129.1, 128.2, 128.1, 127.9, 127.7, 126.1, 125.0, 123.9, 123.2, 121.8, 120.8, 116.7, 109.5,65.7, 55.0.

HRMS (ESI) (m/z): Calcd for $C_{31}H_{22}ClNO_2Na$, $[M+Na]^+$: 498.1237; Found: 498.1250.

Phenyl(2-phenyl-4-(*p*-tolyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]-pyridin-3-yl)methanone (40c)

The compound **40c** was synthesized following the procedure 5, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 ^oC. The reaction afforded **40c** as colourless foam in 47% (26 mg) yield.



IR (neat) ν_{max}: 2924, 1650, 1456, 1122 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 3H), 6.95−6.91 (m, 4H), 6.78 (d, *J* = 5.5 Hz, 2H), 6.35 (s, 1H), 6.31 (s, 1H), 4.98 (d, *J* = 15.0 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 2.33 (s, 3H).

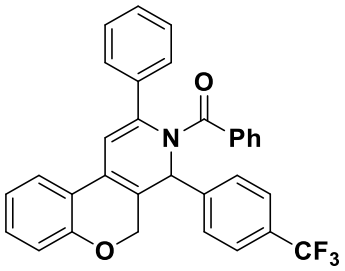
^{13}C NMR (125 MHz, CDCl$_3$): δ 171.2, 153.9, 138.5, 138.4, 136.8, 134.1, 130.3, 129.6, 129.5, 128.3, 128.2, 128.0, 127.7, 127.7, 126.2, 124.9, 124.5, 123.1, 121.7, 116.6, 109.7, 66.0, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{32}H_{25}NO_2Na$, $[M+Na]^+$: 478.1783; Found: 478.1802.

Phenyl(2-phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)methanone (40d)

The compound **40d** was synthesized following the procedure 5, using (*E*)-3-(4-(trifluoromethyl)benzylidene)chroman-4-one (37 mg, 0.12 mmol), ethynylbenzene (37 mg,

0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 °C. The reaction afforded **40d** as colourless foam in 27% (17 mg) yield.



IR (neat) ν_{max}: 3064, 1650, 1603, 1067 cm^{-1}.

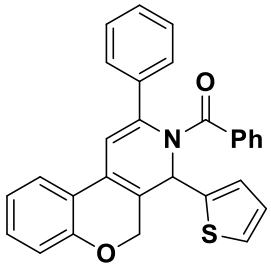
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 6.5 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 3H), 7.16−7.12 (m, 1H), 7.09− 7.05 (m, 3H), 6.97−6.93 (m, 4H), 6.77 (d, *J* = 6.0 Hz, 2H), 6.42 (s, 1H), 6.33 (s,1H), 5.00 (d, *J* = 15.5 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 153.9, 141.3, 139.9, 138.0, 136.4, 136.0, 130.6, 129.8, 128.8, 128.3, 128.2, 128.0, 127.8, 127.2, 126.1, 125.3, 123.4, 123.3, 121.8, 121.4, 120.7, 117.9, 116.7, 109.5, 65.7, 55.2.

HRMS (ESI) (m/z): Calcd for $C_{32}H_{22}F_3NO_2Na$, $[M+Na]^+$: 532.1500; Found: 532.1511.

Phenyl(2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno-[3,4-*c*]pyridin-3-yl)methanone (40e)

The compound **40e** was synthesized following the procedure 5, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (29 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 °C. The reaction afforded **40e** as colourless foam in 34% (18 mg) yield.



IR (neat) ν_{max}: 3063, 1654, 1603, 1449, 1229 cm^{-1}.

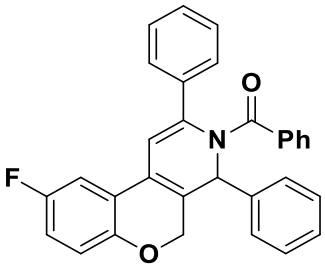
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.32 (d, *J* = 6.0 Hz, 3H), 7.25−7.24 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.07−7.03 (m, 3H), 6.97−6.93 (m, 5H), 6.86 (d, *J* = 3.5 Hz, 2H), 6.51 (s, 1H), 6.32 (s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.92 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 153.9, 140.1, 139.5, 138.4, 130.6, 129.6, 128.4, 128.1, 127.8, 127.7, 127.2, 126.9, 126.8, 124.4, 124.2, 123.3, 121.7, 120.8, 116.7, 65.7, 51.7.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{21}NO_2SNa$, $[M+Na]^+$: 470.1191; Found: 470.1192.

(9-Fluoro-2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl) (phenyl)methanone (40f)

The compound **40f** was synthesized following the procedure 5, using (*E*)-3-benzylidene-6-fluorochroman-4-one (31 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 ^oC. The reaction afforded **40f** as colourless foam in 29% (16 mg) yield.



IR (neat) ν_{max}: 3064, 1687, 1652, 1076, 1023 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66−7.65 (m, 1H,), 7.47 (t, *J* = 8.0 Hz, 1H), 7.32−7.30 (m, 2H), 7.25−7.24 (m, 1H), 7.15 (dd, *J* = 9.0, 3.0 Hz, 2H), 7.07(t, *J* = 7.5 Hz, 2H), 6.98−6.95 (m, 4H), 6.92−6.85 (m, 3H), 6.53 (s, 1H), 6.22 (s,1H), 4.96 (d, *J* = 15.5 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 158.8, 156.9, 149.8, 140.0, 139.9, 138.2, 136.3, 132.2, 130.6, 129.1, 128.6, 128.4, 128.1, 128.0, 127.7, 127.3, 127.0, 126.9, 126.3, 125.4, 117.5, 115.7, 115.5, 110.1, 109.9, 108.6, 69.1, 65.8.

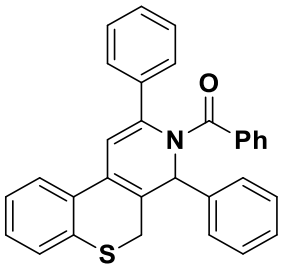
HRMS (ESI) (m/z): Calcd for $C_{29}H_{20}FNO_2SNa$, $[M+Na]^+$: 488.1096; Found: 488.1101.

(2,4-Diphenyl-4,5-dihydro-3*H*-thiochromeno[3,4-*c*]pyridin-3-yl)-(phenyl)methanone (40g)

The compound **40g** was synthesized following the procedure 5, using (*Z*)-3-benzylidenethiochroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in benzonitrile (2 mL) at 50 ^oC. The reaction afforded **40g** as colourless foam in 40% (22 mg) yield.

IR (neat) ν_{max}: 3060, 1655, 1528, 1076 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.66−7.65 (m, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.40−7.37 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.30−7.27 (m, 2H), 7.23−7.22 (m, 1H), 7.14 (t, *J* = 7.5 Hz,



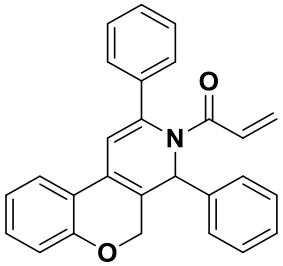
1H), 7.06 (t, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 6.0 Hz, 2H), 6.78 (d, *J* = 5.5 Hz, 2H), 6.52 (s, 1H), 6.29 (s, 1H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.25 (d, *J* = 15.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 139.2, 138.2, 137.2, 136.7, 132.8, 132.7, 132.3, 132.2, 130.3, 129.3, 129.1, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 127.7, 126.4, 126.1, 126.1, 125.2, 112.9, 59.0, 27.4.

HRMS (ESI) (m/z): Calcd for $C_{31}H_{23}NOSNa$, $[M+Na]^+$: 480.1398; Found: 480.1411.

1-(2,4-Diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)-prop-2-en-1-one (40h)

The compound **40h** was synthesized following the procedure 5, using (*Z*)-3-benzylidenethiochroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol) and $BF_3.OEt_2$ (51 mg, 0.36 mmol) in acrylonitrile (2 mL) at 50 ^oC. The reaction afforded **40h** as colourless foam in 28% (14 mg) yield.



IR (neat) ν_{max}: 2922, 1654, 1602, 1038 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.0 Hz, 2H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.35−7.28 (m, 4H), 7.25−7.23 (m, 3H), 7.14−7.13 (m, 2H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.48 (s, 2H), 6.23 (dd, *J* = 16.5, 1.5 Hz, 1H), 5.98− 5.92 (m, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 153.9, 138.7, 137.5, 137.1, 129.8, 129.5, 128.9, 128.9, 128.7, 128.5 128.2, 127.7, 125.8, 125.7, 124.7, 123.1, 121.7, 120.9, 116.5, 111.5, 65.8, 54.2.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{21}NO_2Na$, $[M+Na]^+$: 414.1470; Found: 414.1477.

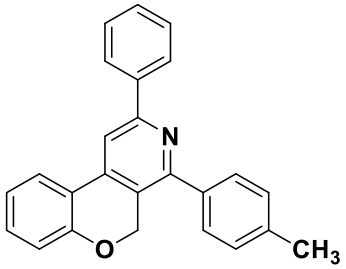
2.14. General procedure for the synthesis of 5*H*-chromeno[3,4-*c*]pyridines (6)

To a mixture of 1 equiv of substituted arylidenechroman-4-one (0.19 mmol), 3 equiv of arylalkyne (0.59 mmol) and 2 equiv of water in CH_3CN (2 mL) at 50 °C, 3 equiv of $BF_3 \cdot OEt_2$ (0.59 mmol) was added. The reaction mixture was allowed to stir for 30 min. It was then

cooled to 0 °C. Then 1.5 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.29 mmol) in CH_3CN (0.5 mL) was slowly added to the reaction mixture and allowed to stir at 50 °C for 6− 12 h. After completion of the reaction, the reaction mixture was again cooled to 0 °C and quenched with an aqueous solution of NaOH (0.2 mL, 3 M). It was then filtered, and the filtrate was extracted with ethyl acetate (3 × 10 mL). The solvent was evaporated in *vacuo* and the residue on silica gel (100 – 200 mesh) column chromatography using a mixture of ethyl acetate – hexane afforded the product.

2-Phenyl-4-(*p*-tolyl)-5*H*-chromeno[3,4-*c*]pyridine (41a)

The compound **41a** was synthesized following the procedure 6, using (*E*)-3-(4-methylbenzylidene)chroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol), $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) and DDQ (41 mg, 0.18 mmol in 0.5 mL of CH_3CN). The reaction afforded **41a** as white solid in 17% (12 mg) yield.



IR (neat) ν_{max}: 3057, 1589, 1366, 1036 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14−8.12 (m, 2H), 7.96 (s, 1H), 7.90 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50−7.48 (m, 4H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.38−7.35 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.16−7.13 (m, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 5.26 (s, 2H), 2.44 (s, 3H).

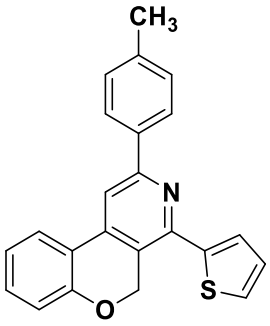
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 155.7, 139.5, 139.3, 138.7, 136.2, 131.4, 129.1, 129.0, 129.0, 128.7, 127.1, 124.2, 122.6, 122.5, 121.7, 117.6, 111.8, 65.8, 21.4.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}NO$, $[M+H]^{+:}$ 350.1545; Found: 350.1544.

4-(Thiophene-2-yl)-2-(*p*-tolyl)-5*H*-chromeno[3,4-*c*]pyridine (41b)

The compound **41b** was synthesized following the procedure 6, using (*E*)-3-(thiophen-2-ylmethylene)chroman-4-one (30 mg, 0.12 mmol), ethynylbenzene (37 mg, 0.36 mmol), H_2O (4 μL, 0.24 mmol), $BF_3.OEt_2$ (51 mg, 0.36 mmol) in CH_3CN (2 mL) and DDQ (41 mg, 0.18 mmol in 0.5 mL of CH_3CN). The reaction afforded **41b** as white solid in 7% (5 mg) yield.

IR (neat) ν_{max}: 3069, 1587, 1367, 1038 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.90 (s, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.38−7.34 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.17−7.12 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 155.4, 148.4, 143.7, 139.4, 139.3, 136.1, 131.5, 129.5, 128.2, 127.6, 127.0, 126.8, 124.1, 122.5, 121.6, 121.4, 117.6, 111.1, 65.5, 21.4.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{18}NOS$, $[M + H]^+$: 356.1109; Found: 356.1111.

2.15. References

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I_2 Catalyzed Diastereoselective Synthesis of Spiroaziridines

3.1. Abstract

Even though spiroheterocycles are considered as emerging drug candidates, synthesis of spiroaziridines has not been well explored so far. Herein, we have developed a metal free I_2 catalyzed protocol for the synthesis of spiroaziridines. The reaction proceeds in a diastereoselective fashion under mild conditions. The synthesis of *N*-alkyl spiroaziridines are achieved using primary amines and easily accessible α,β-unsaturated ketones. This protocol which does not require pre-functionalization of amines is also compatible for the synthesis of simple aziridines.

3.2. Introduction

Aziridines, one of the smallest aza heterocycles, are molecules of high relevance in synthetic organic chemistry. The innate ring strain makes these structural scaffolds important synthons. The synthetic utility of aziridine is well exemplified by the ring opening and ring expansion reactions. Aziridines are used as substrate for the synthesis of amino acids, amino alcohols and various aza heterocycles.[1,2,3] Apart from being an essential building block they are substructures of numerous natural as well as unnatural products of biological significance (**Figure 3.1**). Ficellomycin, an alkaloid with aziridine unit, is an antibiotic.[4] This molecule shows resistance against Gram positive bacteria including the multidrug resistant strains of *Staphylococcus aureus*. On the other hand, the natural products mytomycin C and FR90048 are potent anti-tumor agents.[5,6] The synthetic molecules IV and V, which contain a spiroaziridine unit, are inhibitors of hepatits C virus (**Figure 3.1**). The molecule VI, another aziridine of synthetic origin, is an antibacterial agent.[7] On account of synthetic and medicinal usefulness, aziridines have gained attention of scientific community in various disciplines. Even though numerous protocols are developed for the synthesis of this aza heterocycle any route which gives easy access to this class of molecules is always desirable.[8,9,10]

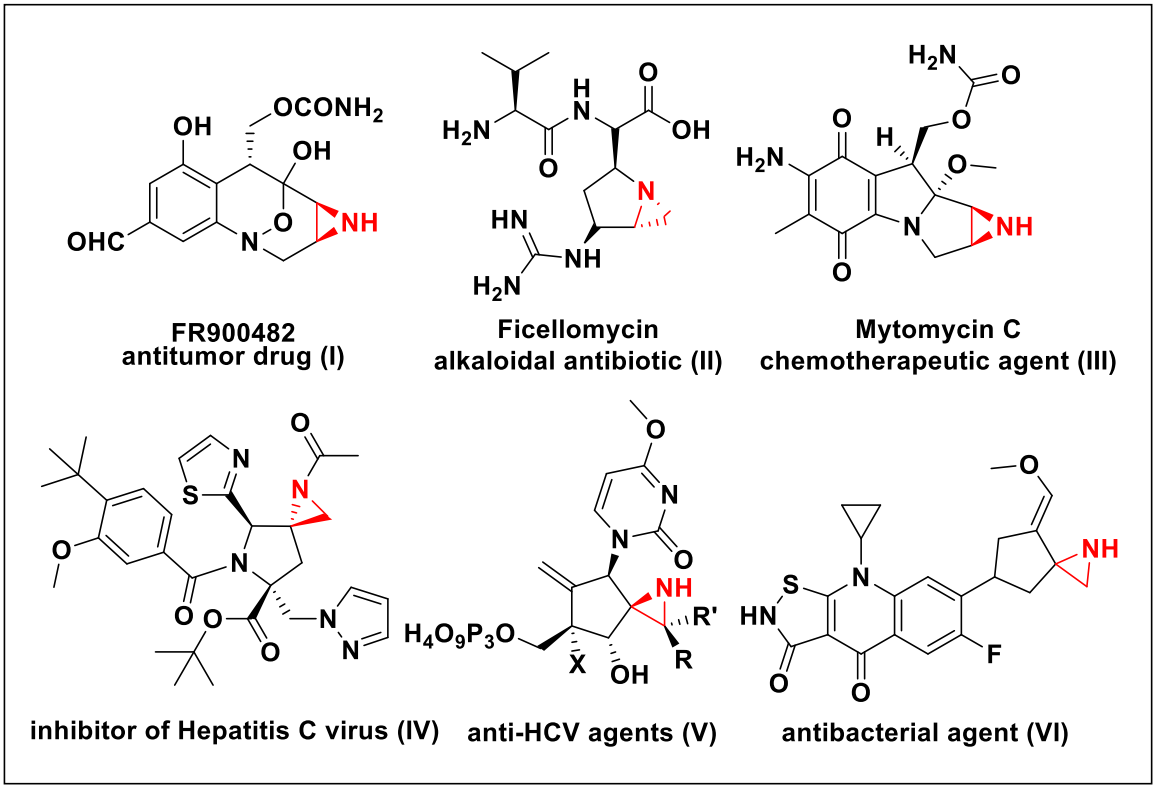
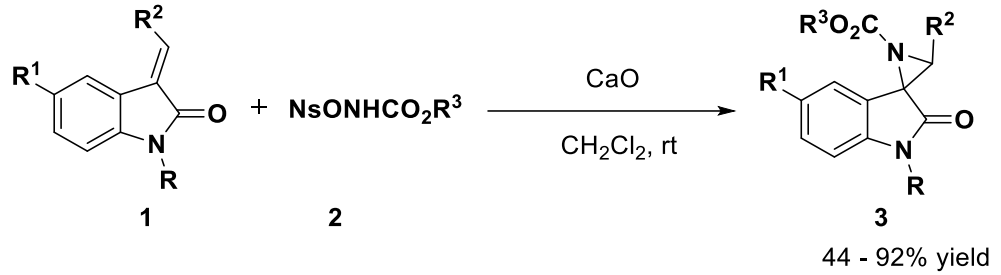


Figure. 3.1. Medicinally important aziridine scaffolds.

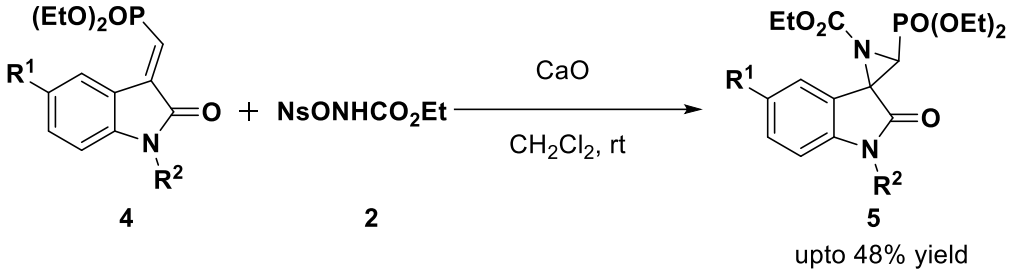
3.2.1. Significance of spiroaziridine and its synthesis

Spirocycles are molecules of structural complexity. This class of compounds consist of two ring systems which shares a single atom. The presence of quaternary carbon center and three dimensionality are the attraction of spiro molecules. On account of these structural features spiranes are considered as potent candidates in drug discovery.[11] Owing to its biological significance, novel protocols are being developed for the synthesis of spirocyclic molecules of various ring sizes.[12]Among the various spirocyclic motifs the three membered spiranes, especially spiroaziridines are the least explored. Considering the biological applications of oxindoles, majority of the protocols are documented on the synthesis of spiroaziridine oxindoles. One of the notable synthetic approach towards spiroaziridine oxindole was reported in 2009, where Ammetto *et al.* demonstrated a direct aziridination of 3-ylidene oxindole **1** (**Scheme 3.1**). The aziridination of the olefin was achieved in the presence of CaO.[13]



Scheme 3.1. CaO mediated synthesis of spiroaziridine oxindole.

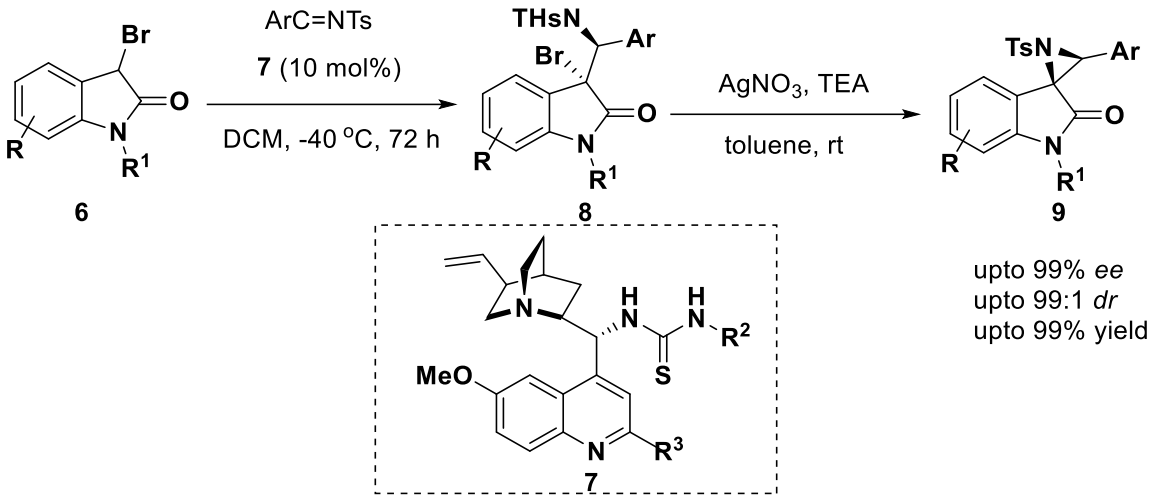
Later in 2011 the same group successfully extended the protocol for the synthesis of aziridine-2-phosphonate spiro-fused with oxindole **5**, under the identical reaction conditions. The reaction was carried out using 3-(Phosphorylmethylene)oxindoles **4** and *N*-{[(4-nitrophenyl)sulfonyl]oxy}-carbamate **2** as the substrates (**Scheme 3.2**).[14]



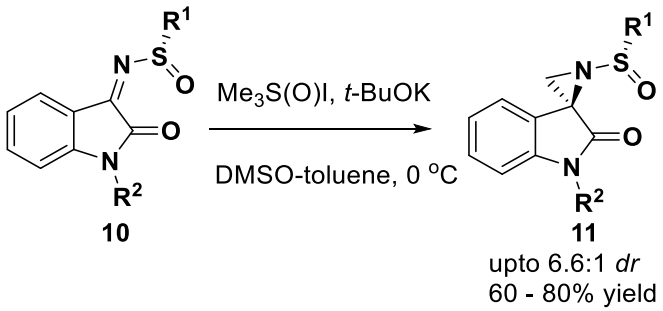
Scheme 3.2. Synthesis of aziridine-2-phosphonate spiro-fused with oxindole.

An organocatalyzed Mannich reaction of 3-bromooxindole **6** with *N*-Ts-imine was reported by Li *et al.* in 2013. The product of this asymmetric synthesis can be easily converted to chiral spiroaziridine oxindole **9** (**Scheme 3.3**).[15]

In 2015, Marsini *et al.* disclosed a diastereoselective protocol for synthesizing *α*-quaternary aziridine-2-carboxylates from readily available substrates. The reaction, which is an Aza-Corey-Chaykovsky aziridination of *N*-tert-butanesulfenyl ketimino ester **10**, provides ready access to spiroaziridine oxindoles **11**(**Scheme 3.4**).[16]

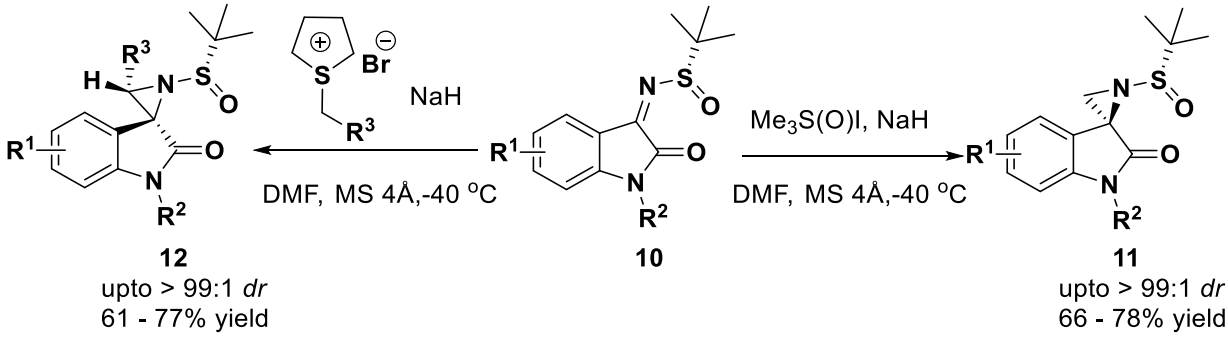


Scheme 3.3. Organocatalyzed synthesis of chiral spiroaziridine oxindole.



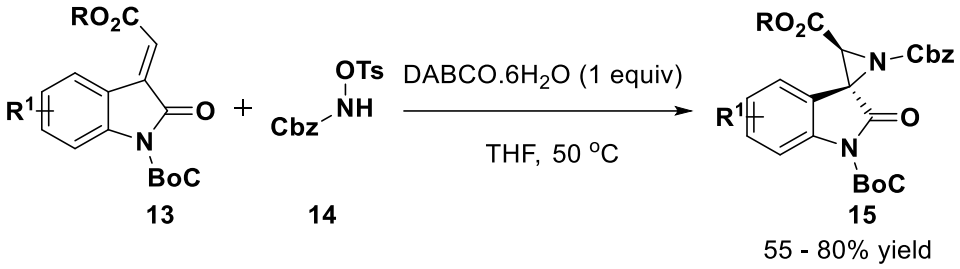
Scheme 3.4. Diastereoselective synthesis of α-quaternary aziridine-2-carboxylates.

In the same year, Hajra *et al.* reported preparation of nonracemic chiral spiroaziridine oxindole **11** following Aza-Corey-Chaykovsky reaction of the same substrate, but with excellent stereoselectivity. Both terminal and substituted products can be attained by changing the sulfur ylide, keeping all the other conditions identical (**scheme 3.5**).[17]



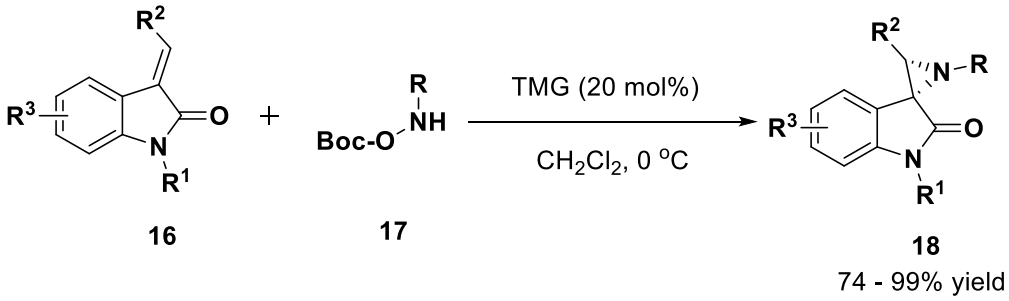
Scheme 3.5. Asymmetric synthesis of spiroaziridine oxindole.

Later Wang *et al.* developed a base promoted domino reaction for the synthesis of spirocyclic aziridine **15** under mild conditions. The spiranes were obtained by reacting methyleneindolinones **13** with *N*-Tosyloxycarbamates **14** in the presence of DABCO.6H_2O. They have also showcased the synthetic utility of the spiroaziridine by preparing bisspirooxindole and fused spirooxindole via annulation strategy (**Scheme 3.6**).[18]



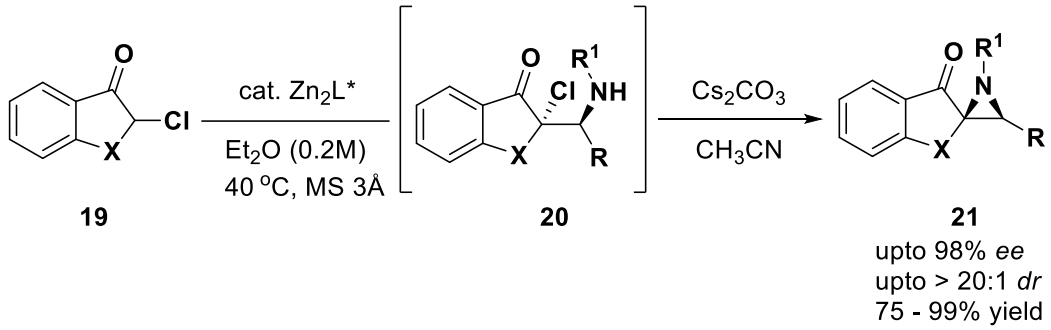
Scheme 3.6. Base mediated spiroaziridine synthesis.

A base catalyzed reaction of 3-ylideneoxindole **16** with O-Boc-hydroxycarbamate **17** affording the product **18** with better yield was disclosed by Liu *et al.* Compared to Wang's method, which requires stoichiometric amounts of base, only catalytic quantity of tetramethylguanidine (TMG) is sufficient for the reaction to proceed (**Scheme 3.7**).[19]



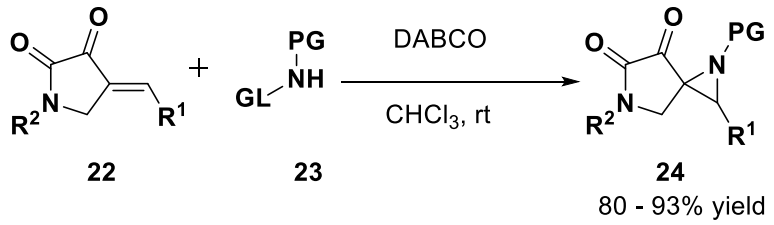
Scheme 3.7. TMG catalyzed synthesis of spiroaziridine.

There are only few protocols reported for the synthesis of spiroaziridine other than spiroaziridine oxindole. To name a few, in 2016 a Zinc pro-phenol catalyzed Aza–Darzen reaction was reported by Trost *et al.* which facilitated enantioselective synthesis of spiroaziridines **21** (**Scheme 3.8**).[20]



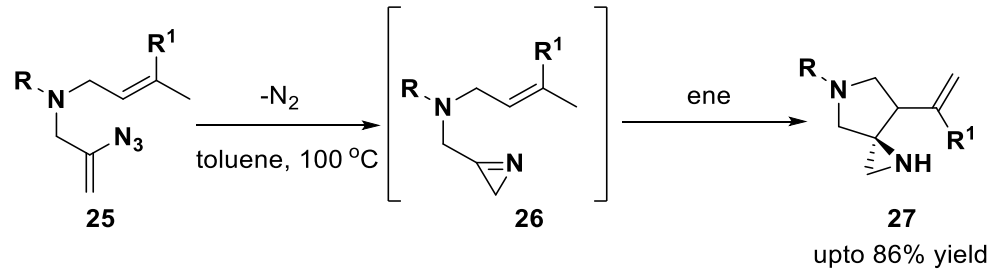
Scheme 3.8. Zinc pro-phenol catalyzed synthesis of spiroaziridine.

Later in 2017 Yang *et al.* developed a base mediated diastereoselective aziridination of electron deficient cyclic enones **22** for the facile synthesis of spiroaziridine pyrrolines **24**. The reaction which utilizes the organic base DABCO, proceeds under mild conditions (**Scheme 3.9**).[21]



Scheme 3.9. DABCO mediated diastereoselective aziridination reaction.

An intramolecular imino-ene reaction was developed by Liu *et al.* demonstrating the importance of protocol that can afford spiro NH aziridines **27**. It involves the in situ generation of 2*H*-azirine **26** from vinyl azide tethered with alkene **25**. The protocol offers high stereoselectivity as well as stereospecificity in the spiro NH aziridine formation (**Scheme 3.10**).[22]

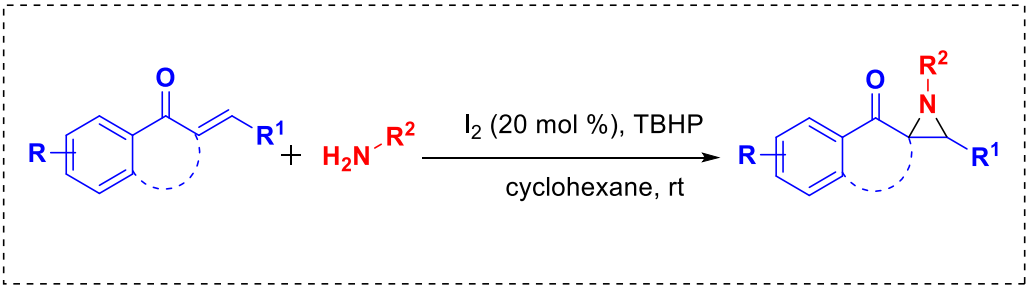


Scheme 3.10. Stereospecific synthesis of spiro NH aziridine.

3.3. Background to the present work

In the last two decade significant advancements have happened in the synthesis of aziridines. The two traditional strategies used in aziridine synthesis are: transfer of a suitable nitrene to C=C bond or transfer of a carbene to C=N bond. But most of the methods developed relying on these strategies has the drawback of narrow substrate scope in terms of *N*-substituents.[8,10] Because, these synthetic routes require an activating group or an electron withdrawing group such as *p*-toluenesulfonyl (Ts) or *p*-nitrophenylsulfonyl (Ns) on the nitrogen atom. The removal of these activating groups is often troublesome to achieve.[23] Therefore, any protocol that gives access to aziridines using readily available unprotected primary amine as the nitrogen source is always desirable.

Owing to our interest in the methodologies that targets the synthesis of heterocycles using readily available substrates, we decided to unravel a protocol that provides accessibility to *N*-alkyl spiroaziridines. Serendipitous finding of Southwick regarding the synthesis of simple aziridines utilizing stoichiometric amount of iodine attracted our attention.[24] Moreover, the popularity that molecular iodine has garnered on account of its reactivity together with environmentally benign nature is commendable. Also the C-C or C-N bond formation mediated by iodine/iodide in combination with an oxidant is an attractive field in organic synthesis.[25,26,27] In the light of these observations, we have developed an operationally simple I_2/TBHP mediated protocol for the diastereoselctive synthesis of *N*-alkyl spiroaziridines from primary amines and easily accessible *α,β*-unsaturated ketones (**Scheme 3.11**).



Scheme 3.11. Iodine catalyzed synthesis of spiroaziridine.

3.4. Results and discussion

For our study (*E*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one (**28a**) and benzylamine (**29a**) were selected as the model substrates. We started our investigation by treating **28a** with **29a** in the presence of iodine and TBHP in EtOAc at 50 ^{o}C. To our delight, the reaction proceeded smoothly affording *trans* isomer **30a** in 41% yield as the sole product. Structure of the product thus obtained was confirmed through various spectroscopic analyses. In the ^{1}H NMR spectrum of **30a**, the peak corresponding to the proton at the stereogenic center is discernible as a singlet at δ 3.73. The benzylic protons adjacent to the nitrogen atoms appeared as two separate doublets at δ 4.47 and δ 4.39. Presence of carbonyl carbon was confirmed by the peak at δ 201.4 in the ^{13}C NMR, which was further supported by the IR absorption value of 1697 cm^{-1}. The HRMS peak at 340.17059 was also in good agreement with the expected $(M+H)^{+}$ value of the product **30a**.

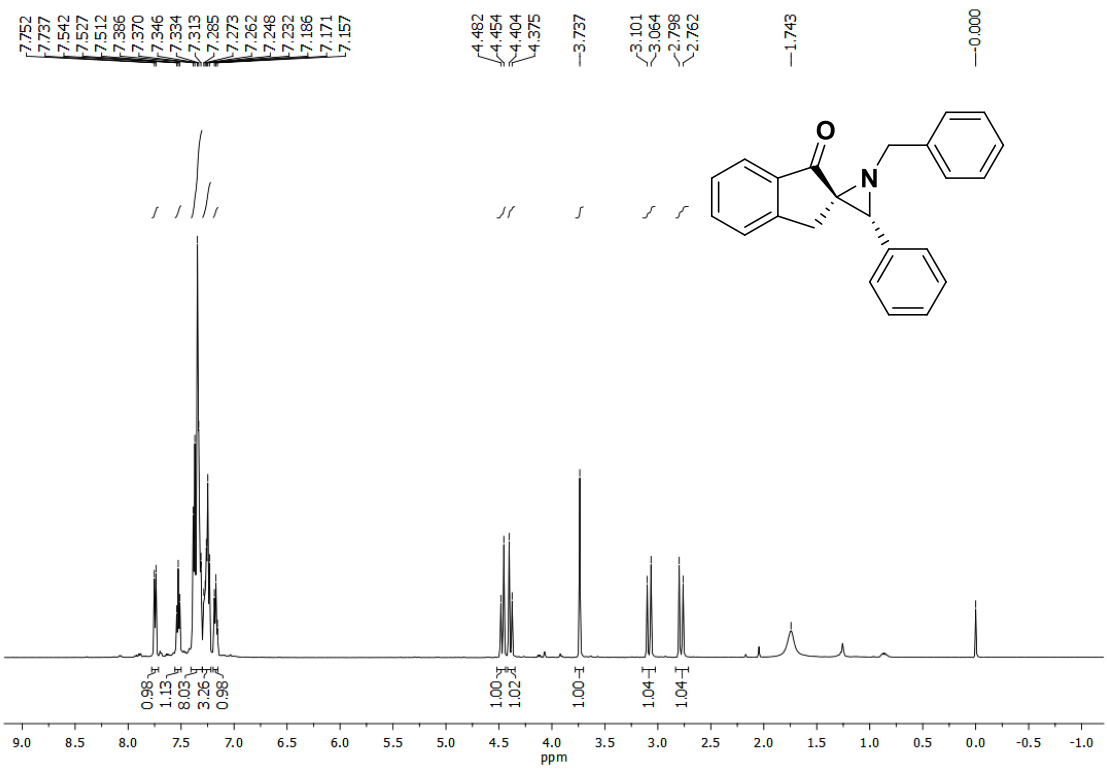


Figure 3.2. ^{1}H NMR **30a**

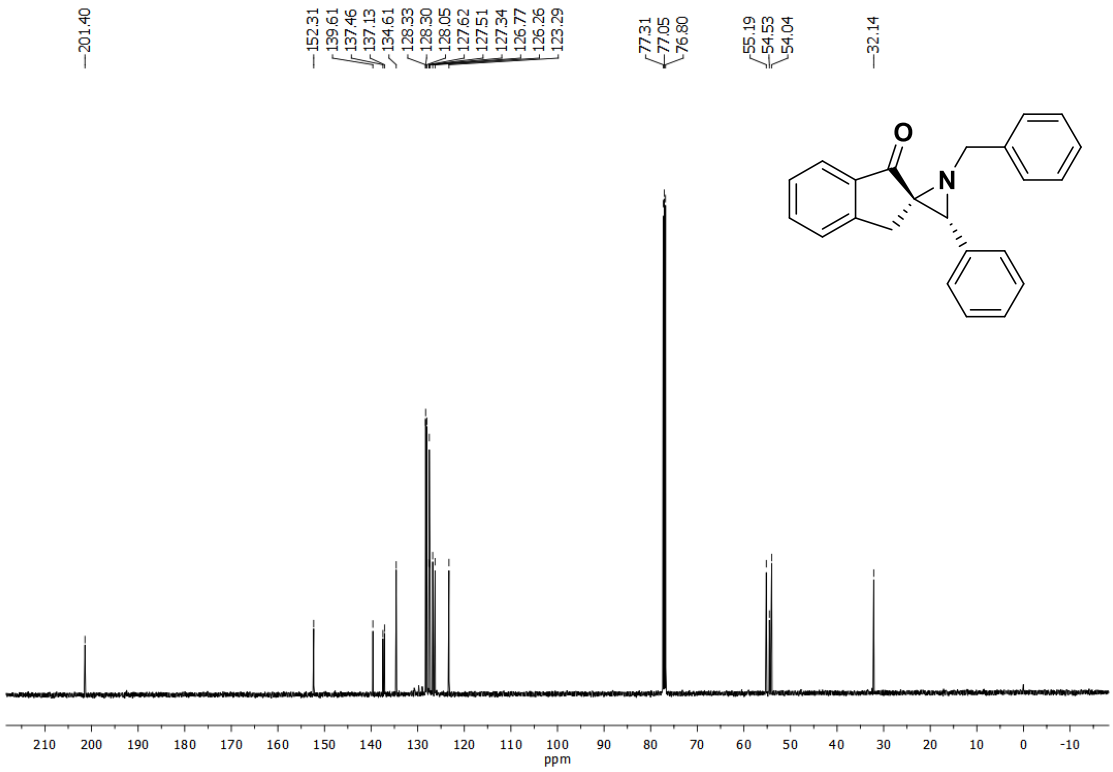


Figure 3.3. ^{13}C NMR of **30a**

The structure and relative stereochemistry of the product was unambiguously confirmed through single crystal X-ray analysis of one of the derivative **30r** (**Figure 3.4**).

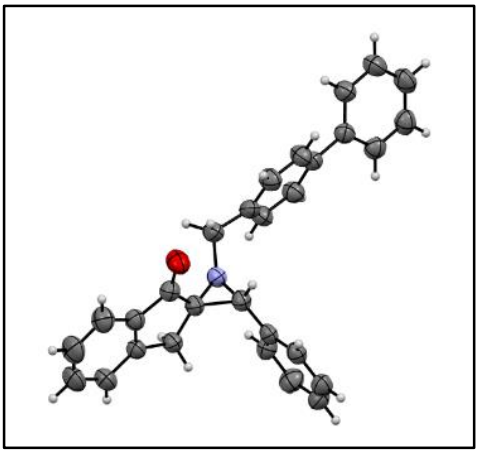
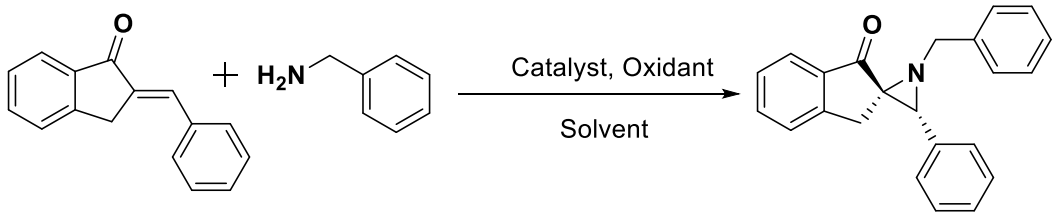


Figure 3.4. Single crystal X-ray structure of **30r** (**CCDC 1949823**)

In pursuit of obtaining optimized conditions we screened various solvents such as MeOH, DMSO, DCM etc (**Table 3.1**). The product **30a** was obtained in better yield when the reaction was carried out in cyclohexane (entry 9). Upon changing the iodine source to TBAI, KI and NaI, a substantial decrease in yield was observed. These observations suggested that molecular iodine is the efficient catalyst for the reaction to proceed smoothly. When the reaction was performed in the presence of iodine alone, only 20% of yield was observed (entry 13). Hence we evaluated various oxidants such as H_2O_2, O_2 and *m*CPBA. This comparative study revealed that TBHP is the better oxidant for the reaction to afford the targeted spiroaziridine **30a** in improved yield (entry 9). A surge in the product yield was observed when the reaction was performed at ambient temperature using 4 equivalents of the primary amine (entry 18). The effect of catalyst loading was also studied and it was found that 20 mol% of iodine gives a better result (**Table 3.2**).

Table 3.1. Optimization of reaction conditions [a]



28a **29a** **(±) 30a**

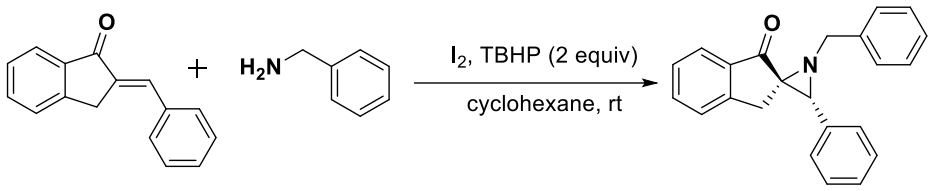
Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	Yield [%][b]
1	I_2	TBHP	EtOAc	50	41
2	I_2	TBHP	MeOH	50	9
3	I_2	TBHP	DMSO	50	trace
4	I_2	TBHP	DCM	50	trace
5	I_2	TBHP	CH_3CN	50	27
6	I_2	TBHP	DCE	50	34
7	I_2	TBHP	THF	50	18
8	I_2	TBHP	toluene	50	trace
9	I_2	TBHP	cyclohexane	50	45
10	TBAI	TBHP	cyclohexane	50	36
11	KI	TBHP	cyclohexane	50	29
12	NaI	TBHP	cyclohexane	50	29

Table 3.1. continues……

Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	Yield [%][b]
13	I_2	—	cyclohexane	50	20
14	I_2	H_2O_2	cyclohexane	50	8
15	I_2	O_2	cyclohexane	50	trace
16	I_2	*m*CPBA	cyclohexane	50	trace
17	I_2	TBHP	cyclohexane	80	trace
18[c]	I_2	TBHP	cyclohexane	rt	61

[a] Reaction conditions: **28a** (0.15 mmol), **29a** (0.30 mmol), catalyst (20 mol%) and oxidant (0.30 mmol), 8 h. [b] Yield of the isolated product. [c] Reaction was carried out using 0.6 mmol of **29a**.

Table 3.2. Optimization of catalyst loading [a]



28a **29a** **(±) 30a**

Entry	Catalyst loading (mol%)	Yield [%][b]
1	10	50
2	20	61
3	30	61
4	40	43

Reaction conditions: [a] **28a** (0.15 mmol), **29a** (0.60 mmol), TBHP (0.30 mmol), 8h. [b] Isolated yield.

With the optimized conditions in hand, next we investigated the feasibility of the reaction for various 2-arylidene-2,3-dihydro-1*H*-inden-1-ones (**Table 3.3**). Initially, we studied the effect of substituents present on the benzylidene ring of the *α,β*-unsaturated ketone. Gratifyingly, the reaction proceeded efficiently for substrates bearing both electron donating and electron withdrawing substituents. The desired spiroaziridines were afforded in moderate yields. This result indicates that the electronic effect has negligible influence on the reaction. To study the effect of steric hindrance on the proposed protocol, we selected *o*-Cl, *m*-Cl and *p*-

Cl substituted benzylidene ketones to react with benzylamine. Regardless of the position, all the expected products were obtained in 44–47% yields. In addition, dimethyl benzylidene and thiophen-3-yl methylene ketones could also transform to the corresponding spiroaziridines **30j** and **30k**, respectively. Apart from the substituent effect on the arylidene ring, the influence of a methoxy and bromo substituted indanone system was also investigated (**30l** and **30m**). Interestingly, when alkylidene-2,3-dihydro-1*H*-inden-1-one reacts with benzylamine under the optimized conditions, formation of diastereomers was observed (**30n**). The chromatographically separable isomers were furnished in a total yield of 75% with a diastereomeric ratio (*dr*) of 1.9:1. This indicates that the diastereoselectivity of the reaction depends on the substituent present at the *β*-position of the enone.

Table 3.3. Substrate scope with respect to 2-aryl/alkylidene-2,3-dihydro-1*H*-inden-1-ones

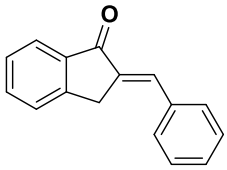
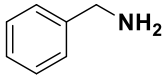
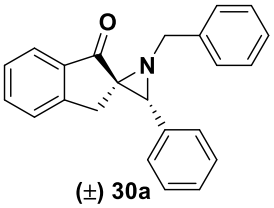
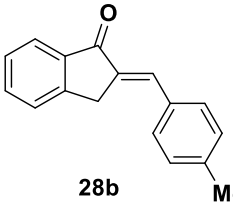
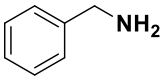
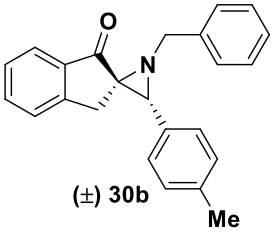
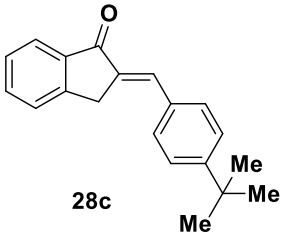
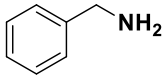
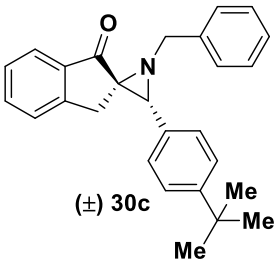
Entry	Unsaturated ketone	Amine	Product	Yield(%)
1	 28a	 29a	 (±) 30a	61
2	 28b	 29a	 (±) 30b	57
3	 28c	 29a	 (±) 30c	48

Table 3.3 continues…….

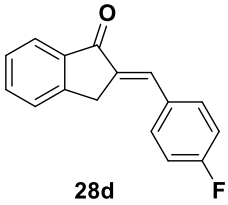
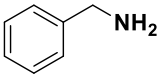
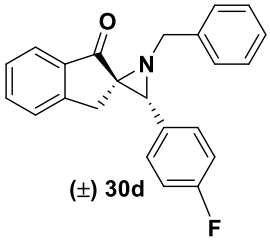
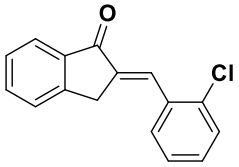
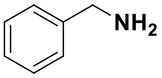
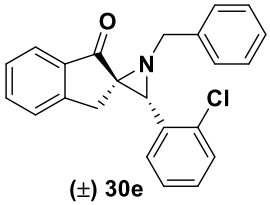
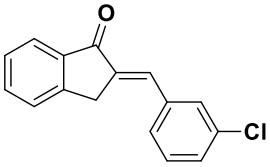
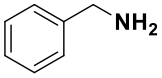
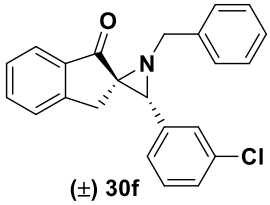
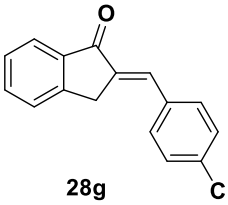
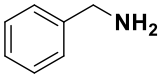
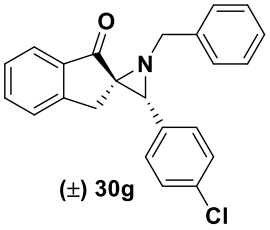
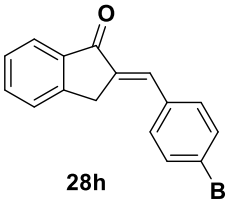
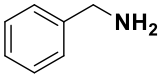
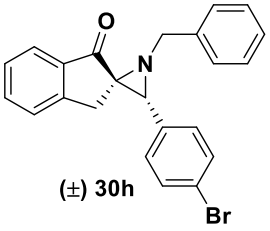
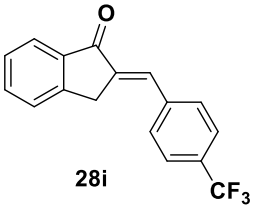
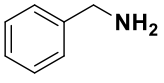
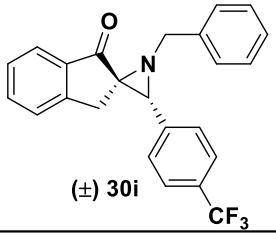
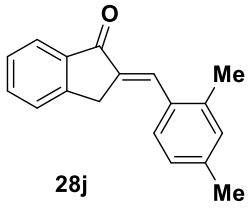
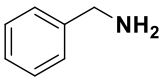
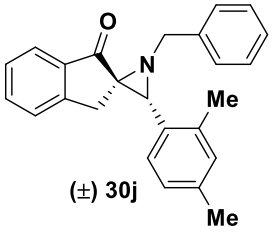
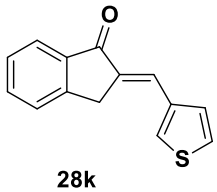
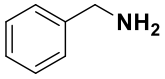
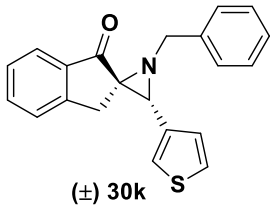
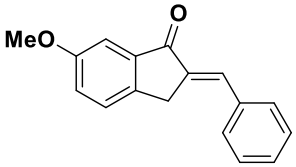
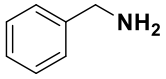
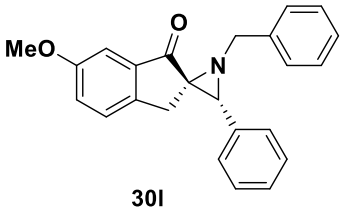
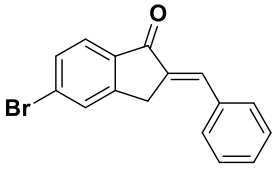
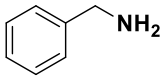
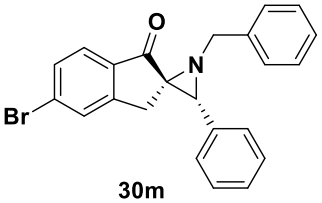
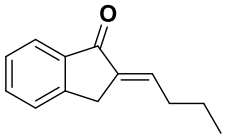
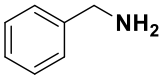
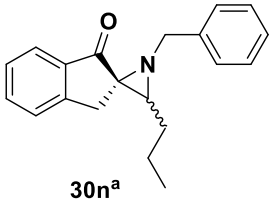
Entry	Unsaturated ketone	Amine	Product	Yield(%)
4	 28d	 29a	 (±) 30d	52
5	 28e	 29a	 (±) 30e	44
6	 28f	 29a	 (±) 30f	47
7	 28g	 29a	 (±) 30g	47
8	 28h	 29a	 (±) 30h	27
9	 28i	 29a	 (±) 30i	49

Table 3.3. continues…….

Entry	Unsaurated ketone	Amine	Product	Yield (%)
10	 **28j**	 **29a**	 **(±) 30j**	37
11	 **28k**	 **29a**	 **(±) 30k**	32
12	 **28l**	 **29a**	 **30l**	36
13	 **28m**	 **29a**	 **30m**	47
14	 **28n**	 **29a**	 **30n[a]** ***dr*= 1.9:1**	75

Reaction conditions: **28** (0.15 mmol), **29a** (0.60 mmol), I_2 (20 mol%) and TBHP (70% aqueous solution, 0.30 mmol) in cyclohexane at rt. Yields of isolated products. [a] *dr* calculated based on the isolated yield.

Furthermore, we explored the applicability of the synthetic strategy with respect to various primary amines (**Table 3.4**). Benzylamines with electron donating and electron withdrawing substituents, 4-phenyl benzylamine and 1-naphthalenemethylamine well tolerated the reaction affording the targeted products in moderate yields (**30o–30s**). As anticipated, the primary amines incorporated with heterocyclic moieties (thiophene and furan)

also afforded the desired products (**30t** and **30u**). In addition, linear and cyclic amines were also found to be compatible (**30v–30x**) under the optimized conditions. Interestingly, propargylamine and the binucleophile, 2-amino ethanol, underwent the transformation furnishing the desired aziridines with an alkyne **30x** and a free hydroxyl **30y** group respectively, providing a synthetic handle for further functionalization.

Table 3.4. Scope of the reaction for various primary amines

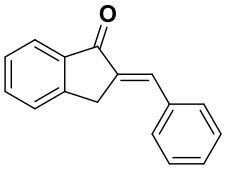
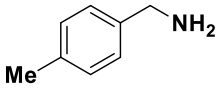
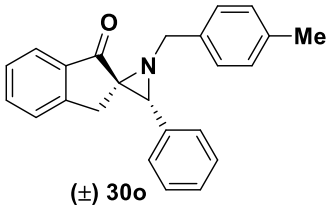
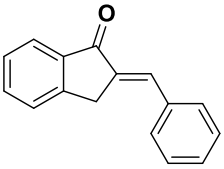
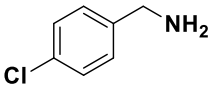
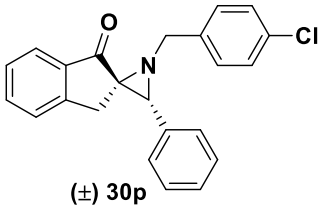
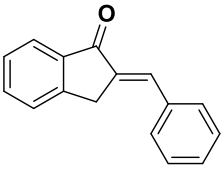
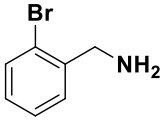
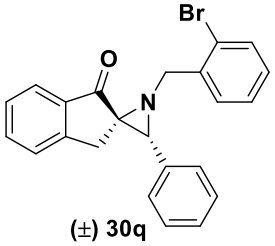
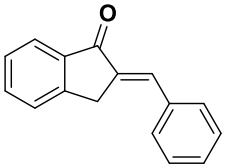
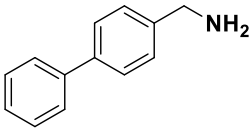
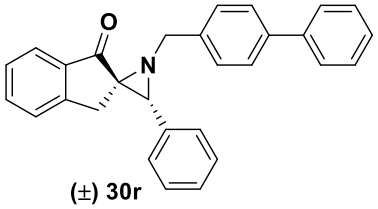
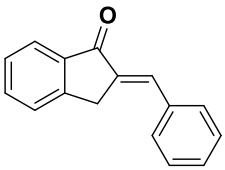
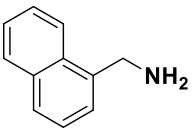
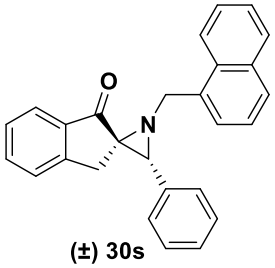
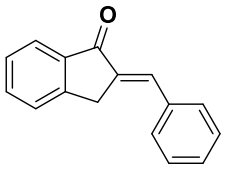
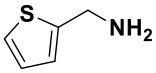
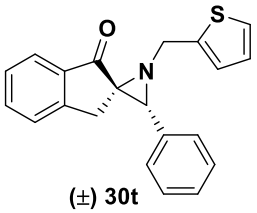
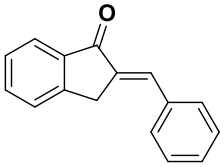
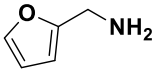
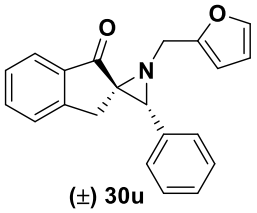
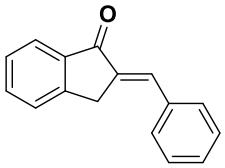
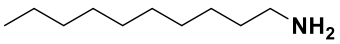
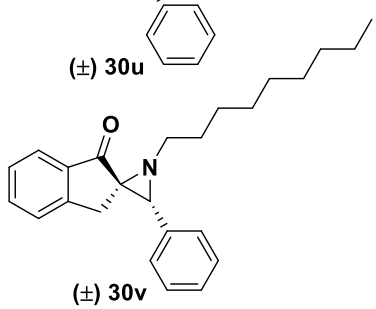
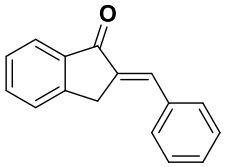
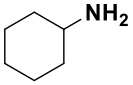
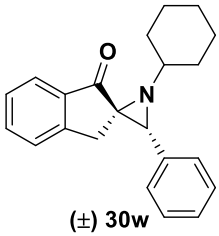
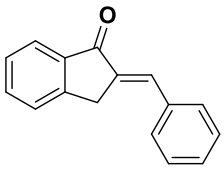
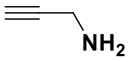
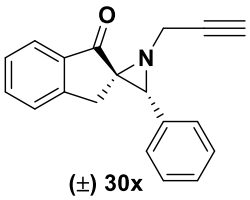
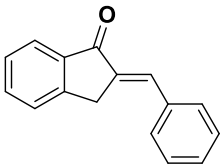
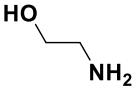
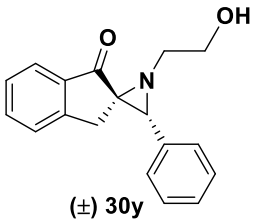
Entry	Unsaturated ketone	Amine	Product	Yield (%)
1	 28a	 29b	 (±) 30o	37
2	 28a	 29c	 (±) 30p	41
3	 28a	 29d	 (±) 30q	54
4	 28a	 29e	 (±) 30r	40
5	 28a	 29f	 (±) 30s	47

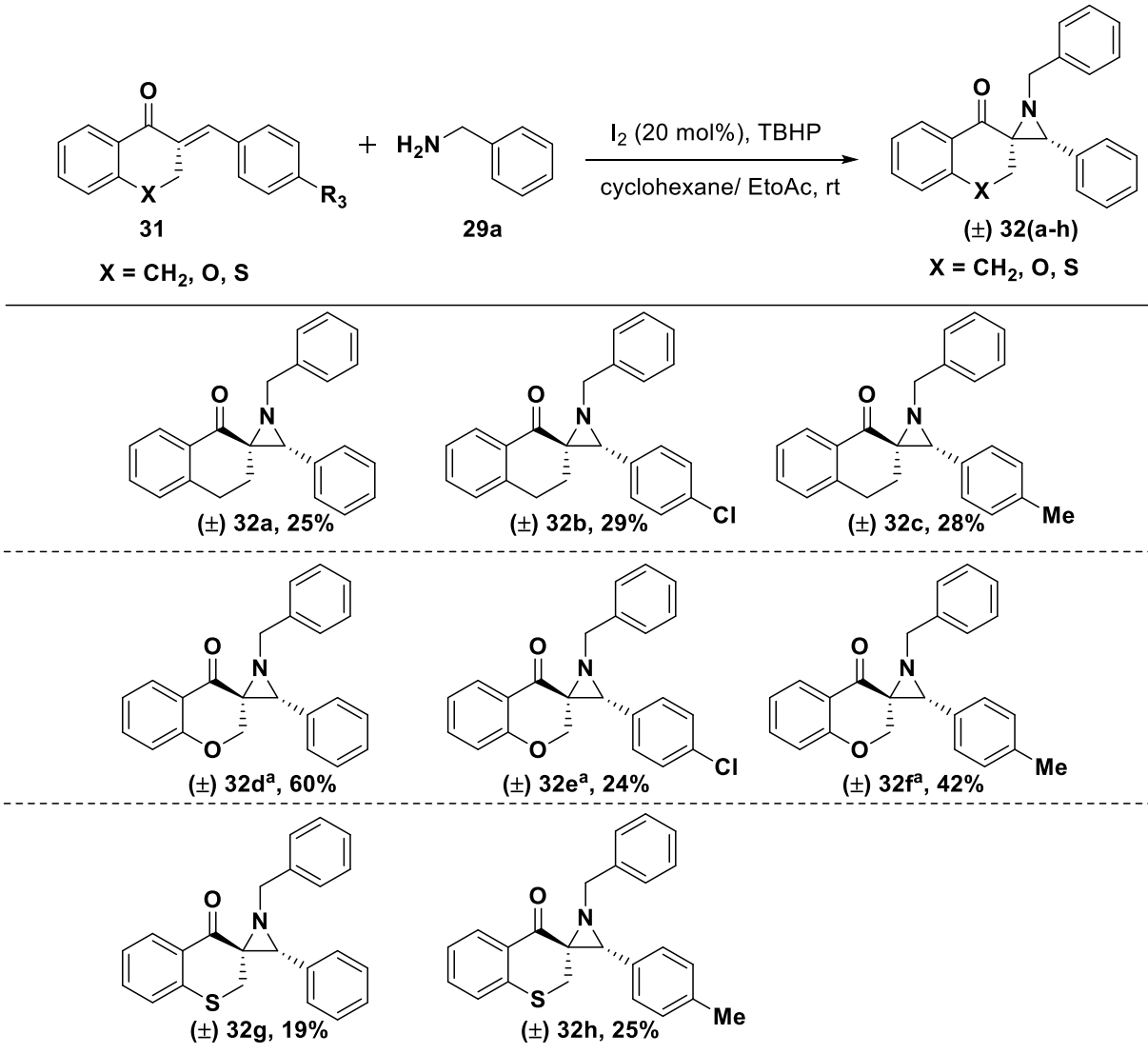
Table 3.4. continues…….

Entry	Unsaurated ketone	Amine	Product	Yield (%)
6	 **28a**	 **29g**	 **(±) 30t**	60
7	 **28a**	 **29h**	 **(±) 30u**	23
8	 **28a**	 **29i**	 **(±) 30v**	45
9	 **28a**	 **29j**	 **(±) 30w**	23
10	 **28a**	 **29k**	 **(±) 30x**	20
11	 **28a**	 **29l**	 **(±) 30y**	53

Reaction conditions: **28a** (0.15 mmol), **29** (0.60 mmol), I_2 (20 mol%) and TBHP (70% aqueous solution, 0.30 mmol) in cyclohexane at rt. Yields of isolated products.

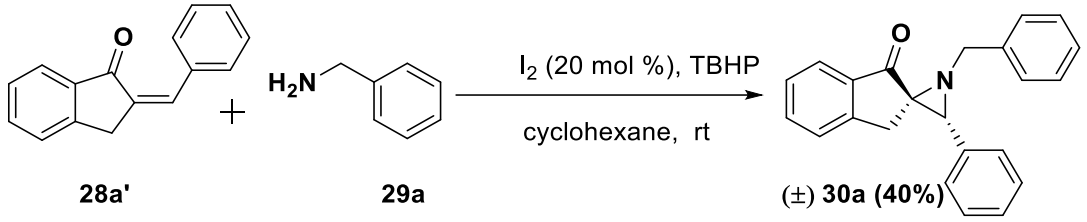
Delighted with the success of spiroaziridine synthesis using arylidene/alkylidene dihydroindenone, we envisioned that the present methodology could be expanded to other fused biologically relevant *α,β*-unsaturated ketones such as arylidene dihydronaphthalen-1-one, arylidene chroman-4-one, and arylidene thiochroman-4-one as well (**Table 3.5**). As expected all the enones could furnish the spiroaziridines under the standard conditions except arylidene chroman-4-ones. A better yield of 60% was obtained for **32d** when the reaction was carried out in EtOAc keeping all other parameters unchanged.

Table 3.5. Scope of the methodology for other fused arylidene ketones



[a] Reaction conditions: **31** (0.15 mmol), **29a** (0.60 mmol), I_2 (20 mol%), and TBHP (0.30 mmol) in cyclohexane at rt. Yields of isolated products. [a] EtOAc is used as the solvent.

Notably, in the case of (*Z*)-3-arylidenethiochroman-4-ones **31g** and **31h**, the *cis* isomer formed as the sole product (**32g** and **32h**). This observation led us conduct an experiment with (*Z*)-2-benzylidene-2,3-dihydro-1*H*-inden-1- one (**28a'**) to check whether the configuration of arylidene ketone plays any significant role in the diastereoselectivity of the reaction (**Scheme 3.12**). We observed the formation of *trans* isomer **30a** from **28a'**. This result indicates that selectivity of the reaction is not influenced by the configuration of the starting material.



Scheme 3.12. Scope of the reaction for arylidene ketone with a *Z* configuration.

Besides, the compatibility of the process for 2-aroylaziridine synthesis using simple *α,β*-unsaturated ketone is also explored. To test our notion, we treated (*E*) chalcone **33a** with benzylamine **29a** under the optimized conditions. Interestingly, we observed the formation of the *trans*-isomer of **34a** in 51% yield (**Table 3.6**). When the catalyst and solvent were switched to TBAI and EtOAc respectively, a mixture of *trans* and *cis* isomers of **34a** was obtained in an improved yield of 82% with a diastereomeric ratio of 2.4 : 1 (entry 2). Structures of both the isomers were confirmed using various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and mass spectrometry. In the ^{1}H NMR spectrum of the *trans* isomer, protons attached to the C_2 and C_3 of aziridine ring were indicated by two doublets observed at δ 3.81 and δ 3.61. Similarly, in the case of *cis* isomer these protons appeared at δ 3.66 and δ 3.47. Coupling constants for these doublets were found to be 2.5 Hz and 7.0 Hz for *trans* and *cis* isomers respectively. In the ^{13}C NMR spectrum of *trans* isomer, carbonyl carbon appeared at δ 195, the two chiral carbons C_2 and C_3 were found to resonate at δ 49.3 and δ 48.2 respectively (**Figure. 3.7**). The identical carbons of *cis* isomer were observed at δ 193, δ 52.1 and δ 49.6. The structures of the products were further confirmed by HRMS spectra.

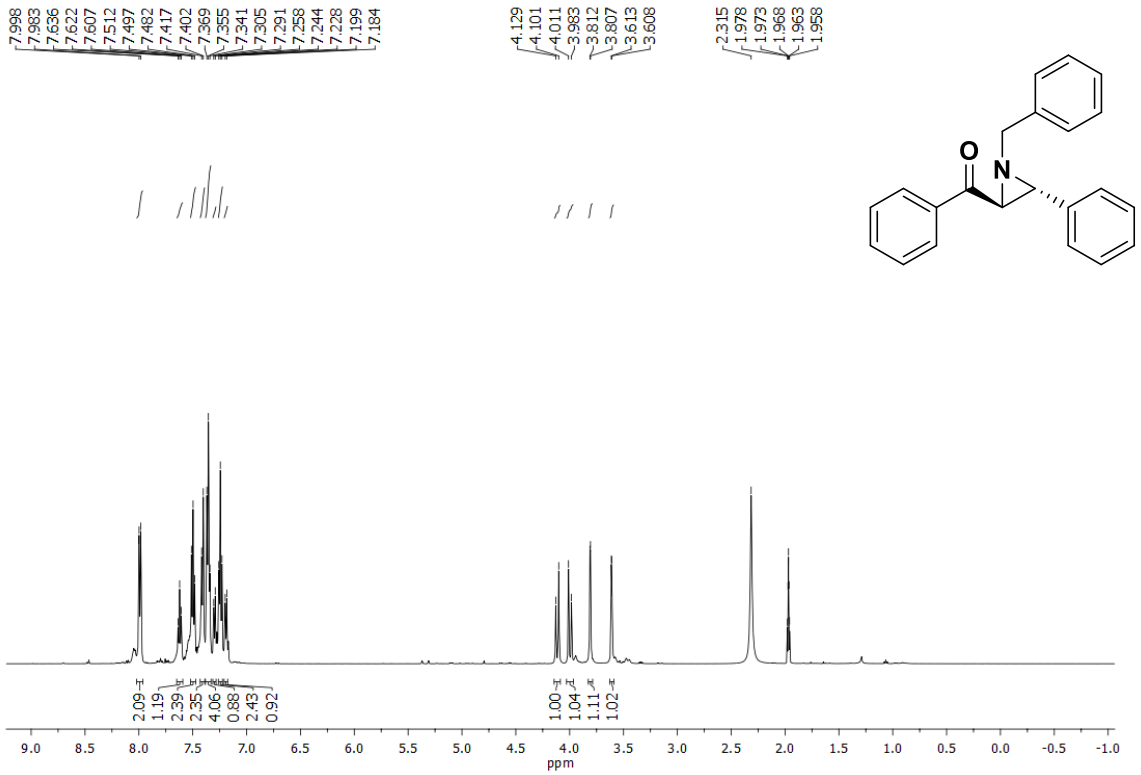


Figure 3.5. ^{1}H NMR of *trans* isomer of **34a**

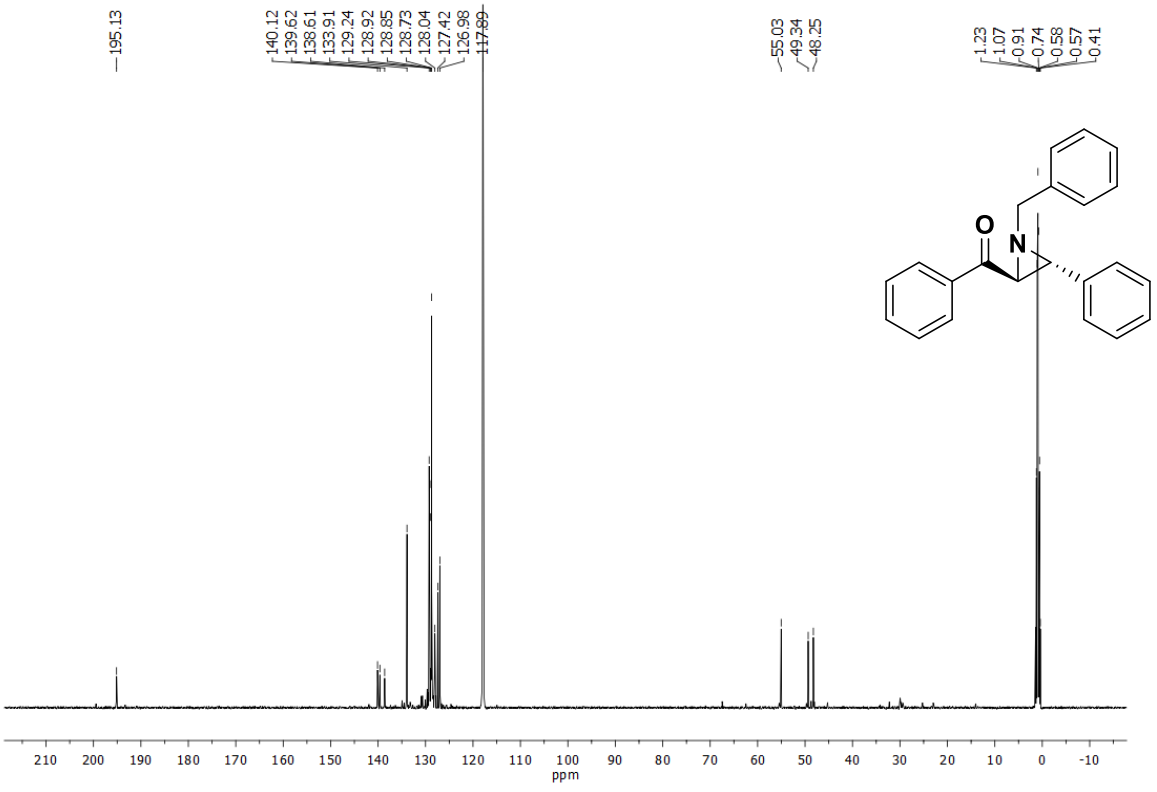


Figure 3.6. ^{13}C NMR of *trans* isomer of **34a**

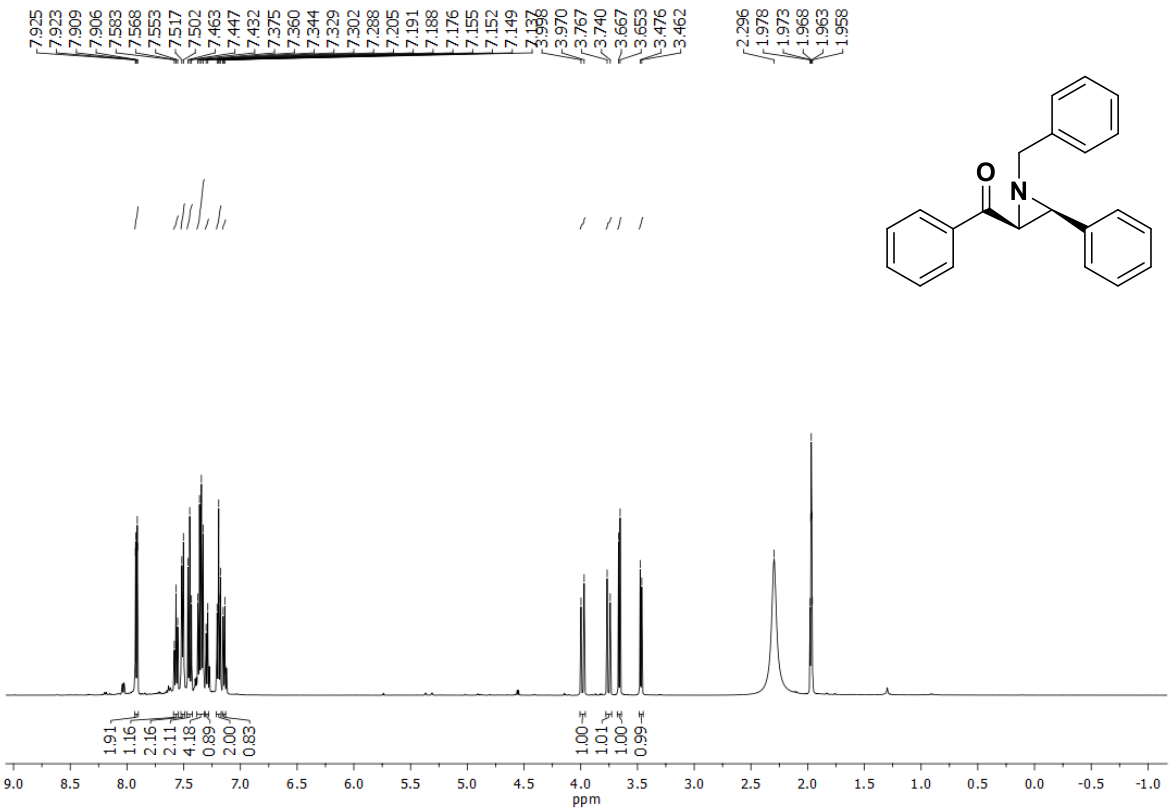


Figure 3.7. ^{1}H NMR of *cis* isomer of **34a**

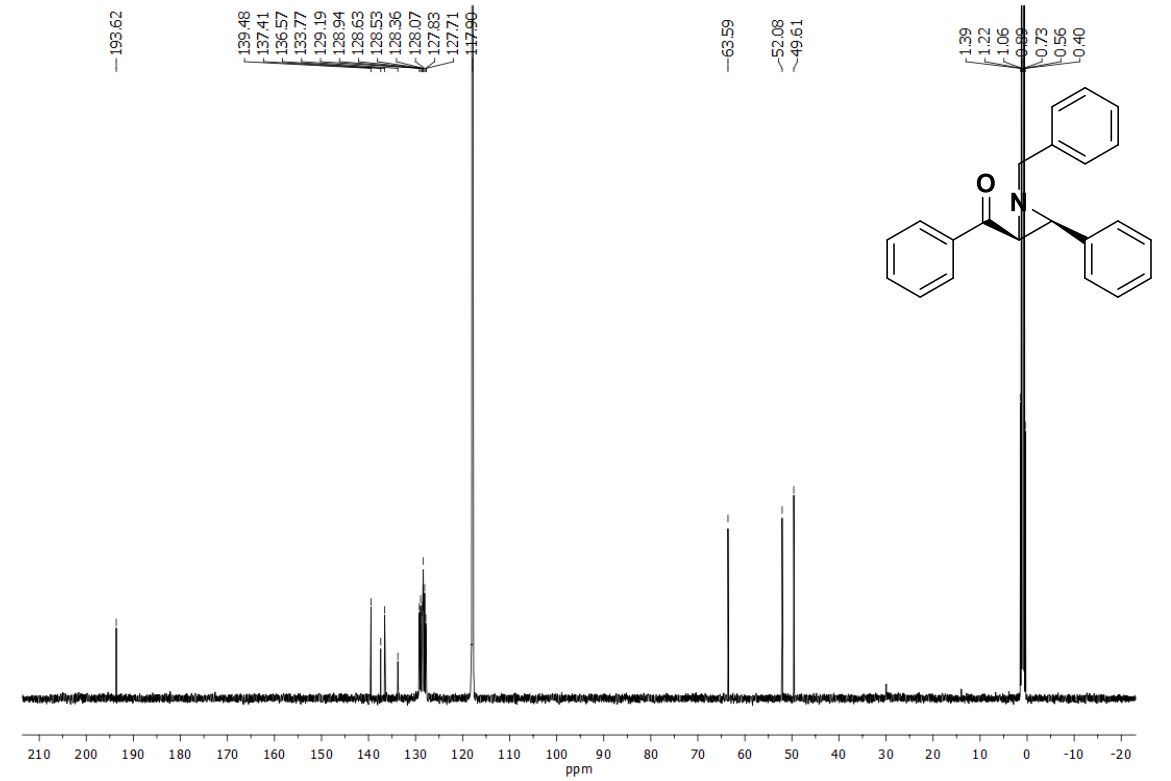


Figure 3.8. ^{13}C NMR of *cis* isomer of **34a**

The structure and relative stereochemistry of the *trans* isomer was unambiguously confirmed through the single crystal X-ray analysis of the derivative **34h**.

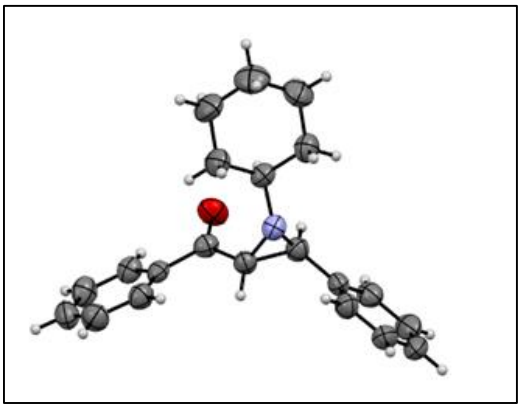
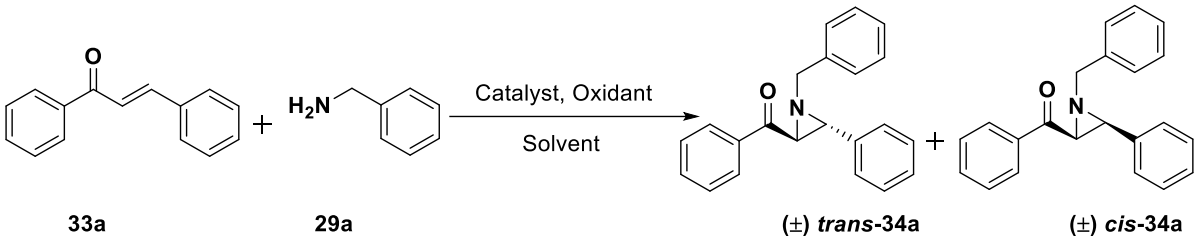


Figure 3.9. Single crystal X-ray structure of **34h** (**CCDC 194982**)

After confirming the structure of the products, we carried out a detailed optimization of the reaction conditions. Initially various solvents were screened and EtOAc was selected as the suitable solvent based on improved yields. We could achieve a shorter reaction time of 1 h on increasing the temperature to 50 °C, without any change in the yield of the reaction (entry 10). Among the different iodinating agents evaluated, molecular iodine turned out to be the better catalyst providing a high yield of 93% (entry 11). From a similar study of oxidants, TBHP emerged as an efficient oxidant for the synthesis of 2-aroylaziridine (entry 11). Sluggish results were obtained when the reaction was performed at both low and high temperatures (entries 16 and 17), but when carried out at 40 °C with 10 mol% loading of the catalyst, the same result as that at 50 °C with 20 mol% of I_2 (yield of 93% and diastereomeric ratio of 2.8 : 1) was obtained (entry 18).

Table 3.6. Optimization of reaction conditions [a]



33a **29a** (±) ***trans*-34a** (±) ***cis*-34a**

Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	*dr*[b]	Yield [%][c]
1[d]	I_2	TBHP	cyclohexane	rt	trans only	51
2	TBHP	TBHP	EtOAc	rt	2.4:1	82
3	TBAI	TBHP	MeOH	rt	4.4:1	71
4	TBAI	TBHP	EtOH	rt	4.8:1	35
5	TBAI	TBHP	CH_3CN	rt	1.1:1	49
6	TBAI	TBHP	DCM	rt	trans only	26
7	TBAI	TBHP	DCE	rt	3.8:1	73
8	TBAI	TBHP	THF	rt	2:1	39
9	TBAI	TBHP	toluene	rt	1.7:1	49
10	TBAI	TBHP	EtOAc	50	2.4:1	82
11	I_2	TBHP	EtOAc	50	2.8:1	93
12	NaI	TBHP	EtOAc	50	3.8:1	53
13	KI	TBHP	EtOAc	50	4.1:1	41
14	I_2	H_2O_2	EtOAc	50	1.5:1	28
15	I_2	*m*CPBA	EtOAc	50	1.6:1	21
16	I_2	TBHP	EtOAc	80	—	trace
17	I_2	TBHP	EtOAc	0	—	trace
18[e]	I_2	TBHP	EtOAc	40	2.8:1	93

[a] Reaction conditions: **33a** (0.20 mmol), **29a** (0.40 mmol), catalyst (20 mol%) and oxidant (0.40 mmol); reactions that are carried out at rt completed within 4 h while those at 50 °C and 40 °C took 1 h to complete. [b] *dr* calculated based on the yields of isolated products. [c] Yields of isolated products. [d] **29a** (4 equiv). [e] Catalyst (10 mol%) and oxidant (0.20 mmol).

With the optimized conditions in hand we explored the generality of the reaction by transforming variously substituted chalcones into corresponding 2-aroylaziridines (**Table 3.7**). Electron neutral (**34a**), electron withdrawing (**34b** and **34c**) and electron donating groups (**34d**–**34f**) bearing chalcones underwent the reaction with moderate to excellent yields from 48 to 93%. The diversity of the reaction for aliphatic amines was also investigated to furnish the desired products in excellent yields with moderate diastereomeric ratios (**34f–34j**). Interestingly, regardless of the substituents on the chalcone and the nature of primary aliphatic amines, the *trans* isomer was formed as the major product in all the cases.

Table 3.7. Scope of 2-aroylaziridine synthesis

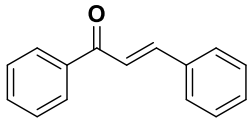
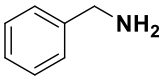
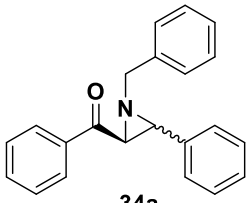
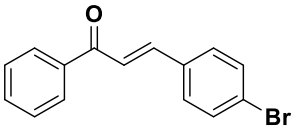
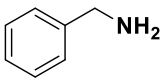
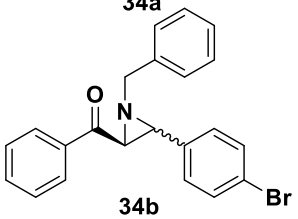
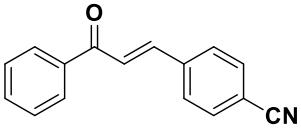
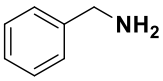
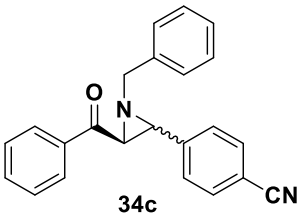
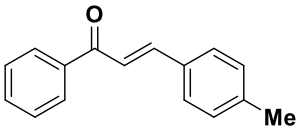
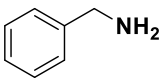
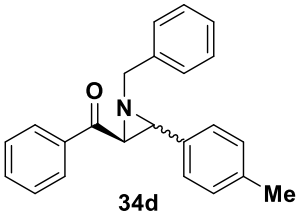
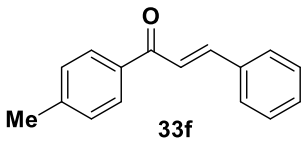
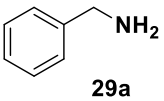
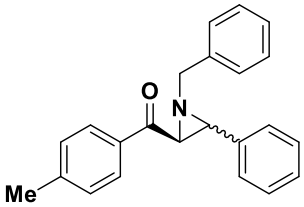
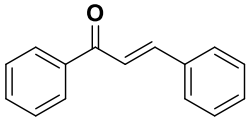
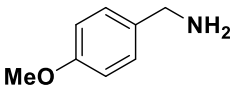
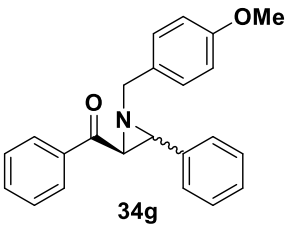
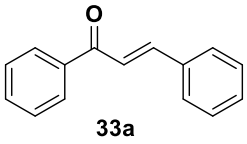
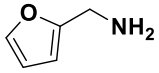
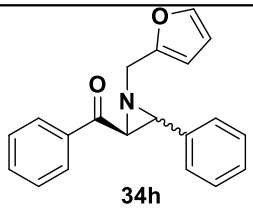
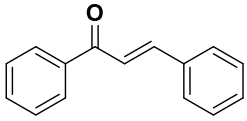
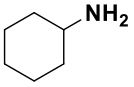
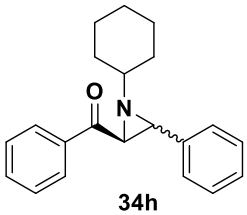
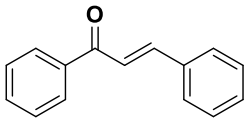
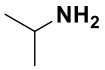
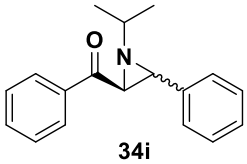
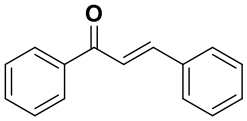
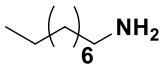
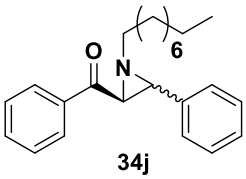
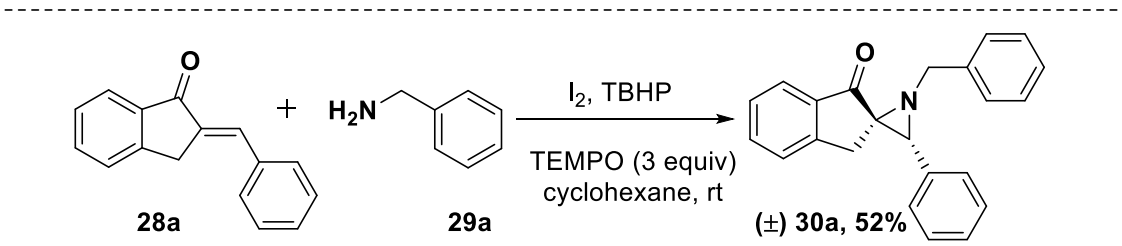
Entry	Unsaturated ketone	Amine	Product	*dr*	Yield (%)
1	 33a	 29a	 34a	2.8:1	93
2	 33b	 29a	 34b	2.8:1	83
3	 33c	 29a	 34c	3.4:1	48
4	 33d	 29a	 34d	2.4:1	68
5	 33f	 29a	 34f	3.5:1	82
6	 33a	 29l	 34g	2.8:1	88

Table 3.7. continues…….

Entry	Unsaurated ketone	Amine	Product	*dr*	Yield (%)
7	 33a	 29h	 34h	2.7:1	82
8	 33a	 29i	 34h	3.1:1	90
9	 33a	 29e	 34i	1.9:1	87
10	 33a	 29h	 34j	2.7:1	92

Reaction conditions: **33** (0.20 mmol), **29** (0.40 mmol), I_2 (10 mol%), and TBHP (0.20 mmol) in EtOAc at 40 °C. Yields of isolated products. *dr* calculated based on the yields of isolated products.

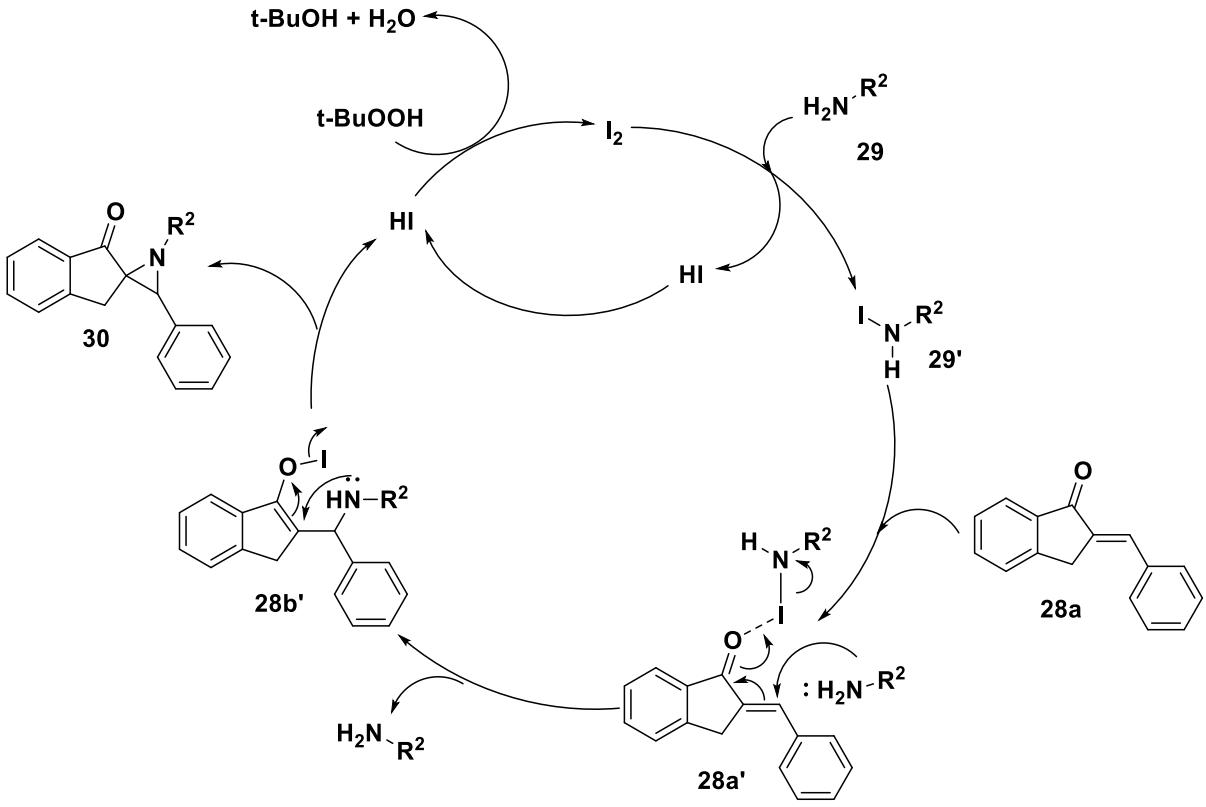
To shed light on the mechanism of the reaction, we have performed a radical trapping experiment under the optimized conditions. There was no substantial decrease in the yield of **30a** when the reaction was carried out in the presence of TEMPO. This observation suggests that the reaction does not proceed through a radical mechanism (**Scheme 3.13**).



Scheme 3.13. Control experiment

3.5. Plausible mechanism

We assume that the reaction proceeds through a mechanism similar to the pathway proposed by Gupta *et al.* (**Scheme 3.14**).[28] Initially the amine interacts with iodine and forms an *N*-iodoamine species. Coordination of *N*-iodoamine with the carbonyl group of **28a** facilitates the aza-Michael addition of another molecule of the amine, generating the intermediate **28b′**. A subsequent intramolecular cyclisation of **28b′** affords the final product **30**. The HI formed in the reaction will be oxidized by TBHP thus regenerating iodine in the catalytic cycle.



Scheme 3.14. Plausible mechanism

3.6. Conclusion

We have developed an operationally simple diastereoselective protocol for the synthesis of *N*-alkyl spiroaziridines. The I_2/TBHP mediated reaction, which proceeds under mild conditions, does not require pre-functionalization of amines. The protocol utilizes unprotected primary

amines as the nitrogen source. This process is compatible for the synthesis of 2-aroylaziridines as well.

3.7. General experimental methods

All the reactions were performed with commercially available best grade chemicals without further purification. All the solvents used were reagent grade and commercially available. Column chromatography was performed using 100 - 200 mesh silica gel and mixture of hexane - ethyl acetate was used for elution of the products. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrometer ($CDCl_3$, $(CD_3)_2CO$ and CD_3CN as solvents). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25)/ $(CD_3)_2CO$ (δ 2.09)/ CD_3CN (δ 1.96). Multiplicities are given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet), m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03)/ $(CD_3)_2CO$ (δ 30.06)/ CD_3CN (δ 1.79). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive - LCMS mass spectrometer by electron spray ionization method with ions given in m/z using Orbitrap analyzer. IR spectra were recorded on Bruker FT-IR spectrometer. Melting points were determined on a Buchi melting point apparatus and are uncorrected.

3.8. General procedure for the synthesis of (*E*)-2-arylidene-2,3-dihydro-1*H*-inden-1-one

One equivalent of aryl aldehyde or heteroaryl aldehyde was added to a solution of one equivalent of indanone in ethanol. 10% aqueous solution of NaOH was added dropwise to the reaction mixture at 0 ^oC and allowed to stir at room temperature for 30 minutes. The precipitate formed was collected by filtration and washed with hexane. The precipitate was dried and used for further reaction.

3.9. Procedure for the synthesis of (*Z*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one

A N_2 - bubbled solution of **28a** in CH_3CN was irradiated using a photochemical reactor at 352 nm for 4h. The solvent was removed under reduced pressure and the product was purified by column chromatography using a mixture of ethyl acetate and hexane (4% ethyl acetate in hexane) as the eluent.

3.10. Procedure for the synthesis of (*E*)-2-alkylidene-2,3-dihydro-1*H*-inden-1-one

One equivalent of butanal was added to a solution of one equivalent of indanone in ethanol. 10% aqueous solution of NaOH was added dropwise to the reaction mixture at 0^{o}C. The reaction was allowed to stir at room temperature by monitoring the TLC. After the completion of the reaction the product was extracted with ethyl acetate (3 x 10 mL). The solvent was evaporated in *vacuo* and the residue on silica gel (100 - 200 mesh) column chromatography using a mixture of hexane and ethyl acetate as eluent yielded the product as pale yellow liquid.

3.11. General procedure for the synthesis of (*E*)-2-arylidene-3,4-dihydronaphthalen-1(2*H*)-one

To a solution of tetralone (1 equiv.) in ethanol, the corresponding aryl aldehyde (1 equiv) was added at 0 ^{o}C. An aqueous solution of NaOH (10%, 10 mL) was added drop wise to this reaction mixture. The solid precipitate formed was collected by filtration and washed with water and hexane. It was dried and used for further reaction.

3.12. General procedure for the synthesis of (*E*)-3-arylidenechroman-4-one/ (*Z*)-3-arylidenethiochroman-4-one

One equivalent of aryl aldehyde was added to a solution of one equivalent of chroman-4-one/thiochroman-4-one in ethanol. 10% aqueous solution of NaOH was added dropwise to the reaction mixture at 0 ^{o}C and allowed to stir at room temperature for 30 minutes. The precipitate formed was collected by filtration and washed with hexane. The precipitate was dried and used for further reaction.

3.13. General procedure for the synthesis of spiroaziridine

Procedure A:

To a mixture of (*E*)-2-aryl/alkylidene-2,3-dihydro-1*H*-inden-1-one (1equiv) and primary amine (4 equiv) 20 mol% of iodine was added. Cyclohexane (2 mL) was added to the reaction mixture followed by the addition of TBHP (2 equiv). The reaction mixture was then allowed to stir at room temperature for 3 - 10 hours by monitoring the TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on column chromatography using a mixture of hexane and ethyl acetate as eluent afforded the product.

Procedure B:

To a mixture of (*E*)-2-arylidene-3,4-dihydronaphthalen-1(2*H*)-one/ (*Z*)-3-arylidenethiochroman-4-one (1 equiv) and benzylamine (4 equiv) 20 mol% of iodine was added. Cyclohexane (2 mL) was added to the reaction mixture followed by the addition of TBHP (2 equiv). The reaction mixture was then allowed to stir at room temperature for 3 – 10 hours by monitoring the TLC. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on column chromatography using a mixture of hexane and ethyl acetate as eluent afforded the product.

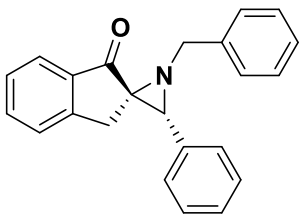
Procedure C:

To a mixture of (*E*)-3-arylidenechroman-4-one (1equiv) and benzylamine (4 equiv) 20 mol% of iodine was added. Ethyl acetate (2 mL) was added to the reaction mixture followed by the addition of TBHP (2 equiv). The reaction mixture was then allowed to stir at room temperature for 2 - 4 hours by monitoring the TLC. After the completion of the reaction, the mixture was washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated in *vacuo*. The residue on column chromatography using a mixture of hexane and ethyl acetate as eluent afforded the product.

3.14. Characterization data of spiroaziridines

1-benzyl-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30a)

The compound **30a** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30a** was obtained as colourless liquid in 61% (30 mg) yield.



IR (neat) ν_{max}: 3031, 1697, 1603, 1494, 1466, 804, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.31 (m, 8H), 7.28 – 7.23 (m, 3H), 7.17 (t, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 14.0 Hz,

1H), 4.39 (d, *J* = 14.5 Hz, 1H), 3.73 (s, 1H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.78 (d, *J* = 18.0 Hz, 1H).

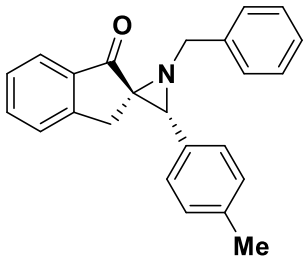
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 152.3, 139.6, 137.5, 137.1, 134.6, 128.3, 128.30, 128.1, 127.6, 127.5, 127.3, 126.8, 126.3, 123.3, 55.2, 54.5, 54.0, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{20}NO$, $(M+H)^+$: 326.15449; Found: 326.15527.

1-benzyl-3-(*p*-tolyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30b)

The compound **30b** was synthesized following the procedure A using (*E*)-2-(4-methylbenzylidene)-2,3-dihydro-1*H*-inden-1-one (36 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30b** was obtained as colourless liquid in 57% (29 mg) yield.

IR (neat) ν_{max}: 3030, 2921, 1698, 1605, 1514, 1495, 1089 cm^{-1}.



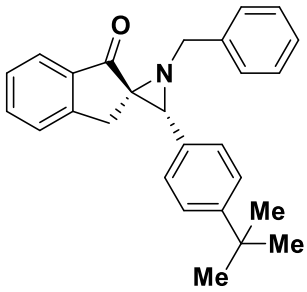
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.37 - 7.31 (m, 4H), 7.23 (d, *J* = 8.0 Hz, 4H), 7.17 - 7.13 (m, 3H), 4.46 (d, *J* = 14.0 Hz, 1H), 4.38 (d, *J* = 14.0 Hz, 1H), 3.70 (s, 1H), 3.07 (d, *J* = 18.5 Hz, 1H), 2.79 (d, *J* = 18.5 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.5, 152.3, 139.7, 137.5, 137.3, 134.5, 134.1, 129.0, 128.3, 128.0, 127.4, 127.3, 126.7, 126.2, 123.3, 55.2, 54.5, 54.1, 32.1, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NO$, $(M+H)^+$: 340.17014; Found: 340.17059.

1-benzyl-3-(4-(tert-butyl)phenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30c)

The compound **30c** was synthesized following the procedure A using (*E*)-2-(4-(tertbutyl)benzylidene)-2,3-dihydro-1*H*-inden-1-one (47 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30c** was obtained as colourless liquid in 48% (25 mg) yield.



IR (neat) ν_{max}: 3030, 2961, 1698, 1648, 1604, 1495 cm^{-1}.

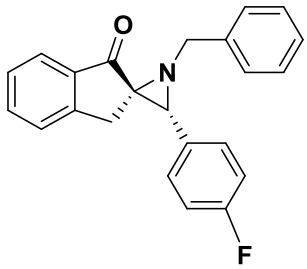
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.56 - 7.50 (m, 1H), 7.38 - 7.31 (m, 6H), 7.27 - 7.23 (m, 4H), 7.17 (t, *J* = 7.5 Hz, 1H), 4.45 (d, *J* = 14.0 Hz, 1H), 4.39 (d, *J* = 14.0 Hz, 1H), 3.71 (s, 1H), 3.08 (d, *J* = 18.0 Hz, 1H), 2.83 (d, *J* = 18.5 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.5, 152.4, 150.6, 139.7, 137.5, 134.5, 134.1, 129.7, 128.3, 128.1, 127.3, 127.2, 126.7, 126.2, 126.0, 125.2, 123.2, 55.2, 54.5, 54.1, 34.6, 32.2, 31.4, 31.1.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{28}NO$, $(M+H)^+$: 382.21709; Found: 382.21669.

1-benzyl-3-(4-(tert-butyl)phenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30d)

The compound **30d** was synthesized following the procedure A using (*E*)-2-(4-fluorobenzylidene)-2,3-dihydro-1*H*-inden-1-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30d** was obtained as colourless liquid in 52% (27 mg) yield.



IR (neat) ν_{max}: 3064, 3031, 2923, 1701, 1606, 1495, 1048 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.32 - 7.25 (m, 4H), 7.23 - 7.19 (m, 3H), 4.45 (d, *J* = 13.5 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 3.90 (s, 1H), 2.95 (d, *J* = 18.0 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 1H).

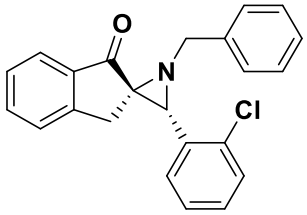
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 152.2, 139.5, 137.3, 135.1, 134.7, 134.3, 129.2, 128.9, 128.8, 128.4, 128.4, 127.4, 126.9, 126.7, 126.2, 123.4, 54.2, 53.4, 53.1, 32.2.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}FNO$, $(M+H)^+$: 344.1557; Found: 344.14557.

1-benzyl-3-(2-chlorophenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30e)

The compound **30e** was synthesized following the procedure A using (*E*)-2-(2-chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-one (39 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature afforded. The product **30e** was obtained as colourless liquid in 44% (25 mg) yield.

IR (neat) ν_{max}: 3066, 3031, 2921, 1702, 1606, 1468, 1048 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.29 (m, 2H), 7.27 – 7.25 (m, 2H), 7.23 - 7.19 (m, 3H), 4.45 (d, *J* = 13.5 Hz, 1H), 4.37 (d, *J* = 13.5 Hz, 1H), 3.90 (s, 1H), 2.95 (d, *J* = 18.0 Hz, 1H), 2.62 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 152.2, 139.5, 137.3, 135.2, 134.6, 134.3, 129.2, 128.9, 128.7, 128.4, 128.4, 127.4, 126.9, 126.7, 126.2, 123.4, 54.2, 53.4, 53.1, 32.2.

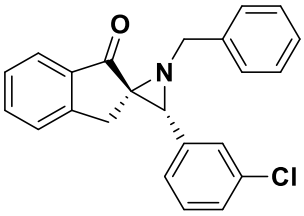
HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}ClNO$, $(M+H)^+$: 360.11552; Found: 360.11652.

1-benzyl-3-(3-chlorophenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30f)

The compound **30f** was synthesized following the procedure A using (*E*)-2-(3-chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-one (39 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30f** was obtained as colourless liquid in 47% (27 mg) yield.

IR (neat) ν_{max}: 3063, 3030, 2919, 1699, 1601, 1494, 1046 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.37- 7.34 (m, 5H), 7.26 – 7.24



(m, 5H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.44 (d, *J* = 14.0 Hz, 1H), S11 4.37 (d, *J* = 14.0 Hz, 1H), 3.69 (s, 1H), 3.08 (d, *J* = 18.0 Hz, 1H), 2.76 (d, *J* = 18.5 Hz, 1H).

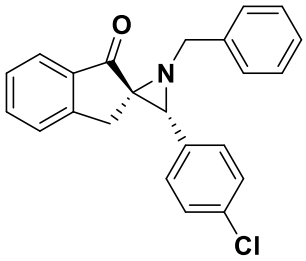
^{13}C NMR (126 MHz, $CDCl_3$): δ 200.9, 152.1, 139.4, 139.3, 137.3, 134.8, 134.4, 129.6, 128.3, 128.1, 127.8, 127.5, 127.4, 126.9, 126.3, 125.8, 123.4, 54.6, 54.1, 53.9, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}ClNO$, $(M+H)^+$: 360.11552; Found: 360.11652.

1-benzyl-3-(4-chlorophenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30g)

The compound **30g** was synthesized following the procedure A using (*E*)-2-(4-chlorobenzylidene)-2,3-dihydro-1*H*-inden-1-one (39 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30g** was obtained as colourless liquid in 47% (27 mg) yield.

IR (neat) ν_{max}: 3063, 3031, 2923, 1699, 1606, 1491, 1047 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.37 - 7.31 (m, 4H), 7.29 (d, *J* = 5.0 Hz, 3H), 7.26 - 7.23 (m, 3H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.45 (d, *J* = 14.0 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 3.69 (s, 1H), 3.06 (d, *J* = 18.0 Hz, 1H), 2.74 (d, *J* = 18.0 Hz, 1H).

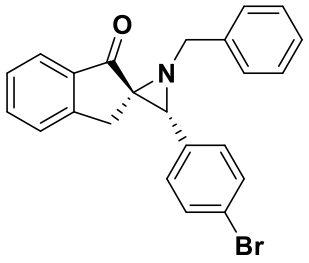
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 152.1, 139.4, 137.4, 135.7, 134.8, 133.4, 128.8, 128.5, 128.3, 128.1, 127.5, 126.9, 126.3, 123.4, 54.5, 54.3, 53.9, 32.0.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}ClNO$, $(M+H)^+$: 360.11552; Found: 360.11680.

1-benzyl-3-(4-bromophenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30h)

The compound **30h** was synthesized following the procedure A using (*E*)-2-(4-bromobenzylidene)-2,3-dihydro-1*H*-inden-1-one (45 mg, 0.15 mmol), benzylamine (65 mg,

0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30h** was obtained as colourless liquid in 27% (16 mg) yield.



IR (neat) ν_{max}: 30362, 3030, 2920, 1699, 1606, 1487, 1047 cm^{-1}.

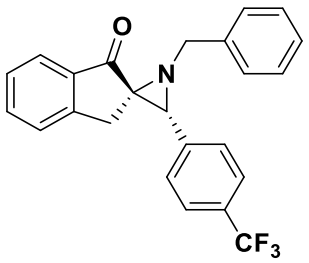
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.35 (m, 4H), 7.28 - 7.23 (m, 4H), 7.20 (t, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 14.0 Hz, 1H), 4.38 (d, *J* = 14.0 Hz, 1H), 3.70 (s, 1H), 3.08 (d, *J* = 18.0 Hz, 1H), 2.77 (d, *J* = 18.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.0, 152.1, 139.4, 137.4, 136.2, 134.7, 131.5, 129.2, 128.3, 128.0, 127.5, 126.9, 126.3, 123.4, 121.5, 54.5, 54.3, 53.9, 32.0.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}BrNO$, $(M+H)^+$: 404.06500; Found: 404.06561, $(M+2)^+$: 406.06296; Found: 406.06360.

1-benzyl-3-(4-(trifluoromethyl)phenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30i)

The compound **30i** was synthesized following the procedure A using (*E*)-2-(4-(trifluoromethyl)benzylidene)-2,3-dihydro-1*H*-inden-1-one (44 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30i** was obtained as colourless liquid in 49% (29 mg) yield.



IR (neat) ν_{max}: 3062, 2925, 1702, 1612, 1323, 1163, 1123, 1065 cm^{-1}.

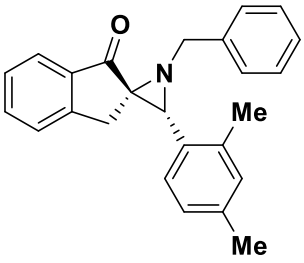
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.38 - 7.32 (m, 4H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.45 (d, *J* = 13.5 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 3.76 (s, 1H), 3.09 (d, *J* = 18.0 Hz, 1H), 2.73 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.8, 152.0, 139.3, 137.3, 134.8, 128.4, 128.1, 127.8, 127.5, 126.9, 126.3, 125.3, 125.3, 123.4, 54.7, 54.1, 53.9, 32.0.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{19}F_3NO$, $(M+H)^+$: 394.14187; Found: 394.14267.

1-benzyl-3-(2,4-dimethylphenyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30j)

The compound **30j** was synthesized following the procedure A using (*E*)-2-(2,4-dimethylbenzylidene)-2,3-dihydro-1*H*-inden-1-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30j** was obtained as colourless liquid in 37% (20 mg) yield.



IR (neat) ν_{max}: 3061, 3030, 2921, 1697, 1607, 1497, 1458, 1048 cm^{-1}.

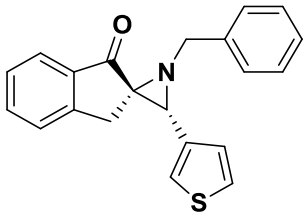
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 - 7.25 (m, 4H), 7.19 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.92 (s, 1H), 4.46 (d, *J* = 13.7 Hz, 1H), 4.39 (d, *J* = 13.7 Hz, 1H), 3.69 (s, 1H), 2.95 (d, *J* = 18.3 Hz, 1H), 2.57 (d, *J* = 18.3 Hz, 1H), 2.29 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.8, 152.3, 139.7, 137.4, 137.12, 136.5, 134.5, 132.5, 130.5, 128.3, 127.3, 127.2, 126.9, 126.6, 126.2, 123.3, 54.4, 54.0, 53.4, 32.2, 21.1, 18.9.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{24}NO$, $(M+H)^+$: 354.18579; Found: 354.18594.

1-benzyl-3-(thiophen-3-yl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30k)

The compound **30k** was synthesized following the procedure A using (*E*)-2-(thiophen-2-ylmethylene)-2,3-dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30k** was obtained as colourless liquid in 32% (16 mg) yield.



IR (neat) ν_{max}: 3063, 3030, 2920, 1696, 1605, 1495, 1466, 1086 cm^{-1}.

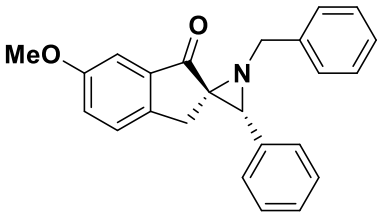
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 6.0 Hz, 4H), 7.19 – 7.11 (m, 4H), 7.08 (t, *J* = 7.0 Hz, 1H), 6.94 (d, *J* = 4.5 Hz, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 4.25 (d, *J* = 14.5 Hz, 1H), 3.64 (s, 1H), 3.01 (d, *J* = 18.0 Hz, 1H), 2.78 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 152.3, 139.6, 139.0, 137.5, 134.6, 128.3, 127.9, 127.4, 126.9, 126.8, 126.3, 125.8, 123.3, 122.5, 54.2, 54.1, 51.7, 32.5.

HRMS (ESI) (m/z): Calcd for $C_{21}H_{18}NOS$, $(M+H)^+$: 332.11091; Found: 332.11093.

1-benzyl-6'-methoxy-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30l)

The compound **30l** was synthesized following the procedure A using (*E*)-2-benzylidene-6-methoxy-2,3-dihydro-1*H*-inden-1-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30l** was obtained as colourless liquid in 36% (20 mg) yield.



IR (neat) ν_{max}: 3083, 3061, 2938, 1695, 1614, 1491, 1279, 1147 cm^{-1}.

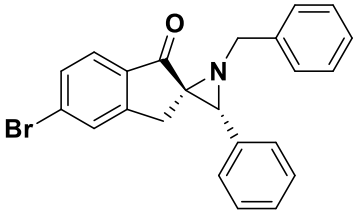
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.34 (m, 4H), 7.31 - 7.24 (m, 4H), 7.22 - 7.18 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 4.49 (d, *J* = 14.0 Hz, 1H), 4.43 (d, *J* = 14.0 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 1H), 3.03 (d, *J* = 18.0 Hz, 1H), 2.73 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 159.3, 145.2, 139.6, 138.5, 137.2, 128.3, 128.0, 127.6, 127.5, 127.0, 126.8, 123.8, 104.7, 55.6, 55.2, 55.2, 54.1, 31.5.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NO_2$, $(M+H)^+$: 356.16505; Found: 356.16556.

1-benzyl-5'-bromo-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30m)

The compound **30m** was synthesized following the procedure A using (*E*)-2-benzylidene-6-bromo-2,3-dihydro-1*H*-inden-1-one (45 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30m** was obtained as colourless liquid in 47% (30 mg) yield.



IR (neat) ν_{max}: 3084, 3061, 2920, 1701, 1596, 1494, 1421, 1051 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 2H), 7.29 – 7.25 (m, 6H), 7.20 - 7.16 (m, 3H), 7.10 (t, *J* = 7.0 Hz, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 4.30 (d, *J* = 14.0 Hz, 1H), 3.66 (s, 1H), 2.97 (d, *J* = 18.5 Hz, 1H), 2.67 (d, *J* = 18.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.2, 153.7, 139.4, 136.8, 136.2, 130.9, 130.1, 129.5, 128.4, 128.3, 128.0, 127.8, 127.5, 126.9, 124.5, 55.4, 54.4, 54.0, 31.8.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}BrNO$, $(M+H)^+$: 404.06500; Found: 404.06543, $(M+2)^+$: 406.06296; Found: 406.06332.

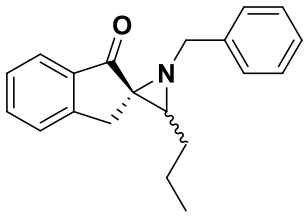
1-benzyl-3-propylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30n)

The compound **30n** was synthesized following the procedure A using (*E*)-2-butylidene-2,3-dihydro-1*H*-inden-1-one (28 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol)., I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The reaction afforded two diastereomers with diastereomeric ratio of 1.9:1. The major isomer was obtained as a colourless liquid in 49% (21 mg) yield and the minor product also as a colourless liquid in 26% (11 mg) yield.

Analytical data of major isomer

IR (neat) ν_{max}: 3030, 2958, 1699, 1607, 1495, 1292, 740, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 2H), 7.26 (m, 2H),



7.19 (t, *J* = 7.0 Hz, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 4.16 (d, *J* = 13.5 Hz, 1H), 3.26 (d, *J* = 18.0 Hz, 1H), 3.15 (d, *J* = 18.0 Hz, 1H), 2.61 (t, *J* = 6.0 Hz, 1H), 1.57 – 1.53 (m, 2H), 1.41 – 1.32 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.5, 152.3, 139.6, 137.7, 134.5, 128.4, 128.3, 127.4, 126.8, 126.2, 123.2, 54.5, 52.9, 51.5, 33.2, 32.5, 20.6, 13.9.

HRMS (ESI) (m/z): Calcd for $C_{20}H_{22}NO$, $(M+H)^+$: 292.17014; Found: 292.17041.

Analytical data of minor isomer

IR (neat) ν_{max}: 3062, 3029, 2958, 1710, 1605, 1494, 1455, 738, 698 cm^{-1}.

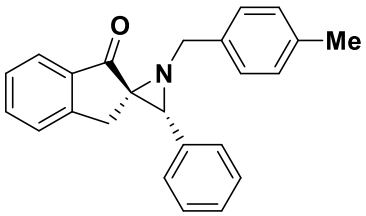
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 3.98 (d, *J* = 14.5 Hz, 1H), 3.81 (d, *J* = 14.5 Hz, 1H), 3.38 (d, *J* = 17.0 Hz, 1H), 3.25 (d, *J* = 17.5 Hz, 1H), 2.26 (t, *J* = 6.5 Hz, 1H), 1.92 - 1.85 (m, 1H), 1.72 - 1.65 (m, 1H), 1.38 - 1.27 (m, 1H), 1.24 - 1.17 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.1, 151.0, 138.7, 137.1, 134.39, 128.4, 127.6, 127.4, 126.9, 126.2, 123.5, 59.7, 56.3, 52.7, 29.5, 28.4, 20.8, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{20}H_{22}NO$, $(M+H)^+$: 292.17014; Found: 292.17020.

1-(4-methylbenzyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30o)

The compound **30o** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), 4-methylbenzylamine (73 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30o** was obtained as colourless liquid in 37% (19 mg) yield.



IR (neat) ν_{max}: 3030, 2921, 1700, 1606, 1466, 1047 cm^{-1}.

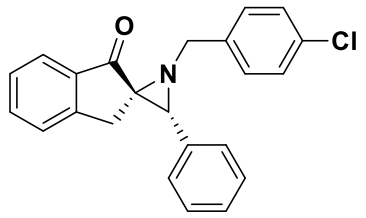
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.26 (d, *J* = 7.5 Hz, 3H), 7.05 (d, *J* = 7.5 Hz, 2H), 4.41 (d, *J* = 14.0 Hz, 1H), 4.34 (d, *J* = 14.0 Hz, 1H), 3.72 (s, 1H), 3.07 (d, *J* = 18.5 Hz, 1H), 2.76 (d, *J* = 18.5 Hz, 1H), 2.26 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 152.3, 137.5, 137.2, 136.6, 136.3, 134.6, 128.9, 128.3, 128.0, 127.6, 127.5, 127.3, 126.2, 123.3, 55.2, 54.5, 53.8, 32.2, 21.1.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NO$, $(M+H)^+$: 340.17014; Found: 340.16971.

1-(4-chlorobenzyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30p)

The compound **30p** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), 4-chlorobenzylamine (85 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30p** was obtained as colourless liquid in 41% (22 mg) yield.



IR (neat) ν_{max}: 3062, 3032, 2922, 1698, 1604, 1491, 1467, 1090, 1048 cm^{-1}.

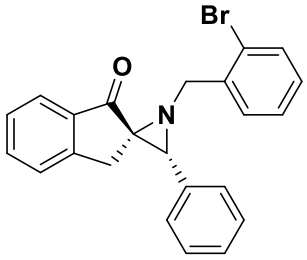
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.37 – 7.28 (m, 9H), 7.21 (d, *J* = 8.0 Hz, 2H), 4.42 (d, *J* = 14.5 Hz, 1H), 4.36 (d, *J* = 14.0 Hz, 1H), 3.71 (s, 1H), 3.05 (d, *J* = 18.0 Hz, 1H), 2.78 (d, *J* = 18.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 152.2, 138.1, 137.3, 136.9, 134.7, 132.5, 129.4, 128.4, 128.4, 127.7, 127.4, 127.4, 126.3, 123.3, 55.1, 54.4, 53.3, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}ClNO$, $(M+H)^+$: 360.11552; Found: 360.11498.

1-(2-bromobenzyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30q)

The compound **30q** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), 2-bromobenzylamine (112 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30q** was obtained as colourless liquid in 54% (33 mg) yield.



IR (neat) ν_{max}: 3062, 3032, 1696, 1603, 1493, 778, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.37 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.26 (m, 6H), 7.22 - 7.18 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 4.47 (d, *J* = 15.5 Hz, 1H), 4.40 (d, *J* = 15.0 Hz, 1H), 3.69 (s, 1H), 3.08 (d, *J* = 18.5 Hz, 1H), 2.75 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 152.2, 139.1, 137.2, 136.9, 134.7, 132.6, 129.2, 128.4, 128.2, 127.7, 127.5, 127.4, 127.4, 126.3, 123.7, 123.4, 55.0, 54.7, 54.1, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}BrNO$, $(M+H)^+$: 404.06500; Found: 404.06485, $(M+2)^+$: 406.06296; Found: 406.06296.

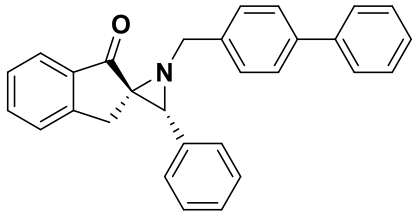
1-([1,1'-biphenyl]-4-ylmethyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30r)

The compound **30r** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), 4-phenylbenzylamine (110 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30r** was obtained as white solid in 40% (24 mg) yield.

MP: 110-112 ^oC

IR (neat) ν_{max}: 3061, 3030, 1699, 1605, 1488, 1048 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.0 Hz, 3H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.43 - 7.35 (m, 9H), 7.32 (d, *J* = 8.0



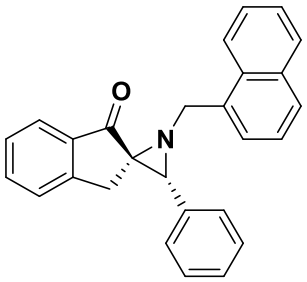
Hz, 1H), 4.53 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 3.78 (s, 1H), 3.14 (d, *J* = 18.0 Hz, 1H), 2.83 (d, *J* = 18.5 Hz, 1H).

^{13}C NMR (126 MHz, CDCl3): δ 201.4, 152.3, 141.0, 139.6, 138.7, 137.5, 137.1, 134.6, 128.7, 128.5, 128.4, 127.6, 127.5, 127.4, 127.1, 127.0, 127.0, 126.3, 123.3, 55.2, 54.6, 53.8, 32.2.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{24}NO$, $((M+H)^+$: 402.18579; Found: 402.18555.

1-(naphthalen-1-ylmethyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30s)

The compound **30s** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3-dihydro-1H-inden-1-one (34 mg, 0.15 mmol), 1-naphthylmethylamine (95 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30s** was obtained as white solid in 47% (26 mg) yield.



IR (neat) ν_{max}: 3055, 1698, 1602, 793, 778, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.36 - 7.26 (m, 8H), 4.92 (d, *J* = 14.5 Hz, 1H), 4.86 (d, *J* = 14.5 Hz, 1H), 3.82 (s, 1H), 3.07 (d, *J* = 18.5 Hz, 1H), 2.78 (d, *J* = 18.5 Hz, 1H).

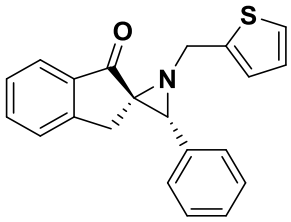
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.5, 152.3, 137.5, 137.2, 135.3, 134.6, 133.7, 132.0, 128.5, 128.3, 127.6, 127.5, 127.5, 127.3, 126.3, 125.8, 125.8, 125.5, 125.4, 124.3, 123.3, 55.2, 54.8, 51.7, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{27}H_{22}NO$, $(M+H)^+$: 376.17014; Found: 376.17242.

3-phenyl-1-(thiophen-2-ylmethyl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30t)

The compound **30t** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), 2-thiophenemethylamine (68 mg, 0.60 mmol),

I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30t** was obtained as colourless liquid in 60% (30 mg) yield.



IR (neat) ν_{max}: 3064, 3032, 2921, 1696, 1605, 1494, 1044 cm^{-1}.

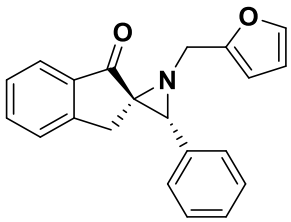
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.27 – 7.18 (m, 6H), 7.21 – 7.18 (m, 1H), 7.05 (d, *J* = 4.5 Hz, 1H), 6.83 (s, 1H),6.79 (s, 1H), 4.53 (s, 2H), 3.66 (s, 1H), 3.03 (d, *J* = 18.5 Hz, 1H), 2.69 (d, *J* = 18.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.2, 152.4, 142.7, 137.4, 136.81, 134.7, 128.3, 127.7, 127.5, 127.4, 126.5, 126.3, 124.9, 124.5, 123.3, 55.0, 54.5, 49.0, 32.0.

HRMS (ESI) (m/z): Calcd for $C_{21}H_{18}NOS$, $(M+H)^+$: 332.11091; Found: 332.11093.

1-(furan-2-ylmethyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30u)

The compound **30u** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), furfurylamine (59 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30u** was obtained as colourless liquid in 23% (11 mg) yield.



IR (neat) ν_{max}: 3063, 3032, 2921, 1697, 1605, 1467, 1073 cm^{-1}.

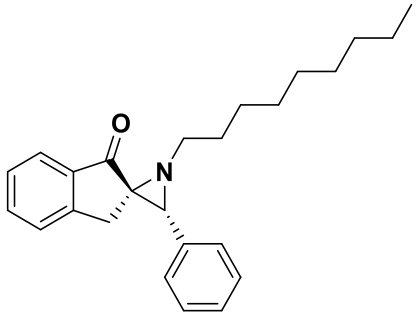
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.25 (m, 7H), 6.21 (s, 1H), 6.13 (s, 1H), 4.43 (d, *J* = 14.5 Hz, 1H), 4.38 (d, *J* = 14.0 Hz, 1H), 3.72 (s, 1H), 3.05 (d, *J* = 18.5 Hz, 1H), 2.76 (d, *J* = 18.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.3, 153.0, 152.3, 141.9, 137.41, 136.8, 134.7, 128.3, 127.7, 127.5, 127.4, 126.3, 123.3, 110.1, 107.3, 54.8, 54.1, 46.8, 31.9.

HRMS (ESI) (m/z): Calcd for $C_{21}H_{18}NO_2$, $(M+H)^+$: 316.13375; Found: 316.13300.

1-nonyl-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30v)

The compound **30v** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), nonylamine (86 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30v** was obtained as colourless liquid in 45% (24 mg) yield.



IR (neat) ν_{max}: 3032, 2924, 1701, 1606, 1464, 1088 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.35 (m, 6H), 7.30 – 7.28 (m, 1H), 3.58 (s, 1H), 3.28 – 3.23 (m, 1H), 3.15 – 3.10 (m, 1H), 3.05 (d, *J* = 18.5 Hz, 1H), 2.77 (d, *J* = 18.5 Hz, 1H), 1.56 – 1.49 (m, 2H), 1.38 - 1.34 (m, 2H), 1.28 - 1.23 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 152.3, 137.6, 137.6, 134.5, 128.3, 127.5, 127.4, 127.3, 126.3, 123.2, 55.2, 54.4, 50.5, 32.3, 31.9, 30.2, 29.5, 29.2, 27.2, 22.7, 14.1.

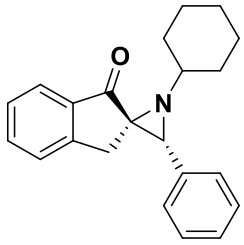
HRMS (ESI) (m/z): Calcd for $C_{25}H_{32}NO$, $(M+H)^+$: 362.24839; Found: 362.24865.

1-cyclohexyl-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30w)

The compound **30w** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), cyclohexylamine (82 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30w** was obtained as colourless liquid in 23% (11 mg) yield.

IR (neat) ν_{max}: 3060, 3032, 2927, 1699, 1605, 1494, 1092, 1042 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* =8.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.33 (m, 5H), 7.28 (s, 1H), 3.63 (s, 1H), 3.33 – 3.25 (m, S21 1H), 3.01 (d, *J* = 18.0 Hz, 1H), 2.77 (d, *J* = 18.0 Hz,



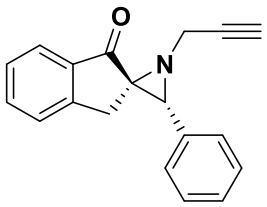
1H), 1.86 - 1.79 (m, 2H), 1.67 (s, 2H), 1.50 – 1.33 (m, 3H), 1.30 – 1.27 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 201.7, 152.2, 137.9, 137.5, 134.5, 128.3, 127.5, 127.4, 127.3, 126.3, 123.3, 56.7, 54.4, 53.9, 32.9, 32.8, 32.7, 26.2, 24.4, 24.1.

HRMS (ESI) (m/z): Calcd for $C_{22}H_{24}NO$, $(M+H)^+$: 318.18579; Found: 318.18616.

3-phenyl-1-(prop-2-yn-1-yl)spiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30x)

The compound **30x** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), propargylamine (34 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30x** was obtained as colourlesss liquid in 20% (8 mg) yield.



IR (neat) ν_{max}: 2916, 1699, 1604, 1493, 752, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.34 (m, 6H), 7.31 - 7.26 (m, 1H), 4.08 (d, *J* = 16.5 Hz, 1H), 4.02 (d, *J*= 16.5 Hz, 1H), 3.63 (s, 1H), 3.12 (d, *J* = 18.5 Hz, 1H), 2.78 (d, *J* = 18.5 Hz, 1H), 2.15 (s, 1H).

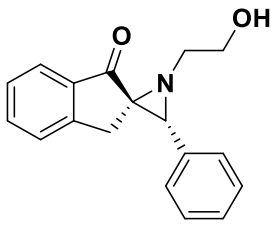
^{13}C NMR (126 MHz, $CDCl_3$): δ 200.9, 152.3, 137.2, 137.1, 134.84, 128.4, 127.8, 127.5, 126.3, 123.4, 80.9, 71.9, 55.1, 53.9, 39.7, 31.9.

HRMS (ESI) (m/z): Calcd for $C_{19}H_{16}NO$, $(M+H)^+$: 274.12319; Found: 274.12332.

1-(2-hydroxyethyl)-3-phenylspiro[aziridine-2,2'-inden]-1'(3'*H*)-one (30y)

The compound **30y** was synthesized following the procedure A using (*E*)-2-benzylidene-2,3- dihydro-1*H*-inden-1-one (34 mg, 0.15 mmol), ethanolamine (37 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **30y** was obtained as white solid in 53% (22 mg) yield.

IR (neat) ν_{max}: 3425, 3064, 3032, 2929, 1699, 1605, 1493, 1070, 1041 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 6.5 Hz, 1H), 3.79 - 3.77 (m, 1H), 3.73 – 3.70 (m, 1H), 3.63 (s, 1H), 3.45 - 3.43 (m, 1H), 3.38 – 3.35 (m, 1H), 3.10 (d, *J* = 18.0 Hz, 1H), 2.82 (d, *J* = 18.0 Hz, 1H), 1.76 (bs, 1H).

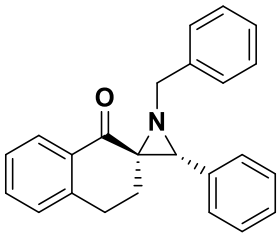
^{13}C NMR (126 MHz, $CDCl_3$): δ 201.2, 152.3, 137.3, 136.8, 134.8, 128.5, 127.8, 127.5, 127.3, 126.3, 123.4, 62.3, 54.4, 54.1, 52.4, 32.1.

HRMS (ESI) (m/z): Calcd for $C_{18}H_{18}NO_2$, $(M+H)^+$: 280.13375; Found: 280.13330.

1-benzyl-3-phenyl-3',4'-dihydro-1'*H*-spiro[aziridine-2,2'-naphthalen]-1'-one (32a)

The compound **34a** was synthesized following the procedure B using (*E*)-2-benzylidene-3,4- dihydronaphthalen-1(2*H*)-one (36 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **34a** was obtained as white solid in 25% (13 mg) yield.

IR (neat) ν_{max}: 3061, 3028, 1666, 1599, 1494, 1453, 1302, 1222, 740, 698 cm^{-1}.



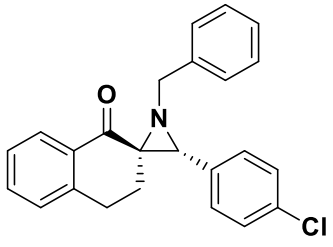
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 - 7.30 (m, 5H), 7.28 – 7.26 (m, 1H), 7.20 – 7.13 (m, 4H), 4.11 (d, *J* = 13.0 Hz, 1H), 4.05 (s, 1H), 3.83 (d, *J* = 13.0 Hz, 1H), 2.85 - 2.80 (m, 1H), 2.69 (d, *J* = 16.0 Hz, 1H), 1.88 (t, *J* = 11.0 Hz, 1H), 1.66 (d, *J* = 13 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.7, 144.6, 139.3, 136.8, 133.9, 133.6, 128.8, 128.4, 128.1, 128.1, 127.9, 127.3, 127.2, 126.9, 126.6, 55.5, 52.1, 51.4, 28.5, 27.5.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NO$, $(M+H)^+$: 340.17014; Found: 340.17062.

1-benzyl-3-(4-chlorophenyl)-3',4'-dihydro-1'*H*-spiro[aziridine-2,2'-naphthalen]-1'-one(32b)

The compound **34b** was synthesized following the procedure B using (*E*)-2-(4-chlorobenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (41 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **34b** was obtained as white solid in 29% (16 mg) yield.



IR (neat) ν_{max}: 3087, 3029, 1668, 1599, 1490, 1305, 1223, 740, 699 cm^{-1}.

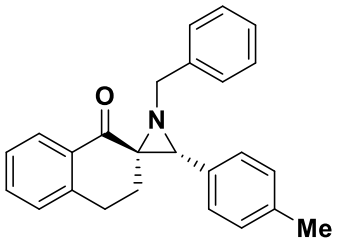
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.25 (m, 7H), 7.17 – 7.14 (m, 4H), 4.06 (d, *J* = 13.0 Hz, 1H), 3.97 (s, 1H), 3.79 (d, *J* = 13.5 Hz, 1H), 2.82 - 2.77 (m, 1H), 2.67 (d, *J* = 16.0 Hz, 1H), 1.85 – 1.79 (m, 1H), 1.63 - 1.57 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.4, 144.5, 139.1, 135.3, 133.8, 133.7, 132.9, 129.2, 128.8, 128.5, 128.3, 128.1, 127.3, 127.1, 126.6, 55.4, 51.5, 51.2, 28.4, 27.5.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{21}ClNO$, $(M+H)^+$: 374.13117; Found: 374.13259.

1-benzyl-3-(*p*-tolyl)-3',4'-dihydro-1'*H*-spiro[aziridine-2,2'-naphthalen]-1'-one (32c)

The compound **34c** was synthesized following the procedure B using (*E*)-2-(4-methylbenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in cyclohexane (2 mL) at room temperature. The product **34c** was obtained as white solid in 28% (15 mg) yield.



IR (neat) ν_{max}: 3059, 3028, 2922, 1666, 1629, 1513, 1454, 1305, 811, 741, 671 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.25 – 7.23 (m, 2H), 7.17 – 7.10 (m, 6H), 4.08 (d, *J* = 13.5 Hz, 1H), 3.98 (s, 1H), 3.81 (d, *J* = 13.5 Hz, 1H), 2.81 (t, *J* = 12.5 Hz, 1H), 2.66 (d, *J* = 16.0 Hz,

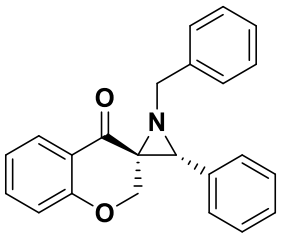
1H), 2.33 (s, 3H), 1.84 (t, *J* = 11.0 Hz, 1H), 1.65 (d, *J* = 13.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9, 144.6, 139.4, 136.8, 133.9, 133.7, 133.5, 128.8, 128.4, 128.1, 127.8, 127.3, 126.9, 126.6, 55.5, 52.1, 51.3, 28.4, 27.5, 21.2.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{24}NO$, $(M+H)^+$: 354.18579; Found: 354.18610.

1-benzyl-3-phenylspiro[aziridine-2,3'-chroman]-4'-one (32d)

The compound **34d** was synthesized following the procedure C using (*E*)-3-benzylidenechroman-4-one (36 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in ethyl acetate (2 mL) at room temperature. The product **34d** was obtained as white solid in 60% (31 mg) yield.



IR (neat) ν_{max}: 3062, 3030, 2919, 1671, 1603, 1578, 1494, 755, 697 cm^{-1}.

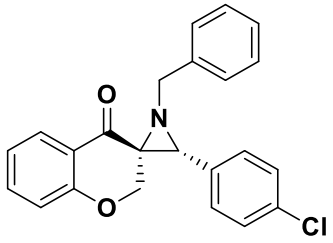
^{1}H NMR (500 MHz, Acetone-d_6): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.40 - 7.30 (m, 4H), 7.34 – 7.21 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 4.27 (d, *J* = 12.5 Hz, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 4.11 (d, *J* = 12.5 Hz, 1H), 4.01 (s, 1H), 3.98 (d, *J* = 13.5 Hz, 1H).

^{13}C NMR (126 MHz, Acetone-d_6): δ 187.4, 161.6, 139.1, 136.2, 135.4, 128.3, 128.2, 128.1, 127.7, 127.6, 126.9, 126.7, 122.8, 121.5, 117.9, 70.8, 54.7, 50.9, 48.3.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{20}NO_2$, $(M+H)^+$: 342.14940; Found: 342.14999.

1-benzyl-3-(4-chlorophenyl)spiro[aziridine-2,3'-chroman]-4'-one (32e)

The compound **34e** was synthesized following the procedure C using (*E*)-3-benzylidenechroman-4-one (36 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in ethyl acetate (2 mL) at room temperature. The product **34e** was obtained as white solid in 24% (14 mg) yield.



IR (neat) ν_{max}: 2990, 1685, 1604, 1578, 1474, 1326, 1307, 757 cm^{-1}.

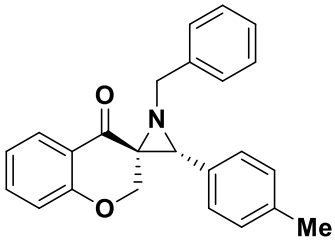
^{1}H NMR (500 MHz, Acetone-d_6): δ 7.72 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.40 - 7.37 (m,1H), 7.31 – 7.29 (m, 2H), 7.24 - 7.19 (m, 4H), 7.06 (d, *J* = 7.5 Hz, 2H), 7.00 – 6.97 (m, 1H), 6.9 – 6.90 (m, 1H), 6.80 (dd, *J* = 8.5, 0.5 Hz, 1H), 4.10 (d, *J* = 12.5 Hz, 1H), 4.01 (d, *J* = 13.5 Hz, 1H), 3.93 (d, *J* = 12.5 Hz, 1H), 3.82 (s, 1H), 3.80 (d, *J* = 13.5 Hz, 1H).

^{13}C NMR (126 MHz, Acetone-d_6): δ 187.1, 161.6, 138.9, 136.3, 134.5, 133.0, 129.4, 128.4, 128.2, 128.1, 126.9, 126.7, 122.8, 121.5, 117.9, 70.7, 54.6, 50.0, 48.4.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}ClNO_2$, $(M+H)^+$: 376.11043; Found: 376.11127.

1-benzyl-3-(*p*-tolyl)spiro[aziridine-2,3'-chroman]-4'-one (32f)

The compound **34f** was synthesized following the procedure C using (*E*)-3-(4-methylbenzylidene)chroman-4-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in ethyl acetate (2 mL) at room temperature. The product **34f** was obtained as white solid in 42% (22 mg) yield.



IR (neat) ν_{max}: 3030, 2922, 1670, 1603, 1512, 1462, 816, 756 cm^{-1}.

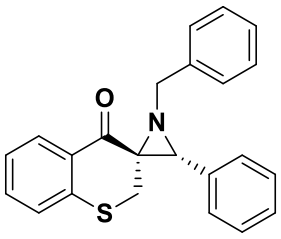
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.47 - 7.44 (m, 1H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.28 – 7.25 (m, 3H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 3H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.15 (d, *J* = 11.0 Hz, 1H), 4.12 (d, *J* = 13.0 Hz, 1H), 3.97 (d, *J* = 17.0 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 188.4, 161.7, 138.8, 137.5, 136.1, 132.1, 129.1, 128.3, 128.2, 127.5, 127.0, 126.9, 122.9, 121.4, 118.1, 71.1, 55.2, 51.3, 48.2, 21.2

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NO_2$, $(M+H)^+$: 356.16505; Found: 356.16553.

1-benzyl-3-phenylspiro[aziridine-2,3'-thiochroman]-4'-one (32g)

The compound **34g** was synthesized following the procedure C using (*Z*)-3-benzylidenethiochroman-4-one (38 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in ethyl acetate (2 mL) at room temperature. The product **34g** was obtained as white solid in 19% (10 mg) yield.



IR (neat) ν_{max}: 3061, 3030, 2923, 1661, 1587, 1493, 1455, 1297, 740, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.39 - 7.32 (m, 7H), 7.30 – 7.28 (m, 1H), 7.24 - 7.21 (m, 4H), 7.19 - 7.16 (m, 1H), 4.20 (s, 1H), 3.97 (d, *J* = 13.5 Hz, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.18 (d, *J* = 14.0 Hz, 1H), 2.60 (d, *J* = 13.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 190.1, 142.6, 138.6, 135.8, 133.3, 132.6, 129.7, 128.8, 128.3, 128.1, 127.9, 127.8, 127.6, 127.1, 125.2, 55.8, 53.4, 50.4, 32.5.

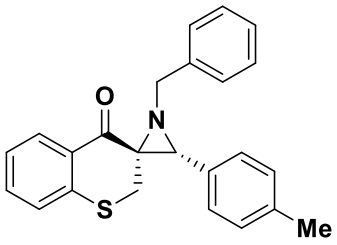
HRMS (ESI) (m/z): Calcd for $C_{23}H_{20}NOS$, $(M+H)^+$: 358.12656; Found: 358.12750.

1-benzyl-3-(*p*-tolyl)spiro[aziridine-2,3'-thiochroman]-4'-one (32h)

The compound **34h** was synthesized following the procedure A using (*Z*)-3-benzylidenethiochroman-4-one (40 mg, 0.15 mmol), benzylamine (65 mg, 0.60 mmol), I_2 (8 mg, 20 mol%) and TBHP (28 mg, 0.30 mmol) in ethyl acetate (2 mL) at room temperature. The product **34h** was obtained as white solid in 25% (13 mg) yield.

IR (neat) ν_{max}: 3063, 3029, 2957, 1686, 1605, 1427, 1307, 749, 699 cm^{-1}.

^{1}H NMR (500 MHz, Acetone-d_6): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 4H), 7.06 (t, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 7.5 Hz, 3H), 3.93 (s, 1H), 3.81 (d, *J* = 13.5 Hz, 1H),



3.66 (d, *J* = 13.5 Hz, 1H), 3.11 (d, *J* = 14.0 Hz, 1H), 2.49 (d, *J* = 14.0 Hz, 1H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, Acetone-d$_6$): δ 189.3, 142.2, 139.0, 137.1, 133.3, 132.9, 132.8, 129.3, 128.9, 128.6, 127.9, 127.8, 127.7, 126.9, 125.2, 55.3, 53.0, 50.3, 31.9, 20.2.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{22}NOS$, $(M+H)^+$: 372.14221; Found: 372.14312.

3.15. General procedure for the synthesis of (*E*)-chalcone

One equivalent of aryl aldehyde was added to a solution of one equivalent of acetophenone in ethanol. 10% aqueous solution of NaOH was added dropwise to the reaction mixture at 0 ^oC and allowed to stir at room temperature for 30 minutes. The precipitate formed was collected by filtration and washed with hexane. The precipitate was dried and used for further reaction.

3.16. General procedure for the synthesis of simple aziridines

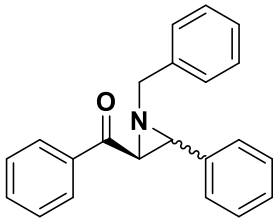
Procedure D:

To a mixture of (*E*)-chalcone (1 equiv) and primary amine (2 equiv) 10 mol% of iodine was added. Ethyl acetate (2 mL) was added to the reaction mixture followed by the addition of TBHP (1 equiv). The reaction mixture was then allowed to stir at 40 ^oC for 1- 2 hours by monitoring the TLC. After the completion of the reaction, the mixture was washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on column chromatography using a mixture of hexane and ethyl acetate as eluent yielded the products.

3.17. Characterization data of simple aziridines

(1-benzyl-3-phenylaziridin-2-yl)(phenyl)methanone (34a)

The compound **34a** was synthesized following the procedure D using (*E*)- chalcone (42 mg, 0.20 mmol), benzylamine (43 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34a** were formed under the reaction conditions. Isolation by column chromatography afforded *trans* and *cis* isomers with a total yield of 93% and *dr* of 2.8:1. The trans isomer was obtained as colourless liquid (43 mg, 69%) and the cis isomer as a white crystalline solid (15 mg, 24%).



Analytical data of *trans* 34a

IR (neat) ν_{max}:3061, 3030, 1664, 1600, 1540, 1493, 695 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 4H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 4.12 (d, *J* = 14.0 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.81 (d, *J* = 2.5 Hz, 1H), 3.61 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 195.1, 140.1, 139.6, 138.6, 133.9, 129.2, 128.9, 128.9, 128.7, 128.0, 127.4, 126.9, 55.0, 49.3, 48.3.

HRMS (ESI) (m/z): Calcd for $C_{22}H_{20}NO$, $(M+H)^+$: 314.15449; Found: 314.15500.

Analytical data of *cis* 34a

MP: 88-90 ºC

IR (neat) ν_{max}: 3061, 3030, 16821598, 1495, 1449, 1222, 732, 694 cm^{-1}.

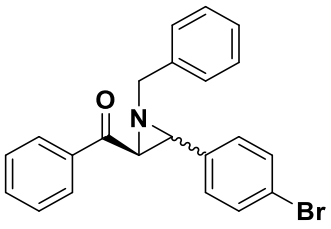
^{1}H NMR (500 MHz, CD_3CN): δ 7.92 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.58 – 7.55 (m, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 15.5, 7.5 Hz, 4H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.20 - 7.17 (m, 2H), 7.15 - 7.13 (m, 1H), 3.98 (d, *J* = 14.0 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.66 (d, *J* = 7.0 Hz, 1H), 3.47 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.6, 139.5, 137.4, 136.6, 133.8, 129.2, 128.9, 128.6, 128.5, 128.4, 128.1, 127.8, 127.7, 63.6, 52.1, 49.6.

HRMS (ESI) (m/z): Calcd for $C_{22}H_{20}NO$, $(M+H)^+$: 314.15449; Found: 314.15518.

(1-benzyl-3-(4-bromophenyl)aziridin-2-yl)(phenyl)methanone (34b)

The compound **34b** was synthesized following the procedure D using (*E*)-3-(4-bromophenyl)-1- phenylprop-2-en-1-one (58 mg, 0.20 mmol), benzylamine (43 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34b** were formed under the reaction conditions. Isolation by column chromatography afforded *trans* and *cis* isomers with a total yield of 83% and *dr* of 2.8:1. The *trans* isomer was obtained as colourless liquid ((48 mg, 61%) and the *cis* isomer as white crystalline solid (17 mg, 22%).



Analytical data of *trans* 34b

IR (neat) ν_{max}: 3088, 3061, 1663, 1593, 1535, 1488, 1070, 1009, 696 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.64 - 7.60 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 4H), 7.33 (t, *J* = 8.5 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 4.10 (d, *J* = 14.0 Hz, 1H), 3.97 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 2.5 Hz, 1H), 3.59 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 194.9, 139.9, 139.1, 138.5, 133.9, 131.9, 129.3, 129.0, 128.9, 128.7, 128.7, 127.5, 121.4, 117.9, 54.9, 48.5, 48.3.

HRMS (ESI) (m/z): Calcd for $C_{22}H_{19}BrNO$, $(M+H)^+$: 392.06500; Found: 392.06531, $(M+2)^+$: 394.06296; Found: 394.06335.

Analytical data of *cis* 34b

MP: 120 - 122 ^oC

IR (neat) ν_{max}: 3084, 3029, 1682, 1581, 1487, 1450, 1224, 734, 695 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.91 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.37 – 7.33 (m, 4H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.27 – 7.25 (m, 2H), 3.96 (d, *J* = 14.0 Hz,

1H), 3.76 (d, *J* = 14.5 Hz, 1H), 3.69 (d, *J* = 7.0 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.5, 139.3, 137.3, 135.9, 133.9, 131.3, 130.1, 129.2, 128.9, 128.6, 128.5, 127.8, 121.2, 63.4, 51.9, 48.9.

HRMS (ESI) (m/z): Calcd for $C_{22}H_{19}BrNO$, $(M+H)^+$: 392.06500; Found: 392.06622, $(M+2)^+$: 394.06296; Found: 394.06433.

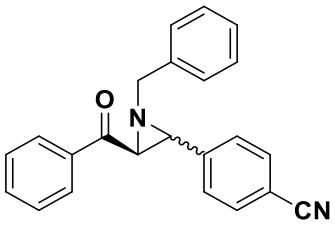
4-(3-benzoyl-1-benzylaziridin-2-yl)benzonitrile (34c)

The compound **34c** was synthesized following the procedure D using (*E*)-4-(3-oxo-3-phenylprop-1-en-1-yl)benzonitrile (47 mg, 0.20 mmol), benzylamine (43 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34c** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 48% and *dr* of 3.4:1. The *trans* isomer was obtained as colourless liquid (25 mg, 37%) and the *cis* isomer as white crystalline solid (7 mg, 11%).

Analytical data of *trans* 34c

IR (neat) ν_{max}: 3063, 3033, 2227, 1668, 1601, 1490, 1450, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 4.11 (d, *J* = 13.8 Hz, 1H), 3.98 (d, *J* = 13.9 Hz, 1H), 3.84 (d, *J* = 2.5 Hz, 1H), 3.69 (d, *J* = 2.3 Hz, 1H).



^{13}C NMR (126 MHz, CD_3CN): δ 194.5, 145.4, 139.8, 138.4, 134.1, 132.8, 129.3, 128.9, 128.8, 128.8, 127.9, 127.6, 119.3, 111.4, 54.9, 48.8, 48.4.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}N_2O$, $(M+H)^+$: 339.14974; Found: 339.15028.

Analytical data of *cis* 34c

MP: 84 - 86 ^{o}C

IR (neat) ν_{max}: 3061, 3031, 2227, 1682, 1607, 1497, 1224, 735, 696 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.90 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 4H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.78 (dd, *J* = 11.5, 4.0 Hz, 2H), 3.55 (d, *J* = 7.1 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 194.5, 145.4, 139.8, 138.4, 134.1, 132.8, 129.3, 128.9, 128.8, 128.8, 127.9, 127.6, 119.3, 111.4, 54.9, 48.8, 48.4.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{19}N_2O$, $(M+H)^+$: 339.14974; Found: 339.15020.

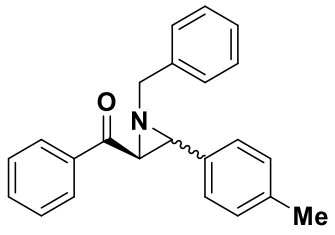
(1-benzyl-3-(*p*-tolyl)aziridin-2-yl)(phenyl)methanone (34d)

The compound **34d** was synthesized following the procedure D using (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one (45 mg, 0.20 mmol), benzylamine (43 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^{o}C. Both *trans* and *cis* isomers of **34d** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 68% and *dr* of 2.4:1. The *trans* isomer was obtained as colourless liquid (31 mg, 48%) and the *cis* isomer as white crystalline solid ((13 mg, 20%).

Analytical data of *trans* 34d

IR (neat) ν_{max}:3060, 3030, 1663, 1602, 1541, 1312, 693 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 7.0 Hz, 2H), 7.29 – 7.22 (m, 5H), 7.19 - 7.15 (m, 2H), 4.10 (d, *J* = 14 Hz, 1H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.79 (d, *J* = 2.5 Hz, 1H), 3.56 (d, *J* = 2.5 Hz, 1H), 2.33 (s, 3H).



^{13}C NMR (126 MHz, CD_3CN): δ 195.3, 140.2, 138.7, 137.8, 136.6, 133.9, 129.5, 129.2, 128.8, 128.7, 127.4, 126.9, 55.1, 49.4, 48.1, 20.8.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO$, $(M+H)^+$: 328.17014; Found: 328.17035.

Analytical data of *cis* 34d

MP: 110 - 112 ^oC

IR (neat) ν_{max}: 3060, 3029, 2977, 1681, 1598, 1495, 1177, 729, 696 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.92 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.58 - 7.55 (m, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.73 (d, *J* = 14.0 Hz, 1H), 3.62 (d, *J* = 7.0 Hz, 1H), 3.42 (d, *J* = 7.0 Hz, 1H), 2.23 (s, 3H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.7, 139.5, 137.6, 137.4, 133.8, 133.5, 129.2, 129.0, 128.9, 128.6, 128.5, 127.9, 127.7, 63.6, 52.1, 49.6, 20.6.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO$, $(M+H)^+$: 328.17014; Found: 328.17126.

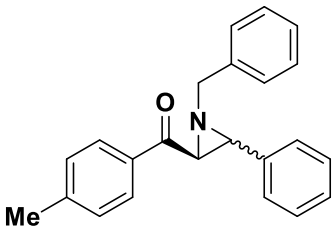
(1-benzyl-3-phenylaziridin-2-yl)(*p*-tolyl)methanone (34e)

The compound **34e** was synthesized following the procedure D using (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (45 mg, 0.20 mmol), benzylamine (43 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34d** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 72% and *dr* of 3.5:1. The *trans* isomer was obtained as colourless liquid (42 mg, 64%) and the *cis* isomer as white solid (12 mg, 18%).

Analytical data of *trans* 34e

IR (neat) ν_{max}: 3061, 3030, 2921, 1663, 1605, 1495, 1176, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 4H), 7.30 (d, *J* = 7.5 Hz, 3H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 4.09 (d, *J* = 14.0 Hz, 1H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 2.0 Hz, 1H), 3.59 (s, 1H), 2.40 (s, 3H).



^{13}C NMR (125 MHz, CD_3CN): δ 194.5, 145.0, 140.2, 139.7, 136.2, 129.9, 129.0, 128.9, 128.7, 127.9, 127.4, 126.9, 54.9, 49.1, 48.2, 21.3.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO$, $(M+H)^+$: 328.17014; Found: 328.17114.

Analytical data of *cis* 34e

MP: 98 - 100 °C

IR (neat) ν_{max}: 3061, 3029, 1680, 1605, 1495, 1177, 1091, 735, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.37 – 7.32 (m, 4H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.18 (m, 2H), 7.15 – 7.13 (m, 1H), 3.97 (d, *J* = 14.0 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.62 (d, *J* = 7.0 Hz, 1H), 3.43 (d, *J* = 7.0 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.0, 144.8, 139.5, 136.7, 134.9, 129.8, 128.9, 128.6, 128.6, 128.3, 128.0, 127.8, 127.7, 63.6, 52.1, 49.4.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO$, $(M+H)^+$: 328.17014; Found: 328.17059.

(1-(4-methoxybenzyl)-3-phenylaziridin-2-yl)(phenyl)methanone (34f)

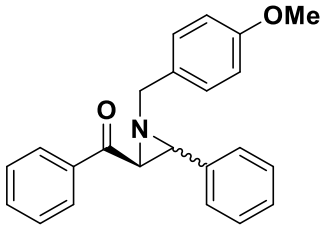
The compound **34f** was synthesized following the procedure D using (*E*)-chalcone (42 mg, 0.20 mmol), 4-methoxybenzylamine (55 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18

mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 °C. Both *trans* and *cis* isomers of **34f** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 88% and *dr* of 2.8:1. The *trans* isomer was obtained as colourless liquid (45 mg, 65%) and the *cis* isomer as pale yellow liquid (16 mg, 23%).

Analytical data of *trans* 34f

IR (neat) ν_{max}: 3059, 1663, 1607, 1512, 1247, 1175, 1028, 696 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.98 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* =8.0 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.02 (d, *J* = 13.5 Hz, 1H), 3.90 (d, *J* = 13.5 Hz, 1H), 3.77 (d, *J* = 2.5 Hz, 1H), 3.71 (s, 3H), 3.60 (d, *J* = 2.0 Hz, 1H).



^{13}C NMR (126 MHz, CD_3CN): δ 195.2, 159.2, 139.7, 138.7, 133.9, 132.0, 130.1, 129.2, 128.8, 128.8, 127.9, 126.9, 114.0, 55.3, 54.5, 49.2, 48.3.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO_2$, $(M+H)^+$: 344.16505; Found: 344.16592.

Analytical data of *cis* 34f

IR (neat) ν_{max}: 3060, 1665, 1610, 1512, 1250, 1177, 1209, 716, 698 cm^{-1}.

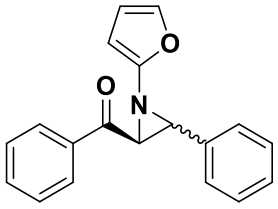
^{1}H NMR (500 MHz, CD_3CN): δ 7.91 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.58 - 7.54 (m, 1H), 7.46 - 7.40 (m, 4H), 7.33 - 7.31 (m, 2H), 7.20 - 7.16 (m, 2H), 7.14 - 7.11 (m, 1H), S33 6.91 - 6.88 (m, 2H), 3.91 (d, *J* = 13.0 Hz, 1H), 3.77 (s, 3H), 3.67 (d, *J* = 13.5 Hz, 1H), 3.63 (d, *J* = 7.0 Hz, 1H), 3.44 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.7, 159.5, 137.4, 136.6, 133.8, 131.7, 129.9, 129.2, 128.5, 128.3, 128.4, 127.8, 114.2, 63.0, 55.4, 51.9, 49.5.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{22}NO_2$, $(M+H)^+$: 344.16505; Found: 344.16544.

(1-(furan-2-ylmethyl)-3-phenylaziridin-2-yl)(phenyl)methanone (34g)

The compound **34g** was synthesized following the procedure D using (*E*)-chalcone (42 mg, 0.20 mmol), furfurylamine (39 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34g** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 82% and *dr* of 2.7:1. The *trans* isomer was obtained as colourless liquid (36 mg, 60%) and the *cis* isomer as pale yellow liquid (13 mg, 22%).



Analytical data of *trans* 34g

IR (neat) ν_{max}: 3032, 1672, 1599, 1448, 1266, 1176, 752, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.38 – 7.33 (m, 5H), 7.29 (t, *J* = 7.0 Hz, 1H), 6.26 – 6.25 (m, 1H), 6.13 (d, *J* = 3.0 Hz, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.80 (d, *J* = 3.0 Hz, 1H), 3.59 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 195.2, 153.6, 142.6, 139.3, 138.7, 133.9, 129.3, 128.9, 128.9, 128.1, 126.9, 110.8, 108.0, 49.4, 47.6, 47.5.

HRMS (ESI) (m/z): Calcd for $C_{20}H_{18}NO_2$, $(M+H)^+$: 304.13375; Found: 304.13355.

Analytical data of *cis* 34g

IR (neat) ν_{max}: 3121, 3060, 2928, 1698, 1598, 1448, 1013, 745, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.91 (dd, *J* = 90, 1.5 Hz, 2H), 7.59 - 7.55 (m, 1H), 7.48 - 7.43 (m, 3H), 7.30 (d, *J* = 7.0 Hz, 2H), 7.20 - 7.17 (m, 2H), 7.16 - 7.12 (m, 1H), 6.40 - 6.37 (m, 2H), 3.90 (d, *J* = 14.0 Hz, 1H), 3.75

(d, *J* = 14.0 Hz, 1H), 3.66 (d, *J* = 7.5 Hz, 1H), 3.48 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.5, 152.9, 143.0, 137.3, 136.4, 133.8, 129.2, 128.5, 128.4, 127.9, 127.8, 108.3, 55.7, 51.5, 49.2.

HRMS (ESI) (m/z): Calcd for $C_{20}H_{18}NO_2$, $(M+H)^+$: 304.13375; Found: 304.13462.

(1-cyclohexyl-3-phenylaziridin-2-yl)(phenyl)methanone (34h)

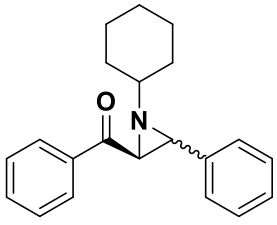
The compound **34h** was synthesized following the procedure D using (*E*)-chalcone (42 mg, 0.20 mmol), cyclohexylamine (55 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34h** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 90% and *dr* of 3.1:1. The *trans* isomer was obtained as crystalline solid (41 mg, 68%) and the *cis* isomer as white solid (13 mg, 22%).

Analytical data of *trans* 34h

MP: 89 - 91 ^oC

IR (neat) ν_{max}: 3062, 3031, 2928, 2854, 1667, 1598, 1495, 1222, 747, 698 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.38 - 7.34 (m, 4H), 7.29 (d, *J* = 6.0 Hz, 1H), 3.71 (s, 1H), 3.49 (s, 1H), 2.59 (s, 1H), 1.83 – 1.76 (m, 2H), 1.61 - 1.55 (m, 2H), 1.43 - 1.39 (m, 1H), 1.32 – 1.21 (m, 4H), 1.09-1.04 (m, 1H).



^{13}C NMR (126 MHz, CD_3CN): δ 195.2, 140.4, 138.8, 133.9, 133.9, 129.4, 128.9, 127.9, 127.1, 58.4, 48.3, 47.5, 33.4, 33.2, 26.4, 24.9, 24.6.

HRMS (ESI) (m/z): Calcd for $C_{21}H_{24}NO$, $(M+H)^+$: 306.18579; Found: 306.18625.

Analytical data of *cis* 34h

MP: 86 - 88 ^oC

IR (neat) ν_{max}: 3063, 3029, 2928, 2854, 1685, 1495, 1177, 737, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): **δ** 7.93 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.58 - 7.54 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J*=7.5 Hz, 2H), 7.21 - 7.18 (m, 2H), 7.15 – 7.12 (m, 1H), 3.48 (d, *J* = 7.0 Hz, 1H), 3.31 (d, *J* = 7.0 Hz, 1H), 1.97 - 1.81 (m, 4H), 1.76 - 1.71 (m, 1H), 1.64 - 1.61 (m, 1H), 1.54 - 1.45 (m, 2H), 1.37 -1.26 (m, 3H).

^{13}C NMR (126 MHz, CD_3CN): **δ** 193.9, 137.5, 137.3, 133.6, 129.1, 128.9, 128.3, 128.1, 127.7, 68.4, 50.7, 48.9, 32.8, 32.3, 26.5, 24.7, 24.7.

HRMS (ESI) (m/z): Calcd for $C_{21}H_{24}NO$, $(M+H)^+$: 306.18579; Found: 306.18643.

(1-isopropyl-3-phenylaziridin-2-yl)(phenyl)methanone (34i)

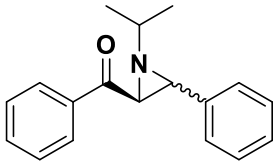
The compound **34i** was synthesized following the procedure D using (*E*)-chalcone (42 mg, 0.20 mmol), isopropylamine (24 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34i** were formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 87% and *dr* of 1.9:1. The *trans* isomer was obtained as colourless liquid (30 mg, 57%) and the *cis* isomer as pale yellow liquid (16 mg, 30%).

Analytical data of *trans* 34i

IR (neat) ν_{max}: 3068, 2976, 1666, 1644, 1175, 695 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): **δ** 8.09 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 3.73 (d, *J* = 1.5 Hz, 1H), 3.49 (d, *J* = 1.5 Hz, 1H), 2.94 - 2.89 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN): **δ** 195.1, 140.2, 138.8, 133.9, 129.4, 128.9, 127.9, 127.0, 50.8, 48.8, 48.1, 22.4.



HRMS (ESI) (m/z): Calcd for $C_{18}H_{20}NO$, $(M+H)^+$: 266.15449; Found: 266.15508.

Analytical data of *cis* 34i

IR (neat) ν_{max}:3062, 2969, 1681, 1598, 1451, 1225, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.94 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.57 – 7.55 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.1 Hz, 2H), 7.21 – 7.18 (m, 2H), 7.15 – 7.12 (m, 1H), 3.48 (d, *J* = 7.0 Hz, 1H), 3.31 (d, *J* = 7.5 Hz, 1H), 2.05- 2.00 (m, 1H), 1.22 (d, *J* = 1.5 Hz, 3H), 1.21 (d, *J* = 2.0 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.8, 137.5, 137.2, 133.6, 129.1, 128.5, 128.3, 128.1, 127.7, 61.1, 51.2, 49.4, 21.9, 21.6.

HRMS (ESI) (m/z): Calcd for $C_{18}H_{20}NO$, $(M+H)^+$: 266.15449; Found: 266.15458.

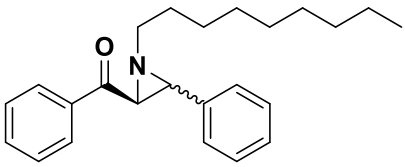
(1-nonyl-3-phenylaziridin-2-yl)(phenyl)methanone (34j)

The compound **34j** was synthesized following the procedure D using (*E*)-chalcone (42 mg, 0.20 mmol), nonylamine (58 mg, 0.4 mmol), I_2 (5 mg, 10 mol%) and TBHP (18 mg, 0.20 mmol) in ethyl acetate (2 mL) at 40 ^oC. Both *trans* and *cis* isomers of **34j** was formed under the reaction conditions. Isolation by column chromatography gave *trans* and *cis* isomers with a total yield of 92% and *dr* of 2.7:1. The *trans* isomer was obtained as colourless liquid (47 mg, 67%) and the *cis* isomer as pale yellow liquid (17 mg, 25%).

Analytical data of *trans* 34j

IR (neat) ν_{max}: 3060, 3030, 2954, 1666, 1600, 1492, 714, 697 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.30 (m, 4H), 7.28 (t, *J* = 7.0 Hz, 1H), 3.67 (d, *J* = 1.5 Hz, 1H), 3.38 (s, 1H), 2.82 – 2.71 (m, 2H), 1.50 - 1.46



(m, 1H), 1.41 - 1.36 (m, 1H), 1.30 – 1.19 (m, 12H), 0.87 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN): δ 194.9, 140.0, 138.6, 133.9, 129.3, 128.9, 127.9, 126.9, 51.6, 48.9, 48.2, 32.2, 30.4, 29.7, 29.5, 27.5, 22.9, 13.9.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{32}NO$, $(M+H)^+$: 350.24839; Found: 350.24895.

Analytical data of *cis* 34j

IR (neat) ν_{max}:2925, 2854, 1685, 1599, 1493, 1224, 698 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.92 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.15 – 7.12 (m, 1H), 3.43 (d, *J* = 7.0 Hz, 1H), 3.24 (d, *J* = 7.0 Hz, 1H), 2.79 - 2.74 (m, 1H), 2.51 - 2.45(m, 1H), 1.67 – 1.61 (m, 2H), 1.48 - 1.42 (m, 2H), 1.35 – 1.28 (m, 10H), 0.90 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, CD_3CN): δ 193.9, 137.6, 136.9, 133.6, 129.1, 128.5, 128.3, 128.1, 127.7, 60.6, 51.8, 49.8, 32.2, 29.9, 29.8, 29.6, 27.6, 22.9.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{32}NO$, $(M+H)^+$: 350.24839; Found: 350.24848.

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One-pot Synthesis of Benzo[*d*]imidazo[2,1-*b*]thiazoles Tethered with Indole Under Metal-free Conditions

4.1. Abstract

Benzo[*d*]imidazo[2,1-*b*]thiazoles are potential synthetic targets owing to its multifaceted applications in various fields of science. We have developed a two-step, one-pot method for the synthesis of highly functionalized benzo[*d*]imidazo[2,1-*b*]thiazoles under metal-free conditions. This protocol gives access to indole tethered, fused heterocycles from easily available substrates. Interestingly, the reaction involves an unusual 1,2-migration of an indole nucleus along with a C_{α}-C_{β} bond cleavage.

4.2. Introduction

Fused bicyclic molecules containing heterocyclic ring systems are compounds of greater prominence in organic chemistry.[1] Various molecules belonging to this class constitute the core unit of many natural alkaloids and pharmaceutically active compounds. Among them sulfur and nitrogen containing molecules have gained greater attention from organic chemists.[2,3,4] Benzo[*d*]imidazo[2,1-*b*]thiazoles are one of the important fused bicyclic scaffolds belonging to this category and are associated with profound biological profile (**Figure 4.1**). For example, Benzo[*d*]imidazo[2,1-*b*]thiazole derivative **(I)** is a potent antitumor agent which is found to be orally active and are effective in the treatment of solid tumor. Benzo[*d*]imidazo[2,1-*b*]thiazole analogue **(II)** possesses antiallergic property and ^{11}C-labelled compound (**III**) is used as flouroprobe in PET imaging of Alzheimer's patients brain.[5,6] Furthermore, compound (**IV**) is an active kinase inhibitor and indole appended analogue (**VI**) is an antimicrobial agent.[7,8] Moreover, derivative (**V**) is a FMS-related tyrosine kinase-3 inhibitor and is in phase II clinical trials.[9] Apart from the biomedical utility, benzothiazole fused imidazole derivatives serve as useful building blocks in organic synthesis and are attractive structural entities in material sciences as well.[10]

On the other hand, indole is a privileged heterocycle endowed with broad spectrum of biological properties.[11] Indole and related analogues have garnered special attention in the scientific field owing to its significance in multiple disciplines. It is a key structural component of various pharmaceuticals, agrochemicals and natural products.[12,13] Thus, incorporation of indole unit into biologically attractive heterocyclic cores such as benzo[*d*]imidazo[2,1-*b*]thiazole can provide novel molecular templates of valuable pharmacological profile. Synthesis and exploration of such molecular hybrids are nowadays getting huge attention from the scientific community. Hence such interventions are anticipated to enrich the field of medicinal chemistry research and pave the path to drug discovery.

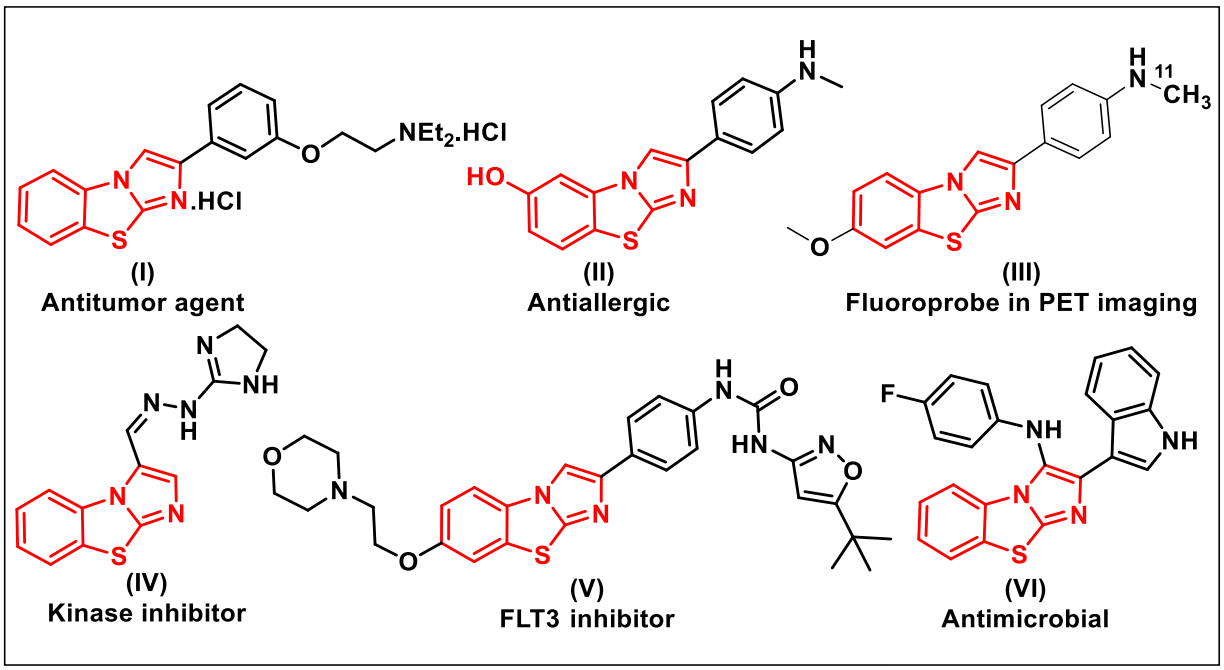
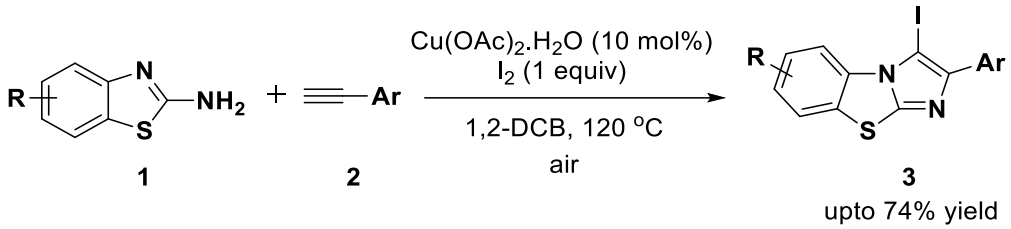


Figure 4.1. Biologically active benzo[*d*]imidazo[2,1-*b*]thiazole derivatives

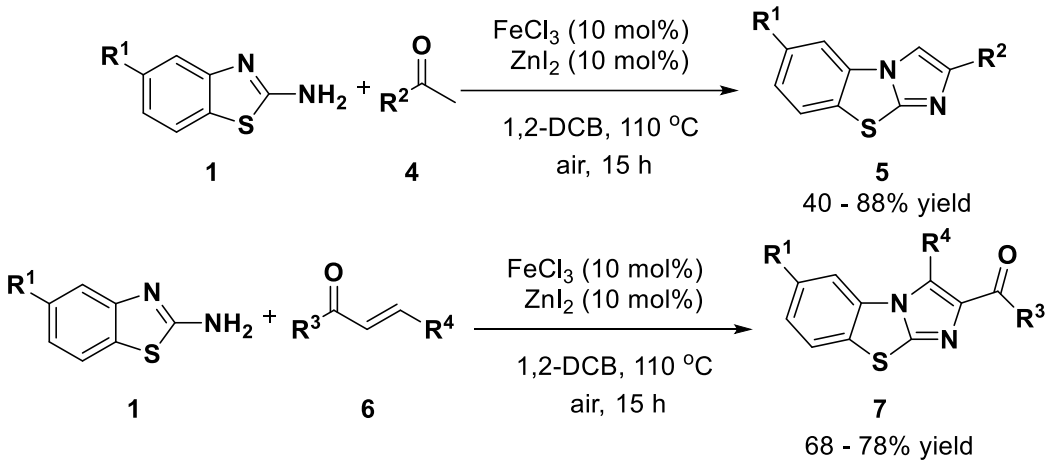
4.3. Synthetic approaches towards benzo[*d*]imidazo[2,1-*b*]thiazole

The biological properties displayed by various derivatives of benzo[*d*]imidazo[2,1-*b*]thiazole has inspired synthetic organic chemist to develop novel protocols to access this fused bicyclic heterocyclic scaffold. In 2013 Samanta *et al*. reported a copper catalyzed synthesis of 2-iodobenzoimidazothiazoles **3** from 2-aminobenzothiazole **1** and aryl alkynes **2** under air atmosphere.[14] The reaction afforded a single regioisomer, 2-iodo derivative, under the optimized reaction conditions.



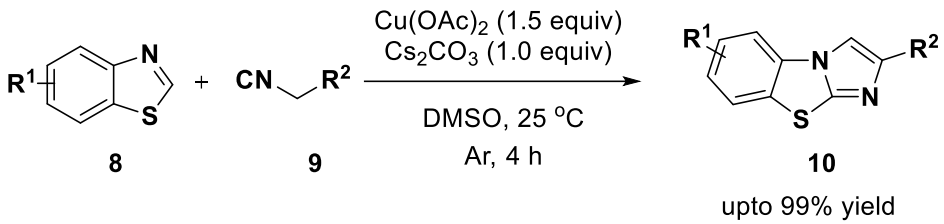
Scheme 4.1. Copper catalyzed synthesis of 2-iodobenzoimidazothiazoles.

In 2014 Mishra *et al*. developed an oxidative amination reaction of aryl methyl ketones **4** with 2-aminobezothiazoles **1** for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles **5**.[15] This oxidative C-H functionalization reaction proceeds in the presence of $FeCl_3/ZnI_2$ catalytic system. The reaction is also compatible with chalcone **6** as the coupling partner, which delivered 2-aroylbenzo[*d*]imidazo[2,1-*b*]thiazoles.



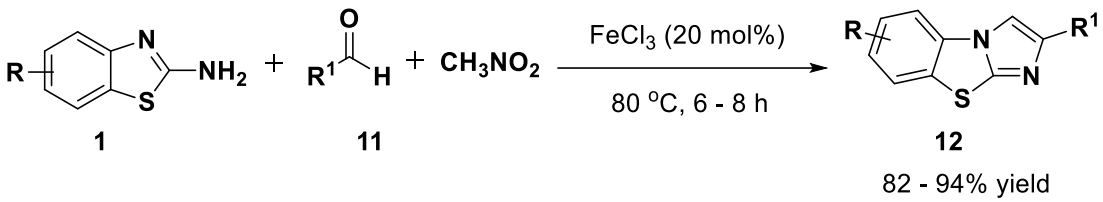
Scheme 4.2. Iron catalyzed synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole.

Later Wang *et al*. disclosed a $Cu(OAc)_2$ and Cs_2CO_3 promoted synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole derivatives **10** under mild reaction conditions.[16] It is a cycloaddition reaction between *α*-methylenyl isocyanide **9** and benzothiazole **1** at room temperature. The reaction involves an unusual rearrangement which proceeds through a C-S bond cleavage and formation of new C-S bond.



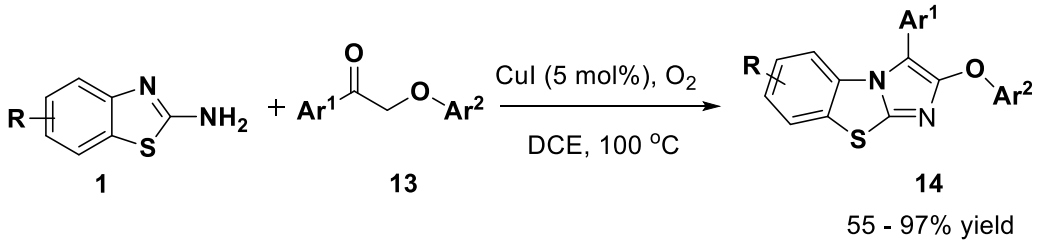
Scheme 4.3. $Cu(OAc)_2$ mediated of benzo[*d*]imidazo[2,1-*b*]thiazole synthesis.

Using $FeCl_3$ as catalyst, a solvent free multicomponent reaction was reported in 2016.[17] The methodology utilizes 2-aminobenzothiazoles **1**, aryl aldehydes **11** and nitromethane as the substrates to afford benzo[*d*]imidazo[2,1-*b*]thiazoles **12**. The reaction which proceeds under air atmosphere involves condensation reaction between 2-aminobenzothizole and aldehyde followed by nucleophilic attack of nitromethane forming the aza-Henry product. Subsequent intramolecular cyclization and denitration affords the final product.



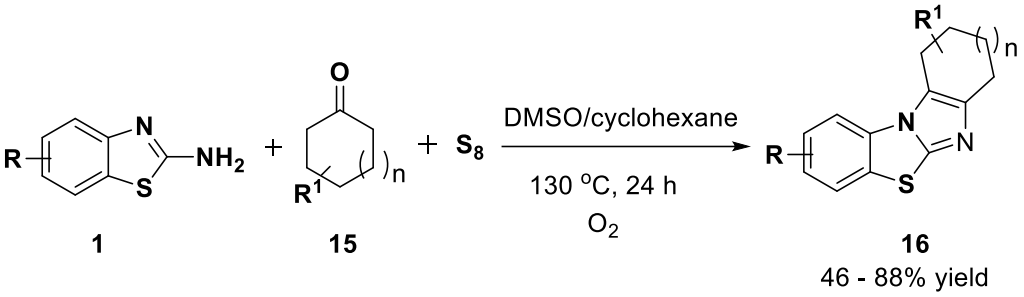
Scheme 4.4. $FeCl_3$ catalyzed multicomponent reaction for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole.

In 2017 a copper catalyzed synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles **14** tethered with oxophenyl group was unravelled by Zhang *et al*.[18] They have used lignin derived compound **13** as the coupling partner for 2-aminobenzothiazole **1** to accomplish the reaction. The protocol requires molecular oxygen for the regeneration of the copper catalyst during the reaction. The sole byproduct formed in the reaction is water.



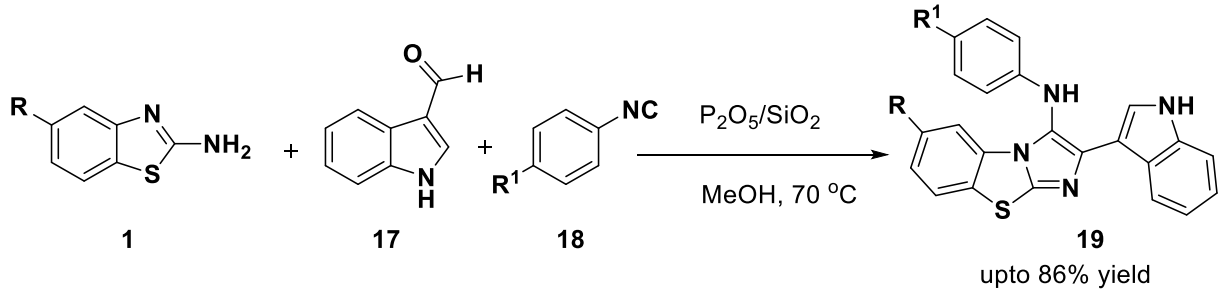
Scheme 4.5. Synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles tethered with oxophenyl group.

In the same year Xie *et al*. developed an oxidative cyclization reaction of 2-aminobenzothiazoles **1** with cyclic ketones **15** in the presence of elemental sulfur.[19] The reaction is performed in the presence of oxygen which act as a co-oxidant to afford the fused bicyclic molecule **16** in high yield. The efficiency of this synthetic transformation is highly influenced by the solvent system, which is a mixture of cyclohexane and DMSO.



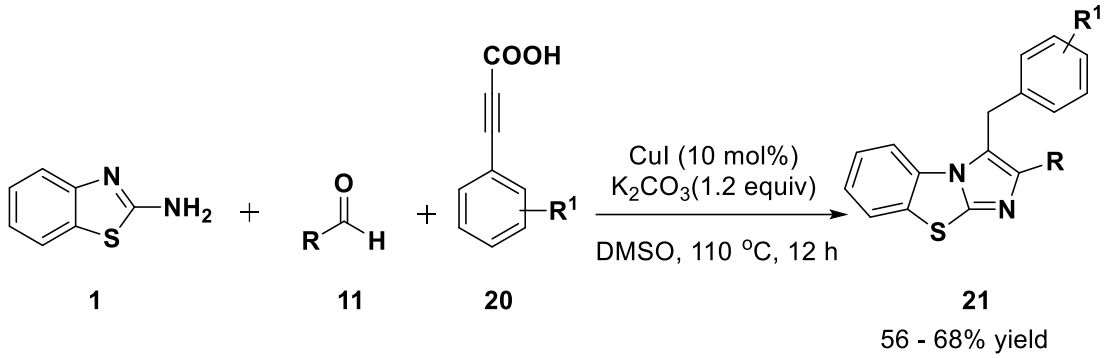
Scheme 4.6. Elemental sulfur mediated synthesis of benzothiazole fused imidazole.

In 2018, a one-pot strategy for the synthesis of 3-aminoimidazo[2,1-*b*](1,3)benzothiazoles **19** bearing an indole at the C2 carbon was reported.[20] The reaction is carried out in the presence of a heterogeneous catalyst, P_2O_5 supported on SiO_2. The substrates used for the reaction are 2-aminobenzothiazole **1**, indole-3-carboxaldehyde **17** and aryl isocyanide **18**.



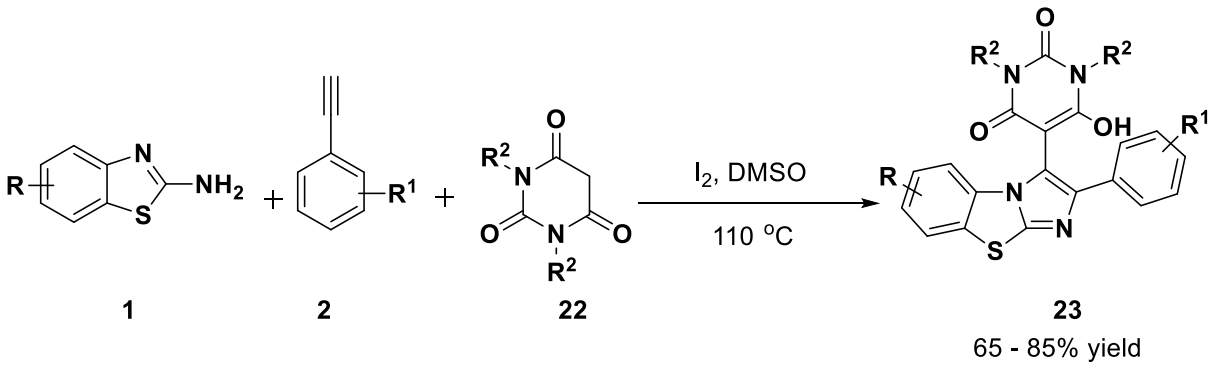
Scheme 4.7. Multicomponent synthesis of 3-aminoimidazo[2,1-*b*](1,3)benzothiazoles.

Later in 2019, Wu *et al*. disclosed a CuI catalyzed multicomponent reaction for the construction of 2,3-disubstituted benzo[*d*]imidazo[2,1-*b*]thiazoles **21** from 2-aminobenzothiazoles **1**, aldehydes **11** and alkynecarboxylic acids **20**.[21] The protocol involves condensation, decarboxylation, A^3 coupling and 5-exo-dig-cyclization reaction. This one pot multicomponent reaction requires K_2CO_3 as an additive to furnish the product.



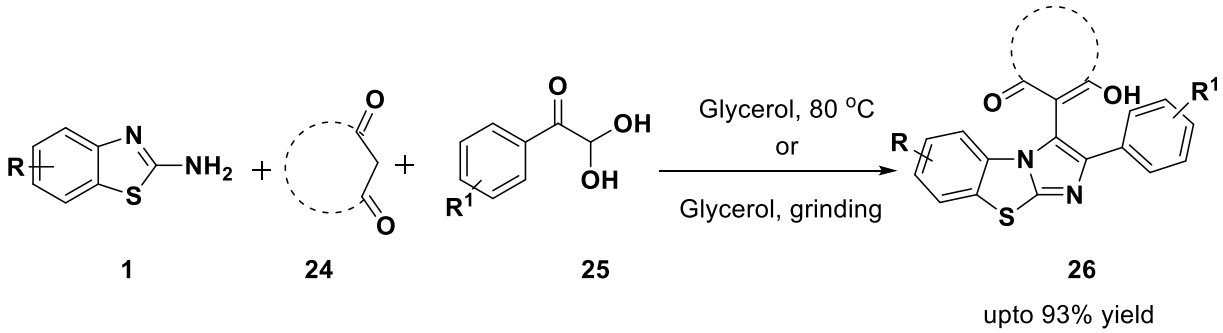
Scheme 4.8. CuI catalyzed synthesis of 2,3-disubstituted benzo[*d*]imidazo[2,1-*b*]thiazoles.

In the same year an I_2/DMSO mediated multicomponent reaction for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole **23** bearing barbituric acid was reported by Jana *et al*.[6] The reaction utilizes barbituric acid **22**, 2-aminobenzothiazole **1** and aryl alkynes **2** or aryl methyl ketones as the substrates. It is an oxidative cyclization reaction which can be performed either under conventional heating or microwave irradiation.



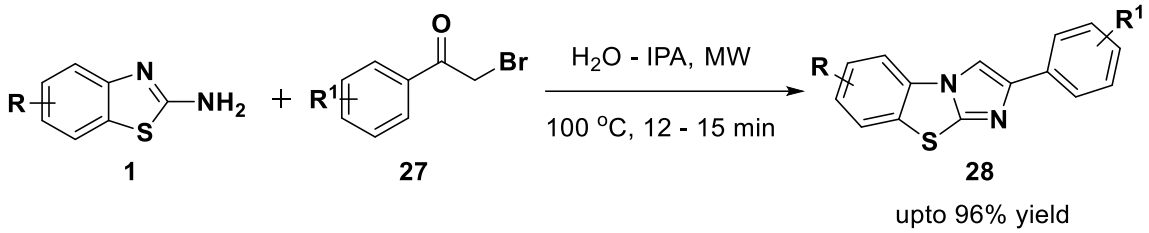
Scheme 4.9. I_2/DMSO mediated synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole.

Meena *et al*. devised a three component reaction involving phenyl glyoxal **25**, 2-aminobenzothiazole **1** and cyclic 1,3-diketone **24** under catalyst free conditions which furnishes multifunctionalized benzo[*d*]imidazo[2,1-*b*]thiazoles **26** in excellent yield.[22] The reaction can be performed under heating condition or by grinding, using ethylene glycol or ethanol as solvent. High yield, shorter reaction time and environmentally benign conditions are the notable features of this multicomponent strategy.



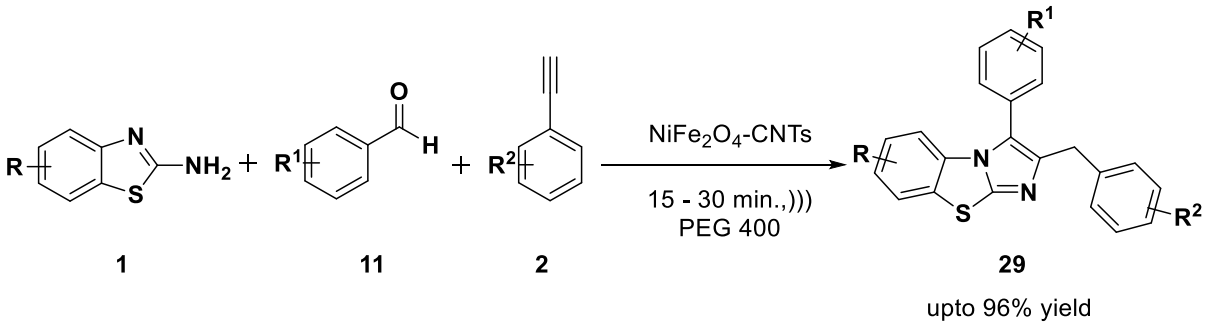
Scheme 4.10. Catalyst free synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole.

Recently, a transition metal free synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles **28** from *α*-haloketones **27** and 2-aminobenzothiazoles **1** in water was reported by Mukku *et al*.[23] This heteroannulation reaction proceeds under microwave irradiation and does not require column chromatographic purification. It is an environmentally benign protocol which gives ready access to the fused heterocycles within a shorter reaction time of about 15 minutes.



Scheme 4.11. Synthesis of benzo[*d*]imidazo[2,1-*b*] under microwave irradiation.

Geedkar *et al*. introduced a sonication assisted multicomponent reaction of 2-aminobenzothiazoles **1** with arylaldehydes **11** and terminal alkynes **2** under heterogeneous catalysis for the preparation of functionalized benzothiazole fused imidazole **29**.[24] They have used multi-walled carbon nanotubes bearing nickel-ferrite magnetic nanoparticles ($NiFe_2O_4$-CNTs) as the catalyst to accomplish the synthesis. The protocol involves condensation reaction, A^3 coupling and 5-*exo*-dig cyclization reaction.

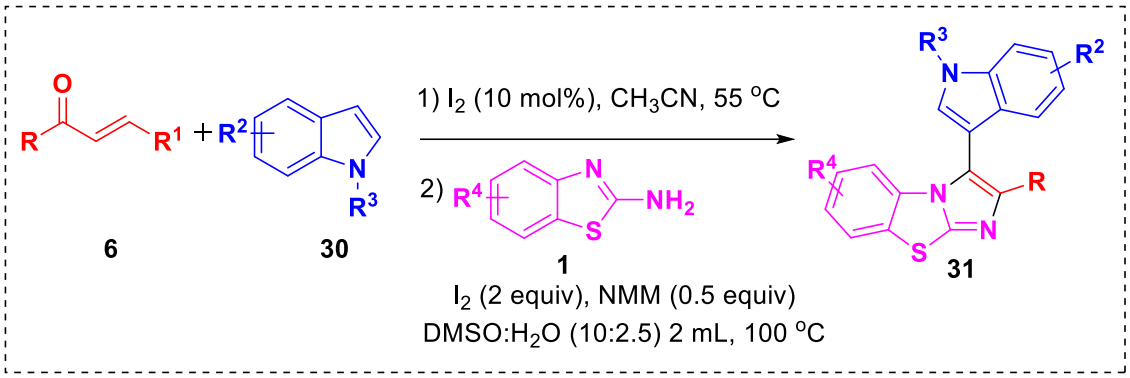


Scheme 4.12. Sonication assisted synthesis of benzothiazole fused imidazole.

4.4. Background to the present work

Despite the multifaceted significance of benzo[*d*]imidazo[2,1-*b*]thiazoles in different areas of science, medicinal chemistry in particular, only few methods are developed for its synthesis. Especially, protocols for the synthesis of highly functionalized benzothiazole fused imidazoles are less in numbers. From the literature survey it is evident that most of the methods reported has either used transition metal catalysts or expensive starting materials. Moreover, till now there is only a single protocol reported for the synthesis of benzothiazole fused imidazole bearing indole ring. This reaction affords the product with indole at C2 carbon atom.[20] Interestingly, there is no protocol developed so far, to construct benzo[*d*]imidazo[2,1-*b*]thiazole tethered with an indole nucleus at the C3 carbon. Thus, any synthetic approach which gives access to such an attractive structural framework from easily available substrates are always desirable.

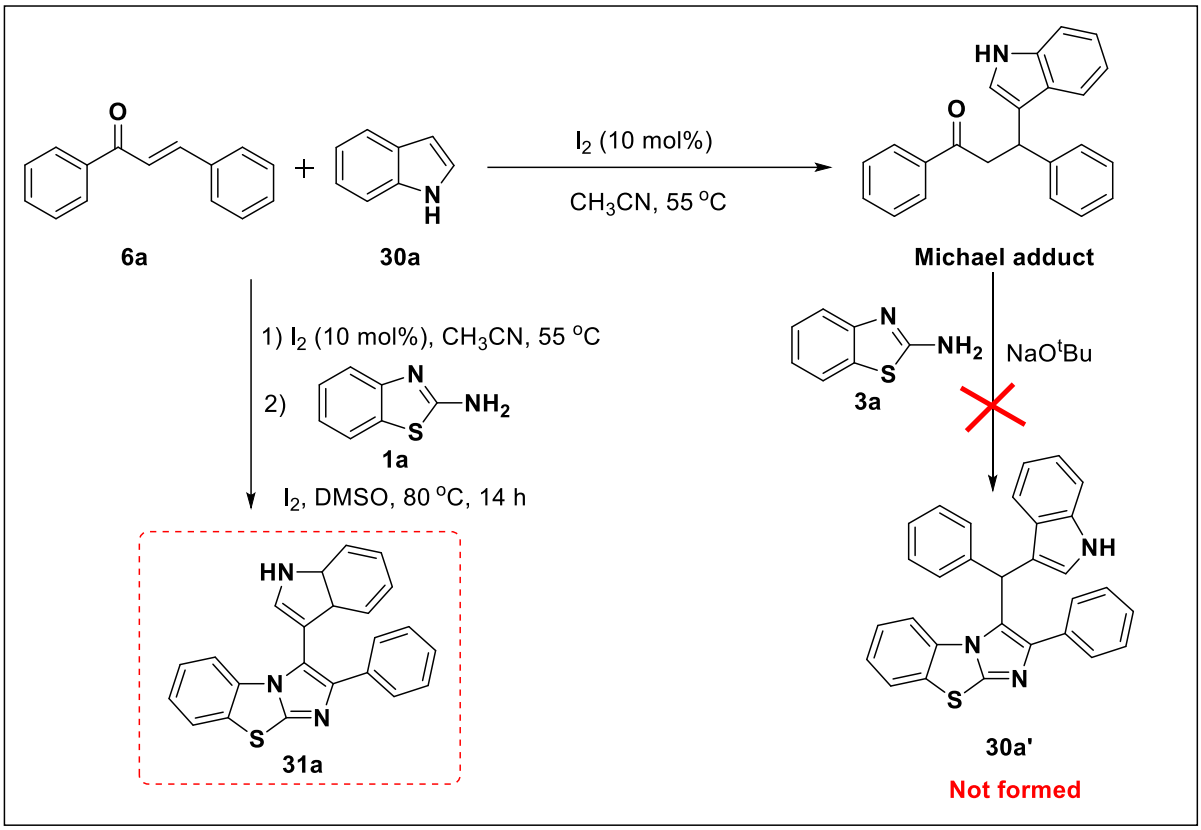
Owing to the pharmacological potential offered by fused heterocyclic nuclei in drug discovery process, we have developed a transition metal free, two step one-pot protocol for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole tethered with an indole nucleus. We have used readily accessible substrates such as *α,β*-unsaturated ketones, 2-aminobenzothiazoles and indoles for the reaction. Interestingly our protocol involves an unusual 1,2- indole migration.



Scheme 4.13. Two step, one-pot synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole.

4.5. Results and discussion

Inspired by the high biological profile associated with benzo[*d*]imidazo[2,1-*b*]thiazole and indole nucleus, we targeted the synthesis of benzothiazole fused imidazole bearing an indole nucleus. For our study we have selected chalcone **6a** as our starting material. Since, chalcone can easily undergo Michael addition reaction with indole in the presence of catalytic amount of iodine, which is an already established reaction, we have anticipated that sequential addition of 2-aminobenzothiazole **1a** to the reaction mixture in the presence of a base such as NaO^{t}Bu may furnish 3-((1*H*-indol-3-yl)(phenyl)methyl)benzo[*d*]imidazo[2,1-*b*]thiazole **30a′**. However, to our dismay the reaction failed to furnish the targeted product. Next, we tried an I_2/DMSO condition at an elevated temperature of 80 °C, which is suitable for the *α*-iodination, so that cyclocondensation reaction will be more feasible. The reaction was carried out in such a way that, we have added 2-aminobenzothiazole to the reaction mixture without the isolation of the Michael adduct, just by evaporating off the acetonitrile. It was then followed by the addition of 1 equivalent of molecular iodine and 2 mL of DMSO. After stirring the reaction at 80 °C for 14 hours we observed the formation of a product (**Scheme 4.14**). Interestingly, during the characterization studies using various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and mass spectrometry, we found that the indole is migrating from *β* carbon to *α* carbon along with a C_α-C_β bond cleavage.



Scheme 4.14. Preliminary observations

From the ^{1}H NMR it is evident that the product contains only aromatic protons which appeared in the range of δ 6.79 – 7.68 (**Figure 4.2**). The indole N-H appeared as a singlet at δ 9.06. Importantly, spectral interpretations point out that peaks corresponding to protons of an aromatic ring are missing from the ^{1}H NMR. Similarly, both *β* carbon and carbon atoms of phenyl ring attached to the *β* carbon are not observed in the ^{13}C NMR spectrum of **31a**. Moreover, the HRMS analysis was also in good agreement with the observation. From the spectroscopic interpretation the structure of the product was confirmed as 3-(1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole **31a**.

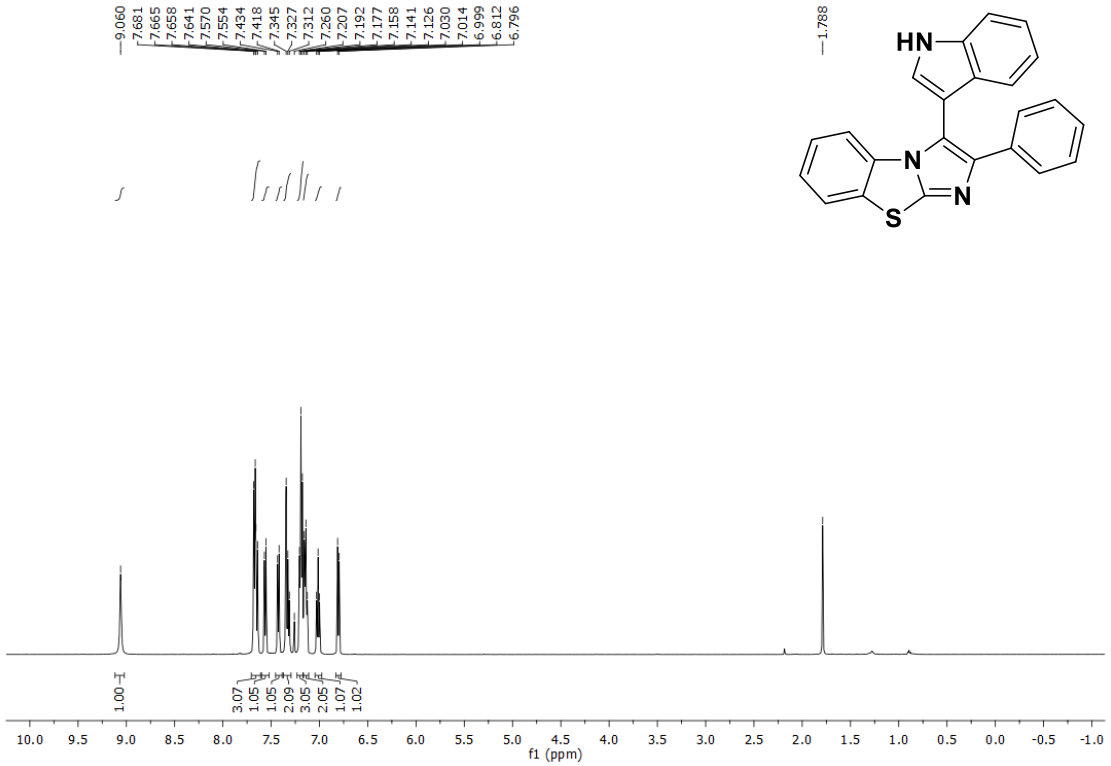


Figure 4.2. ^{1}H NMR of **31a**

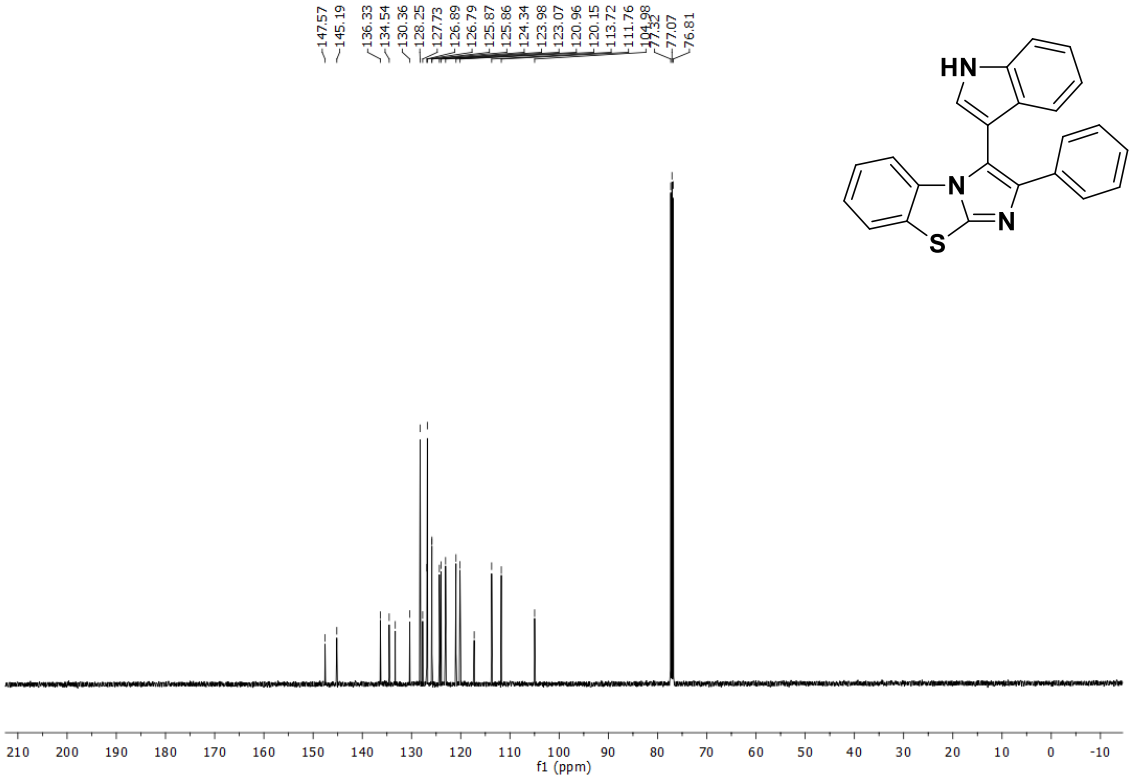
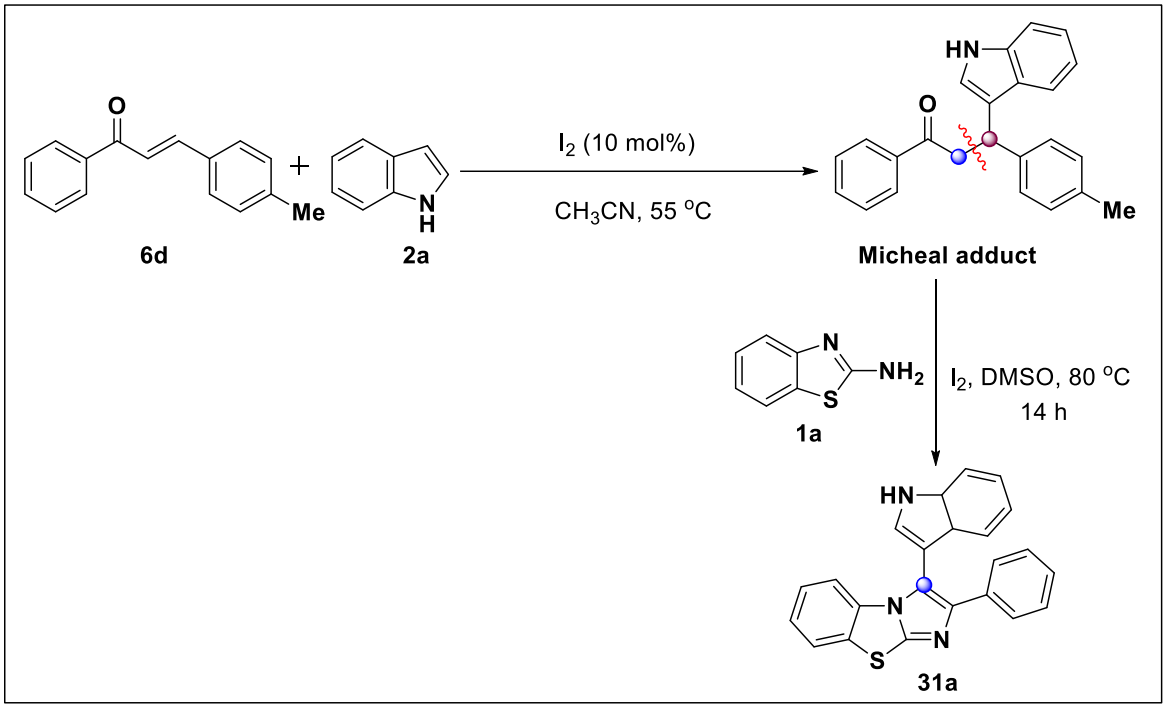


Figure 4.3. ^{13}C NMR of **31a**

To further confirm the loss of the phenyl ring associated with β carbon, we have performed a reaction using chalcone bearing methyl group at the phenyl ring attached to the double bond (**Scheme 4.15**). The product thus obtained had identical ^{1}H NMR and ^{13}C NMR spectra. Moreover, the structure of the product was unambiguously confirmed using single crystal X- ray analysis of the analogue **31b** (**Figure 4.4**).



Scheme 4.15. Structural characterization studies.

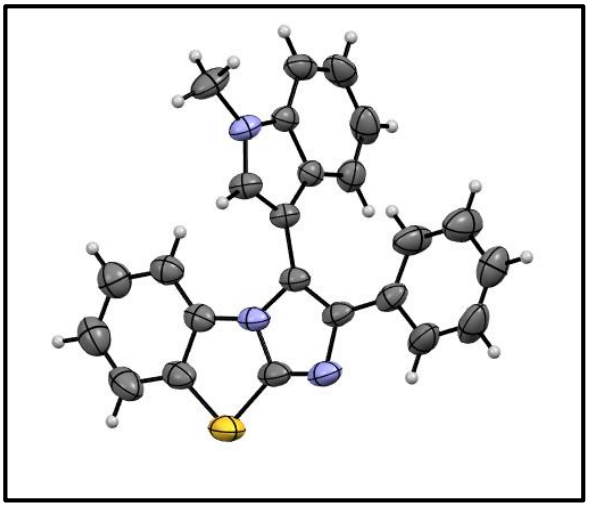
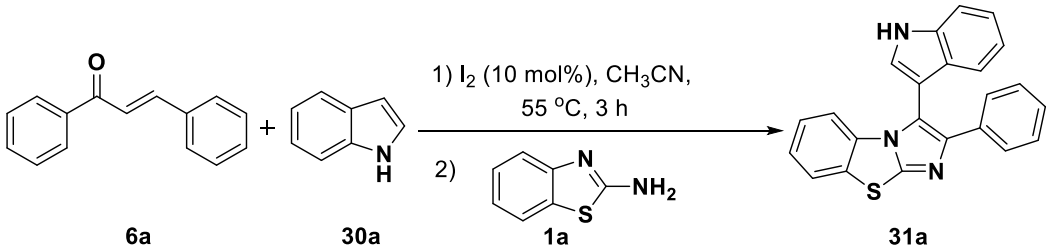


Figure 4.4. Single crystal X-ray structure of **31b** (**CCDC 2177316**).

After confirming the structure of the product, we commenced optimization of the reaction conditions by taking chalcone **6a**, 1*H*-indole **30a** and 2-aminobenzothiazole **1a** as the model substrates (**Table 4.1**). Initially the reaction was carried out in DMSO in the presence of 1 equiv of molecular iodine at 80 ^{o}C and the product **31a** was obtained in 23% yield (entry 1). On decreasing the temperature to 70 ^{o}C, there was no increment in the yield of the reaction (entry 2). But an increase in the temperature to 100 ^{o}C resulted in 33% yield (entry 3). Next, we carried out screening of various solvents, which includes 1,4-dioxane, toluene, DMF and DMA. It was found that DMSO is inevitable for the reaction to proceed. An evaluation of various iodine sources such as TBAI, NIS and PIDA failed to afford the product in better yield compared to that of I_2. When we increased the equivalents of iodine from 1 to 2, an enhancement in the reactivity was observed (entry 11). Further, we tried an inert atmosphere for the reaction, using dry DMSO under argon supply. Interestingly, a sudden decline in the product yield to 16% was observed (entry 12). This indicated that some amount of water is also necessary for the reaction to commence smoothly. Thus, effect of a mixture of DMSO and H_2O on the efficiency of the reaction was investigated. To our delight, a mixture of 10/2.5 mL (v/v) of DMSO/H_2O (80% DMSO/H_2O mixture) turned out to be crucial in the formation of the product with better yield (entry 15). Further, we studied influence of various bases on the reactivity of the substrates. Initially, inorganic base, Cs_2CO_3 was used for the optimization, which failed to afford the product even in trace quantity (entry 17). Later, a screening of organic bases such as DBU, DBN, DMAP, Et_3N, morpholine, *N*-methylmorpholine (NMM), 2,6-luitidine etc. was conducted. To our delight, addition of 0.5 equivalents of *N*-methylmorpholine resulted in a maximum yield of 63% (entry 23). Additionally, different equivalents of *N*-methylmorpholine was also evaluated. But 50 mol% was turned out to be suitable for better result. Moreover, an increment in the 2-aminobenzothiazole loading was found to be detrimental for the reaction (entry 29).

Table 4.1. Optimization of reaction conditions [a]



Iodine source, Temperature, solvent

Sl.No.	Iodine source	Solvent	Base	Temperature [°C]	Yield [%][b]
[c]1	I_2	DMSO	-	80	23
[c]2	I_2	DMSO	-	70	23
[c]3	I_2	DMSO	-	100	33
[c]4	I_2	1,4-Dioxane	-	100	ND
[c]5	I_2	Toluene	-	100	ND
[c]6	I_2	DMF	-	100	ND
[c]7	I_2	DMA	-	100	ND
8	TBAI	DMSO	-	100	ND
9	NIS	DMSO	-	100	Trace
10	PIDA	DMSO	-	100	Trace
11	I_2	DMSO	-	100	45
[d]12	I_2	DMSO	-	100	16
13	I_2	DMSO:H_2O (10:1)	-	100	34
14	I_2	DMSO:H_2O (10:2)	-	100	40
15	I_2	DMSO:H_2O (10:2.5)	-	100	46
16	I_2	DMSO:H_2O (10:3)	-	100	31
17	I_2	DMSO:H_2O (10:2.5)	Cs_2CO_3	100	ND
18	I_2	DMSO:H_2O (10:2.5)	DBU	100	43
19	I_2	DMSO:H_2O (10:2.5)	DBN	100	41
20	I_2	DMSO:H_2O (10:2.5)	DMAP	100	59
21	I_2	DMSO:H_2O (10:2.5)	Et_3N	100	53
22	I_2	DMSO:H_2O (10:2.5)	Morpholine	100	55

Table 4.1. continues…….

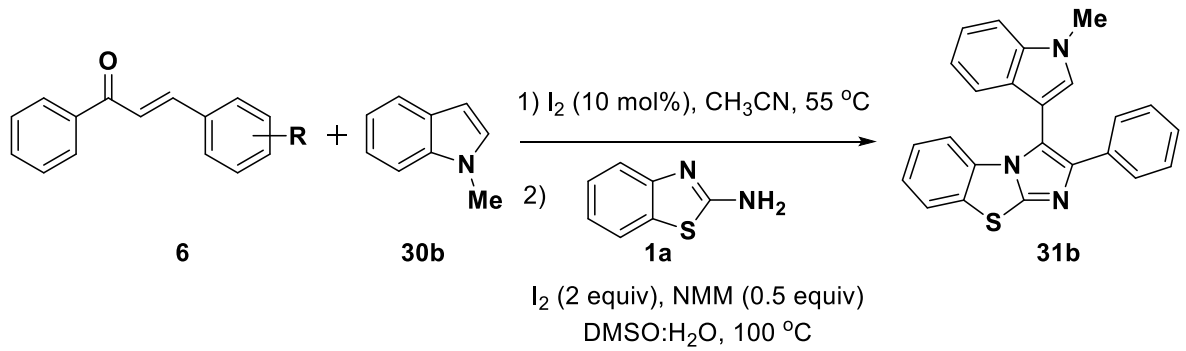
Sl.No.	Iodine source	Solvent	Base	Temperature [°C]	Yield [%]
23	I_2	DMSO:H_2O (10:2.5)	*N*-Methylmorpholine	100	63
24	I_2	DMSO:H_2O (10:2.5)	2,6-Lutidine	100	56
25	I_2	DMSO:H_2O (10:2.5)	Piperidine	100	52
26	I_2	DMSO:H_2O (10:2.5)	TMEDA	100	54
[e]27	I_2	DMSO:H_2O (10:2.5)	*N*-Methylmorpholine	100	52
[f]28	I_2	DMSO:H_2O (10:2.5)	*N*-Methylmorpholine	100	53
[g]29	I_2	DMSO:H_2O (10:2.5)	*N*-Methylmorpholine	100	48

[a] Reaction conditions: **6a** (0.25 mmol), **30a** (0.25 mmol), **1a** (0.25 mmol), Iodine source (0. 50 mmol), base (0.125 mmol), solvent (2 mL), dry DMSO is used in the preparation of solvent mixture. [b] Yield of the product isolated. [c] I_2 (0.25 mmol, 1 equiv). [d] used dry DMSO (2 mL). [e] *N*-Methylmorpholine (1 equiv). [f] *N*-methylmorpholine (0.4 eqiv.). [g] **1a** (2 equiv)

Since there is a C_α-C_β bond cleavage, along with the loss of phenyl ring attached to the β carbon, we assume that it is cleaving apart as benzaldehyde. Hence, we sought to study the effect of various substituents present on the phenyl ring of the chalcone on the C-C bond cleavage and leaving ability of substituted benzaldehydes (**Table 4.2**). From a detailed analysis of various α,β -unsaturated ketones bearing both electron donating and electron withdrawing substituents, we found that better yield is obtained for the unsubstituted phenyl ring (entry 1).

With the optimized conditions in hand, we investigated the scope of *N*-protected indoles for the present synthetic transformation (**Table 4.3**). *N*-methyl, allyl and benzyl indoles were found to be compatible under the optimized reaction conditions. Among them, *N*-methyl indole and *N*-benzyl indole afforded the desired products (**31b** and **31d**) in a better yield of 69%. Apart from *N*-alkyl indoles, 1*H*-indole protected with an aryl group also successfully underwent the reaction (**31e**). Next, we studied the effect of various substituents present at different positions on the indole ring. Fortunately, 1*H*-indole bearing both electron donating (Me and OMe) as well as electron withdrawing substituents (F, Cl and Br) could afford the desired products (**31e – 31o**) under the optimized conditions. It is noteworthy that, regardless of the position of the substituent, all the substrates were found to be suitable for this protocol.

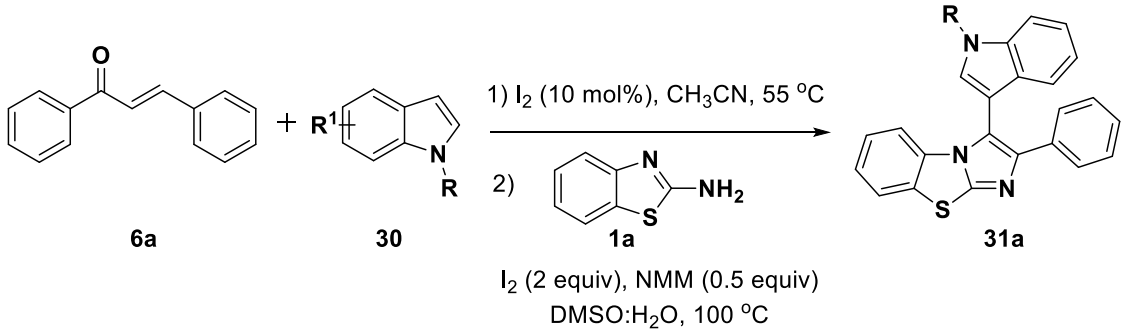
Table 4.2. Evaluation of electronic effect of substituents present on the phenyl ring



Sl.No.	R	Yield [%]
1	**4-H**	69
2	**4-F**	64
3	**4-Br**	47
4	**4-Cl**	55
5	**4-CF_3**	42
6	**4-NO_2**	67
7	**4-CN**	ND
8	**4-Me**	47
9	**2-OMe**	37
10	**4-OH**	ND

Reaction conditions: **6** (0.25 mmol), **30b** (0.25 mmol), **1a** (0.25 mmol), I_2 used in second step (0.50 mmol), NMM (0.125 mmol), DMSO: H_2O (10: 2.5, 2 mL), 100 °C, 14 h.

Table 4.3. Scope of indole



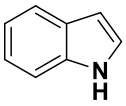
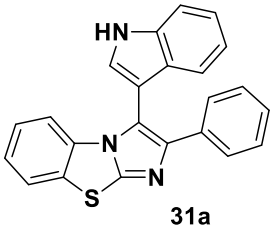
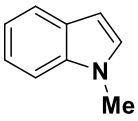
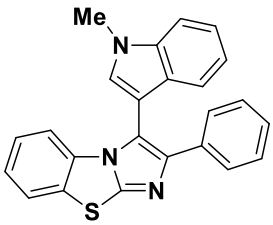
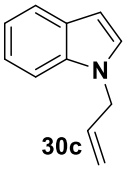
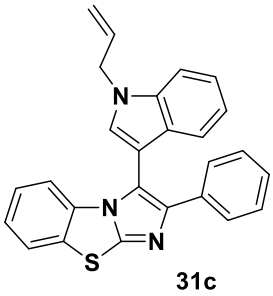
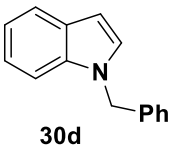
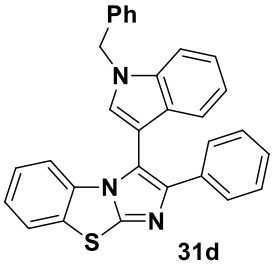
Sl.No.	Indole	Product	Yield [%]
1.	 30a	 31a	63
2.	 30b	 31b	69
3.	 30c	 31c	56
4.	 30d	 31d	69

Table 4.3. continues…….

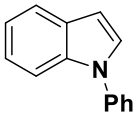
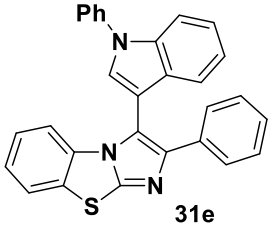
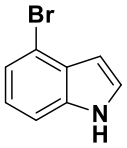
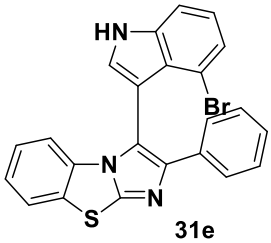
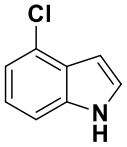
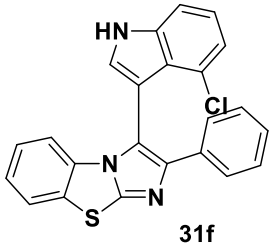
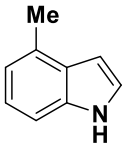
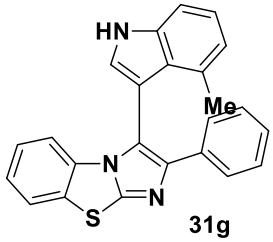
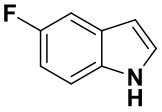
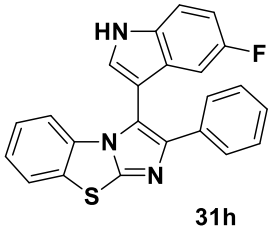
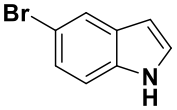
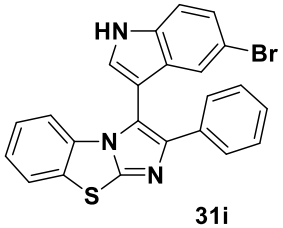
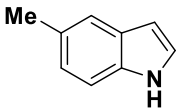
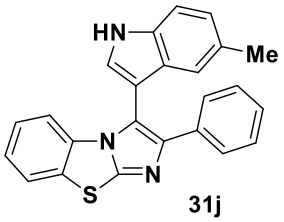
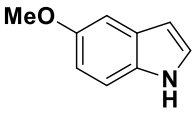
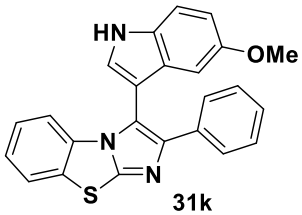
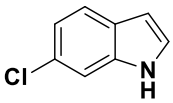
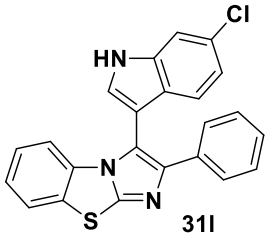
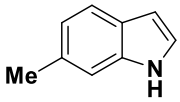
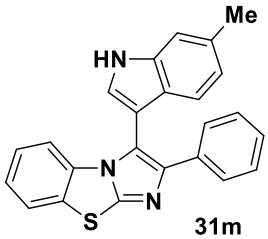
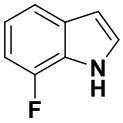
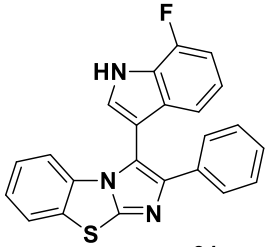
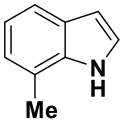
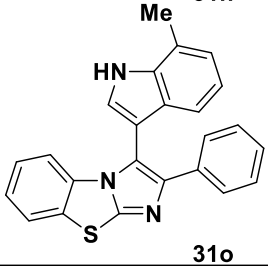
Sl.No.	Indole	Product	Yield [%]
5.	 30e	 31e	57
6.	 30e	 31e	62
7.	 30f	 31f	35
8.	 30g	 31g	32
9.	 30h	 31h	58
10.	 30i	 31i	58

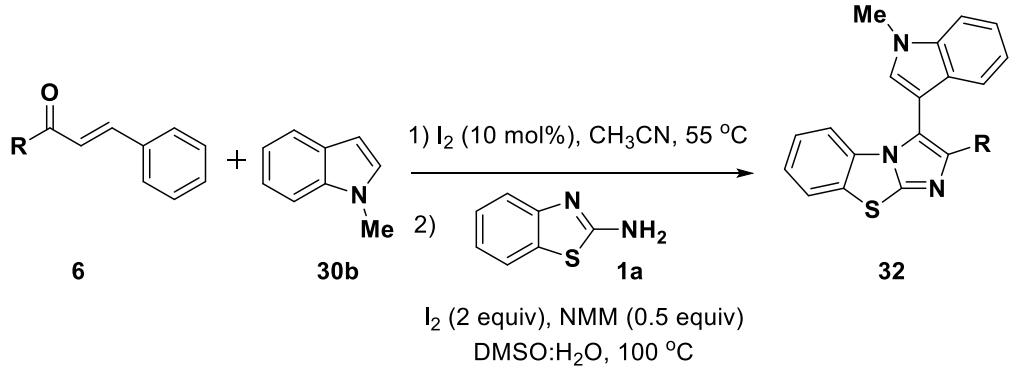
Table 4.3. continues…….

Sl.No.	Indole	Product	Yield [%]
11.	 30j	 31j	53
12.	 30e	 31k	38
13.	 30f	 31l	30
14.	 30g	 31m	42
15.	 30h	 31n	48
16.	 30i	 31o	56

Reaction conditions: **6a** (0.25 mmol), **30** (0.25 mmol), **1a** (0.25 mmol), I_2 used in step two (0.50mmol), NMM (0.125 mmol), DMSO: H_2O (10: 2.5, 2 mL), 100 ^oC, 14 h.

Later, we explored the generality of the reaction with chalcone. Since the aromatic ring adjacent to the double bond is cleaving apart, the investigation was centered on the electronic effect of aroyl ring of the chalcone. Delightfully, all the substrates bearing various substituents, except *p*-bromo (**6d**) and *p*-nitro (**6g**), furnished the anticipated benzo[*d*]imidazo[2,1-*b*]thiazoles tethered with indole in better yield of 49 – 62%. The lower yield of 17% observed for both *p*-bromo and *p*-nitro substituents is attributed to the poor reactivity of the respective chalcones in the Michael addition step. Interestingly, we were able to synthesis 3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole incorporated with a thiophene nucleus (**32g**) in 59% yield, by selecting (*E*)-3-phenyl-1-(thiophen-3-yl)prop-2-en-1-one as the starting material. In addition to chalcone, we have extended the scope of the reaction for other *α,β* -unsaturated ketones such as benzylideneacetone (**6i**) and dibenzylideneacetone (**6j**). Fortunately, the desired products were obtained in moderate yields under the optimal reaction conditions.

Table 4.4. Scope of unsaturated ketones



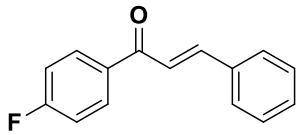
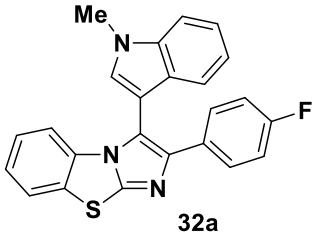
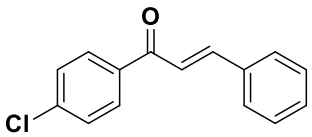
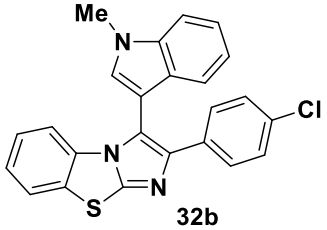
Sl.No.	Unsaturated ketone	Product	Yield [%]
1.	 6b	 32a	60
2.	 6c	 32b	55

Table 4.4. continues…….

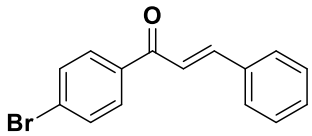
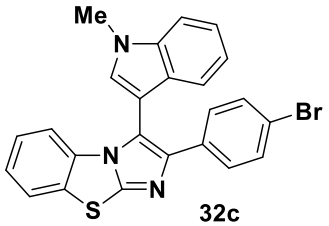
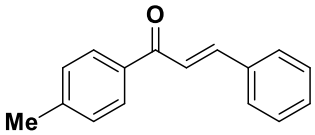
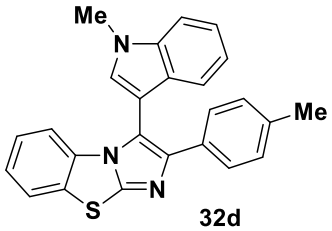
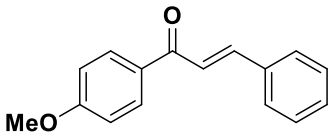
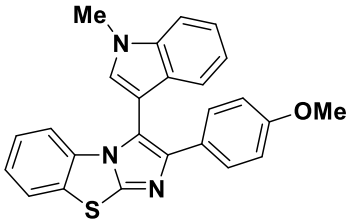
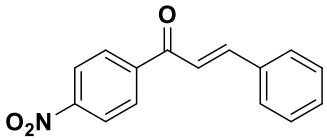
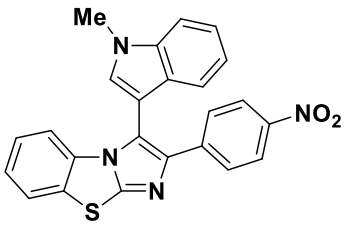
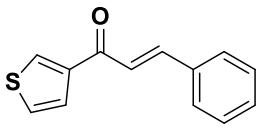
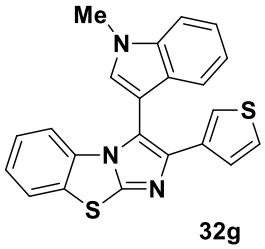
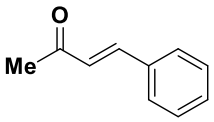
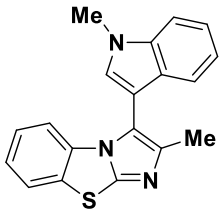
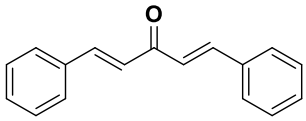
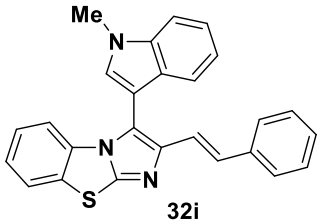
Sl.No.	Unsaturated ketone	Product	Yield [%]
3.	 6d	 32c	17
4.	 6e	 32d	49
5.	 6f	 32e	62
6.	 6g	 32f	17
7.	 6h	 32g	59

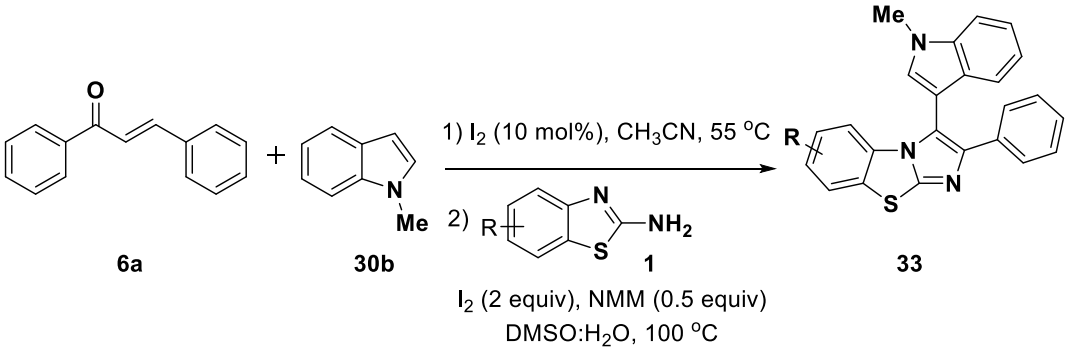
Table 4.4. continues…….

Sl.No.	Unsaturated ketone	Product	Yield [%]
8.	 6i	 32h	42
9.	 6j	 32i	43

Reaction conditions: **6** (0.25 mmol), **30a** (0.25 mmol), **1a** (0.25 mmol), I_2 used in step two (0.50 mmol), NMM (0.125 mmol), DMSO: H_2O (10: 2.5, 2 mL), 100 ^oC, 14 h.

To further inspect the scope of this two-step, one-pot reaction, 2-aminobenzothiazoles bearing electron donating and electron withdrawing substituents were evaluated. Satisfyingly, 2-aminobenzothiazoles bearing F, Cl, Br, Me and OMe substituents at the 6th position underwent the reaction smoothly and afforded the expected products in moderate to good yields of 52 – 74%. On the other hand, 2-aminobenzothiazole containing Me and OMe groups at the 4th position furnished the desired tricycles in lower yield compared to that of substituents at the 6th position.

Table 4.5. Scope of 2-aminobenzothiazoles



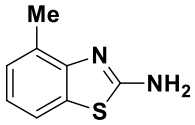
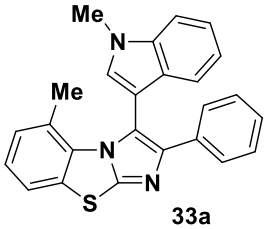
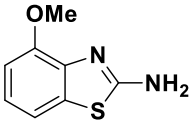
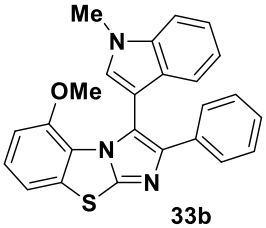
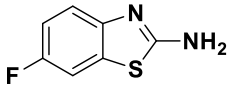
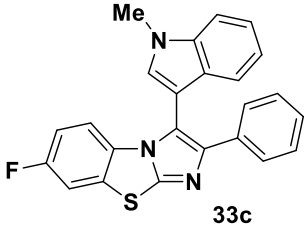
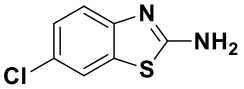
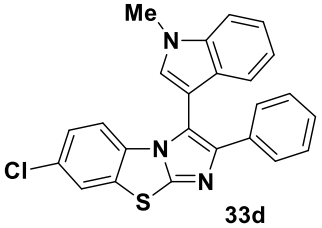
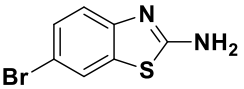
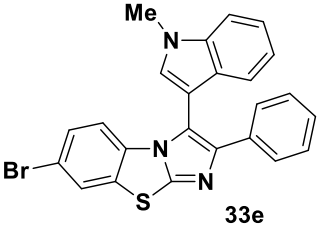
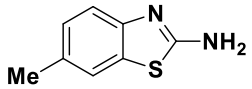
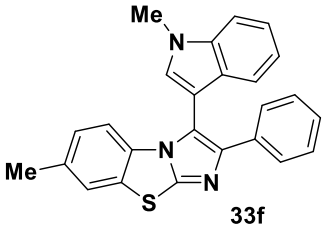
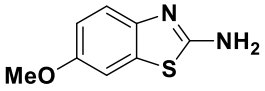
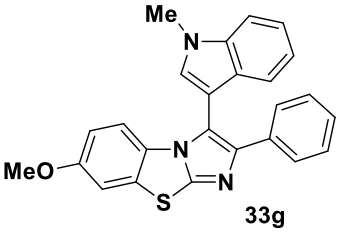
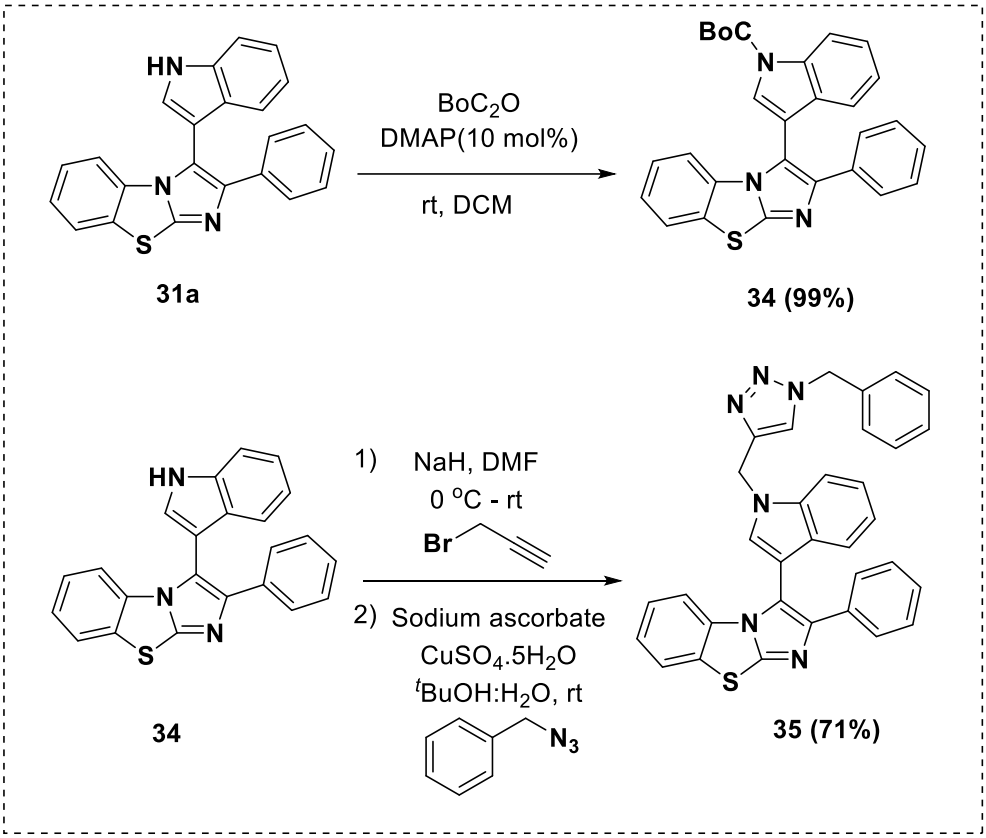
Sl.No.	2-aminobenzothiazoles	Product	Yield [%]
1.	 1b	 33a	19
2.	 1c	 33b	56
3.	 1d	 33c	52
4.	 1e	 33d	66
5.	 1f	 33e	57

Table 4.5. continues…….

Sl.No.	2-aminobenzothiazoles	Product	Yield [%]
6.	 1g	 33f	66
7.	 1h	 33g	74

Reaction conditions: **6a** (0.25 mmol), **30b** (0.25 mmol), **1** (0.25 mmol), I_2 used in step two (0.50 mmol), NMM (0.125 mmol), DMSO: H_2O (10: 2.5, 2 mL), 100 ^oC, 14 h.

In order to showcase the synthetic utility of the tricyclic product, we have carried out few reactions on 3-(1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole. Since the molecule contains a free NH-group, we have performed a Boc protection on **31a** which resulted in the formation of **34** in 99% yield. Furthermore, we have propargylated **31a** and subjected to click reaction with benzyl azide to afford the corresponding triazole **35**. This single molecule contains multiple heterocyclic nuclei such a benzothiazole, imidazole, indole and triazole ring.



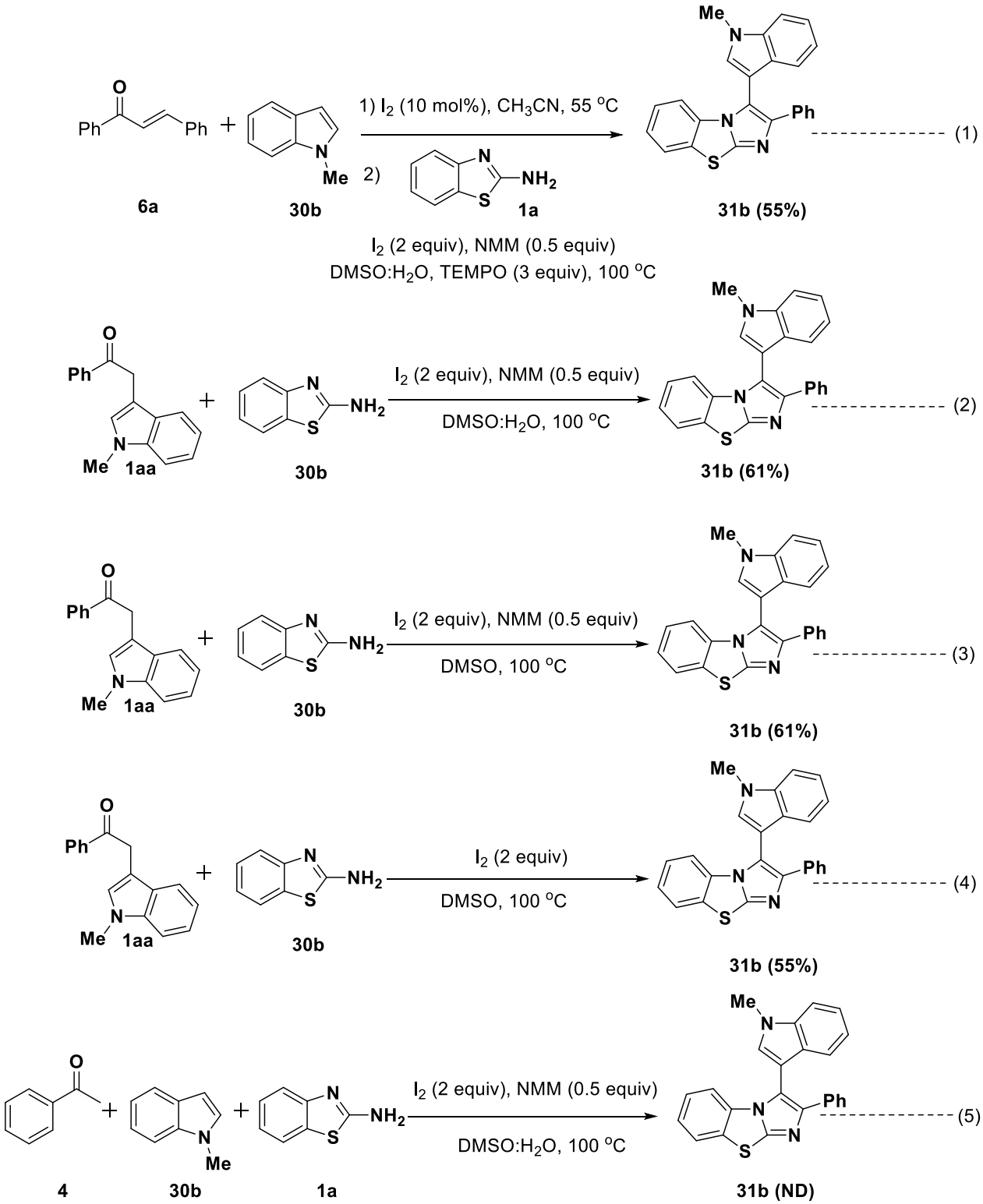
Scheme 4.16. Synthetic utility of benzo[*d*]imidazo[2,1-*b*]thiazoles

4.6. Plausible Mechanism

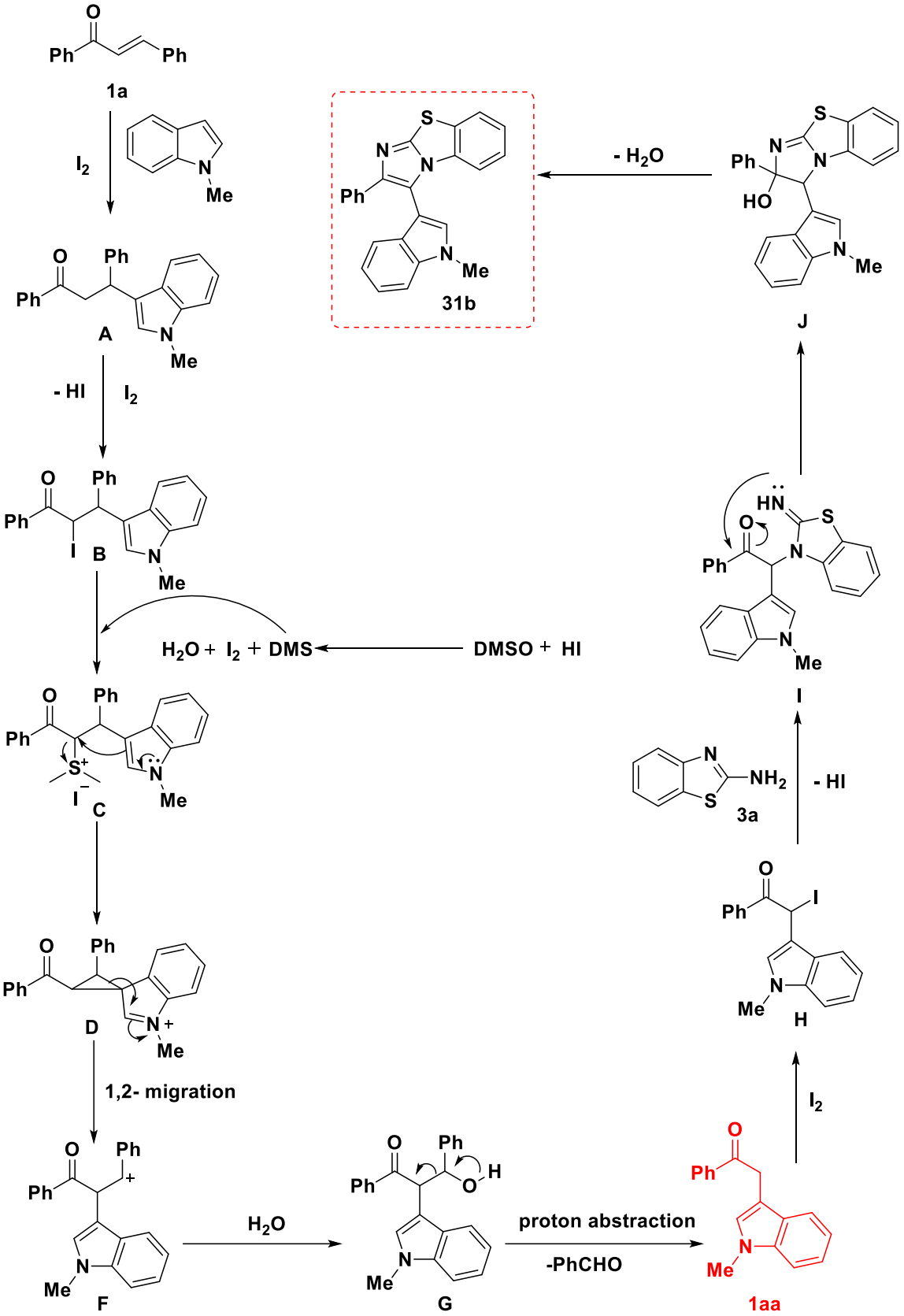
To get an insight into the mechanistic pathway, we have performed a series of control experiments (**Scheme 4.17**). Initially a reaction was carried out in the presence of radical inhibitor TEMPO, which resulted in the formation of the product in 55% yield. This observation rules out the possibility of a radical pathway. Since the reaction involves 1,2-indole migration and C_α-C_β bond cleavage, we have assumed that the reaction might be proceeding through an intermediate **1aa**. Hence, **1aa** was reacted with 2-aminobenzothiazole under the optimized conditions. Fortunately, the reaction afforded the targeted product in 60% yield. When the reaction was carried out in dry DMSO in the absence of water, identical yield was obtained. The product was obtained in a considerable yield of 55% in the presence of I_2 and DMSO alone at 100 ^{o}C. This observation implies that, base might be enhancing the reactivity of 2-aminobenzothiazole, thereby leading to a better yield. We have also checked the possibility of one step three component reaction for furnishing the product by treating

acetophenone with *N*-methyl indole and 2-aminobenzothiazole under the optimized conditions. But the reaction could not afford the product, even in trace quantities.

Based on the control experiments and literature reports we have proposed a plausible mechanism for the reaction (**Scheme 4.18**).[25,26,27] First step of the reaction is the formation of Michael adduct **A** in the presence of catalytic amount of I_2. The second step of the one-pot reaction starts with an α-iodination of **A** forming the intermediate **B**. The nucleophilic attack of dimethyl sulfide (DMS) on **B** leads to the formation of sulfonium intermediate **C**. The intramolecular nucleophilic attack of indole generates a cyclopropane intermediate **D**. Then, subsequent C-C bond cleavage of cyclopropane ring and migration of indole from β carbon to α carbon generates a carbocation **F**, which on attack by water forms intermediate **G**. Further, **G** undergoes a C-C bond cleavage followed by proton abstraction resulting in the formation of **1aa** and benzaldehyde. Subsequently, α-iodination of **1aa** followed by nucleophilic attack by the endocyclic nitrogen atom of 2-aminobenzothiazole affords intermediate **I**. Intramolecular cyclization of **I** generates the intermediate **J**. Finally, loss of water from **J** furnishes the desired product.



Scheme 4.17. Control experiments



Scheme 4.18. Plausible mechanism

4.7. Conclusion

We have developed a two-step, one pot protocol for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole tethered with an indole nucleus at the C3 carbon atom. The reaction which proceeds under metal-free conditions, utilizes readily accessible substrates such as α,*β*-unsaturated ketones, indoles and 2-aminobenzothiazoles. Notably, the reaction involves a 1,2-indole migration along with C_{α}-C_{β} bond cleavage. Further, the reaction is compatible with both protected as well as unprotected indole.

4.8. General experimental methods

All the reactions were performed with commercially available best grade chemicals without further purification. All the solvents used were reagent grade and commercially available. Column chromatography was performed using neutral alumina (Al_2O_3) and mixtures of hexane – ethyl acetate were used for elution of the products. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrometer ($CDCl_3$ and $(CD_3)_2SO$ as solvents). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of $CDCl_3$ (δ 7.25) and $(CD_3)_2SO$ (δ 2.50) Multiplicities are given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet), m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm). Mass spectra were recorded under EI/HRMS at 60,000 resolution using Thermo Scientific Exactive- LCMS mass spectrometer by electron spray ionization method with ions given in m/z using Orbitrap analyzer. IR spectra were recorded on Bruker FT-IR spectrometer. Melting points were determined on a Buchi melting point apparatus and are uncorrected.

4.9. General procedure for the synthesis of *α,β* -unsaturated ketone (1)

One equivalent of aryl aldehyde was added to a solution of one equivalent of acetophenone in ethanol. 10% aqueous solution of NaOH was added dropwise to the reaction mixture at 0 ^{o}C and allowed to stir at room temperature for 30 minutes. The precipitate formed was collected by filtration and washed with hexane. The precipitate was dried and used for further reaction.

4.10. General procedure for the synthesis of *N*-alkyl indole derivatives (2)

Indole (4.268 mmol) was weighed out into a 50 mL round bottom flask, to which crushed KOH (12.804 mmol) was added. Then 10 mL of DMSO was added to it and allowed to stir at room temperature. Corresponding alkyl bromide (8.536 mmol) was added to this mixture and stirring was continued at the room temperature. Progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The product was isolated by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent.

4.11. Procedure for the synthesis of 1-phenyl-1*H*-indole (3)

To a mixture of 1*H*-indole (4.2 mmol), iodobenzene (3.0 mmol), copper(I)iodide (0.6 mmol) and Cs_2CO_3 (6.0 mmol), 6 mL of DMF was added. Then the solution was stirred at 120 ^oC for 16 hours. Next, the reaction mixture was extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The product was isolated by column chromatography on silica gel using a mixture of hexane and ethyl acetate as eluent.

4.12. General procedure for the synthesis of benzo[*d*]imidazo[2,1-*b*]thiazole tethered with indole (4)

To a mixture of 1 equiv (0.25 mmol) of *α,β* -unsaturated ketone and 1 equiv (0.25 mmol) of indole, 10 mol% of iodine was added followed by the addition of 2 mL of CH_3CN. Then the reaction mixture was allowed to stir at 55 ^oC for 0.5 to 3 hours. Completion of the reaction was monitored by TLC. After the completion of the first step, solvent was evaporated in *vacuo* and the reaction mixture was kept in vacuum pump for 15 minutes. Later, 1 equiv (0.25 mmol) of 2-aminobenzothiazole was added to the reaction mixture. A 2 mL solution of 2 equiv (0.5 mmol) of iodine and 0.5 equiv (0.125 mmol) of *N*-methylmorpholine in DMSO: H_2O (10: 2.5, v/v) mixture was added to the reaction mixture. It was then allowed to stir at 100 ^oC for 14 hours. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on alumina column chromatography using mixture of hexane and ethyl acetate as eluent, afforded the product.

4.13. Control experiments

4.13.1 Experiment 1

To a mixture of *α,β* -unsaturated ketone (1 equiv, 0.25 mmol) and indole (1 equiv, 0.25 mmol), 10 mol% of iodine (0.1 equiv, 0.025 mmol) was added followed by the addition of 2 mL of CH_3CN. Then the reaction mixture was allowed to stir at 55 ^oC for 0.5 to 3 hours. Completion of the reaction was monitored by TLC. After the completion of the first step, solvent was evaporated in *vacuo* and the reaction mixture was kept in vacuum pump for 15 minutes. Later, 2-aminobenzothiazole (1 equiv, 0.25 mmol) was added to the reaction mixture. A 2 mL solution of iodine (2 equiv, 0.5 mmol) and *N*-methylmorpholine (0.5 equiv, 0.125 mmol) in DMSO: H_2O (10: 2.5, v/v) mixture was added to the reaction mixture followed by the addition of TEMPO (3 equiv, 0.75 mmol). It was then allowed to stir at 100 ^oC for 14 hours. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on alumina column chromatography using mixture of hexane and ethyl acetate as eluent, afforded the product in 55% yield.

4.13.2. Experiment 2

A round bottom flask was charged with **1aa** (1 equiv, 0.25 mmol) and 2-aminobenzothiazole (1 equiv, 0.25 mmol) at room temperature. Then, 2 mL solution of iodine (2 equiv, 0.5 mmol) and *N*-methylmorpholine (0.5 equiv, 0.125 mmol) in DMSO: H_2O (10: 2.5, v/v) mixture was added to it. The reaction mixture was stirred at 100 ^oC for 14 hours. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on alumina column chromatography using mixture of hexane and ethyl acetate as eluent, afforded the product in 61% yield.

4.13.3. Experiment 3

A round bottom flask was charged with **1aa** (1 equiv, 0.25 mmol) and 2-aminobenzothiazole (1 equiv, 0.25 mmol) at room temperature. Then, 2 mL solution of iodine (2 equiv, 0.5 mmol) and *N*-methylmorpholine (0.5 equiv, 0.125 mmol) in DMSO was added to it. The reaction mixture was stirred at 100 ^oC for 14 hours. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and

brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on alumina column chromatography using mixture of hexane and ethyl acetate as eluent, afforded the product in 61% yield.

4.13.4. Experiment 4

A round bottom flask was charged with **1aa** (1 equiv, 0.25 mmol), 2-aminobenzothiazole (1 equiv, 0.25 mmol) and iodine (2 equiv, 0.5 mmol) at room temperature. Then, 2 mL of DMSO was added to it. The reaction mixture was stirred at 100 ^oC for 14 hours. After the completion of the reaction, the mixture was extracted with ethyl acetate and washed with aqueous solution of sodium thiosulfate and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The residue on alumina column chromatography using mixture of hexane and ethyl acetate as eluent, afforded the product in 55% yield.

4.13.5. Experiment 5

A round bottom flask was charged with acetophenone (1 equiv, 0.25 mmol), 1-methyl-1*H*-indole (1 equiv,0.25 mmol) and 2-aminobenzothiazole (1 equiv, 0.25 mmol). and iodine (2 equiv, 0.5 mmol) at room temperature. Then, 2 mL solution of iodine (2 equiv, 0.5 mmol) and *N*-methylmorpholine (0.5 equiv, 0.125 mmol) in DMSO: H_2O (10: 2.5, v/v) mixture was added to it. The reaction mixture was stirred at 100 ^oC for 14 hours. The desired product was not formed even in trace quantities.

4.14. Characterization data of the compounds

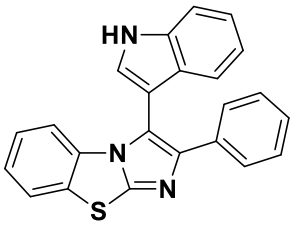
3-(1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31a)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1*H*-indole (30 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 63% (59 mg) yield.

MP: 116 - 118 ^oC

IR (neat) ν_{max}: 3388, 1706, 1490, 1373, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.68 - 7.64 (m, 3H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.31 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 3H), 7.15 - 7.12 (m, 2H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H).



^{13}C NMR (126 MHz, $CDCl_3$): δ 147.6, 145.2, 136.3, 134.5, 133.3, 130.4, 128.3, 127.7, 126.9, 126.8, 125.9, 125.9, 124.3, 123.9, 123.1, 120.9, 120.2, 117.3, 113.7, 111.8, 104.9.

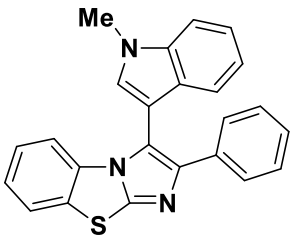
HRMS (ESI) (m/z): Calcd for $C_{23}H_{16}N_3S$, $(M+H)^+$: 366.10649; Found: 366.10690.

3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31b)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 69% (63 mg) yield.

MP: 228 - 230 ^oC

IR (neat) ν_{max}: 1709, 1593, 1488, 1379, 743 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.5 Hz, 3H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.15 (m, 6H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.95 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.2, 137.2, 134.6, 133.4, 130.4, 129.9, 128.3, 128.2, 126.8, 125.7, 124.2, 123.9, 122.6, 120.6, 120.4, 117.2, 113.7, 109.8, 103.5, 33.3.

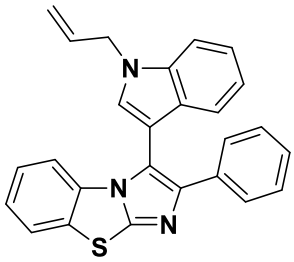
HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3S$, $(M+H)^+$: 380.12214; Found: 380.12192.

3-(1-allyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31c)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-allyl-1*H*-indole (39 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 56% (53 mg) yield.

MP: 96 - 98 ^oC

IR (neat) ν_{max}: 1494, 1381, 746 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (t, *J* = 7.0 Hz, 3H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 4.0 Hz, 1H), 7.13 – 7.04 (m, 5H), 6.96 – 6.93 (m, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.01 – 5.94 (m, 1H), 5.18 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.04 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.77 (d, *J* = 5.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.1, 136.6, 134.6, 133.3, 133.0, 130.5, 129.3, 128.4, 128.2, 126.8, 126.7, 125.8, 124.3, 123.9, 122.7, 120.8, 120.5, 117.5, 117.1, 113.6, 110.2, 103.9, 48.9.

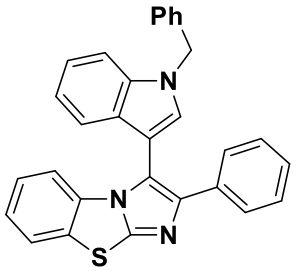
HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}N_3S$, $(M+H)^+$: 406.13779; Found: 406.13834.

3-(1-benzyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31d)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-benzyl-1*H*-indole (51 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a white solid in 69% (79 mg) yield.

MP: 171 - 173 ^oC

IR (neat) ν_{max}: 1709, 1595, 1492,1380, 739 cm^{-1}.



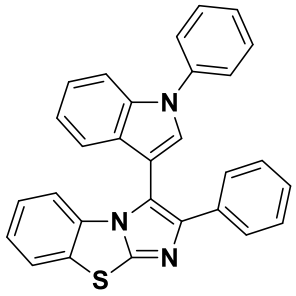
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 – 7.67 (m, 3H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.31 (m, 5H), 7.23 – 7.18 (m, 6H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.5Hz, 1H), 5.46 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.1, 137.1, 136.8, 134.5, 133.3, 130.5, 129.6, 128.9, 128.5, 128.2, 127.9, 126.9, 126.8, 126.7, 125.7, 124.3, 124.0, 122.9, 120.9, 120.5, 117.1, 113.7, 110.3, 104.2, 50.4.

HRMS (ESI) (m/z): Calcd for $C_{30}H_{22}N_3S$, $(M+H)^+$: 456.15344; Found: 456.15457.

2-phenyl-3-(1-phenyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (31e)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-phenyl-1*H*-indole (48 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as pale yellow solid in 57% (63 mg) yield.



MP: 110 - 112 ^{o}C

IR (neat) ν_{max}: 1711, 1596, 1498, 1378, 746 cm^{-1}.

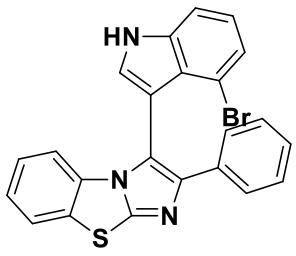
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.5 Hz, 1H), 7.71 – 7.67 (m, 3H), 7.58 – 7.57 (m, 4H), 7.52 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.24 – 7.16 (m, 5H), 7.08 – 7.05 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.8, 145.4, 139.1, 136.4, 134.5, 133.3, 130.5, 129.9, 129.8, 129.1, 128.9, 128.3, 127.1, 126.9, 126.8, 125.9, 124.5, 124.4, 124.1, 123.5, 121.6, 120.7, 116.6, 113.7, 111.1, 106.2.

HRMS (ESI) (m/z): Calcd for $C_{29}H_{20}N_3S$, $(M+H)^+$: 442.13779; Found: 442.13843.

3-(4-bromo-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31f)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 4-bromo-1*H*-indole (49 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (25% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 62% (36 mg) yield.



MP: 296 - 298 ^{o}C

IR (neat) ν_{max}: 1707,1552, 1490, 1374, 743 cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ 12.06 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.24 - 7.20 (m, 3H), 7.16 (t, *J* = 8.0 Hz, 3H), 6.50 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ 146.4, 145.2, 137.9, 135.2, 133.3, 129.9, 129.7, 128.7, 127.1, 126.7, 126.5,

126.0, 125.5, 125.0, 124.3, 123.9, 117.6, 113.1, 112.7, 112.6, 103.4.

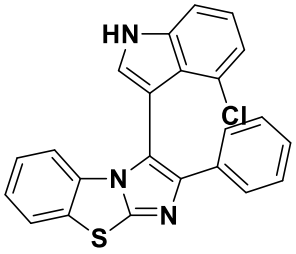
HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}BrN_3S$, $(M+H)^+$: 444.01701; Found: 444.01440.

3-(4-chloro-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31g)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 4-chloro-1*H*-indole (38 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 35% (33 mg) yield.

MP: 280 - 282 ^oC

IR (neat) ν_{max}: 1707, 1600, 1489, 1375,742 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.66 – 7.62 (m, 3H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 3H), 7.15 (t, *J* = 8.5 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3, 145.5, 137.4, 134.7, 133.5, 130.4, 128.2, 127.1, 126.9, 126.8, 126.6, 125.8, 125.2, 124.2, 124.0, 123.8, 121.7, 116.9, 113.1, 110.5, 104.7.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}ClN_3S$, $(M+H)^+$: 400.06752; Found: 400.06814.

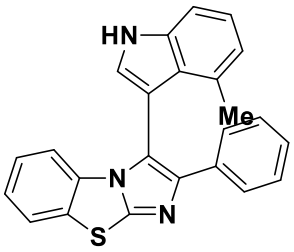
3-(4-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31h)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 4-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a yellow solid in 32% (30 mg) yield.

MP: 249 - 251 ^oC

IR (neat) ν_{max}: 1705,1583, 1490, 1375, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz,



1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 3H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 2.02 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.1, 145.1, 136.6, 134.6, 133.3, 131.3, 130.4, 129.0, 128.3, 126.8, 126.6, 125.9, 125.7, 124.4, 124.1, 123.2, 122.0, 118.5, 113.2, 109.5, 104.9, 18.4.

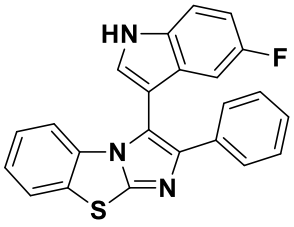
HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3S$, $(M+H)^+$: 380.12214; Found: 380.12170.

3-(5-fluoro-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31i)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 5-flouro-1*H*-indole (34 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product as a yellow solid in 58% (56 mg) yield.

MP: 257 - 259 ^oC

IR (neat) ν_{max}: 1707, 1586, 1489, 1374, 747cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 7.67 - 7.62 (m,3H), 7.48 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.14 (m, 4H), 7.09 – 7.03 (m, 3H), 6.78 (d, *J* = 8.0 Hz, 1H).

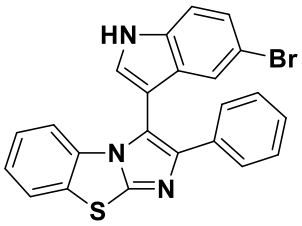
^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6, 157.7, 147.8, 145.4, 134.4, 133.2, 132.7, 130.4, 128.3, 127.5, 126.9, 126.7, 125.9, 124.4, 124.1, 116.4, 113.4, 112.6, 112.5, 111.9, 111.7, 105.1, 104.9.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}FN_3S$, $(M+H)^+$: 384.09707; Found: 384.09668.

3-(5-bromo-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31j)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 5-bromo-1*H*-indole (49 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol).

The crude product was purified by column chromatography (25% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 58% (64 mg) yield.



MP: 262 - 264 ^{o}C

IR (neat) ν_{max}: 1707, 1587, 1489, 1372, 743 cm^{-1}.

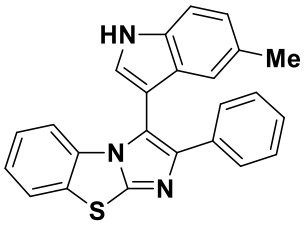
^{1}H NMR (500 MHz, DMSO): δ 11.95 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.58 (d, *J* = 7.5 Hz, 3H), 7.39 (s, 1H), 7.32 (dd, *J* = 2.0, 8.5 Hz, 2H), 7.24 - 7.19 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ 147.2, 144.5, 135.6, 134.8, 133.1, 130.0, 129.5, 128.7, 127.3, 126.7, 126.4, 125.5, 125.3, 125.2, 121.4, 117.2, 114.9, 113.2, 113.0, 102.9.

HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}BrN_3S$, $(M+H)^+$: 444.01701; Found: 444.01646.

3-(5-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31k)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 5-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 53% (50 mg) yield.



MP: 232 - 234 ^{o}C

IR (neat) ν_{max}: 1725, 1586, 1492, 1376, 746 cm^{-1}.

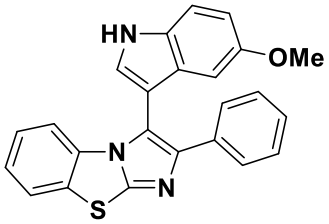
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.70 - 7.66 (m, 3H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.32 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 4H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.1, 134.6, 134.6, 133.3, 130.4, 128.2, 128.1, 126.8, 126.7, 125.9, 125.8, 124.8, 124.3, 123.9, 119.6, 117.4, 113.7, 111.3, 104.5, 21.5.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3S$, $(M+H)^+$: 380.12214; Found: 380.12274.

3-(5-methoxy-1H-indol-3-yl)-2-phenylbenzo[d]imidazo[2,1-b]thiazole (31l)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 5-methoxy-1*H*-indole (37 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 38% (38 mg) yield.



MP: 113 - 115 ^{o}C

IR (neat) ν_{max}: 1707, 1586, 1488, 1374, 700 cm^{-1}.

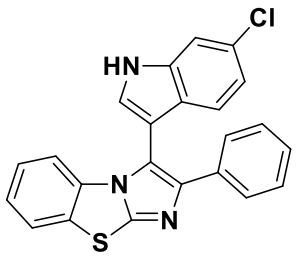
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 3H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 2.5 Hz, 1H), 7.22 - 7.18 (m, 3H), 7.15 (t, *J* = 7.5 Hz,1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 9.0, 2.0 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 3.65 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.1, 147.5, 144.9, 134.4, 133.3, 131.2, 130.4, 128.3, 128.3, 126.9, 126.7, 126.2, 125.9, 124.4, 123.9, 117.2, 113.9, 113.7, 112.5, 104.8, 101.1, 55.8.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3OS$, $(M+H)^+$: 396.11706; Found: 396.11700.

3-(6-chloro-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31m)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 4-chloro-1*H*-indole (38 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 30% (30 mg) yield.



MP: 293 - 295 ^{o}C

IR (neat) ν_{max}: 1715, 1601, 1490, 1375, 749 cm^{-1}.

^{1}H NMR (500 MHz, DMSO): δ 11.87 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.64 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.23 - 7.20 (m, 4H), 7.18 - 7.14 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (126 MHz, DMSO): δ 147.1, 144.5, 137.3, 134.8, 133.0, 129.9, 129.0, 128.7, 127.4, 127.3, 126.8, 126.4, 125.5, 125.2, 120.9, 120.8, 117.4, 113.1, 112.5, 103.5.

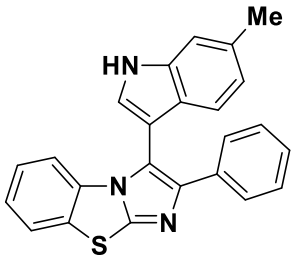
HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}ClN_3S$, $(M+H)^+$: 400.06752; Found: 400.06860.

3-(6-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31n)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 6-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 42% (40 mg) yield.

MP: 223 - 225 ºC

IR (neat) ν_{max}: 1709, 1601, 1491, 1374, 747 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 7.58 - 7.55 (m, 3H), 7.26 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 3H), 7.07 (d, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.7, 136.8, 134.6, 133.3, 133.0, 130.4, 128.2, 126.8, 126.7, 125.9, 125.6, 125.1, 124.3, 123.9, 122.8, 119.8, 117.4, 113.7, 111.6, 104.9, 21.8.

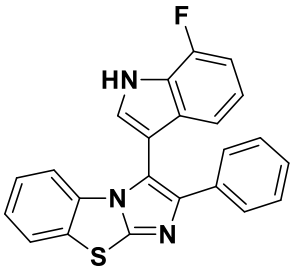
HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3S$, $(M+H)^+$: 380.12214; Found: 380.12228.

3-(7-fluoro-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31o)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 7-flouro-1*H*-indole (34 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 48% (46 mg) yield.

MP: 207 - 209 ºC

IR (neat) ν_{max}: 1707, 1583, 1491, 1375, 737 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 2H), 7.40 (s, 1H), 7.28 - 7.18 (m, 5H), 7.08 – 7.05 (m, 3H), 6.80 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.7, 148.7, 147.8, 145.4, 134.3, 133.2, 130.4, 128.3, 127.0, 126.8, 126.4, 125.9, 124.4, 124.1, 121.4, 121.4, 115.9, 115.9, 113.5, 108.1, 107.9, 106.1,

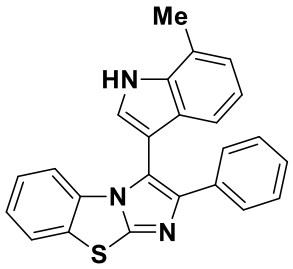
HRMS (ESI) (m/z): Calcd for $C_{23}H_{15}FN_3S$, $(M+H)^+$: 384.09707; Found: 384.09357.

3-(7-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (31p)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 7-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 56% (53 mg) yield.

MP: 266 - 268 ^oC

IR (neat) ν_{max}: 1707, 1590, 1491, 1375, 745 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.68 - 7.66 (m, 3H), 7.36 (s, 1H), 7.29 (d, *J* = 9.5 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 3H), 7.16 (t, *J* = 6.5 Hz, 2H), 7.09 - 7. 02 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 2.66 (s, 3H).

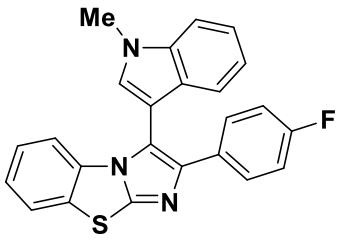
^{13}C NMR (126 MHz, $CDCl_3$): δ 147.5, 145.1, 135.9, 134.6, 133.3, 130.4, 128.2, 127.3, 126.8, 126.8, 125.8, 125.4, 124.3, 123.9, 123.7, 121.1, 120.8, 117.9, 117.4, 113.7, 105.6, 16.76.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{18}N_3S$, $(M+H)^+$: 380.12214; Found: 380.12347.

2-(4-fluorophenyl)-3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32a)

The reaction was performed according to procedure 4 with (*E*)-1-(4-fluorophenyl)-3-phenylprop-2-en-1-one (57 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column

chromatography (10% ethyl acetate in hexane) to afford the desired product as a white solid in 60% (60 mg) yield.



MP: 239 - 241 ^{o}C

IR (neat) ν_{max}: 1710, 1587, 1497, 1378, 742 cm^{-1}.

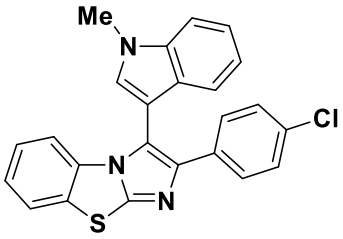
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.20 – 7.17 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.89 - 6.86 (m, 2H), 6.79 (d, *J* = 8.5 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.9, 160.9, 147.5, 144.3, 137.2, 133.3, 130.8, 130.4, 129.9, 128.4, 128.2, 125.8, 124.3, 123.9, 122.7, 120.7, 120.3, 116.9, 115.2, 114.9, 113.6, 109.9, 103.2, 33.39.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}FN_3S$, $(M+H)^+$: 398.11272; Found: 398.11325.

2-(4-chlorophenyl)-3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32b)

The reaction was performed according to procedure 4 with (*E*)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (60 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a yellow solid in 55% (56 mg) yield.



MP: 281 - 283 ^{o}C

IR (neat) ν_{max}: 1711, 1594, 1491, 1377, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 13.0, 8.0 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 3H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H).

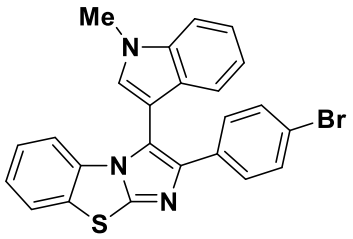
^{13}C NMR (126 MHz, $CDCl_3$): δ 147.7, 144.1, 137.3, 133.2, 133.1, 132.5, 130.4, 129.9, 128.4, 128.1, 127.9,

125.8, 124.4, 124.0, 122.8, 120.7, 120.2, 117.4, 113.7, 109.9, 103.1, 33.3.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}ClN_3S$, $(M+H)^+$: 414.08317; Found: 414.08449.

2-(4-bromophenyl)-3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32c)

The reaction was performed according to procedure 4 with (*E*)-1-(4-bromophenyl)-3-phenylprop-2-en-1-one (71 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a pale yellow solid in 17% (19 mg) yield.



MP: 318 - 320 ^oC

IR (neat) ν_{max}: 1707, 1530, 1491, 1373, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.52 – 7.49 (m, 3H), 7.39 – 7.35 (m, 2H), 7.31 – 7.29 (m, 2H), 7.21 – 7.18 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.04 – 7.07 (m, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.7, 144.1, 137.2, 133.6, 133.2, 131.3, 130.4, 129.9, 128.3, 128.1, 125.8, 124.4, 124.0, 122.8, 120.7, 120.7, 120.2, 117.5, 113.7, 109.9, 103.1, 33.3.

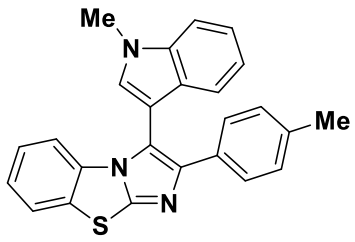
HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}BrN_3S$, $(M+H)^+$: 458.03266; Found: 458.03271.

3-(1-methyl-1*H*-indol-3-yl)-2-(*p*-tolyl)benzo[*d*]imidazo[2,1-*b*]thiazole (32d)

The reaction was performed according to procedure 4 with (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-one (55 mg, 0.25 mmol), 1-methylindole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a white solid in 49% (48 mg) yield.

MP: 261 - 263 ^oC

IR (neat) ν_{max}: 1710, 1531, 1481, 1377, 743 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.19 - 7.12 (m, 3H), 7.0 1 - 6.98 (m, 3H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.91 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 145.3, 137.2, 136.5, 133.4, 131.8, 130.4, 130.0, 128.9, 128.4, 126.6, 125.7, 124.2, 123.9, 122.6, 120.6, 120.4, 116.7, 113.6, 109.8, 103.6, 33.3, 21.2.

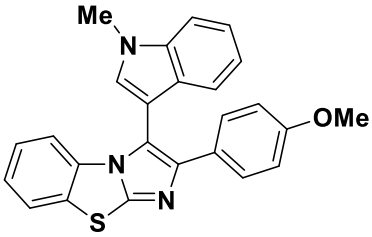
HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3S$, $(M+H)^+$: 394.13779; Found: 394.13790.

2-(4-methoxyphenyl)-3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32e)

The reaction was performed according to procedure 4 with (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (59 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 62% (63 mg) yield.

MP: 239 - 241 ^oC

IR (neat) ν_{max}: 1612, 1497, 1378, 741cm^{-1}.



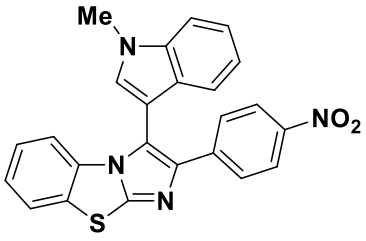
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.58 - 7.55 (m, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.19 - 7.12 (m, 3H), 7.02 - 6.98 (m, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.77 - 6.72 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 147.3, 145.1, 137.2, 133.4, 130.3, 130.0, 128.4, 127.9, 127.4, 125.7, 124.1, 123.9, 122.6, 120.6, 120.4, 116.1, 113.6, 113.5, 109.8, 103.6, 55.2, 33.3.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3OS$, $(M+H)^+$: 410.13271; Found: 410.13351.

3-(1-methyl-1*H*-indol-3-yl)-2-(4-nitrophenyl)benzo[*d*]imidazo[2,1-*b*]thiazole (32f)

The reaction was performed according to procedure 4 with (*E*)-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one (63 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as yellow solid in 17% (18 mg) yield.



MP: 304 - 306 ^{o}C

IR (neat) ν_{max}: 1711, 1596, 1494, 1337, 744 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.96 (d, *J* = 9.0 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.31 (dd, *J* = 16.5, 8.0 Hz, 2H), 7.18 - 7.07 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 148.4, 146.2, 142.9, 141.2, 137.3, 133.0, 130.5, 129.8, 127.7, 126.8, 125.9, 124.9, 124.1, 123.7, 123.1, 121.0, 120.1, 119.7, 113.9, 110.1, 102.6, 33.4.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}N_4O_2S$, $(M+H)^+$: 425.10722; Found: 425.10699.

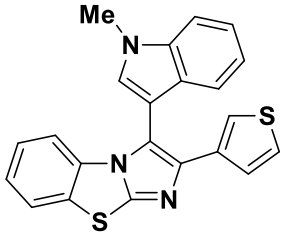
3-(1-methyl-1*H*-indol-3-yl)-2-(thiophen-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32g)

The reaction was performed according to procedure 4 with (*E*)-3-phenyl-1-(thiophen-3-yl)prop-2-en-1-one (53 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as yellow solid in 59% (56 mg) yield.

MP: 214 - 216 ^{o}C

IR (neat) ν_{max}: 1709, 1589, 1480, 1385, 742 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 4.0 Hz, 1H), 7.12 - 7.09 (m,



2H), 7.06 - 7.03 (m, 2H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$); δ 147.4, 142.1, 137.2, 135.9, 133.3, 130.4, 130.2, 128.2, 126.5, 125.8, 124.9, 124.2, 123.9, 122.7, 120.8, 120.7, 120.3, 116.4, 113.5, 109.8, 103.2, 33.3.

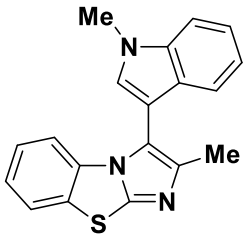
HRMS (ESI) (m/z): Calcd for $C_{22}H_{16}N_3S$, $(M+H)^+$: 386.07856; Found: 386.07892.

2-methyl-3-(1-methyl-1*H*-indol-3-yl)benzo[*d*]imidazo[2,1-*b*]thiazole (32h)

The reaction was performed according to procedure 4 with (*E*)-4-phenylbut-3-en-2-one (36 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (20% ethyl acetate in hexane) to afford the desired product as pale yellow solid in 42% (33 mg) yield.

MP: 136 - 138 ^oC

IR (neat) ν_{max}: 1698, 1589, 1475, 1399, 739 cm^{-1}.



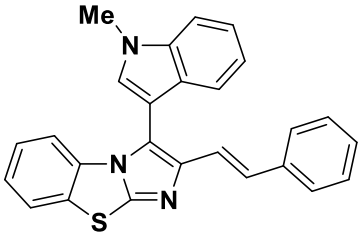
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 2H), 7.12 (s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.96 - 6.91 (m, 2H), 3.85 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 142.9, 137.0, 133.4, 130.1, 129.8, 129.7, 129.0, 128.3, 125.5, 123.9, 123.8, 122.4, 120.4, 120.2, 117.6, 113.6, 109.7, 103.2, 33.2, 13.8.

HRMS (ESI) (m/z): Calcd for $C_{19}H_{16}N_3S$, $(M+H)^+$: 318.10649; Found: 318.10648.

(*E*)-3-(1-methyl-1*H*-indol-3-yl)-2-styrylbenzo[*d*]imidazo[2,1-*b*]thiazole (32i)

The reaction was performed according to procedure 4 with (*1E*,*4E*)-1,5-diphenylpenta-1,4-dien-3-one (58 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-aminobenzothiazole (37 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as pale yellow solid in 43% (43 mg) yield.



MP: 221 - 223 °C

IR (neat) ν_{max}: 1710, 1594, 1486, 1378, 741 cm^{-1}.

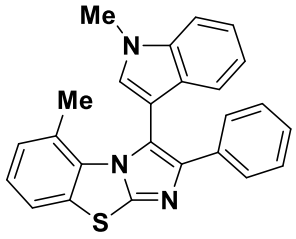
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.42 (s, 1H), 7.38 - 7.35 (m, 3H), 7.34 - 7.30 (m, 2H), 7.24 - 7.21 (m, 2H), 7.17 - 7.09 (m, 3H), 7.03 – 6.97 (m, 2H), 6.89 (d, *J* = 16.0 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 148.7, 144.2, 137.8, 137.1, 133.1, 130.4, 130.2, 128.5, 128.2, 128.1, 127.1, 126.4, 125.8, 124.3, 123.9, 122.7, 120.6, 120.6, 119.7, 119.4, 113.9, 109.8, 102.3, 33.3.

HRMS (ESI) (m/z): Calcd for $C_{26}H_{20}N_3S$, $(M+H)^+$: 406.13779; Found: 406.13796.

5-methyl-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33a)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-4-methylbenzothiazole (41 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a colourless liquid in 19% (19 mg) yield.



IR (neat) ν_{max}: 1711, 1601, 1501, 1333, 739 cm^{-1}.

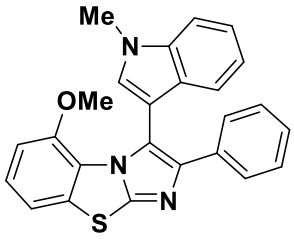
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 6.0 Hz, 3H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.15 – 7.13 (m, 6H), 6.92 (d, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 148.6, 145.8, 136.7, 134.9, 134.1, 131.1, 130.8, 130.6, 129.8, 127.9, 127.2, 126.6, 125.7, 124.3, 122.5, 121.7, 120.7, 119.9, 118.4, 109.7, 106.4, 33.2, 21.3.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3S$, $(M+H)^+$: 394.13779; Found: 394.13916.

5-methoxy-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33b)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-4-methoxybenzothiazole (45 mg, 0.25 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to afford the desired product as a yellow solid in 56% (57 mg) yield.



MP: 189 - 191 ºC

IR (neat) ν_{max}: 1713, 1581, 1500, 1343, 742 cm^{-1}.

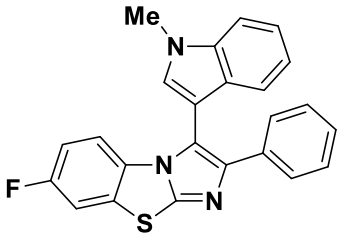
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.46 - 7.44 (m, 2H), 7.32 - 7.28 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.19 - 7.13 (m, 5H), 7.04 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 2.70 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.9, 147.6, 145.5, 136.8, 135.1, 131.8, 131.0, 129.9, 127.9, 127.2, 126.5, 125.2, 124.1, 121.7, 120.3, 119.9, 119.1, 115.8, 109.0, 108.5, 107.2, 54.5, 32.9.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3OS$, $(M+H)^+$: 410.13271; Found: 410.13403.

7-fluoro-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33c)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-6-flourobenzothiazole (42 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 52% (52 mg) yield.



MP: 208 - 210 ºC

IR (neat) ν_{max}: 1497, 1377, 1257, 1212, 747 cm^{-1}.

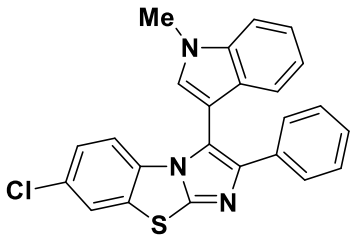
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40 - 7.35 (m, 3H), 7.20 - 7.13 (m, 5H), 6.75 - 6.69 (m, 2H), 3.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.3, 158.3, 147.1, 145.1, 137.2, 134.5, 131.8, 131.7, 129.9, 128.2, 126.9, 126.7, 122.7, 120.7, 120.2, 117.2, 114.4, 113.4, 113.2, 111.1, 110.9, 109.9, 103.0, 33.3.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}FN_3S$, $(M+H)^+$: 398.11272; Found: 398.11206.

7-chloro-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33d)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-6-chlorobenzothiazole (46 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 66% (67 mg) yield.



MP: 216 - 218 ^oC

IR (neat) ν_{max}: 1711, 1602, 1494, 1379, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.5 Hz, 3H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.38 - 7.34 (m, 2H), 7.21 – 7.12 (m, 5H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.2, 145.4, 137.2, 134.4, 131.9, 129.9, 129.7, 128.2, 128.1, 126.9, 126.8, 126.1, 123.6, 122.8, 120.7, 120.2, 117.3, 114.3, 109.9, 102.9, 33.3.

HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}ClN_3S$, $(M+H)^+$: 414.08317; Found: 414.08478.

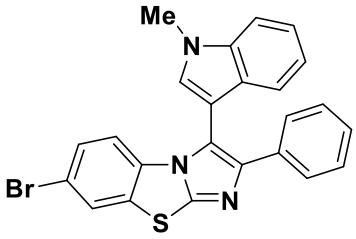
7-bromo-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33e)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-6-bromobenzothiazole (57 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 57% (65 mg) yield.

MP: 220 – 222 ^oC

IR (neat) ν_{max}: 1710, 1602, 1493, 1378, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.38 - 7.35 (m, 2H), 7.21 - 7.14 (m, 5H), 7.12 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H).



^{13}C NMR (126 MHz, $CDCl_3$): δ 147.1, 145.4, 137.2, 134.4, 132.3, 132.2, 129.9, 128.9, 128.2, 128.1, 126.9, 126.8, 126.4, 122.8, 120.7, 120.2, 117.3, 116.9, 114.7, 109.9, 102.9, 33.3.

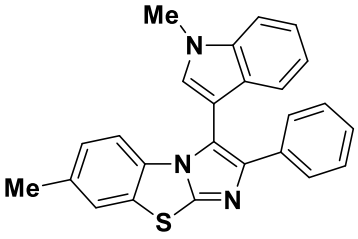
HRMS (ESI) (m/z): Calcd for $C_{24}H_{17}BrN_3S$, $(M+H)^+$: 458.03266; Found: 458.03299.

7-methyl-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33f)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-6-methylbenzothiazole (41 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 66% (65 mg) yield.

MP: 214 - 216 ºC

IR (neat) ν_{max}: 1711, 1601, 1493, 1380, 736 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 - 7.17 (m, 3H), 7.15 - 7.11 (m, 2H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3, 144.9, 137.2, 134.7, 134.3, 131.3, 130.5, 129.9, 128.3, 128.2, 126.7, 126.7, 124.0, 122.6, 120.5, 120.4, 117.1, 113.3, 109.7, 103.5, 33.3, 21.2.

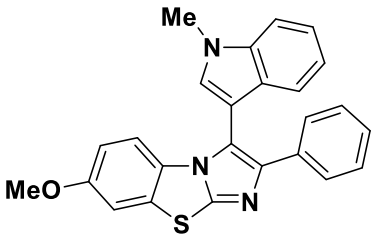
HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3S$, $(M+H)^+$: 394.13779; Found: 394.13858.

7-methoxy-3-(1-methyl-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (33g)

The reaction was performed according to procedure 4 with (*E*) chalcone (52 mg, 0.25 mmol), 1-methyl-1*H*-indole (33 mg, 0.25 mmol) and 2-amino-6-methoxybenzothiazole (45 mg, 0.25 mmol). The crude product was purified by column chromatography (15% ethyl acetate in hexane) to afford the desired product as a white solid in 74% (76 mg,) yield.

MP: 201 - 203 ºC

IR (neat) ν_{max}: 1710, 1602, 1495, 1390, 742 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.12 (m, 6H), 6.66 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.7, 146.8, 144.6, 137.2, 134.8, 131.7, 129.9, 128.3, 128.2, 127.6, 126.7, 126.6, 122.6, 120.6, 120.4, 117.0, 114.2, 112.8, 109.8, 108.5, 103.5, 55.8, 33.2.

HRMS (ESI) (m/z): Calcd for $C_{25}H_{20}N_3OS$, $(M+H)^+$: 410.13271; Found: 410.13190.

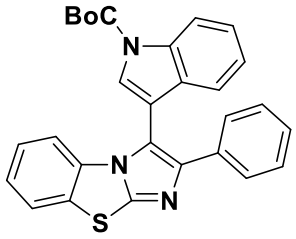
4.15. Procedure for the synthesis of *N*-Boc derivative

***tert*-butyl 3-(2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazol-3-yl)-1*H*-indole-1-carboxylate (34)**

To a solution of **31a** (0.08 mmol) in 1 mL of DCM, 10 mol% of 4-dimethylaminopyridine (0.008 mmol) was added at room temperature. Then a solution of di-*tert*-butyl dicarbonate (0.12 mmol) in 1 mL of DCM was added to the reaction mixture. The reaction was stirred at room temperature for 30 minutes. After the completion of the reaction, it was then quenched with 2 mL, 0.1N HCl and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The product was isolated by column chromatography on neutral alumina using a mixture of hexane and ethyl acetate as eluent. The product was obtained as white solid 99% (38 mg) yield.

MP: 185 - 187 ^oC

IR (neat) ν_{max}: 1735, 1497, 1449, 1377, 747 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.0 Hz, 1H), 7.70 (s, 1H), 7.60 – 7.57 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.18 – 7.16 (m, 5H), 7.00 (t, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 1.62 (s, 9H).

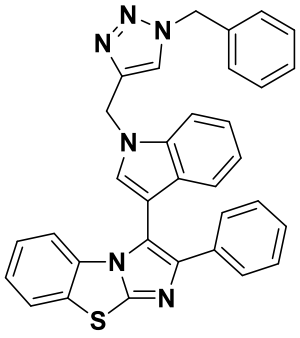
^{13}C NMR (126 MHz, $CDCl_3$): δ 149.5, 148.1, 145.9, 135.5, 134.1, 133.0, 130.4, 130.2, 128.4, 127.2, 127.0, 126.8, 125.97, 125.5, 124.5, 124.1, 123.7, 120.4, 115.6, 115.0, 113.6, 110.06, 84.7, 28.2.

HRMS (ESI) (m/z): Calcd for $C_{28}H_{23}N_3O_2S$, $(M+H)^+$: 466.15892; Found: 466.15881.

4.16. Procedure for the synthesis of triazole appended analogue

3-(1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-indol-3-yl)-2-phenylbenzo[*d*]imidazo [2,1-b]thiazole (35)

To a solution of **31a** (0.27 mmol) in DMF (2 mL), NaH (0.55 mmol) was added at 0 ^oC. The reaction mixture was allowed to stir for 1 hour at 0 ^oC. Then, propargyl bromide (0.55 mmol) was added slowly and stirred at room temperature for 2 hours. After the completion of the reaction, it was then quenched with water and extracted with ethyl acetate. Then, the organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. To the crude product, benzyl azide (0.12 mmol) was added. It was then dissolved in 3 mL of ^{t}BuOH: H_2O (1:2) mixture. Then, $CuSO_4.5H_2O$ (0.01 mmol) and sodium-L-sacorbate (0.04 mmol) were added. Next, the reaction mixture was stirred at room temperature and progress of the reaction was monitored using TLC. After the completion of the reaction, it was extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated in *vacuo*. The product was isolated by column chromatography on neutral alumina using a mixture of hexane and ethyl acetate as eluent. The product was obtained as white solid in 71% (104 mg) yield.



MP: 79 - 81 ^oC

IR (neat) ν_{max}: 1493, 1457, 1377, 1257, 747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.25 - 7.21 (m, 5H), 7.09 - 7.05 (m, 4H), 7.03 - 6.97 (m, 4H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.48 - 5.32 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 147.6, 145.2, 144.7, 136.4, 134.6, 134.3, 133.2, 130.4, 129.2, 129.1, 128.9, 128.5, 128.1, 127.9, 126.8, 125.8, 124.3, 123.9, 123.0, 121.5, 121.0, 120.5, 116.9, 113.7, 110.2, 104.6, 54.3, 42.4.

HRMS (ESI) (m/z): Calcd for $C_{33}H_{25}N_6S$, $(M+H)^+$: 537.18614; Found:537.18640.

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ABSTRACT

Name of the Student**: Ms. Ashitha K. T.**
Registration No**.:** 10CC15A39002
Faculty of Study**:** Chemical Sciences
Year of Submission**:** 2022
AcSIR academic centre/CSIR Lab**:** CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)
Name of the Supervisors**: Dr. Sasidhar B. S.**

Title of the thesis: **Transition Metal Free Transformations of *α,β*-Unsaturated Ketones to Heterocycles of Medicinal Relevance**

Heterocycles are one of the largest class of molecules in organic chemistry. Heterocyclic molecules have wide range of applications in our life. The biological properties associated with them have always attracted the attention of the scientific community. Hence, development of new synthetic methods to construct diverse heterocyclic moieties is an ever growing area of interest. One of the prominent synthetic tool used in this regard is transition metal catalyzed reactions. However, the toxicity of transition metals has become a major concern when it comes to the synthesis of molecules of medicinal relevance. Thus, development of transition metal free reactions is preferred nowadays. On the other hand *α,β*-unsaturated ketones are important building blocks in synthetic organic chemistry. Molecules of this class possess multiple reaction sites and are used as precursors for the synthesis of various heterocycles.

Chapter 1 gives a brief introduction to the significance of transition metal-free reactions in the synthesis of various heterocycles using *α,β*-unsaturated ketones as the substrate. We have documented some of the relevant synthetic methods devised for the construction of diverse heterocyclic entities in recent times.

Chapter 2 deals with a $BF_3.OEt_2$ mediated annulation reaction of arylidenones with alkynes and nitriles. The reaction affords *N*-substituted chromeno/pyrano fused pyridines under mild conditions. This annulation strategy has broad substrate scope and is process friendly. The method is also valid for the construction of thiochromeno[3,4-*c*]pyridines and thiopyrano[3,4-*c*]pyridine derivatives as well. In addition, a one-pot synthesis of 5*H*-chromeno[3,4-*c*]pyridines was successfully achieved.

In **Chapter 3** we have disclosed an iodine catalyzed diastereoselective method for the synthesis of spiroaziridine. The reaction which proceeds under mild conditions, utilizes *α,β*-unsaturated ketones and primary aliphatic amines as the substrates. Notably, the reaction does not require pre functionalization of the amine. Moreover, this methodology is suitable for the synthesis of simple aziridine as well.

Benzo[*d*]imidazo[2,1-*b*]thiazoles are potential synthetic targets owing to its multifaceted applications in various fields of science. Hence synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles is the subject matter of **Chapter 4**. We have developed a one-pot, two-step method for the synthesis of highly functionalized benzo[*d*]imidazo[2,1-*b*]thiazoles under metal-free conditions. This protocol gives access to indole tethered, tricycle from easily available substrates. Interestingly, the reaction involves an unusual 1,2-migration of indole nucleus along with a C_α-C_β bond cleavage. Furthermore, the reaction is compatible with both protected as well as unprotected indole and has broad substrate scope.

LIST OF PUBLICATIONS

Publications emanated from thesis

(1) **Ashitha, K. T.**; Praveen Kumar, V.; Fathimath Salfeena, C. T.; Sasidhar, B. S. $BF_3{\cdot}OEt_2$-mediated tandem annulation: A strategy to construct functionalized chromeno- and pyrano-fused pyridines. *J. Org. Chem.* **2018**, *83*, 113–124.

(2) **Ashitha, K. T.**; Vinaya, P. P.; Krishna, A.; Vincent, D. C.; Jalaja, R.; Varughese, S.; Somappa, S. B. I_2/TBHP mediated diastereoselective synthesis of spiroaziridines. *Org. Biomol. Chem.* **2020**, *18*, 1588–1593.

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Other pulications

(1) Fathimath Salfeena, C. T.; **Ashitha, K. T.**; Sasidhar, B. S. $BF_3{\cdot}Et_2O$ Mediated one-step synthesis of N-substituted-1,2-dihydropyridines, indenopyridines and 5,6-dihydroisoquinolines. *Org. Biomol. Chem.* **2016**, *14*, 10165–10169.

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§: equal contribution.

(9) Lakshmi, S.; **Ashitha, K. T.**; Sasidhar, B. S.; Priya, S. Detailed molecular pharmacokinetic and gene expression evaluations of identified lead NIIST-AC 1 against breast cancer cell line MDA-MB 231. [Manuscript under preparation].

PATENT -NOT RELATED TO THESIS

(1) Lakshmi, S.; **Ashitha, K. T**.; Sasidhar, B. S.; Raghu, K. G.; Priya, S. Pyrazole amide based compounds and uses against breast cancer thereof. [Patent filed- PCT, application no: **PCT/IN2022/051006. Filed on: 16-Nov-2022**].

CONTRIBUTION TO ACADEMIC CONFERENCES

(1) $BF_3 \cdot OEt_2$-Mediated tandem annulation: A strategy to construct functionalized chromeno and pyrano fused pyridines. **Ashitha K. T**., Fathimath Salfeena C. T., Valmiki Praveen Kumar and Sasidhahr B. S. **Poster presentation** at *XIV J-NOST Conference for Research Scholars* held at CSIR-IICT, Hyderabad, India, 28 November – 1 December, 2018.

(2) Nitriles: a valuable synthon in nitrogen containing-heterocyclic and building block synthesis. **Ashitha K. T**., Fathimath Salfeena C. T., Valmiki Praveen Kumar and Sasidhahr B. S. **Poster presentation** at the *CSIR- Inter Institutional Students Conference (SU-CHEM Yuva,)* held at CSIR-IICT, Hyderabad, India, 24-26 July,2019. [**Best poster presentation award**]

(3) I_2/TBHP mediated diastereoselective synthesis of spiroaziridines, **Ashitha, K. T.**; Vinaya, P. P.; Krishna, **Oral presentation** at 32nd Kerala Science Congress held at Yuvakshetra Institute of Management Studies, Mundoor, Palakkad, kerala, India. 25-27 January, 2020.

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BF_3·OEt_2-Mediated Tandem Annulation: A Strategy To Construct Functionalized Chromeno- and Pyrano-Fused Pyridines

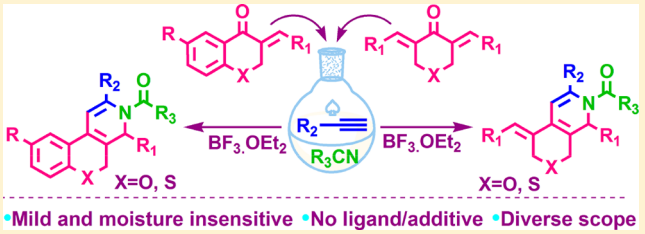
K.T. Ashitha, V. Praveen Kumar, C.T. Fathimath Salfeena, and B. S. Sasidhar*

Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram 695 019, India

Academy of Scientific and Innovative Research (AcSIR), CSIR-NIIST, Thiruvananthapuram 695 019, India

Supporting Information

ABSTRACT: A simple and efficient one-pot annulation of arylidenones, alkynes, and nitriles in the presence of BF_3·OEt_2 is described. A highly functionalized variety of N-substituted pyridine-fused chromeno and pyrano derivatives were obtained with satisfactory yields under mild reaction conditions. The method was proven to be valid for the synthesis of a diverse library of chromeno[3,4-*c*]pyridines, thiochromeno[3,4-*c*]pyridines, pyrano[3,4-*c*]pyridines, and thiopyrano[3,4-*c*]pyridine derivatives from readily accessible substrates. This experimentally simple protocol provides structurally complex, biologically relevant heterocycles in a one-pot operation.



INTRODUCTION

Chromone is an essential class of oxygen-containing heterocyclic compounds. Chromones are among the most exciting discoveries in the field of natural products which have successfully led to the development of many approved drugs and clinical trial agents[1] (Figure 1). In fact, this class of compounds is known to have a broad spectrum of medicinal properties, including antitumor,[2] antibacterial,[3] anti-HIV,[4] acetyl-CoA carboxylase (ACC) inhibitor,[5] etc. Many pharmacologically relevant natural products such as hematoxylin, riparichromene, clausenin, and calanolide A have been synthesized from the versatile intermediate chromanone.[6] On the other hand, pyridine as a privileged *N*-heterocycle is associated with various natural products and pharmaceuticals.[7] Interestingly, more than 100 currently marketed drugs contain this core.[8]

The medicinal properties of these compounds are associated with their bi- and tricyclic molecular hybrids. Consequently, a variety of chimeric structures of chromones[1d,9] and pyridines[8,10] have been prepared and evaluated for therapeutic applications. In 1997, Unangst et al. synthesized chromeno-[3,4-*c*]pyridin-5-ones by a cyclocondensation of an appropriate phenol with a piperidone ester under strongly acidic conditions.[11] Zhou et al. reported microwave-assisted, cobalt-catalyzed intramolecular [2 + 2 + 2] cyclization of dialkynylnitriles to pyrano[3,4-*c*][1,6]naphthyridines.[12] Panda and co-workers demonstrated one-pot cyclization for the preparation of cyclic ethers from their diols via a tandem oxidation−reduction protocol. The protocol was also generalized for the synthesis of pyrano[3,4-*c*]pyridine derivative.[13] In the total synthesis of camptothecin and SN-38, an important precursor, (*S*)-4-ethyl-4-hydroxy-8-methoxy-1*H*-pyrano[3,4-*c*]-pyridin-3(4*H*)-one, was achieved through the multistep process starting from 2-methoxypyridine-3-carboxylic acid.[14] These highlighted methods mainly possess drawbacks such as unavailability of starting substrates and multistep synthesis.

The generation of hybrid pharmacophore through the fusion of medicinally active chromenones/pyranones and pyridines will undoubtedly enrich the structural template. Therefore, the development of these enriched structural templates through multiple bond-forming transformations involving multicomponent reactions (MCRs) in one pot is the key to generating molecular diversity. The significance of applications of MCRs in the drug discovery process,[15] total synthesis,[16] and the development of various strategies for the construction of new chemical entities is quite evident.[17]

Owing to the aforementioned biological importance of pyridines, related hybrids, and our interest in the design and development[18] of medicinally essential heterocycles, recently we have unraveled a one-pot multicomponent cascade synthesis of pyridine appended heterocycles from the readily accessible arylidenones, alkynes, and nitriles.[19] This simple protocol has led us now to report the diverse library of chromeno[3,4-*c*]pyridines, thiochromeno[3,4-*c*]pyridines, pyrano[3,4-*c*]pyridines, and thiopyrano[3,4-*c*]pyridines.

RESULTS AND DISCUSSION

In sharp contrast to the well-documented approaches to access either chromeno[4,3-*b*]pyridines[10b,20] or chromeno[3,2-*c*]-pyridines,[21] we report a one-pot, multicomponent cascade annulation for the construction of chromeno[3,4-*c*]pyridines.

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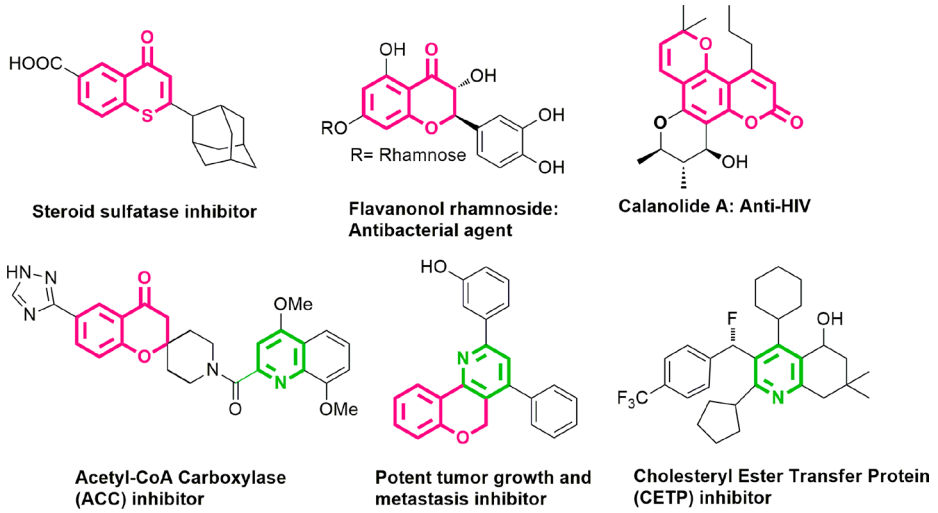
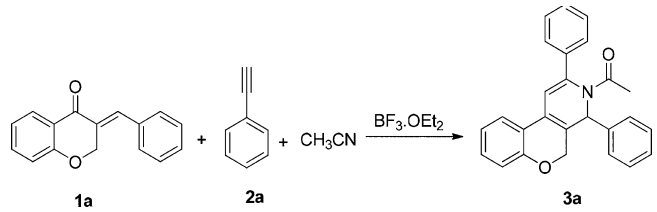


Figure 1. Medicinally relevant chromane, thiochromane, and pyridine derivatives.

Table 1. Optimization of the Reaction Conditions[a]



entry	**1a** (equiv)	**2a** (equiv)	Lewis acid	solvent	temp (°C)	yield[b] (%)
1	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_3CN	rt	12
2	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_3CN	50	22
3	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	toluene + CH_3CN (2 equiv)	50	trace
4	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	DCE + CH_3CN (2 equiv)	50	trace
5	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	DCM + CH_3CN (2 equiv)	50	trace
6	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	THF + CH_3CN (2 equiv)	50	0
7	1	1	$BF_3{\cdot}OEt_2$ (1 equiv)	DMF + CH_3CN (2 equiv)	50	0
8	1	1	$AlCl_3$	CH_3CN	50	0
9	1	1	$GaBr_3$	CH_3CN	50	0
10	1	1	$ZnCl_2$	CH_3CN	50	0
11.	1	1	I_2	CH_3CN	50	0
12	1	1	CF_3COOH	CH_3CN	50	0
13	1	1	PTSA	CH_3CN	50	0
14	1	1	$PhB(OH)_2$	CH_3CN	50	0
15	1	1	$Sc(OTf)_3$	CH_3CN	50	0
16	1	1	$Cu(OTf)_2$	CH_3CN	50	0
17	1	1	$Zn(OTf)_2$	CH_3CN	50	0
18	1	1	$BF_3{\cdot}OEt_2$ (1 equiv) + $AuPPh_3$ (20 mol %)	CH_3CN	50	20
19	1	1	$BF_3{\cdot}OEt_2$ + $AuCl_3$	CH_3CN	50	23
20	1	1	$BF_3{\cdot}OEt_2$ + $AuCl_3{\cdot}H_2O$	CH_3CN	50	21
21	1	1	$BF_3{\cdot}OEt_2$ + $Cu(OAc)_2$	CH_3CN	50	0
22	1	1	$BF_3{\cdot}OEt_2$ + I_2	CH_3CN	50	0
23	1	2	$BF_3{\cdot}OEt_2$ (1 equiv)	CH_3CN	50	30
24	1	3	$BF_3{\cdot}$ OEt_2 (1 equiv)	CH_3CN	50	42
25	1	3	BF_3 ${\cdot}OEt_2$ (2 equiv)	CH_3CN	50	56
26	1	3	$BF_3{\cdot}OEt_2$ (3 equiv)	CH_3CN	50	66

[a]Unless otherwise specified, all of the reactions were carried out at 50 °C, **1a** (0.12 mmol), H_2O (0.24 mmol) in 2 mL of CH_3CN. [b]Isolated yield.

As an extension of our recent report,[16] the feasibility of this annulation reaction was first tested using 1 equiv of (*E*)-3-benzylidenechroman-4-one (**1a**), phenylacetylene (**2a**), and acetonitrile in the presence of 1 equiv of $BF_3{\cdot}OEt_2$ at 50 °C, which presumably afforded 1-(2,4-diphenyl-4,5-dihydro-3*H*-chromeno[3,4-*c*]pyridin-3-yl)ethanone (**3a**) in 22% of yield (Table 1, entry 2). The model reaction was also examined for various Lewis acids like $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, $La(OTf)_3$, etc. However, the reaction did not afford the expected product. Bronsted acids TFA, benzoic acid, and

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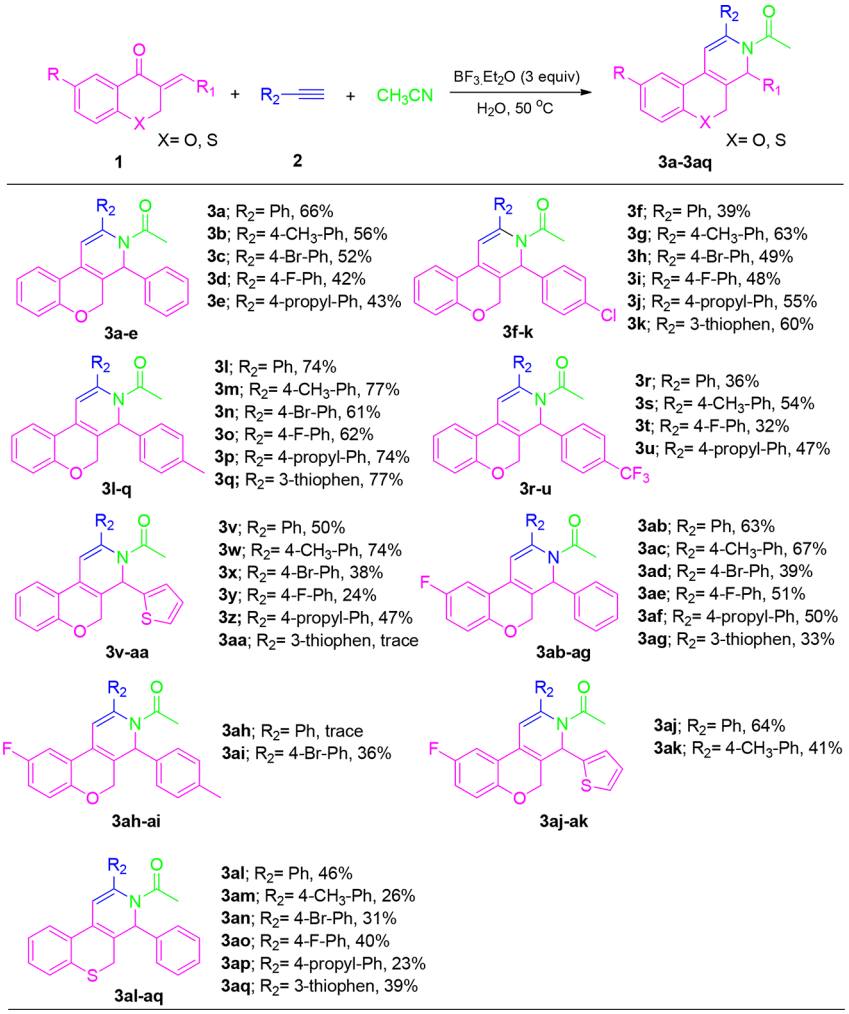
Scheme 1. Scope of the Reaction for *N*-Acetylated, Chromeno-, and Thiochromeno[3,4-*c*]pyridines



phenylboronic acid, etc., failed to furnish the product even in trace amounts. Addition of 2 equiv of acetonitrile in the presence of other solvents such as toluene, DCE, and DCM afforded the product in meager yields, while THF and DMF did not show any positive result (Table 1, entries 3−7). When we tried to optimize with carbophilic Lewis acids, such as $AuCl_3$, $AuPPh_3$, $AuCl_3H_2O$, $Cu(OAc)_2$ and I_2 as additives, along with the $BF_3{\cdot}OEt_2$, we could not find any marked improvement in the reaction. Further, the reaction was observed at varying temperatures. A low yield of about 12% was obtained for the room temperature reaction. On increasing the temperature from 50 °C, the reaction started to produce some byproducts which apparently resulted in poor yields. From the optimization parameters listed in Table 1, an addition of three equivalent of $BF_3{\cdot}OEt_2$, with three equivalent of an alkyne, without any cosolvent (Table 1, entry 26) at 50 °C emerges as the optimized condition, furnishing the highest yield (66%) of the targeted chromeno[3,4-*c*]pyridine.

With the optimized reaction conditions in hand, all of the subsequent reactions of (*E*)-3-arylidenechroman-4-one (1 equiv) and aryl or heteroaryl alkynes (3 equiv) were performed in the presence of $BF_3{\cdot}OEt_2$ (3 equiv) at 50 °C in acetonitrile for 10−90 min. After completion of the reaction as evident from TLC, the product extracted with ethyl acetate and purified by column chromatography to obtain pure chromeno-[3,4-*c*]pyridine derivatives (**3**). The generality of this three-component annulation was well explored for substituted (*E*)-3-arylidenechroman-4-one, aromatic acetylenes, bearing a series of electron-withdrawing and electron-donating substituents and heteroaryl ring thiophene. 6-Fluoroarylidene chromanones were also generalized with the variety of arylidene and alkynes in the presence of acetonitrile. These different, electronically substituted varied reagents reacted efficiently under the optimized conditions to afford the corresponding chromeno-[3,4-*c*] pyridines in acceptable yields (Scheme 1). We turned our attention to assessing the scope of this annulation reaction with arylidene thiochromanone, alkynes bearing a series of electron-withdrawing and electron-donating substituents. In all cases, the methodology worked well to synthesize the targeted thiochromeno[3,4-*c*]pyridines (**3al−aq**) in moderate to good yields (Scheme 1). From our observations, we found that the yields of the thiochromeno[3,4-*c*]pyridines are lower than those of the chromeno[3,4-*c*]pyridines. It may be attributed to the basicity of heteroatom sulfur as compared to that of oxygen.

The successful annulation of chromeno[3,4-*c*]pyridines and thiochromeno[3,4-*c*]pyridines led us to examine the reactivity of (3*E*,5*E*)-3,5-diarylidenedihydro-2*H*-pyran-4(3*H*)-one and (3*Z*,5*Z*)-3,5-diarylidenedihydro-2*H*-thiopyran-4(3*H*)-one with various substituted alkynes and acetonitrile under the same optimized condition. Pyranone and thiopyranone diarylidenes (**4**) derived from phenyl and thiophenes were utilized for the

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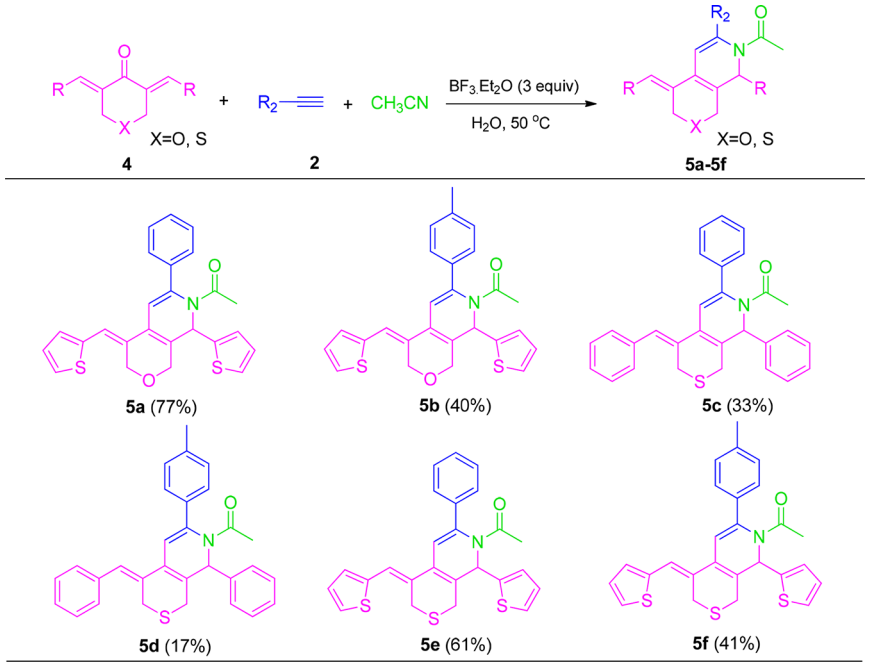
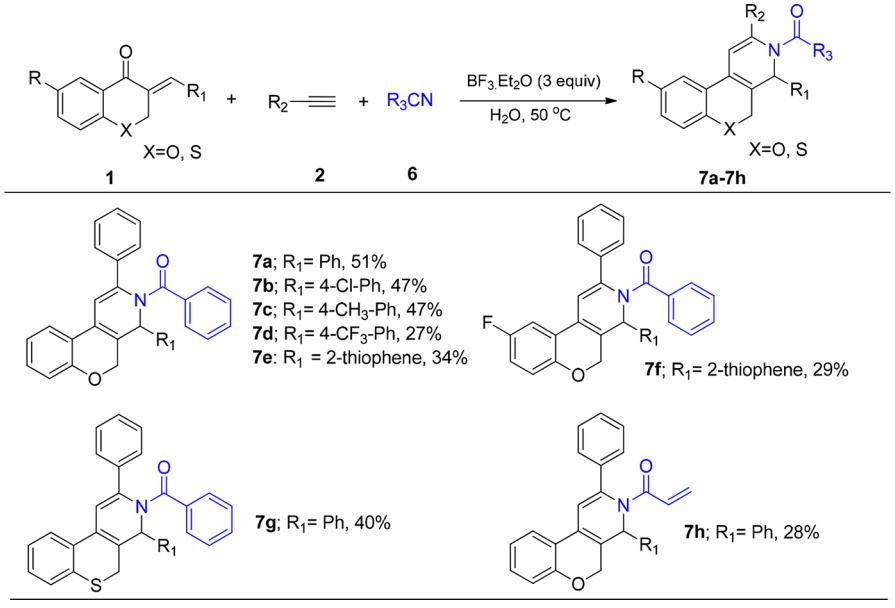
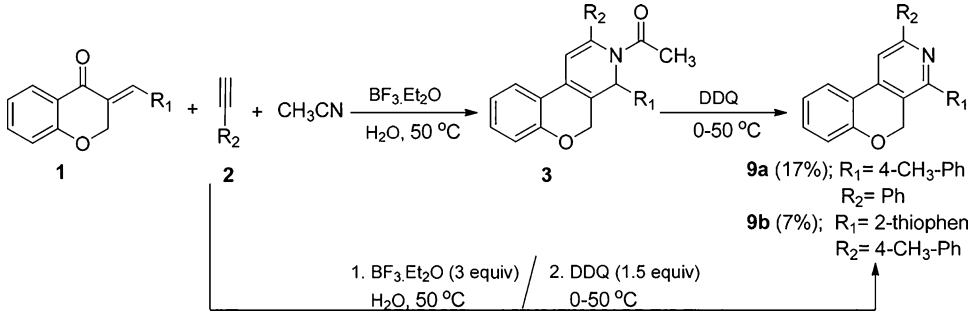
Scheme 2. Generality of Pyrano- and Thiopyrano[3,4-*c*]pyridine Synthesis



Scheme 3. Scope of Nitriles for [3,4-*c*]Pyridine Synthesis



Scheme 4. One-Pot Synthesis of 5*H*-Chromeno[3,4-*c*]pyridines



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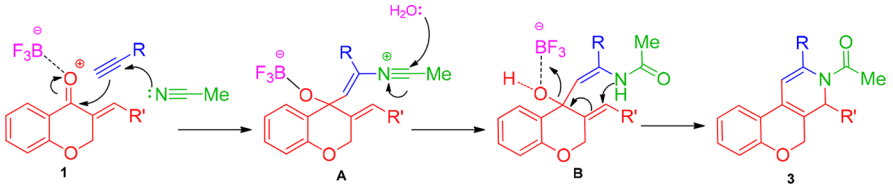
Scheme 5. Plausible Mechanism of Chromeno[3,4-*c*]pyridine Formation



three-component cascade annulation. To our delight, we obtained the new molecular templates of pyrano[3,4-*c*]-pyridines and thiopyrano[3,4-*c*]pyridines (**5**) in acceptable yields (Scheme 2). Delighted with the success of the broad diversity of arylidenones and alkynes, we further explored the compatibility of other nitrile sources such as benzonitrile and acrylonitrile. As targeted, we successfully obtained *N*-substituted chromeno- and thiochromeno-fused pyridines (**7**) under mild and straightforward reaction conditions in acceptable yields (Scheme 3). Finally, under the DDQ oxidation conditions, product **3** (**3l** and **3w**) was successfully transformed into the corresponding 5*H*-chromeno[3,4-*c*]-pyridines of biological relevance (Scheme 4).

Based on the aforementioned experimental results, a plausible mechanistic pathway is outlined in Scheme 5. Being oxophilic in nature, $BF_3{\cdot}OEt_2$ coordinates to the carbonyl oxygen of arylidene ketone **1**, favoring the carbonyl group to undergo 1,2 addition by phenylacetylene. This is followed by the attack of acetonitrile to phenyl acetylene leading to the formation of intermediate **A**. Hydrolysis of nitrile group of intermediate **A** under acidic conditions leads to the creation of intermediate **B** which on subsequent intramolecular cyclization of amide nitrogen affords the product **3**.

CONCLUSION

In conclusion, a simple and efficient $BF_3{\cdot}OEt_2$-mediated cascade annulation of arylidenones, alkynes, and nitriles have been developed. This reaction affords a highly generalized and straightforward way to construct *N*-substituted chromeno-, thiochromeno-, pyrano-, and thiopyrano[3,4-*c*]pyridines under mild conditions and tolerates a wide range of functional groups. In addition, a one-pot synthesis of 5*H*-chromeno[3,4-*c*]pyridines was successfully achieved. Notably, the reaction is process friendly, with easily accessible substrates and without any inert conditions. A plausible mechanism of the reaction has proposed. Our protocol will aid in the generation of a diverse library of fused pyridine hybrids with potential biological significance. Further investigation for the construction of other heterocyclic appended fused pyridines via this annulation reaction is in progress at our laboratory.

EXPERIMENTAL SECTION

General Experimental Methods. All the reactions are performed with commercially available best grade chemicals without further purification. All of the solvents used are reagent-grade and commercially available. Column chromatography was performed using 100−200 mesh silica gel, and mixtures of hexane−ethyl acetate were used for elution of the products. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.25, singlet). Multiplicities are given as s (singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublet); dt (doublet of triplet); m (multiplet). Coupling constants are reported as *J* values in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). HRMS analysis was recorded on a Thermo Scientific Exactive-LCMS instrument by electron spray ionization method with ions given in *m*/*z* using Orbitrap analyzer. IR spectra were recorded on a Bruker FT-IR spectrometer.

*General Procedure for the Synthesis of Arylideneehroman-4-ones and Thiochroman-4-ones (**1**).*[22] To a solution of chroman-4-one/thiochroma-4-one (4.0 mmol) in ethanol was added corresponding aryl or hetero aryl aldehyde (4.40 mmol) at 0 °C. An aqueous solution of NaOH (10%, 10 mL) was added dropwise to this reaction mixture. The solid precipitate formed was collected by filtration and washed with water and hexane. It was dried and used for further reaction.

*General Procedure for the Synthesis of (3E,5E)-3,5-Diarylidenedihydro-2H-pyran-4(3H)-one/(3Z,5Z)-3,5-Diarylidenedihydro-2H-thiopyran-4(3H)-one (**4**).*[22] To a solution of dihydro-2*H*-pyran-4(3*H*)-one/dihydro-2*H*-thiopyran-4(3*H*)-one (2.00 mmol) in ethanol was added the corresponding aryl or hetero aryl aldehyde (2.20 mmol) at 0 °C. An aqueous solution of NaOH (10%, 10 mL) was added dropwise to this reaction mixture. The solid precipitate formed was collected by filtration and washed with water and hexane. It was dried and used for further reaction.

*General Procedure for $BF_3{\cdot}OEt_2$-Mediated One-Pot Synthesis of N-Acetylated Chromeno[3,4-c]pyridines/Thiochromeno[3,4-c]-pyridines (**3**).* To a mixture of 1 equiv of substituted arylidenechroman-4-one/thiochroman-4-one (0.12 mmol) and 3 equiv of aryl- or heteroarylalkyne (0.36 mmol) in acetonitrile (2 mL) with 2 equiv of water at 50 °C added 3 equiv of $BF_3{\cdot}OEt_2$ (0.36 mmol). The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), evaporated in vacuo, and purified by column chromatography using 100−200 mesh silica gel with ethyl acetate/hexane as the eluent to afford the corresponding *N*-acetylated fused pyridines as the product.

*1-(2,4-Diphenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)-ethanone (**3a**).* Yield: 30 mg, 66% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1661, 1601, 1036. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.35−7.29 (m, 3H), 7.28−7.26 (m, 4H), 7.22 (td, *J* = 8.0, 1.5 Hz, 1H), 7.13 (s, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.52 (s, 1H), 6.44 (s, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 153.9, 138.5, 138.3, 137.2, 129.5, 129.0, 128.8, 128.6, 128.5, 128.1, 125.8, 124.7, 123.0, 121.7, 120.9, 116.5, 112.0, 65.8, 53.5, 24.7. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{21}NO_2Na$ 402.1470, found 402.1461.

*1-(4-Phenyl-2-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3b**).* Yield: 26 mg, 56% yield, as a colorless foam. R_f = 0.21 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3061, 1666, 1604, 1116. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.49 (m, 2H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.34−7.27 (m, 3H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 3H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 2.30 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.9, 138.8, 138.3, 137.2, 135.7, 133.2, 129.7, 129.4, 128.8, 128.6, 128.4, 128.3, 128.1, 125.7, 125.5, 124.7, 123.1, 121.7, 121.0, 116.5, 111.3, 65.8, 53.5, 24.8, 21.2. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{27}H_{23}NO_2Na$ 416.1626, found 416.1620.

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*1-(2-(4-Bromophenyl)-4-phenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3c**).* Yield: 29 mg, 52% yield, as a colorless foam. R_f = 0.19 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1669, 1586, 1072, 1040. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50−7.46 (m, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.37 (dd, J = 8.0, 1.5 Hz, 1H), 7.34−7.29 (m, 3H), 7.22 (td, J = 8.0, 1.5 Hz, 1H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.99 (d, J = 7.0 Hz, 2H), 6.91 (dd, J = 8.0, 1.0 Hz, 1H), 6.50 (s, 1H), 6.44 (s, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 153.8, 137.5, 137.2, 137.0, 132.2, 129.6, 128.9, 128.6, 128.0, 127.2, 126.4, 124.7, 123.0, 122.7, 121.7, 120.7, 116.6, 112.6, 65.7, 53.5, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}BrNO_2Na$ 480.0575, found 480.0580.

*1-(2-(4-fluorophenyl)-4-phenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3d**).* Yield: 20 mg, 42% yield, as a colorless foam. R_f = 0.16 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3065, 1667, 1599,1098. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50−7.49 (m, 2H), 7.38 (dd, J = 7.5, 1.5 Hz, 1H), 7.35−7.29 (m, 3H), 7.21 (td, J = 8.0, 1.5 Hz, 1H), 7.09 (s, 2H), 7.02 (td, J = 7.5, 1 Hz, 1H), 6.96 (t, J = 9.0 Hz, 2H), 6.91 (dd, J = 8.0, 0.5 Hz, 1H), 6.51 (s, 1H), 6.39 (s, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.76 (d, J = 15.0 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 153.8, 137.2, 137.1, 134.7, 134.7, 133.7, 131.6, 129.5, 128.9, 128.6, 128.1, 127.5, 127.4, 125.8, 124.7, 123.0, 121.7, 120.8, 116.6, 116.2, 116.0, 112.0, 65.7, 53.5, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}FNO_2Na$ 420.1376, found 420.1376.

*1-(4-Phenyl-2-(4-propylphenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3e**).* Yield: 22 mg, 43% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1666, 1606, 1040. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.0 Hz, 2H), 7.39 (dd, J = 7.5, 1.5 Hz, 1H), 7.34−7.28 (m, 3H), 7.21 (td, J = 8.0, 1.5 Hz, 1H), 7.08−7.00 (m, 5H), 6.91 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 6.40 (s, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 2.54−2.51 (m, 2H), 1.71 (s, 3H), 1.60−1.56 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.9, 143.5, 138.4, 137.3, 135.9, 129.4, 129.1, 128.8, 128.4, 128.1, 125.7, 125.4, 124.7, 123.1, 121.7, 121.0, 116.5, 111.2, 65.8, 53.5, 37.7, 24.7, 24.4, 13.8. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{29}H_{27}NO_2Na$ 444.1939, found 444.1943.

*1-(4-(4-Chlorophenyl)-2-phenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3f**).* Yield: 19 mg, 39% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1666, 1593, 1091; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.5 Hz, 2H), 7.40 (dd, J = 8.0, 1.5 Hz, 1H), 7.31−7.28 (m, 5H), 7.22 (td, J = 8.0, 1.5 Hz, 1H), 7.12 (s, 2H), 7.03 (td, J = 7.5, 1 Hz, 1H), 6.92 (dd, J = 8.5, 1.0 Hz, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.71 (d, J = 15.0 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 153.8, 138.3, 138.3, 135.8, 134.4, 129.6, 129.1, 129.1, 128.8, 125.7, 125.1, 125.0, 123.1, 121.8, 120.7, 116.6, 111.8, 65.6, 52.8, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}ClNO_2Na$ 436.1080, found 436.1089.

*1-(4-(4-Chlorophenyl)-2-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3g**).* Yield: 32 mg, 63% yield, as a colorless foam. R_f = 0.28 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3035, 1667, 1588, 1091. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.5 Hz, 2H), 7.39 (dd, J = 7.5, 1.5 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 (td, J = 8.0, 1.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.02 (td, J = 7.5, 1.0 Hz, 3H), 6.91 (dd, J = 8.5, 1.0 Hz, 1H), 6.46 (s, 1H), 6.40 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.71 (d, J = 15.0 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 153.9, 139.0, 138.3, 135.8, 135.5, 134.3, 129.8, 129.6, 129.6, 129.0, 125.6, 125.0, 124.8, 123.1, 121.8, 120.8, 116.6, 111.2, 65.6, 52.8, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{22}ClNO_2Na$ 450.1237, found 450.1233.

*1-(2-(4-Bromophenyl)-4-(4-chlorophenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3h**).* Yield: 29 mg, 49% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2928, 1666, 1588, 1269, 1091. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (dd, J = 8.5, 2.0 Hz, 4H), 7.37 (dd, J = 7.5, 1.5 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.23 (td, J = 8.0, 1.5 Hz, 1H), 7.03 (td, J = 7.5, 1.0 Hz, 1H), 6.99 (d, J = 7.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 6.44 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.70 (d, J = 15.0 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 153.8, 137.2, 137.1, 135.6, 134.5, 133.6, 132.3, 131.6, 129.8, 129.5, 129.2, 127.1, 125.6, 124.9, 123.1, 122.9, 121.8, 120.6, 116.6, 112.4, 65.5, 52.8, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{19}BrClNO_2Na$ 514.0185, found 514.0177.

*1-(4-(4-Chlorophenyl)-2-(4-fluorophenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3i**).* Yield: 25 mg, 48% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3068, 1669, 1600, 1092. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.23 (td, J = 8.0, 1.5 Hz, 1H), 7.09 (s, 2H), 7.04−6.97 (m, 3H), 6.92 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 6.39 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.71 (d, J = 15.0 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 163.9, 161.9, 153.8, 137.1, 135.7, 134.5, 129.7, 129.5, 129.1, 127.5, 127.4, 124.9, 123.1, 121.8, 120.6, 116.6, 116.3, 116.1, 111.8, 65.6, 52.9, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{19}ClFNO_2Na$ 454.0986, found 454.0995.

*1-(4-(4-Chlorophenyl)-2-(4-propylphenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3j**).* Yield: 30 mg, 55% yield, as a colorless foam. R_f = 0.28 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1668, 1588, 1091. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 7.5 Hz, 1H), 7.26 (d, J = 5.5 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.12 (s, 5H), 7.01 (t, J = 7.5 Hz, 1H), 6.93−6.89 (m, 2H), 6.65 (s, 1H), 6.41 (s, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.84 (d, J = 15.5 Hz, 1H), 2.57−2.54 (m, 2H), 1.70 (s, 3H), 1.63−1.58 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 143.6, 140.4, 138.2, 135.9, 129.5, 129.1, 126.8, 126.8, 126.5, 125.9, 125.2, 124.2, 123.2, 121.7, 120.8, 116.5, 110.7, 65.6, 49.7, 37.7, 24.8, 24.4, 13.8. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{29}H_{26}ClNO_2Na$ 478.1550, found 478.1553.

*1-(4-(4-Chlorophenyl)-2-(thiophene-3-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3k**).* Yield: 30 mg, 60% yield, as a colorless foam. R_f = 0.21 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3106, 1666, 1596, 1090. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 8.5 Hz, 2H), 7.36 (dd, J = 8.0, 1.5 Hz, 1H), 7.29−7.27 (m, 3H), 7.22 (td, J = 8.0, 1.5 Hz, 1H), 7.03−7.00 (m, 2H), 6.92−6.90 (m, 2H), 6.42 (s, 2H), 4.87 (d, J = 15.5 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.8, 140.1, 135.9, 134.3, 133.6, 130.9, 129.6, 129.5, 129.4, 129.0, 127.2, 125.3, 125.0, 125.0, 123.1, 122.0, 121.8, 120.7, 65.7, 52.7, 24.1. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{24}H_{18}ClNO_2SNa$ 442.0644, found 442.0636.

*1-(2-Phenyl-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3l**).* Yield: 35 mg, 74% yield, as a colorless foam. R_f = 0.26 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3060, 1666, 1596, 1090. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 3H), 7.27−7.25 (m, 3H), 7.21 (td, J = 8.0, 1.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 4H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (dd, J = 8.0, 1.0 Hz, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 2.30 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 153.8, 138.6, 138.3, 138.2, 134.2, 129.5, 129.4, 129.0, 128.6, 128.1, 126.1, 125.8, 124.5, 123.0, 121.7, 121.0, 116.5, 111.9, 65.8, 53.3, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{23}NO_2Na$ 416.1626, found 416.1637.

*1-(2,4-Di-p-tolyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)-ethanone (**3m**).* Yield: 38 mg, 77% yield, as a colorless foam. R_f = 0.28 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3031, 1666, 1606, 1041. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39−7.37 (m, 3H), 7.20 (td, J = 7.5, 1.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.04−6.99 (m, 3H), 6.90 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 6.39 (s, 1H), 4.88 (d, J = 15.0 Hz, 1H), 4.75 (d, J = 15.0 Hz, 1H), 2.30 (s, 6H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.8, 138.7, 138.2, 138.1, 135.8, 134.1, 129.9, 129.7, 129.5, 129.4, 128.0, 125.7, 124.5, 123.0, 121.7, 121.0, 116.5, 111.2, 65.8, 53.2, 24.8, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{28}H_{25}NO_2Na$ 430.1783, found 430.1761.

*1-(2-(4-Bromophenyl)-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3n**).* Yield: 35 mg, 61% yield, as a colorless

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foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1666, 1587, 1072. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 8.5 Hz, 2H), 7.37−7.34 (m, 3H), 7.21 (td, J = 8.0, 1.5 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.02 (td, J = 7.5, 1.0 Hz, 3H), 6.91 (dd, J = 8.0, 1.0 Hz, 1H), 6.46 (s, 1H), 6.43 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.74 (d, J = 15.5 Hz, 1H), 2.31 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 138.4, 137.5, 137.1, 133.9, 132.2, 129.6, 129.5, 128.0, 127.2, 126.7, 124.5, 123.0, 122.6, 121.7, 120.7, 116.6, 112.5, 65.8, 53.3, 24.8, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{22}BrNO_2Na$ 494.0732, found 494.0721.

*1-(2-(4-Fluorophenyl)-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3o**).* Yield: 31 mg, 62% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1667, 1600, 1042. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 7.5 Hz, 3H), 7.21 (td, J = 8.0, 2.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 4H), 7.01 (td, J = 7.5, 1.0 Hz, 1H), 6.97 (t, J = 9.0 Hz, 2H), 6. 91 (dd, J = 8.0, 1.0 Hz, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 4.87 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 2.31 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 163.8, 161.8, 153.8, 138.3, 137.2, 134.8, 134.1, 129.6, 129.5, 128.0, 127.5, 127.5, 126.1, 124.5, 123.0, 121.7, 120.8, 116.5, 116.2, 116.0, 111.9, 65.8, 53.3, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{22}FNO_2Na$ 434.1532, found 434.1530.

*1-(2-(4-Propylphenyl)-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3p**).* Yield: 39 mg, 74% yield, as a colorless foam. R_f = 0.30 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2958, 1666, 1588, 1228. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 3H), 7.20 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.08−7.07 (m, 4H), 7.01 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 6.40 (s, 1H), 4.88 (d, J = 15.0 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 2.55−2.52 (m, 2H), 2.30 (s, 3H), 1.70 (s, 3H), 1.61−1.56 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.9, 143.5, 138.4, 138.1, 136.0, 134.3, 129.5, 129.3, 129.0, 128.0, 125.7, 124.5, 123.0, 121.6, 121.0, 116.5, 111.1, 65.9, 53.3, 37.7, 24.7, 24.3, 21.2, 13.8. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{30}H_{29}NO_2Na$ 458.2096, found 458.2086.

*1-(2-(Thiophene-3-yl)-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3q**).* Yield: 37 mg, 77% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3103, 1663, 1587, 1041. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.34 (m, 3H), 7.25 (dd, J = 5.0, 3.0 Hz, 1H), 7.20 (td, J = 8.0, 1.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.02−6.99 (m, 2H), 6.94 (dd, J = 5.0, 1.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 4.5 Hz, 2H), 4.87 (d, J = 15.0 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 2.29 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 153.8, 140.4, 138.1, 134.3, 133.6, 129.5, 129.4, 127.8, 127.0, 126.1, 125.5, 124.5, 123.0, 122.0, 121.7, 120.9, 116.5, 110.7, 65.9, 53.1, 24.2, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}NO_2SNa$ 422.1191, found 422.1196.

*1-(2-Phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3r**).* Yield: 19 mg, 36% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3064, 1665, 1609, 1067. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.41 (dd, J = 7.5, 1.0 Hz, 1H), 7.31−7.29 (m, 3H), 7.23 (dd, J = 7.5, 1.5 Hz, 1H), 7.13 (s, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.55 (s, 1H), 6.45 (s, 1H), 4.90 (d, J = 15.5 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 153.9, 141.4, 138.4, 138.1, 129.8, 129.1, 128.9, 128.6, 125.9, 125.8, 125.7, 125.3, 124.5, 123.2, 121.9, 120.7, 116.6, 111.8, 65.6, 53.0, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{20}F_3NO_2Na$ 470.1344, found 470.1335.

*1-(2-(p-Tolyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3s**).* Yield: 30 mg, 54% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3066, 1663, 1166, 1067. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.41 (dd, J = 7.5, 1.5 Hz, 1H), 7.23 (td, J = 8.0, 1.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.05−7.02 (m, 3H), 6.92 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 2.31 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 153.9, 141.4, 139.1, 138.4, 135.3, 129.8, 129.7, 128.6, 125.8, 125.8, 125.6, 125.3, 124.2, 123.2, 121.8, 120.7, 116.6, 111.0, 65.6, 53.0, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{28}H_{22}F_3NO_2Na$ 484.1500, found 484.1487.

*1-(2-(4-Fluorophenyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3t**).* Yield: 18 mg, 32% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3073, 1666, 1601, 1067. ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (q, J = 8.5 Hz, 4H), 7.39 (d, J = 7.5 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.10 (s, 2H), 7.05 (d, J = 7.5 Hz, 1H), 7.02−6.98 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 6.41 (s, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.72 (d, J = 15.5 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 164.0, 162.0, 153.9, 141.3, 137.3, 134.3, 129.8, 128.5, 127.5, 127.4, 125.9, 125.9, 125.3, 124.6, 123.1, 121.9, 120.6, 116.7, 116.4, 116.2, 111.7, 65.5, 53.0, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{19}F_4NO_2Na$ 488.1250, found 488.1256.

*1-(2-(4-Propylphenyl)-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3u**).* Yield: 28 mg, 47% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3056, 1666, 1606, 1065. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 8.0, 1.5 Hz, 1H), 7.25−7.21 (m, 1H), 7.10 (d, J = 8.5 Hz, 2H), 7.04 (td, J = 7.5, 1.5 Hz, 3H), 6.92 (dd, J = 8.0, 1.0 Hz, 1H), 6.54 (s, 1H), 6.42 (s, 1H), 4.89 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 2.56−2.53 (m, 2H), 1.73 (s, 3H), 1.62−1.57 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 153.9, 143.9, 141.5, 138.5, 135.5, 129.7, 129.2, 128.6, 125.8, 125.8, 125.7, 125.3, 124.2, 123.2, 121.8, 120.8, 116.6, 111.0, 65.6, 53.0, 37.7, 24.7, 24.3, 13.8. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{30}H_{26}F_3NO_2Na$ 512.1813, found 512.1823.

*1-(2-Phenyl-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]-pyridin-3-yl)ethanone (**3v**).* Yield: 23 mg, 50% yield, as a colorless foam. R_f = 0.23 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2922, 1648, 1605, 1033. ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (dd, J = 7.5, 1.5 Hz, 1H), 7.31−7.28 (m, 3H), 7.27 (dd, J = 5.5, 1.5 Hz, 1H), 7.22−7.18 (m, 3H), 7.13 (d, J = 3.5 Hz, 1H), 7.01 (td, J = 7.5, 1.5 Hz, 1H), 6.93 (dd, J = 5.5, 4.0 Hz 1H), 6.90 (dd, J = 8.0, 1.0 Hz, 1H), 6.66 (s, 1H), 6.45 (s, 1H), 4.89 (d, J = 15.0 Hz, 1H), 4.83 (d, J = 15.0 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 153.9, 140.3, 138.5, 138.1, 129.6, 129.0, 128.8, 128.7, 126.8, 126.8, 126.6, 126.0, 125.6, 124.2, 123.2, 121.7, 120.7, 116.6, 111.5, 65.6, 49.7, 33.6, 24.8. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{24}H_{19}NO_2SNa$ 408.1034, found 408.1028.

*1-(4-(Thiophene-2-yl)-2-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3w**).* Yield: 35 mg, 74% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3069, 1665, 1606, 1040. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (dd, J = 7.5, 1.5 Hz, 1H), 7.25 (dd, J = 5.0, 1.0 Hz, 1H), 7.20 (td, J = 8.0, 1.5 Hz, 1H), 7.16 (s, 5H), 7.01 (td, J = 7.5, 1.5 Hz, 1H), 6.92 (dd, J = 5.5, 1.5 Hz, 1H), 6.89 (dd, J = 8.0, 1.0 Hz, 1H),6.65 (s, 1H), 6.41 (s, 1H), 4.88 (d, J = 15.5 Hz, 1H), 4.83 (d, J = 15.5 Hz, 1H), 2.32 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 140.3, 138.9, 138.1, 135.7, 129.7, 129.5, 126.8, 126.7, 126.5, 125.9, 125.3, 124.2, 123.2, 121.7, 120.8, 116.5, 110.8, 65.6, 49.7, 24.8, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}NO_2SNa$ 422.1191, found 422.1188.

*1-(2-(4-Bromophenyl)-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3x**).* Yield: 21 mg, 38% yield, as a colorless foam. R_f = 0.23 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1670, 1586, 1072; ^1H NMR (500 MHz, $CDCl_3$): 7.45 (d, J = 8.5 Hz, 2H), 7.37 (dd, J = 7.5, 1.3 Hz, 1H), 7.27 (dd, J = 5.0, 1.0 Hz, 1H), 7.21 (td, J = 8.0, 1.5 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 7.09 (d, J = 6.0 Hz, 2H), 7.01 (td, J = 7.5, 1.1 Hz, 1H), 6.93 (dd, J = 5.10, 3.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.0 Hz, 1H), 6.65 (s, 1H), 6.45 (s, 1H), 4.88 (d, J = 15.0 Hz, 1H), 4.83 (d, J = 15.5 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 153.8, 140.0, 137.4, 137.0, 132.3, 129.7, 127.4, 126.9, 126.7, 126.1, 124.1, 123.2, 122.8, 121.8, 120.6, 116.6, 112.1, 65.5, 49.6, 24.8. HRMS (ESI-

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Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{24}H_{18}BrNO_2SNa$ 486.0139, found 486.0132.

*1-(2-(4-Fluorophenyl)-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3y**).* Yield: 12 mg, 24% yield, as a colorless foam. R_f = 0.37 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3072, 1670, 1599, 1229. ^{1}H NMR (500 MHz, $CDCl_3$): δ7.37 (dd, J = 7.5, 1.5 Hz, 1H), 7.28 (dd, J = 5.5, 1.5 Hz, 1H), 7.23−7.19 (m, 3H), 7.13 (d, J = 3.5, Hz, 1H), 7.06−6.99 (m, 3H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.0 Hz, 1H), 6.65 (s, 1H), 6.40 (s, 1H), 4.89 (d, J = 15.5 Hz, 1H), 4.83 (d, J = 15.0 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 163.9, 161.9, 153.8, 140.2, 137.0, 134.7, 129.6, 127.8, 127.7, 126.9, 126.6, 125.6, 124.2, 123.1, 121.7, 120.6, 116.6, 116.2, 116.1, 111.5, 65.5, 49.7, 24.8. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{24}H_{18}FNO_2SNa$ 426.0940, found 426.0930.

*1-(2-(4-Propylphenyl)-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3z**).* Yield: 24 mg, 47% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3070, 1667, 1606, 1040. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.5 Hz, 1H), 7.26−7.25 (m, 1H), 7.20 (td, J = 8.0, 1.5 Hz, 1H), 7.12 (s, 5H), 7.01 (t, J = 7.5 Hz, 1H), 6.92 (dd, J = 5.0, 3.5 Hz1H), 6.90 (d, J = 8.0 Hz, 1H), 6.65 (s, 1H), 6.42 (s, 1H), 4.89 (d, J = 15.0 Hz, 1H), 4.84 (d, J = 15.0 Hz, 1H), 2.55 (t, J = 7.5 Hz, 2H), 1.70 (s, 3H), 1.63−1.57 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 153.8, 143.6, 140.4, 138.2, 135.9, 129.5, 129.1, 126.8, 126.8, 126.5, 125.9, 125.2, 124.2, 123.2, 121.7, 120.8, 116.5, 110.7, 65.6, 49.7, 37.7, 26.9, 24.8, 24.4, 13.8. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{27}H_{25}NO_2SNa$ 450.1504, found 450.1512.

*1-(4-(Thiophene-2-yl)-2-(thiophene-3-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3aa**).* Yield: trace. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{22}H_{17}NO_2S_2Na$ 414.0598, found 414.0599.

*1-(9-Fluoro-2,4-diphenyl-4,5-dihydro-3H-chromeno[3,4-c]-pyridin-3-yl)ethanone (**3ab**).* Yield: 30 mg, 63% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1665, 1591, 1074; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.0 Hz, 2H), 7.36−7.30 (m, 3H), 7.28−7.27 (m, 3H), 7.13 (s, 2H), 7.09 (dd, J = 9.0, 3.0 Hz, 1H), 6.92−6.88 (m, 1H), 6.86 (dd, J = 9.0, 5.5 Hz, 1H), 6.53 (s, 1H), 6.34 (s, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.74 (d, J = 15.5 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 158.8, 156.9, 149.7, 138.7, 138.3, 137.0, 129.0, 128.9, 128.8, 128.6, 128.1, 127.0, 125.8, 124.2, 122.1, 117.4, 117.3, 115.5, 115.3, 111.4, 109.8, 109.6, 65.8, 53.4, 24.7. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{26}H_{20}FNO_2Na$ 420.1376, found 420.1368.

*1-(9-Fluoro-4-phenyl-2-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ac**).* Yield: 33 mg, 67% yield, as a colorless foam. R_f = 0.22 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3060,1667, 1589, 1025. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 7.0 Hz, 2H), 7.34−7.27 (m, 3H), 7.10−7.07 (m, 3H), 7.02 (s, 2H), 6.89 (td, J = 8.5, 3.0 Hz, 1H), 6.85 (dd, J = 9.0, 5.0 Hz, 1H), 6.52 (s, 1H), 6.30 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.73 (d, J = 15.5 Hz, 1H), 2.30 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 139.0, 138.8, 137.0, 135.5, 129.7, 128.9, 128.5, 128.1, 125.7, 124.4, 122.2, 122.1, 117.4, 117.3, 115.4, 115.3, 110.7, 109.8, 109.6, 65.9, 53.4, 24.8, 21.2. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{27}H_{22}FNO_2Na$ 434.1532, found 434.1522.

*1-(2-(4-Bromophenyl)-9-fluoro-4-phenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ad**).* Yield: 22 mg, 39% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1669, 1489, 1073, 1032. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 7.0 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.35−7.30 (m, 3H), 7.07 (dd, J = 9.0, 3.0 Hz, 1H), 6.99 (d, J = 7.0 Hz, 2H), 6.91 (td, J = 8.5, 3.0 Hz, 1H), 6.86 (dd, J = 9.0, 5.5 Hz, 1H), 6.52 (s, 1H), 6.35 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.73 (d, J = 15.5 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 158.8, 156.9, 149.7, 137.6, 137.2, 136.8, 132.3, 129.0, 128.7, 128.0, 127.2, 124.3, 122.9, 117.4, 117.4, 115.6, 115.5, 112.0, 109.8, 109.6, 65.8, 53.4, 24.7. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{26}H_{19}BrFNO_2Na$ 498.0481, found 498.0472.

*1-(9-Fluoro-2-(4-fluorophenyl)-4-phenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ae**).* Yield: 25 mg, 51% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3064, 1669, 1597, 1099, 1024. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 7.0 Hz, 2H), 7.36−7.29 (m, 3H), 7.09−7.06 (m, 3H), 6.98 (t, J = 9.0 Hz, 2H), 6.90 (td, J = 9.0, 3.0 Hz, 1H), 6.86 (dd, J = 9.0, 5.0 Hz, 1H), 6.52 (s, 1H), 6.29 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.73 (d, J = 15.5 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 163.9, 161.9, 158.8, 156.9, 149.7, 137.6, 136.9, 129.0, 128.7, 128.0, 127.5, 127.4, 127.1, 117.4, 117.3, 116.3, 116.1, 115.6, 115.4, 111.4, 109.8, 109.6, 65.8, 53.4, 24.7. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{26}H_{19}F_2NO_2Na$ 438.1282, found 438.1265.

*1-(9-Fluoro-4-phenyl-2-(4-propylphenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3af**).* Yield: 26 mg, 50% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1669, 1591, 1549, 1041. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 7.0 Hz, 2H), 7.35−7.29 (m, 3H), 7.08 (d, J = 6.5 Hz, 3H), 7.04 (s, 2H), 6.90 (t, J = 8.5 Hz, 1H), 6.87−6.83 (m, 1H), 6.52 (s, 1H), 6.31 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.74 (d, J = 15.5 Hz, 1H), 2.54 (t, J = 8.0 Hz, 2H), 1.71 (s, 3H), 1.61−1.56 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 143.7, 138.8, 137.1, 135.7, 129.1, 128.9, 128.5, 128.1, 126.7, 125.7, 124.4, 122.1, 117.4, 117.3, 115.4, 115.2, 110.6, 109.8, 109.6, 65.9, 53.4, 37.7, 24.8, 24.4, 13.8. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{29}H_{26}FNO_2Na$ 462.1845, found 462.1848.

*1-(9-Fluoro-4-phenyl-2-(thiophene-3-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ag**).* Yield: 16 mg, 33% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3066, 1664, 1490, 1079. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 7.0 Hz, 2H), 7.34−7.26 (m, 4H), 7.05 (dd, J = 9.0, 3.0 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.93 (d, J = 5.5 Hz, 1H), 6.89 (dd, J = 8.5, 3.0 Hz, 1H), 6.86 (dd, J = 8.5, 5.0 Hz, 1H), 6.48 (s, 1H), 6.32 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.75 (d, J = 15.5 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 158.8, 156.9, 149.7, 140.1, 137.2, 134.1, 128.9, 128.5, 127.8, 127.1, 125.4, 124.3, 122.2, 117.4, 117.3, 115.5, 115. 3, 110.2, 109.8, 109.6, 65.9, 53.3, 24.2. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{24}H_{18}FNO_2SNa$ 426.0940, found 426.0929.

*1-(9-Fluoro-2-phenyl-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ah**).* Yield: trace. HRMS (ESI-Orbitrap) m/z: [M − 1]$^+$ calcd for $C_{27}H_{22}FNO_2$ 410.1556, found 410.1546.

*1-(2-(4-Bromophenyl)-9-fluoro-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ai**).* Yield: 21 mg, 36% yield, as a colorless foam. R_f = 0.23 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3058, 1666, 1589, 1073. ^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.0 Hz, 2H), 7.26 (d, J = 1.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 5.0 Hz, 1H), 6.91−6.83 (m, 2H), 6.48 (s, 1H), 6.34 (s, 1H), 4.84 (d, J = 15.0 Hz, 1H), 4.72 (d, J = 15.0 Hz, 1H), 2.32 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.7, 158.8, 156.8, 149.7, 138.5, 137.5, 137.3, 133.7, 132.3, 129.7, 127.9, 127.2, 124.1, 122.8, 121.9, 121.9, 117.4, 117.3, 115.6, 115.4, 112.0, 109.8, 109.6, 65.8, 53.2, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{27}H_{21}BrFNO_2Na$ 512.0637, found 512.0627.

*1-(9-Fluoro-2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3aj**).* Yield: 31 mg, 64% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3070, 1666, 1590, 1177. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.30 (m, 3H), 7.28 (dd, J = 5.0, 1.5 Hz, 1H), 7.22 (s, 2H), 7.12 (d, J = 3.5 Hz, 1H), 7.09 (dd, J = 9.0, 3.0 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.90 (td, J = 9.0, 3.0 Hz, 1H), 6.85 (dd, J = 9.0, 5.0 Hz, 1H), 6.68 (s, 1H), 6.35 (s, 1H), 4.86 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 15.0 Hz, 1H) 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 158.8, 156.9, 149.71, 140.0, 138.5, 138.3, 129.1, 126.9, 126.7, 126.0, 123.8, 121.9, 121.9, 117.4, 117.4, 115.7, 115.5, 110.9, 109.9, 109.8, 65.6, 49.6, 24.8. HRMS (ESI-Orbitrap) m/z: [M + Na]$^+$ calcd for $C_{24}H_{18}FNO_2SNa$ 426.0940, found 426.0940.

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*1-(9-Fluoro-4-(thiophene-2-yl)-2-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)ethanone (**3ak**).* Yield: 21 mg, 41% yield, as a colorless foam. R_f = 0.22 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3071, 1670, 1492, 1031. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26−7.25 (m, 1H), 7.12−7.11 (m, 5H), 7.08 (dd, J = 9.0, 3.0 Hz, 1H), 6.93 (dd, J = 5.0, 3.5 Hz, 1H), 6.90−6.86 (m, 1H), 6.84 (dd, J = 9.0, 5.0 Hz,1H) 6.67 (s, 1H), 6.32 (s, 1H), 4.85 (d, J = 15.5 Hz, 1H), 4.80 (d, J = 15.0 Hz, 1H), 2.33 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 158.8, 156.9, 149.7, 149.7, 140.0, 139.1, 138.6, 135.5, 129.8, 126.8, 126.6, 126.5, 125.9, 117.4, 117.3, 115.6, 115.4, 110.2, 110.0, 109.8, 65.7, 49.6, 24.8, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{25}H_{20}FNO_2SNa$ 440.1096, found 440.1087.

*1-(2,4-Diphenyl-4,5-dihydro-3H-thiochromeno[3,4-c]pyridin-3-yl)ethanone (**3al**).* Yield: 22 mg, 46% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR(neat, cm^{-1}): 3059, 1667, 1596, 1032. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 7.5 Hz, 2H), 7.51 (dd, J = 7.5, 1.5 Hz, 1H), 7.36−7.33 (m, 3H), 7.31 (d, J = 7.5 Hz, 1H), 7.26−7.24 (m, 4H), 7.22 (dd, J = 3.0, 2.0 Hz, 1H), 7.20 (dd, J = 7.5, 1.5 Hz, 1H), 7.13 (s, 1H), 6.62 (s, 1H), 6.40 (s, 1H), 3.83 (d, J = 16.0 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 138.4, 137.7, 137.3, 133.6, 132.6, 132.2, 131.6, 129.2, 128.9, 128.7, 128.5, 128.4, 128.1, 127.8, 127.5, 126.1, 125.8, 125.1, 115.1, 57.0, 27.3, 24.6. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{21}NOSNa$ 418.1242, found 418.1232.

*1-(4-Phenyl-2-(p-tolyl)-4,5-dihydro-3H-thiochromeno[3,4-c]-pyridin-3-yl)ethanone (**3am**).* Yield: 13 mg, 26% yield, as a colorless foam. R_f = 0.21 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2925, 1663, 1371, 1039. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 8.0, 1.5 Hz, 1H), 7.36−7.32 (m, 3H), 7.29 (d, J = 7 Hz, 1H), 7.23−7.21 (m, 1H), 7.19 (dd, J = 7.5, 1.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 7.0 Hz, 2H), 6.61 (s, 1H), 6.36 (s, 1H), 3.83 (d, J = 16.0 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 2.29 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 138.6, 137.7, 137.3, 135.5, 133.6, 132.6, 132.3, 131.6, 129.6, 129.2, 128.7, 128.4, 128.4, 128.0, 127.8, 127.2, 126.1, 125.7, 125.1, 114.4, 57.0, 27.3, 24.6, 21.1. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{23}NOSNa$ 432.1398, found 432.1406.

*1-(2-(4-Bromophenyl)-4-phenyl-4,5-dihydro-3H-thiochromeno-[3,4-c]pyridin-3-yl)ethanone (**3an**).* Yield: 18 mg, 31% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3059, 1668, 1584, 1072, 1035; ^1H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 7.0 Hz, 2H), 7.48 (dd, J = 8.0, 2.0 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.37−7.34 (m, 2H), 7.33−7.30 (m, 2H), 7.23 (dd, J = 7.5, 2.0 Hz 1H), 7.20 (dd, J = 7.5, 1.5 Hz, 1H), 6.99 (d, J = 7.5 Hz, 2H), 6.61 (s, 1H), 6.40 (s, 1H), 3.82 (d, J = 15.5 Hz, 1H), 3.14 (d, J = 15.5 Hz, 1H), 1.74 (s, 3H); ^{13}CNMR (125 MHz, $CDCl_3$): δ 171.7, 137.3, 137.1, 136.6, 132.6, 132.2, 132.1, 129.1, 128.8, 128.6, 128.3, 128.2, 128.1, 127.9, 127.1, 126.1, 125.1, 122.6, 115.7, 56.9, 27.3, 24.6. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}BrNOSNa$ 496.0347, found 496.0346.

*1-(2-(4-Fluorophenyl)-4-phenyl-4,5-dihydro-3H-thiochromeno-[3,4-c]pyridin-3-yl)ethanone (**3ao**).* Yield: 20 mg, 40% yield, as a colorless foam. R_f = 0.22 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3061, 1668, 1598, 1077, 1034. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, J = 7.0 Hz, 2H), 7.49 (dd, J = 8.0, 2.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 3H), 7.32 (d, J = 7.0 Hz, 1H), 7.23 (td, J = 8.0, 2.0 Hz, 2H), 7.09 (s, 2H), 6.96 (t, J = 8.5 Hz, 2H), 6.61 (s, 1H), 6.35 (s, 1H), 3.83 (d, J = 16.0 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 171.8, 163.8, 161.8, 137.2, 132.6, 132.2, 129.1, 128.8, 128.5, 128.3, 128.1, 127.9, 127.5, 127.4, 126.1, 125.1, 116.1, 116.0, 115.1, 57.0, 27.3, 24.6. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{20}FNOSNa$ 436.1147, found 436.1149.

*1-(4-Phenyl-2-(4-propylphenyl)-4,5-dihydro-3H-thiochromeno-[3,4-c]pyridin-3-yl)ethanone (**3ap**).* Yield: 12 mg, 23% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3058, 1668,1605, 1035. ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 7.5 Hz, 2H), 7.51 (dd, J = 7.5, 1.5 Hz, 1H), 7.36−7.33 (m, 3H), 7.30 (d, J = 7.5 Hz, 1H), 7.23−7.18 (m, 2H), 7.07−7.03 (m, 4H), 6.61 (s, 1H), 6.36 (s, 1H), 3.83 (d, J = 15.5 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 2.54−2.51 (m, 2H), 1.72 (s, 3H), 1.60−1.56 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 143.4, 137.8, 137.4, 135.8, 132.6, 132.3, 129.0, 128.7, 128.4, 128.3, 128.0, 127.8, 127.1, 126.1, 125.7, 125.1, 114.3, 57.0, 37.7, 27.4, 24.6, 24.4, 13.8. HRMS (ESI-Orbitrap) m/z: $[M-1]^+$calcd for $C_{29}H_{27}NOS$ 436.1735, found 437.1741.

*1-(4-Phenyl-2-(thiophene-3-yl)-4,5-dihydro-3H-thiochromeno-[3,4-c]pyridin-3-yl)ethanone (**3aq**).* Yield: 18, 39% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3103, 1670, 1588, 1230. ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 7.0 Hz, 2H), 7.47−7.45 (m, 1H), 7.36 (dd, J = 7.5, 2.0 Hz, 2H), 7.33 (d, J = 7.5 Hz, 2H), 7.25−7.24 (m, 1H), 7.23−7.20 (m, 2H), 7.02 (d, J = 1.5 Hz, 1H), 6.92 (dd, J = 5.0, 1.0 Hz, 1H), 6.56 (s, 1H), 6.37 (s, 1H), 3.83 (d, J = 15.5 Hz, 1H), 3.15 (d, J = 16.0 Hz, 1H), 1.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 140.2, 137.5, 132.6, 132.2, 129.1, 128.7, 128.3, 128.1, 128.1, 127.8, 127.4, 126.9, 126.1, 125.5, 125.1, 121.8, 113.9, 56.9, 27.5, 24.0. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{24}H_{19}NOS_2Na$ 424.0806, found 424.0803.

*General Procedure for $BF_3{\cdot}OEt_2$-Mediated Synthesis of N-Acetylated Pyrano/Thiopyranopyridines (**5**).* To a mixture of 1 equiv of (3*E*,5*E*)-3,5-diarylidenedihydro-2*H*-pyran-4(3*H*)-one/(3*Z*,5*Z*)-3,5-diarylidene dihydro-2*H*-thiopyran-4(3*H*)-one (0.12 mmol) and 3 equiv of aryl- or heteroarylalkyne (0.36 mmol) in acetonitrile (2 mL) with 2 equiv of water at 50 °C was added 3 equiv of $BF_3{\cdot}OEt_2$ (0.36 mmol). The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), evaporated in vacuo, and purified by column chromatography using 100−200 mesh silica gel with ethyl acetate/hexane as the eluent to afford the corresponding *N*-acetylated pyridine as the product.

*(Z)-1-(6-Phenyl-8-(thiophene-2-yl)-4-(thiophene-2-ylmethylene)-3,4-dihydro-1H-pyrano[3,4-c]pyridin-7(8H)-yl)ethanone (**5a**).* Yield: 40 mg, 77% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1668, 1587, 1097, 1040. ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 5.0, Hz, 1H), 7.31 (d, J = 6.5 Hz, 3H), 7.26−7.25 (m, 1H), 7.20 (d, J = 4.0 Hz, 2H), 7.09−7.06 (m, 2H), 7.04 (d, J = 3.5 Hz, 1H), 6.93 (dd, J = 5.0, 3.5 Hz, 1H), 6.89 (s,1H), 6.61 (s,1H), 6.43 (s, 1H), 4.95 (dd, J = 14.5, 1.5 Hz, 1H), 4.71 (dd, J = 14.5, 1.5 Hz, 1H), 4.36 (s, 2H), 1.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 140.3, 139.4, 138.5, 137.2, 133.1, 132.9, 129.0, 128.7, 128.6, 128.4, 127.6, 126.8, 126.6, 126.4, 126.1, 115.6, 111.9, 66.1, 65.9, 50.0, 24.7. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{25}H_{21}NO_2S_2Na$ 454.0911, found 454.0911.

*(Z)-1-(8-(Thiophene-2-yl)-4-(thiophene-2-ylmethylene)-6-(p-tolyl)-3,4-dihydro-1H-pyrano[3,4-c]pyridin-7(8H)-yl)ethanone (**5b**).* Yield: 21 mg, 40% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1669, 1587, 1183. ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 5.5, 1.0 Hz, 1H), 7.24 (dd, J = 5.0 Hz, 1.0 Hz, 1H), 7.10 (s, 3H), 7.08 (dd, J = 5.0, 4.0 Hz, 2H), 7.06−7.02 (m, 2H), 6.92 (dd, J = 5.0, 3.5 Hz, 1H), 6.88 (s, 1H), 6.60 (s, 1H), 6.39 (s, 1H), 4.94 (dd, J = 14.5, 1.5 Hz, 1H), 4.71 (dd, J = 14.5, 2.0 Hz, 1H), 4.36 (s, 2H), 2.32 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.4, 140.3, 139.4, 138.8, 137.2, 135.7, 132.7, 129.7, 129.1, 128.4, 127.6, 126.7, 126.7, 126.6, 126.3, 125.9, 125.8, 115.5, 112.4, 111.1, 66.13, 65.9, 50.0, 24.7, 21.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{26}H_{23}NO_2S_2Na$ 468.1068, found 468.1074.

*(Z)-1-(4-Benzylidene-6,8-diphenyl-3,4-dihydro-1H-thiopyrano-[3,4-c]pyridin-7(8H)-yl)ethanone (**5c**).* Yield: 17 mg, 33% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3058, 1665, 1599, 1054, 1030. ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 8.0 Hz, 2H), 7.34−7.28 (m, 7H), 7.24−7.23 (m, 2H), 7.08 (s, 2H), 6.96 (s, 1H), 6.48 (s, 1H), 6.41 (s, 1H), 3.74 (d, J = 14.5 Hz, 1H), 3.69 (d, J = 14.5 Hz, 1H) 3.50 (d, J = 18.5 Hz, 1H), 3.36 (d, J = 18.5 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ171.7, 138.4, 137.3, 136.8, 136.5, 131.5, 131.4, 129.6, 129.3, 128.9, 128.8, 128.5, 128.3, 128.2, 127.3, 125.8, 125.6, 115.0, 57.7, 29.2, 27.1,24.5. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{29}H_{25}NOSNa$ 458.1555, found 458.1560.

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*(Z)-1-(4-Benzylidene-8-phenyl-6-(p-tolyl)-3,4-dihydro-1H-thiopyrano[3,4-c]pyridin-7(8H)-yl)ethanone (**5d**).* Yield: 9 mg, 17% yield, as a colorless foam. R_f = 0.18 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3028, 1665, 1607, 1033. ^1H NMR (500 MHz, $CDCl_3$): δ7.44 (d, *J* = 7.5 Hz, 3H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 5H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 7.0 Hz, 2H), 6.95 (s, 1H), 6.47 (s, 1H), 6.37 (s, 1H), 3.73 (d, *J* = 14.5 Hz, 1H), 3.69 (d, *J* = 14.5 Hz, 1H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.37 (d, *J* = 18.5 Hz, 1H), 2.29 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ171.8, 138.6, 137.3, 136.8, 136.5, 135.5, 131.4, 131.2, 129.7, 129.6, 129.3, 128.7, 128.5, 128.2, 127.2, 125.7, 125.5, 114.3, 57.6, 29.2, 27.1, 24.6, 21.2. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{30}H_{27}NOSNa$ 472.1711, found 472.1710.

*(Z)-1-(6-Phenyl-8-(thiophene-2-yl)-4-(thiophene-2-ylmethylene)-3,4-dihydro-1H-thiopyrano[3,4-c]pyridin-7(8H)-yl)ethanone (**5e**).* Yield: 33 mg, 61% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3069, 1666, 1592, 1036. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.30−7.29 (m, 3H), 7.26 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.20 (d, *J* = 6.0 Hz, 2H), 7.14 (d, *J* = 3.5 Hz, 1H), 7.10−7.07 (m, 2H), 7.00 (s, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.62 (s, 1H), 6.38 (s, 1H), 3.86 (s, 2H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.41 (d, *J* = 18.0 Hz, 1H), 1.68 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.2, 140.2, 139.5, 138.3, 136.6, 132.2, 129.5, 129.1, 129.0, 129.0, 128.6, 127.4, 126.9, 126.7, 126.6, 126.4, 126.1, 118.7, 114.5, 53.9, 28.6, 27.6, 24.6. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{25}H_{21}NOS_3Na$ 470.0683, found 470.0683.

*(Z)-1-(8-(Thiophene-2-yl)-4-(thiophene-2-ylmethylene)-6-(p-tolyl)-3,4-dihydro-1H-thiopyrano[3,4-c]pyridin-7(8H)-yl)ethanone (**5f**).* Yield: 24 mg, 43% yield, as a colorless foam. R_f = 0.15 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3026, 1667, 1510, 1038. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 5.0, 1 Hz, 1H), 7.24 (dd, *J* = 5.5, 1.5 Hz, 1H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.10−7.06 (m, 6H), 6.99 (s, 1H), 6.92 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.61 (s, 1H), 6.34 (s, 1H), 3.86 (s, 2H), 3.48 (d, *J* = 18.5 Hz, 1H), 3.41(d, *J* = 18.0 Hz, 1H), 2.32 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 140.3, 139.6, 138.7, 136.6, 135.5, 132.0, 129.6, 129.2, 128.9, 127.4, 126.9, 126.7, 126.5, 126.3, 126.0, 118.7, 113.8, 53.9, 31.6, 28.6, 27.6, 24.6, 21.2. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{23}NOS_3Na$ 484.0839, found 484.0834.

*General Procedure for BF_3·OEt_2-Mediated Synthesis of N-Substituted Chromeno/Thiochromenopyridines (**7**).* To a mixture of 1 equiv of substituted arylidenechroman-4-one/thiochroman-4-one (0.12 mmol) and 3 equiv of aryl- or heteroarylalkyne (0.36 mmol) in the respective nitrile (2 mL) with 2 equiv of water at 50 °C was added 3 equiv of BF_3·OEt_2 (0.36 mmol). The reaction mixture was then allowed to stir for 10−90 min by monitoring the TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 10 mL), evaporated in vacuo, and purified by column chromatography using 100−200 mesh silica gel with ethyl acetate/hexane as the eluent to afford the product.

*(2,4-Diphenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)-(phenyl)methanone (**7a**).* Yield: 27 mg, 51% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3062, 1675, 1485, 1028. ^1H NMR (500 MHz, $CDCl_3$): δ7.69 (d, *J* = 7.5 Hz, 2H), 7.46 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 3H), 6.96−6.91 (m, 4H), 6.77 (d, *J* = 6.5 Hz, 2H), 6.39 (s, 1H), 6.32 (s, 1H), 5.00 (d, *J* = 15.5 Hz, 1H), 4.84 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 153.9, 139.8, 138.4, 137.2, 136.7, 130.3, 129.5, 128.9, 128.6, 128.4, 128.2, 128.0, 127.8, 127.7, 126.1, 124.7, 124.6, 123.1, 121.7, 120.9, 116.6, 109.7, 65.9, 55.6. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{23}NO_2Na$ 464.1626, found 464.1629.

*(4-(4-Chlorophenyl)-2-phenyl-4,5-dihydro-3H-chromeno[3,4-c]-pyridin-3-yl)(phenyl)methanone (**7b**).* Yield: 27 mg, 47% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3059, 1651, 1599, 1091, 1016. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 6.5, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.27−7.25 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.07−7.04 (m, 3H), 6.95 (t, *J* = 7.0 Hz, 4H), 6.76 (d,*J* = 6.0 Hz, 2H), 6.34 (s, 1H), 6.31 (s, 1H), 4.98 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 153.9, 139.7, 138.2, 136.5, 135.7, 134.5, 130.5, 129.9, 129.7, 129.1, 128.2, 128.1, 127.9, 127.7, 126.1, 125.0, 123.9, 123.2, 121.8, 120.8, 116.7, 109.5,65.7, 55.0. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{22}ClNO_2Na$ 498.1237, found 498.1250.

*Phenyl(2-phenyl-4-(p-tolyl)-4,5-dihydro-3H-chromeno[3,4-c]-pyridin-3-yl)methanone (**7c**).* Yield: 26 mg, 47% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2924, 1650,1456, 1122. ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.23 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 3H), 6.95−6.91 (m, 4H), 6.78 (d, *J* = 5.5 Hz, 2H), 6.35 (s, 1H), 6.31 (s, 1H), 4.98 (d, *J* = 15.0 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 153.9, 138.5, 138.4, 136.8, 134.1, 130.3, 129.6, 129.5, 128.3, 128.2, 128.0, 127.7, 127.7, 126.2, 124.9, 124.5, 123.1, 121.7, 116.6, 109.7, 66.0, 21.2. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{32}H_{25}NO_2Na$ 478.1783, found 478.1802.

*Phenyl(2-phenyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)methanone (**7d**).* Yield: 17 mg, 27% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3064, 1650, 1603, 1067. ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 6.5 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 3H), 7.16−7.12 (m, 1H), 7.09−7.05 (m, 3H), 6.97−6.93 (m, 4H), 6.77 (d, *J* = 6.0 Hz, 2H), 6.42 (s, 1H), 6.33 (s,1H), 5.00 (d, *J* = 15.5 Hz, 1H), 4.80 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 153.9, 141.3, 139.9, 138.0, 136.4, 136.0, 130.6, 129.8, 128.8, 128.3, 128.2, 128.0, 127.8, 127.2, 126.1, 125.3, 123.4, 123.3, 121.8, 121.4, 120.7, 117.9, 116.7, 109.5, 65.7, 55.2. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{32}H_{22}F_3NO_2Na$ 532.1500, found 532.1511.

*Phenyl(2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno-[3,4-c]pyridin-3-yl)methanone (**7e**).* Yield: 18 mg, 34% yield, as a colorless foam. R_f = 0.20 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3063, 1654, 1603, 1449, 1229. ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.32 (d, *J* = 6.0 Hz, 3H), 7.25−7.24 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.07−7.03 (m, 3H), 6.97−6.93 (m, 5H), 6.86 (d, *J* = 3.5 Hz, 2H), 6.51 (s, 1H), 6.32 (s, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.92 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 153.9, 140.1, 139.5, 138.4, 130.6, 129.6, 128.4, 128.1, 127.8, 127.7, 127.2, 126.9, 126.8, 124.4, 124.2, 123.3, 121.7, 120.8, 116.7, 65.7, 51.7. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{29}H_{21}NO_2SNa$ 470.1191, found 470.1192.

*(9-Fluoro-2-phenyl-4-(thiophene-2-yl)-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl) (phenyl)methanone (**7f**).* Yield: 16 mg, 29% yield, as a colorless foam. R_f = 0.22 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3064, 1687, 1652, 1076, 1023. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66−7.65 (m, 1H,), 7.47 (t, *J* = 8.0 Hz, 1H), 7.32−7.30 (m, 2H), 7.25−7.24 (m, 1H), 7.15 (dd, *J* = 9.0, 3.0 Hz, 2H), 7.07(t, *J* = 7.5 Hz, 2H), 6.98−6.95 (m, 4H), 6.92−6.85 (m, 3H), 6.53 (s, 1H), 6.22 (s,1H), 4.96 (d, *J* = 15.5 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 158.8, 156.9, 149.8, 140.0, 139.9, 138.2, 136.3, 132.2, 130.6, 129.1, 128.6, 128.4, 128.1, 128.0, 127.7, 127.3, 127.0, 126.9, 126.3, 125.4, 117.5, 115.7, 115.5, 110.1, 109.9, 108.6, 69.1, 65.8. HRMS (ESI-Orbitrap) *m*/*z*: [M + Na]$^+$ calcd for $C_{29}H_{20}FNO_2SNa$ 488.1096, Found 488.1101.

*(2,4-Diphenyl-4,5-dihydro-3H-thiochromeno[3,4-c]pyridin-3-yl)-(phenyl)methanone (**7g**).* Yield: 22 mg, 40% yield, as a colorless foam. R_f = 0.25 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 3060, 1655, 1528, 1076. ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.66−7.65 (m, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.40−7.37 (m, 3H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.30−7.27 (m, 2H), 7.23−7.22 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 6.0 Hz, 2H), 6.78 (d, *J* = 5.5 Hz, 2H), 6.52 (s, 1H), 6.29 (s, 1H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.25 (d, *J* = 15.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 139.2, 138.2, 137.2, 136.7, 132.8, 132.7, 132.3, 132.2, 130.3, 129.3, 129.1, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 127.7, 127.7, 126.4, 126.1, 126.1,

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125.2, 112.9, 59.0, 27.4. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$calcd for $C_{31}H_{23}NOSNa$ 480.1398, found 480.1411.

*1-(2,4-Diphenyl-4,5-dihydro-3H-chromeno[3,4-c]pyridin-3-yl)-prop-2-en-1-one (**7h**).* Yield: 13 mg, 28% yield, as a colorless foam. R_f = 0.30 (hexane/ethyl acetate = 90/10). IR (neat, cm^{-1}): 2922, 1654, 1602, 1038. ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.0 Hz, 2H), 7.41 (dd, J = 8.0, 1.5 Hz, 1H), 7.35−7.28 (m, 4H), 7.25−7.23 (m, 3H), 7.14−7.13 (m, 2H), 7.03 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (dd, J = 8.0, 1.0 Hz, 1H), 6.48 (s, 2H), 6.23 (dd, J = 16.5, 1.5 Hz, 1H), 5.98−5.92 (m, 1H), 5.32 (d, J = 10.5 Hz, 1H), 4.90 (d, J = 15.5 Hz, 1H), 4.77 (d, J = 15.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 153.9, 138.7, 137.5, 137.1, 129.8, 129.5, 128.9, 128.9, 128.7, 128.5 128.2, 127.7, 125.8, 125.7, 124.7, 123.1, 121.7, 120.9, 116.5, 111.5, 65.8, 54.2. HRMS (ESI-Orbitrap) m/z: $[M + Na]^+$ calcd for $C_{27}H_{21}NO_2Na$ 414.1470, found 414.1477.

*General Procedure for the Synthesis of 5H-Chromeno[3,4-c]pyridines (**9**).* To a mixture of 1 equiv of substituted arylidenechroman-4-one (0.19 mmol) and 3 equiv of arylalkyne (0.59 mmol) in acetonitrile (2 mL) with 2 equiv of water at 50 °C was added 3 equiv of $BF_3{\cdot}OEt_2$ (0.59 mmol). The reaction mixture was allowed to stir for 30 min. It was then cooled to 0 °C followed by the slow addition of 1.5 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.29 mmol) in acetonitrile (0.5 mL) and allowed to stir at 50 °C for 6−12 h. After completion of the reaction, the reaction mixture was again cooled to 0 °C and quenched with an aqueous solution of NaOH (0.2 mL, 3 M). It was then filtered, and the filtrate was extracted with ethyl acetate (3 × 10 mL), evaporated in vacuo, and purified by column chromatography using 100−200 mesh silica gel with ethyl acetate/hexane as the eluent to afford the product.

*2-Phenyl-4-(p-tolyl)-5H-chromeno[3,4-c]pyridine (**9a**).* Yield: 12 mg, 17% yield, as a white solid. R_f = 0.40 (hexane/ethyl acetate = 95/5). IR (neat, cm^{-1}): 3057, 1589, 1366, 1036. ^1H NMR (500 MHz, $CDCl_3$): δ 8.14−8.12 (m, 2H), 7.96 (s, 1H), 7.90 (dd, J = 8.0, 1.5 Hz, 1H), 7.50−7.48 (m, 4H), 7.43 (t, J = 7.5 Hz, 1H), 7.38−7.35 (m, 1H), 7.32 (d, J = 7.5 Hz, 2H), 7.16−7.13 (m, 1H), 7.04 (d, J = 8.5 Hz, 1H), 5.26 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 155.7, 139.5, 139.3, 138.7, 136.2, 131.4, 129.1, 129.0, 129.0, 128.7, 127.1, 124.2, 122.6, 122.5, 121.7, 117.6, 111.8, 65.8, 21.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{25}H_{20}NO$ 350.1545, found 350.1544.

*4-(Thiophene-2-yl)-2-(p-tolyl)-5H-chromeno[3,4-c]pyridine (**9b**).* Yield: 5 mg, 7% yield, as a white solid. R_f = 0.36 (hexane/ethyl acetate = 95/5). IR (neat, cm^{-1}): 3069, 1587, 1367, 1038. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.0 Hz, 2H), 7.90 (s, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.50 (dd, J = 5.0, 1.0 Hz, 1H), 7.38−7.34 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.17−7.12 (m, 3H), 7.05 (d, J = 8.0 Hz, 1H), 5.47 (s, 2H), 2.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 156.4, 155.4, 148.4, 143.7, 139.4, 139.3, 136.1, 131.5, 129.5, 128.2, 127.6, 127.0, 126.8, 124.1, 122.5, 121.6, 121.4, 117.6, 111.1, 65.5, 21.4. HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{18}NOS$ 356.1109, found 356.1111.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02463.

^1H, ^{13}C NMR spectra of all the newly synthesized compounds and HRMS data of **3aa** and **3ah** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: drsasidharbs@niist.res.in.

ORCID

B. S. Sasidhar: 0000-0003-1546-2083

Notes

The authors declare no competing financial interest.

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CORRECTION

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Correction: I_2/TBHP mediated diastereoselective synthesis of spiroaziridines

Kizhakkan Thiruthi Ashitha,[a,b] Puthiya Purayil Vinaya,[a] Ajay Krishna,[a] Deepthy Cheeran Vincent,[a] Renjitha Jalaja,[a,b] Sunil Varughese[a] and Sasidhar Balappa Somappa*[a,b]

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The authors regret that there was an error in the address for affiliation b. The correct address is '[b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India', as included in this correction.

The Royal Society of Chemistry apologises for these errors and any consequent inconvenience to authors and readers.

[a]*Organic Chemistry Section, Chemical Sciences and Technology Division, Council of Scientific and Industrial Research (CSIR)-National Institute for Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram-695019, India. E-mail: drsasidharbs@niist.res.in*

[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*

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I_2/TBHP mediated diastereoselective synthesis of spiroaziridines†

Kizhakkan Thiruthi Ashitha,[a,b] Puthiya Purayil Vinaya,[a] Ajay Krishna,[a] Deepthy Cheeran Vincent,[a] Renjitha Jalaja,[a,b] Sunil Varughese[a] and Sasidhar Balappa Somappa *[a,b]

Eventhough spiroheterocycles are considered as emerging drug candidates, synthesis of spiroaziridines has not been well explored so far. Herein, we disclose an efficient I_2/TBHP mediated diastereoselective synthesis of *N*-alkyl spiroaziridines from primary amines and easily accessible α,β-unsaturated ketones. The reaction is also compatible for the synthesis of 2-aroylaziridines.

Aziridines have an essential place in the arena of synthetic organic chemistry. The high reactivity imparted by the inherent ring strain makes this three-membered nitrogen heterocycle a versatile synthon. The synthetic utility of aziridines to be transformed into useful structural motifs is well established by ring expansion and ring opening reactions.[1] Apart from being essential building blocks they are substructures of numerous natural and unnatural products of biological significance (Fig. 1).[2,7] Thus, synthesis of aziridines has been an area of interest.[3]

However, despite the significance of azaspirocycles as emerging drug candidates, synthesis of spiroaziridines has not been well explored so far.[4] Most of the methods reported dealt with the construction of spiroaziridine oxindoles.[5] To name a few exceptions, in 2016, a zinc pro-phenol catalysed Aza–Darzen reaction was reported by Trost *et al.* and it facilitated enantioselective synthesis of spiroaziridines.[6] Later in 2017, Yang *et al.* developed a base mediated diastereoselective aziridination of electron deficient cyclic enones for the facile synthesis of spiroaziridine pyrrolines.[7] An intramolecular imino-ene reaction was developed by Liu *et al.* demonstrating the importance of a protocol that can afford spiro NH aziridines.[8]

In the last two decades, significant advancements have been made in the synthesis of aziridines, and the two traditional strategies used for aziridine synthesis are either the transfer of a suitable nitrene to a C=C bond or the transfer of a carbene to a C=N bond. But most of the methods developed relying on these strategies have the drawback of narrow substrate scope in terms of *N*-substituents,[3] because these synthetic routes require an activating group/an electron withdrawing group such as a *p*-toluenesulfonyl (Ts) or *p*-nitrophenylsulfonyl (Ns) group on the nitrogen atom. The removal of these activating groups is often challenging to achieve.[9] Therefore a protocol that gives access to *N*-alkyl substituted aziridines using a readily available unprotected primary amine as the nitrogen source is always desirable.

Owing to our interest in the methodologies that target the synthesis of heterocycles using readily available substrates,[10] we decided to unravel a protocol that provides access to *N*-alkyl spiroaziridines. A serendipitous finding of Southwick regarding the synthesis of simple aziridines utilizing a stoichiometric amount of iodine attracted our attention.[11] Moreover, the

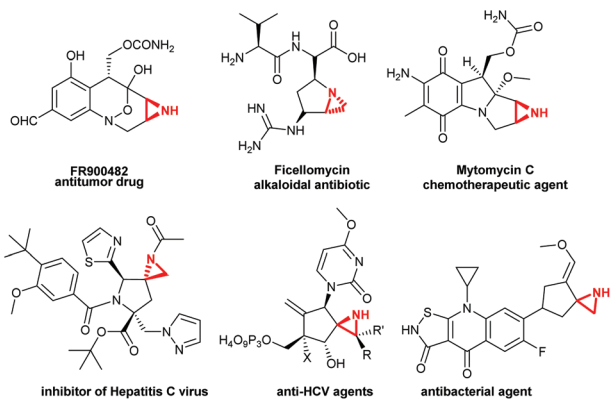


Fig. 1 Medicinally important aziridine scaffolds.

[a]*Organic Chemistry Section, Chemical Sciences and Technology Division, Council of Scientific and Industrial Research (CSIR)-National Institute for Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram-695019, India. E-mail: drsasidharbs@niist.res.in*

[b]*Academy of Scientific and Innovative Research (AcSIR), New Delhi-110001, India*

†Electronic supplementary information (ESI) available: Experimental procedures, optimization table, and ^{1}H and ^{13}C NMR spectra of all new compounds. X-ray crystal structure data for **3r** and **7h** (CIF). CCDC 1949821 and 1949823. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob02711d

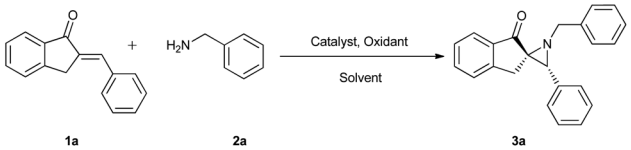
popularity that molecular iodine has garnered on account of its reactivity together with environmentally benign nature is commendable. Also the C–C or C–N bond formation mediated by iodine/iodide in combination with an oxidant is an attractive field in organic synthesis.[12] In the light of these observations we have developed an operationally simple I_2/TBHP mediated protocol for the diastereoselctive synthesis of *N*-alkyl spiroaziridines from primary amines and easily accessible α,β-unsaturated ketones.

Results and discussion

For our study (*E*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one (**1a**) and benzylamine (**2a**) were selected as the model substrates. We started our investigation by treating **1a** with **2a** in the presence of iodine and TBHP in EtOAc at 50 °C. To our delight, the reaction proceeded smoothly affording *trans* isomer **3a** in 41% yield as the sole product (Table 1, entry 1). In pursuit of obtaining optimized conditions we screened various solvents such as MeOH, DMSO, DCM *etc*. The product **3a** was obtained in better yield when the reaction was carried out in cyclohexane (entry 9). Upon changing the iodine source to TBAI, KI and NaI, a substantial decrease in the yield was observed. These observations suggested that molecular iodine is an efficient catalyst for the reaction to proceed smoothly. When the reaction was performed in the presence of iodine alone, only 20% of yield was observed (entry 13). Hence we evaluated various oxidants such as H_2O_2, O_2 and mCPBA. This comparative study demonstrated that TBHP is a better oxidant for the reaction to afford the targeted spiroaziridine **3a** in improved yield (entry 9). A surge in the product yield was observed when the reaction was performed at ambient temperature using 4 equivalents of the primary amine (entry 18). The effect of catalyst loading was also studied and it was found that 20 mol% of iodine gives a better result (Table S1, ESI†).

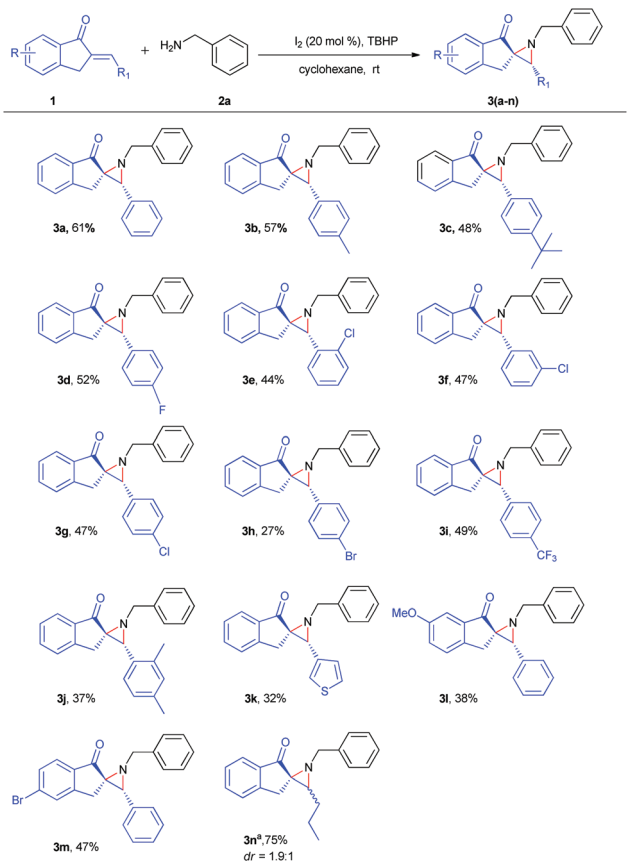
With the optimized conditions in hand, we next investigated the feasibility of the reaction for various 2-arylidene-2,3-dihydro-1*H*-inden-1-ones (Scheme 1). Initially, we studied the effect of substituents present on the benzylidene ring of the α,β-unsaturated ketone. Gratifyingly, the reaction proceeded efficiently for substrates bearing both electron donating and electron withdrawing substituents. The desired spiroaziridines were afforded in moderate to good yields. This result indicates that the electronic effect has negligible influence on the reaction. To study the effect of steric hindrance on the proposed protocol, we allowed *o*-Cl, *m*-Cl and *p*-Cl substituted benzylidene ketones to react with benzylamine. Regardless of the position, all the expected products were obtained in 44–47% yields. In addition, dimethyl benzylidene and thiophen-3-yl-

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	Yield[b] [%]
1	I_2	TBHP	EtOAc	50	41
2	I_2	TBHP	MeOH	50	9
3	I_2	TBHP	DMSO	50	Trace
4	I_2	TBHP	DCM	50	Trace
5	I_2	TBHP	CH_3CN	50	27
6	I_2	TBHP	DCE	50	34
7	I_2	TBHP	THF	50	18
8	I_2	TBHP	Toluene	50	Trace
9	I_2	TBHP	Cyclohexane	50	45
10	TBAI	TBHP	Cyclohexane	50	36
11	KI	TBHP	Cyclohexane	50	29
12	NaI	TBHP	Cyclohexane	50	29
13	I_2	—	Cyclohexane	50	20
14	I_2	H_2O_2	Cyclohexane	50	8
15	I_2	O_2	Cyclohexane	50	Trace
16	I_2	mCPBA	Cyclohexane	50	Trace
17	I_2	TBHP	Cyclohexane	80	Trace
18[c]	I_2	TBHP	Cyclohexane	rt	61

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), catalyst (20 mol%), and oxidant (0.3 mmol), 8 h. [b] Yield of the isolated product. [c] Reaction was carried out using 0.6 mmol of **2a**.

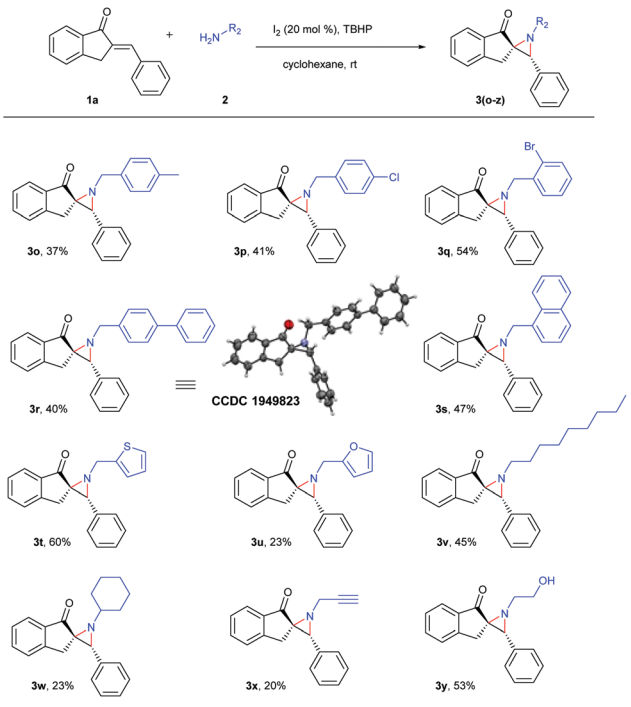


Scheme 1 Substrate scope with respect to 2-aryl/alkylidene-2,3-dihydro-1*H*-inden-1-ones. Reaction conditions: **1** (0.15 mmol), **2a** (0.60 mmol), I_2 (20 mol%), and TBHP (70% aqueous solution, 0.30 mmol) in cyclohexane at rt. Yields of isolated products. [a] dr calculated based on the isolated yield.

methylene ketones could also transform to the corresponding spiroaziridines **3j** and **3k**, respectively.

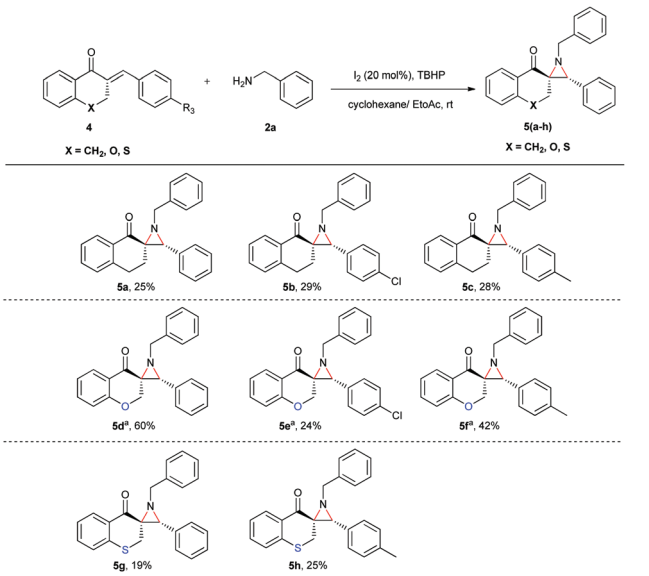
Apart from the substituent effect on the arylidene ring, the influence of a methoxy and bromo substituted indanone system was also investigated (**3l** and **3m**). Interestingly, when alkylidene-2,3-dihydro-1*H*-inden-1-one reacts with benzylamine under the optimized conditions, formation of diastereomers was observed (**3n**). The chromatographically separable isomers were furnished in a total yield of 75% with a diastereomeric ratio of 1.9 : 1. This indicates that the diastereoselectivity of the reaction depends on the substituent present at the β-position of the enone.

Furthermore, we explored the applicability of the synthetic strategy with respect to various primary amines (Scheme 2). Benzylamines with electron donating and electron withdrawing substituents, 4-phenyl benzylamine and 1-naphthalenemethylamine, well tolerated the reaction affording the targeted products in moderate to good yields (**3o–3s**). The structure of **3r** was unambiguously confirmed by single-crystal X-ray analysis. As anticipated, the primary amines incorporated with heterocyclic moieties (thiophene and furan) afforded the desired products in 60% and 23% yields, respectively. In addition, linear and cyclic amines were also found to be compatible (**3v–3x**). Interestingly, propargylamine and the binucleophile, 2-amino ethanol, underwent the transformation furnishing the desired aziridines with an alkyne and a free hydroxyl group providing a synthetic handle for further functionalization (**3x** and **3y**).

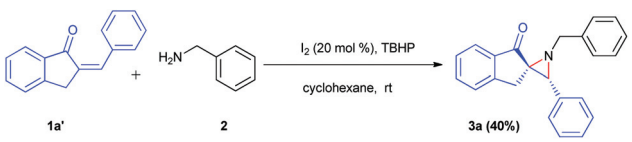


Scheme 2 Scope of reaction for a diversity of amines. Reaction conditions: **1a** (0.15 mmol), **2** (0.60 mmol), I_2 (20 mol%), and TBHP (70% aqueous solution, 0.30 mmol) in cyclohexane at rt. Yields of isolated products.

Delighted with the success of spiroaziridine synthesis using arylidene/alkylidene dihydroindenone, we envisioned that the present methodology could be expanded to other fused biologically relevant α,β-unsaturated ketones such as arylidene dihydronaphthalen-1-one, chroman-4-one, and thiochroman-4-one as well (Scheme 3). All the enones could furnish the spiroaziridines under the standard conditions except arylidene chroman-4-ones. A better yield of 60% was obtained for **5d** when the reaction was carried out in EtOAc keeping all other parameters unchanged. Notably, in the case of (*Z*)-3-arylidenethiochroman-4-ones **4g** and **4h**, the *cis* isomer formed as the sole product (**5g** and **5h**). This observation made us conduct an experiment with (*Z*)-2-benzylidene-2,3-dihydro-1*H*-inden-1-one (**1a′**) to check whether the configuration of arylidene ketone plays any significant role in the diastereoselectivity of the reaction (Scheme 4). We observed the formation of *trans* isomer **3a** from **1a′**. This result indicates that selectivity is driven by the stereochemical stability of the final product. The *trans* configuration of **3a** obtained from **1a′** was confirmed by carrying out NOE difference analysis of the product (Fig. S111, ESI†).

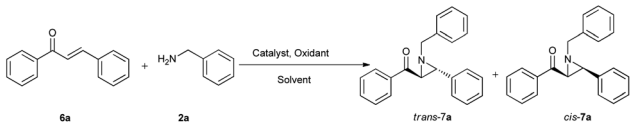


Scheme 3 Scope of the methodology for fused arylidene ketones. Reaction conditions: **4** (0.15 mmol), **2a** (0.60 mmol), I_2 (20 mol%), and TBHP (0.30 mmol) in cyclohexane at rt. Yields of isolated products. [a] EtOAc is used as the solvent.



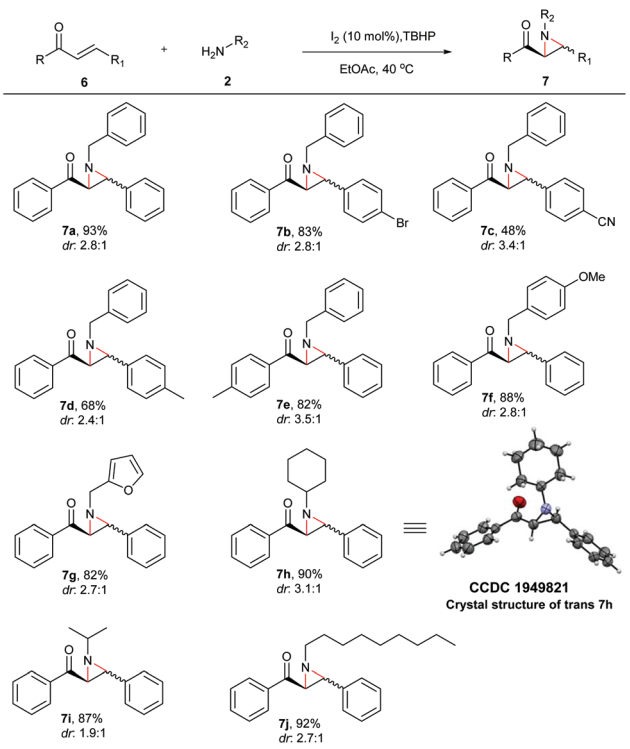
Scheme 4 Scope of the reaction for arylidene ketone with a *Z* configuration. Reaction conditions: **1a′** (0.15 mmol), **2** (0.60 mmol), I_2 (20 mol%), and TBHP (70% aqueous solution, 0.30 mmol) in cyclohexane at rt. Yield of the isolated product.

Table 2 Optimization of 2-aroylaziridine synthesis[a]



Entry	Catalyst	Oxidant	Solvent	Temperature [°C]	dr[b]	Yield[c] [%]
1[d]	I_2	TBHP	Cyclohexane	rt	Trans only	51
2	TBAI	TBHP	EtOAc	rt	2.4 : 1	82
3	TBAI	TBHP	MeOH	rt	4.4 : 1	71
4	TBAI	TBHP	EtOH	rt	4.8 : 1	35
5	TBAI	TBHP	CH_3CN	rt	1.1 : 1	49
6	TBAI	TBHP	DCM	rt	Trans only	26
7	TBAI	TBHP	DCE	rt	3.8 : 1	73
8	TBAI	TBHP	THF	rt	2 : 1	39
9	TBAI	TBHP	Toluene	rt	1.7 : 1	49
10	TBAI	TBHP	EtOAc	50	2.4 : 1	82
11	I_2	TBHP	EtOAc	50	2.8 : 1	93
12	NaI	TBHP	EtOAc	50	3.8 : 1	53
13	KI	TBHP	EtOAc	50	4.1 : 1	41
14	I_2	H_2O_2	EtOAc	50	1.5 : 1	28
15	I_2	mCPBA	EtOAc	50	1.6 : 1	21
16	I_2	TBHP	EtOAc	80	—	Trace
17	I_2	TBHP	EtOAc	0	—	Trace
18[e]	I_2	TBHP	EtOAc	40	2.8 : 1	93

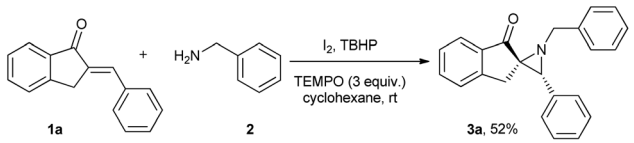
[a] Reaction conditions: **5a** (0.2 mmol), **2a** (0.4 mmol), catalyst (20 mol%), and oxidant (0.4 mmol); reactions were carried out at rt completed within 4 h while those at 50 °C and 40 °C took 1 h to complete. [b] dr calculated based on the yields of isolated products. [c] Yields of isolated products. [d] **2a** (4 equiv.). [e] Catalyst (10 mol%) and oxidant (0.2 mmol).



Scheme 5 Scope of 2-aroylaziridine synthesis. Reaction conditions: **6** (0.20 mmol), **2** (0.40 mmol), I_2 (10 mol%), and TBHP (0.20 mmol) in EtOAc at 40 °C. Yields of isolated products. dr calculated based on the yields of isolated products.

Besides, the compatibility of the process for 2-aroylaziridine synthesis from a simple α,β-unsaturated ketone is also explored. To test our notion, we treated (*E*) chalcone **6a** with benzylamine **2a** under the optimized conditions. Interestingly, we observed the formation of the *trans*-isomer of **7a** in 51% yield (Table 2). When the catalyst and solvent were switched to TBAI and EtOAc, respectively, during the optimization, a mixture of *trans* and *cis* isomers of **7a** was obtained in an improved yield of 82% with a diastereomeric ratio of 2.4 : 1 (entry 2). After screening various solvents, EtOAc was selected as the suitable solvent based on improved yields. We could achieve a shorter reaction time of 1 h on increasing the temperature to 50 °C without any change in the yield of the reaction (entry 10). Among the different iodinating agents evaluated, molecular iodine turned out to be the better catalyst providing a high yield of 93% (entry 11). From a similar study of oxidants, TBHP emerged as an efficient oxidant for the synthesis of 2-aroylaziridine (entry 11). Sluggish results were obtained when the reaction was performed at both low and high temperatures (entries 16 and 17). However, when carried out at 40 °C with 10 mol% loading of the catalyst, the same result as that at 50 °C with 20 mol% of I_2 (yield of 93% and diastereomeric ratio of 2.8 : 1) was obtained (entry 18).

With the optimized conditions in hand we explored the generality of the reaction by transforming variously substituted chalcones into corresponding 2-aroylaziridines (Scheme 5). Electron neutral (**7a**), electron withdrawing (**7b** and **7c**) and electron donating groups (**7d–7f**) bearing chalcones underwent the reaction with moderate to excellent yields from 48 to 93%.



Scheme 6 Control experiment.

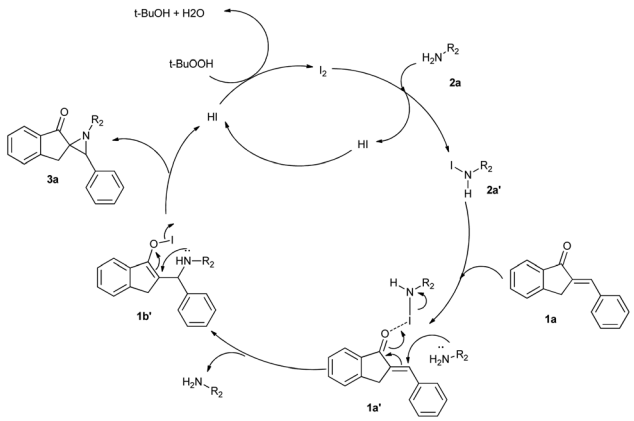


Fig. 2 Plausible mechanism.

The diversity of the reaction for aliphatic amines was also investigated to furnish the desired products in excellent yields with moderate diastereomeric ratios (**7f–7j**). Interestingly, regardless of the chalcone's substitution and the nature of primary aliphatic amines, the *trans* isomer was formed as the major product. The *trans* configuration of the major isomer of **7h** was unambiguously confirmed by single-crystal X-ray analysis.

To shed light on the mechanism of the reaction we have performed a radical trapping experiment under the optimized conditions. There was no substantial decrease in the yield of **3a** when the reaction was carried out in the presence of TEMPO. This observation suggests that the reaction does not proceed through a radical mechanism (Scheme 6).

We assume that the reaction proceeds through a mechanism similar to the pathway proposed by Gupta *et al.* (Fig. 2).[13] Initially the amine interacts with iodine and forms an *N*-iodoamine species. Coordination of *N*-iodoamine with the carbonyl group of **1a** facilitates the Aza-Michael addition of another molecule of the amine, generating the intermediate **1b′**. A subsequent intramolecular cyclisation of **1b′** affords the final product **3a**. The HI formed in the reaction will be oxidized by TBHP thus regenerating iodine in the catalytic cycle.

Conclusions

In conclusion we have developed an operationally simple diastereoselective protocol for the synthesis of *N*-alkyl spiroaziridines. The I_2/TBHP mediated reaction, which proceeds under mild conditions, does not require pre-functionalization of amines. This utilizes unprotected primary amines as the nitrogen source. This process is compatible for the synthesis of 2-aroylaziridines as well.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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ORGANIC CHEMISTRY FRONTIERS

REVIEW

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Recent advances in the transition metal-free synthesis of heterocycles from α,β-unsaturated ketones

Kizhakkan Thiruthi Ashitha,[a,b] Ajay Krishna M. S.,[a,b] Basavaraja D.[a,b] and Sasidhar B. Somappa *[a,b]

Heterocyclic compounds are an inevitable part of our life. These important classes of molecules have a wide range of applications starting from life-sustaining drugs to agrochemicals. Numerous methods, including metal and non-metal mediated protocols, are documented to synthesise complex and straightforward heterocyclic entities. The metal-free protocols have more significance over the metal-catalyzed ones when the toxicity associated with the metal catalyst is considered. On the other hand, α,β-unsaturated ketones are essential building blocks in synthetic organic chemistry. The presence of multiple reaction sites makes conjugated carbonyls suitable substrates for constructing a vast array of heterocycles and carbocycles. Herein, the review's primary focus is to highlight the transition metal-free methodologies developed for synthesising various heterocyclic compounds by utilising α,β-unsaturated ketones as valuable synthons during the period of 2009 to 2020.

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1. Introduction

Heterocycles are one of the practical classes of organic molecules which play a pivotal role in the sustenance of life.[1] These are significant structural motifs found in various natural products and are known for a broad spectrum of biological

[a]Organic Chemistry Section, Chemical Sciences and Technology Division, Council of Scientific and Industrial Research (CSIR)-National Institute for Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram-695019, India.
E-mail: drsasidharbs@niist.res.in
[b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

Kizhakkan Thiruthi Ashitha

Kizhakkan Thiruthi Ashitha was born in Kozhikode district of Kerala, India. She obtained her B.Sc. degree in Chemistry from St. Joseph's College, Kozhikode, in 2012 and M.Sc. from the same college in 2014. She qualified the CSIR-UGC national eligibility test in 2014 with a research fellowship. Currently, she is a Senior Research Fellow and pursuing her PhD at CSIR-NIIST, Thiruvananthapuram, Kerala, under the guidance of Dr Sasidhar B. S. Her area of research is in the development of new methodologies for the synthesis of novel heterocyclic systems of biological relevance. Her research focus includes medicinal chemistry as well.

Ajay Krishna M. S.

Ajay Krishna M. S. completed integrated BSc-MSc in applied chemistry at Sahyadri Science College, Kuvempu University, Shivamogga, Karnataka, in the year 2017. After that, he joined as a project assistant at CSTD, CSIR-National Institute for Interdisciplinary Science and Technology (NIIST), Thiruvananthapuram, Kerala in the year 2019 in the CSIR project under the guidance of Dr Sasidhar B. S. Presently he is pursuing his PhD in Chemical Sciences under the guidance of Dr Sasidhar B. S. at CSIR-NIIST. His area of interest is the isolation and identification of bioactive molecules from natural resources and the development of novel synthetic methodologies for therapeutic applications.

properties.[2,3] Apart from the medicinal utility, numerous heterocyclic compounds are used as agrochemicals, dyestuff, sensitizers, antioxidants, developers, and copolymers. Owing to the pharmaceutical and industrial relevance, a plethora of protocols have been contributed by the scientific community towards the synthesis of various heterocycles. On the other hand, α,β-unsaturated ketones are important building blocks in synthetic organic chemistry (Fig. 1).[4–6] Molecules of this class possess multiple reaction sites, including both nucleophilic and electrophilic centers (Fig. 2). Considering the potential of enones to undergo reactions such as oxidation, hydrogenation,[7,8] 1,2 addition, conjugate addition[9,10] and cycloaddition,[11] they are utilized as necessary starting materials in various synthetic methodologies.

Nowadays, transition metal-free reactions have drawn significant interest among synthetic organic chemists. The quest to explore alternatives to transition metal catalysts is mainly attributed to the toxicity inherent with such systems, especially when it comes to synthesising heterocycles of biological relevance. Moreover, the requirement of drastic reaction conditions, tedious purification procedures, and high cost are some of the drawbacks of transition metal-catalyzed protocols. Additionally, special additives, co-catalysts and prefunctionalized starting materials are required in many cases.[12] It is noteworthy that, until now only few drugs have been synthesised *via* metal free methods (Fig. 3).[6b,13] Hence, protocols which proceed under metal-free conditions are always desirable among the scientific community. The current review focuses on the recent advances in the transition metal-free synthesis of heterocyclic molecules using α,β-unsaturated ketones.

2. Synthesis of nitrogen-containing heterocycles

Nitrogen-containing molecules constitute an important class of structural scaffolds among various heterocycles. It is found that around 75% of the currently marketed drugs are nitrogen containing heterocyclic molecules.[14,15] Thus, the synthesis of nitrogen heterocycles is an area of ever-growing interest among organic chemists. As a result, numerous protocols are being developed for accessing various N-heterocycles.

2.1 Synthesis of five-membered nitrogen heterocycles

2.1.1 Synthesis of pyrrole and its derivatives. Pyrrole is an important five-membered heterocyclic compound. Like any other N-heterocyclic scaffold, pyrrole and its derivatives are inherited with valuable biological properties.[16,17] In 2011, Li *et al.* reported a metal-free strategy for synthesising pyrroles **3** (Scheme 1).[18] They demonstrated the pyrrole synthesis using

Basavaraja D.

Basavaraja D. was born in the Raichur district of Karnataka, India. He obtained a B.Sc. degree in Chemistry from Laxmi Venkatesh Desai (LVD) College, Raichur, and M.Sc. from Gulbarga University, Gulbarga, Karnataka, in the year 2016. He qualified the CSIR-UGC national eligibility test in 2016 with a research fellowship. Presently he is a Senior Research Fellow and pursuing his Ph.D. at CSIR-NIIST, Thiruvananthapuram, Kerala, under Dr Sasidhar B. S. His area of research interest is the design and synthesis of spiro and heterocyclic based molecular templates of medicinal significance.

Sasidhar B. Somappa

Sasidhar B. Somappa received an M.Sc. in Organic Chemistry (2006) and Ph.D. in Organic and Medicinal Chemistry (2012) from Gulbarga University, Kalaburagi, India, under the supervision of Professor J. S. Biradar. Prior to his Ph.D., he had industrial stints at leading pharmaceutical industries (2006–2008). In 2012, he joined as a Scientist at Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Kerala, India. Presently, he is a Senior Scientist and an Assistant Professor (AcSIR). He has published over 60 peer-reviewed articles and reviews with an impact factor of >250 that have been cited over 1300 times. His research interests include the development of novel synthetic methodologies for the heterocycles of medicinal relevance, improved processes for Active Pharmaceutical Ingredients (APIs) and speciality chemicals, and target based drug design via *synthetic and natural product based approaches. He is a recipient of multiple awards and fellowships, including the prestigious CSIR Young Scientist Award (2019) from CSIR, India, Kerala State Young Scientist Award (2017) from KSCSTE, Kerala, India and Young Associate of Indian Academy of Sciences (2019), from Indian Academy of Sciences, India.*

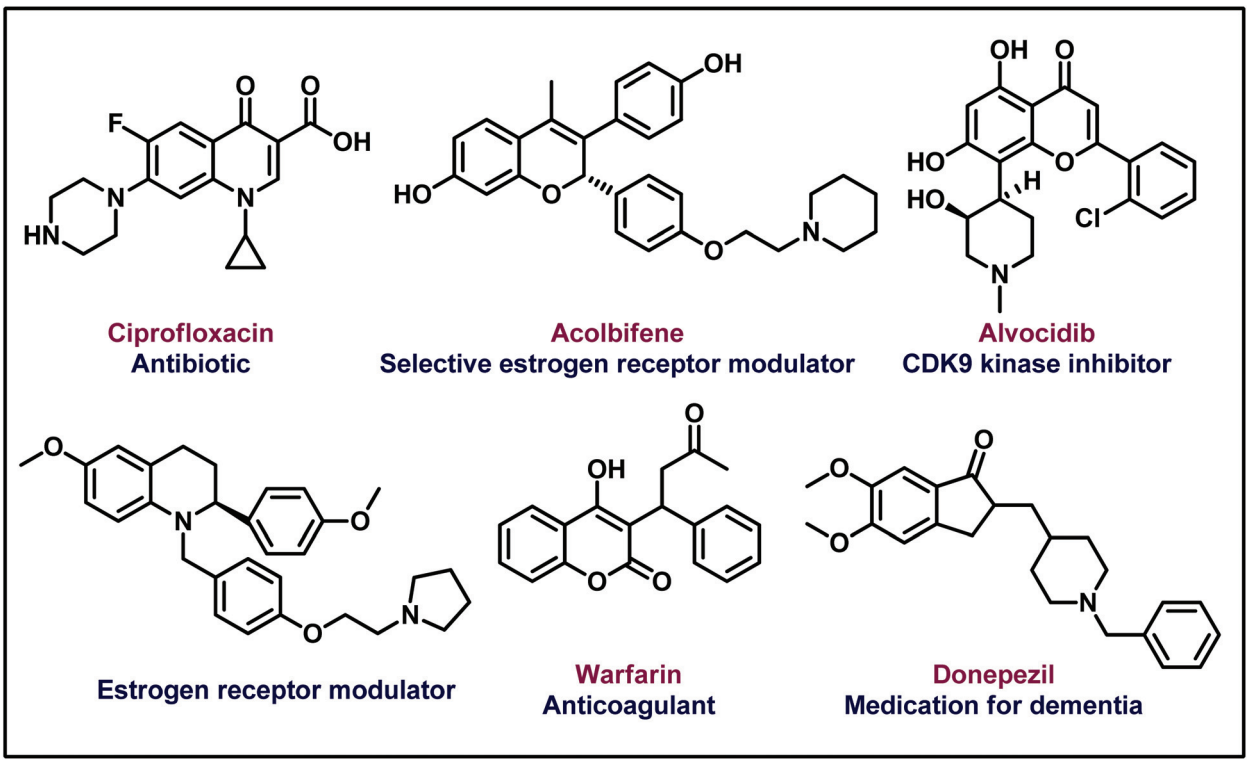


Fig. 1 Drugs and clinical candidates with process chemistry involving α,β-unsaturated ketone as one of the intermediates.

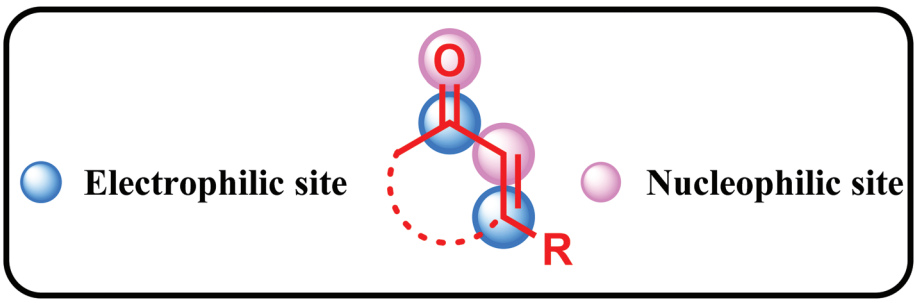


Fig. 2 Reactive sites of α,β-unsaturated ketones.

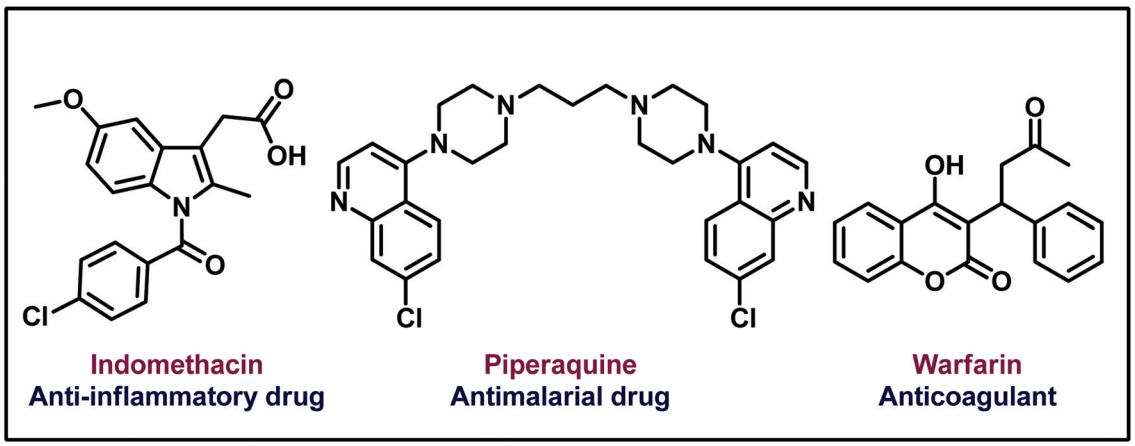
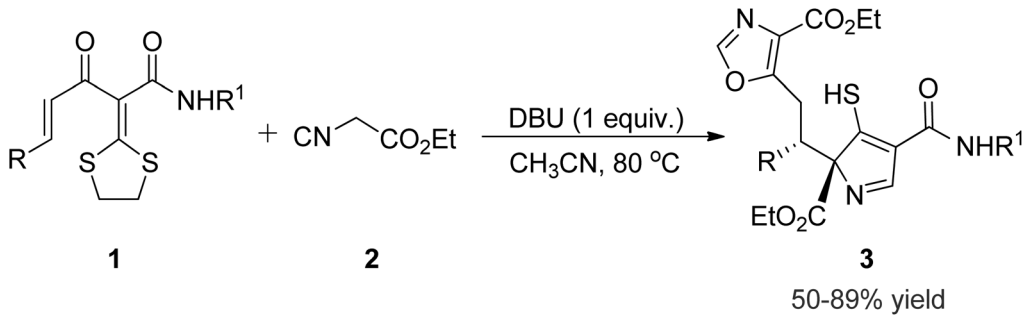


Fig. 3 Drugs synthesised *via* metal free process chemistry.



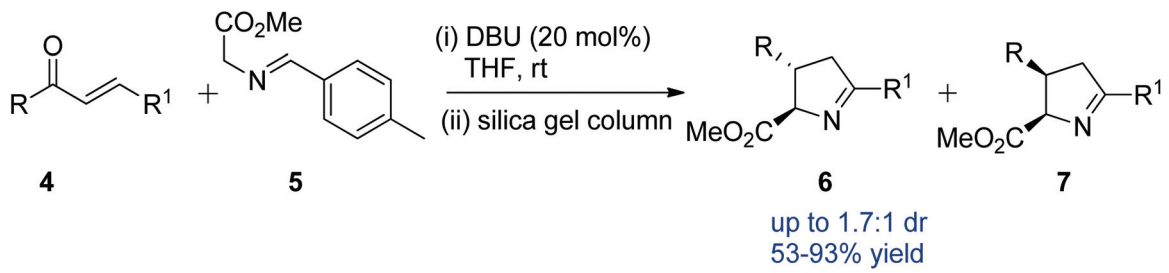
Scheme 1 DBU mediated domino process for the synthesis of C_2-tethered pyrroles/oxazoles.

divinyl ketone **1** and ethyl isocyanoacetate **2** as the starting materials. It is a DBU mediated domino process that proceeds *via* [5 + 1] annulation, ring-opening, and double isocyanide cyclisation sequence. The method facilitates the synthesis of C_2-tethered pyrrole/oxazole pair, involving the formation of four C–C and one C–O bond in a regio and diastereoselective fashion.

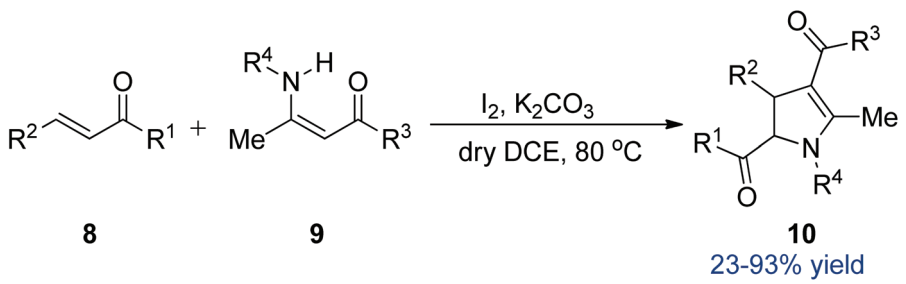
Later in 2012, Zhang *et al.* unravelled a single step, DBU catalysed method for the synthesis of 3,4-dihydro-2*H*-pyrroles (**6** and **7**) using enones **4** and *N*-(4-chlorobenzylidene)-glycine methyl ester **5** as the substrates (Scheme 2). This reaction involves the formation of a Michael adduct in the presence of the catalytic amount of base. Further, conversion of the Michael adduct to the product as well as its purification occurs during silica gel column chromatography.[19]

Li and co-workers reported an iodine mediated synthesis of polysubstituted *trans*-2,3-dihydropyrroles **10** in 2015 (Scheme 3). The environmentally benign method utilises chalcones **8** and *β*-enamine ketones **9** as the starting materials.[20] The synthesis of 2,3-dihydropyrroles proceeds through molecular iodine mediated Michael addition of enamine to the chalcone followed by intramolecular cyclisation reaction.

Later in 2018, Wen *et al.* devised an organocatalyzed asymmetric synthesis of dihydropyrroles **14** from enones **8** and glycine esters **11**.[21] The authors have developed a novel chiral aldehyde catalyst to activate *α*-position of the glycine ester. The reaction is highly beneficial for the synthesis of the dihydropyrroles, as it affords the product with high yield, diastereoselectivity and enantioselectivity. The reaction is assumed to proceed through the formation of an imine from glycine ester and catalyst. Later, the imine undergoes nucleophilic addition reaction with enone (Scheme 4). Finally, intramolecular condensation reaction furnishes the product. It is found that the hydroxyl group present on the chiral catalyst **12** plays a crucial role in the imine formation and addition of nucleophile.



Scheme 2 DBU catalysed single-step synthesis of 3,4-dihydro-2*H*-pyrroles.



Scheme 3 Iodine mediated synthesis of polysubstituted *trans*-2,3-dihydropyrroles.