Diastereoselective Construction of Structurally Diverse Spirooxindoles via Annulation of Morita-Baylis-Hillman Adducts of Isatin

A thesis

submitted in partial fulfillment of the requirements
of the degree of

Doctor of Philosophy

By

Prakash Kashinath Warghude

ID: 20163475

Indian Institute of Science Education and Research Pune

2022

This thesis is dedicated to...

My parents

And

My beloved family

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान पुणे
INDIAN INSTITUTE OF SCIENCE EDUCATION AND RESEARCH PUNE
An Autonomous Institution of the Ministry of Education, Govt. of India

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CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled "***Diastereoselective Construction of Structurally Diverse Spirooxindoles via Annulation of Morita-Baylis-Hillman Adducts of Isatin***" submitted by **Prakash Kashinath Warghude** and the research was carried out by the candidate at Indian Institute of Science Education and Research (IISER), Pune, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other University or institution.

Date: 24/03/2022
Place: Pune (Maharashtra)

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DECLARATION

I declare that, this written submission represents my ideas in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date: 24/03/2022 Prakash Kashinath Warghude

Place: Pune (Maharashtra) (ID: 20163475)

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"The truth is - no matter how "self-made" you think you are, you are really made by many who have invested in your life. Be known as a thankful and grateful person… and be known as the person that is investing in others to build them up, as well. It's your way of paying back the debt that others have invested in you."
*(Writer: **Josh Hatcher, Manlihood: The 12 Pillars of Masculinity**)*

Finally, I thank the almighty God for giving this wonderful life full of opportunities

Prakash Kashinath Warghude

CONTENTS

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Chapter 3: ***Enantioselective Synthesis of Spirooxindole Dihydrofuran Fused Pyrazolones via [3+2] annulation of Morita-Baylis–Hillman Carbonate with Pyrazolone 4, 5-diones***

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List of Abbreviations

Å	angstrom (s)
ACN	acetonitrile
Ag	argentums (Silver)
Ar	aryl
β-ICD	beta-isocupreidine
BHT	butylated hydroxytoluene
Bn	benzyl
^{t}Boc	*tert*-butoxycarbonyl
bs	broad singlet
C	carbon
°C	degree Celsius
Calcd.	calculated
Cat.	catalytic
cm^{-1}	wavenumber(s)
Cu	copper
d	day (s); doublet (spectral)
DCC	*N, N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DFT	density functional theory
DMAP	*N, N'*-dimethylaminopyridine
DIPEA	*N, N*-diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
E	electrophile
equiv.	equivalent

ESI	electrospray ionisation
EtOAc	ethyl acetate
EWG	electron withdrawing group
g	gram(s)
FTIR	fourier transform infrared
H	hydrogen
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
^{i}Pr	isopropyl
J	Spin coupling constant
kcal	kilocalories
LB	Lewis Base
M	multiplet (spectral)
m	meta
M	molar (mol L^{-1})
MBH	Morita-Baylis-Hillman
MBHCs	Morita-Baylis-Hillman Carbonates
m/z	mass- to-charge ratio
Me	methyl
mg	milligram
min	minute(s)
mL	millilitres
mmL	microlitre
MS	molecular seives
mmol	millimole
mol	mole
m.p.	melting point
MTBE	methyl tert-butyl ether
N	nitrogen
NHC	*N*-heterocyclic carbenes
NMR	nuclear magnetic resonance

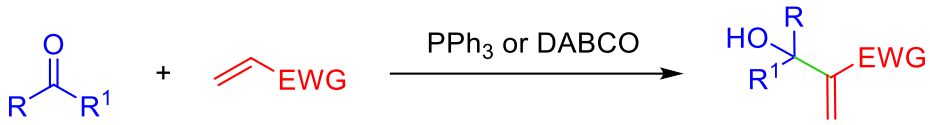
Nu	nucleophile
O	oxygen
o	ortho
ORTEP	Oak Ridge Thermal-Ellipsoid Plot Program
p	para
P	phosphorus
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor
rt	room temperature
S	sulphur
s	singlet (NMR)
t	triplet (NMR)
t-, tert-	tertiary (branched alkyl chain)
Ti	Titanium
td	triplet of doublet
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TS	transition state
UV	ultraviolet
X	heteroatom
XRD	X-ray diffraction
δ	chemical shift in ppm downfield from trimethylsilane

SYNOPSIS

The thesis entitled "***Diastereoselective Construction of Structurally Diverse Spirooxindoles via Annulation of Morita-Baylis-Hillman Adducts of Isatin***" comprises of five main chapters

Chapter 1: *Regio-divergent Organocatalytic Reactions of Morita-Baylis-Hillman (MBH) Adducts to Access Spirocarbocyclic Compounds*

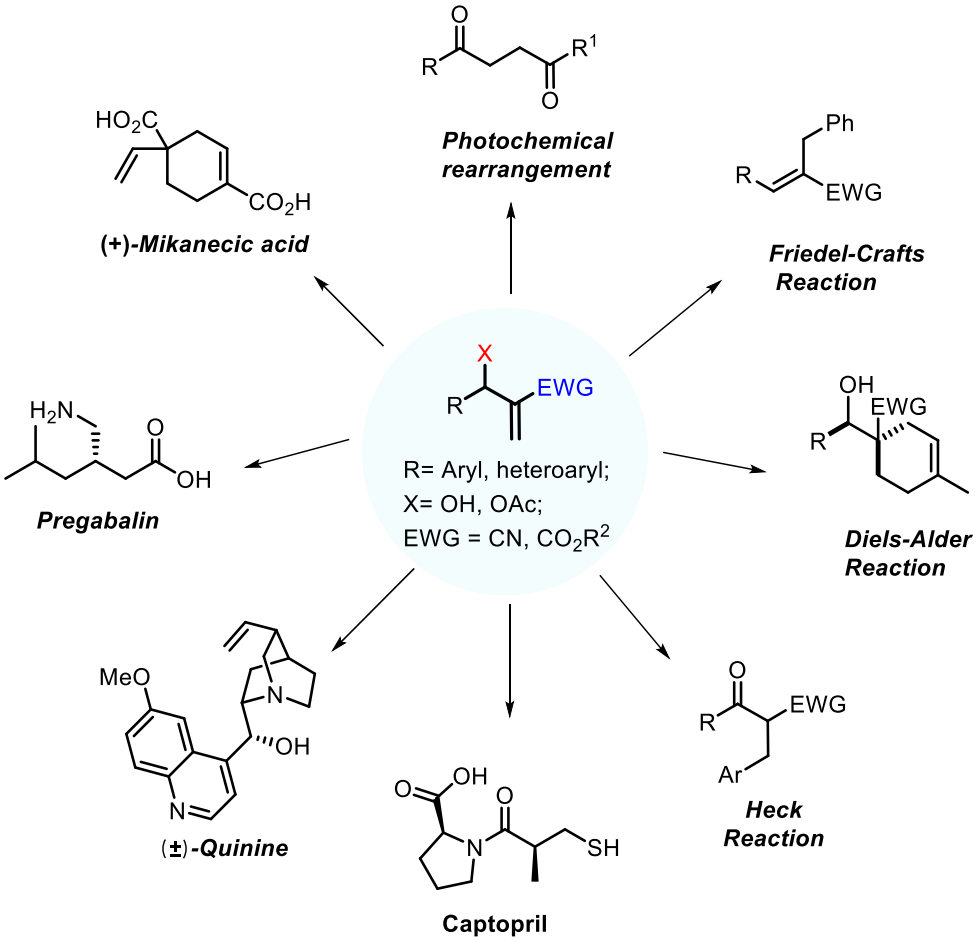
This introductory chapter presents a brief overview on Morita-Baylis-Hillman (MBH) reaction and the utility of MBH adduct in organic synthesis. Among the various carbon-carbon bond forming reactions, the Morita-Baylis-Hillman (MBH) reaction has emerged as one of the most important and useful methods to construct C-C and C-X bonds very effectively under mild reaction conditions. The classical Morita-Baylis-Hillman (MBH) reaction forms the carbon-carbon (C-C) bond between α-position of an activated alkene and aldehyde in presence of nucleophilic catalyst such as tertiary amine or phosphine (Scheme 1.1).



R = aryl, alkyl, heteroaryl; R^1 = H, aryl, CO_2R^3
EWG = CO_2R^3, CHO, CN, *etc.*

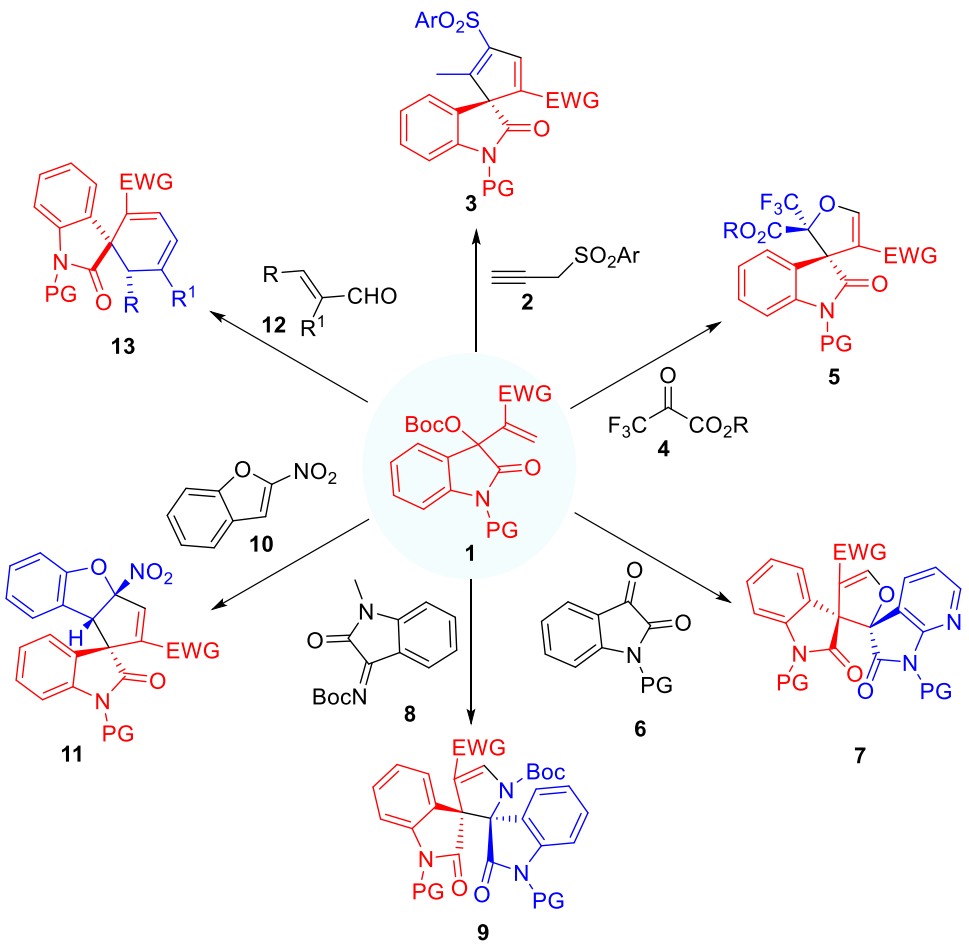
Scheme 1.1 The classical Morita-Baylis-Hillman (MBH) Reaction

The MBH reaction products (MBH adducts) are highly functionalized with different functional groups (allylic alcohol, activated alkene and electron withdrawing group) in a close proximity. Due to the dense functionalities, the MBH adducts have been used as a versatile precursor in various types of synthetic transformations such as photochemical reaction, Friedel-Craft reaction, Diels-Alder reaction, Heck reaction, etc. Moreover, these MBH adducts have also been used in the synthesis of bioactive as well as medicinally relevant compounds like captopril (hypertension), quinine, pregabalin, (+)-Mikanecic acid (Scheme 1.2).



Scheme 1.2 Utility of Morita-Baylis-Hillman (MBH) Adducts

Besides these transformations, MBH carbonates are known to undergo various types of annulation reactions, which are useful in synthesizing structurally diverse spirocyclic compounds. Particularly, isatin-derived MBH carbonates **1** have turned out to be very useful substrates for the construction of biologically relevant spirocyclic compounds such as cyclopentadiene oxindole **3**, spirooxindole dihydrofuran **5**, bis-spirooxindole **7** and spirooxindole dihydropyrrole **9** via [3 + 2] annulation with propargyl sulfones **2**, trifluoropyruvate **4**, *N*-alkylisatin **6** and isatin derived *N*-Boc-ketimine **8** substrates respectively. In addition, MBH carbonates **1** undergo dearomative cycloaddition as well as electrocyclic cyclization by reacting with the 2-nitrobenzofurans **10** and α, β-unsaturated aldehydes **12** to give respective compounds **11** and **13** (Scheme 1.3).



Scheme 1.3 Synthetic application of Morita-Baylis-Hillman (MBH) carbonates of isatin

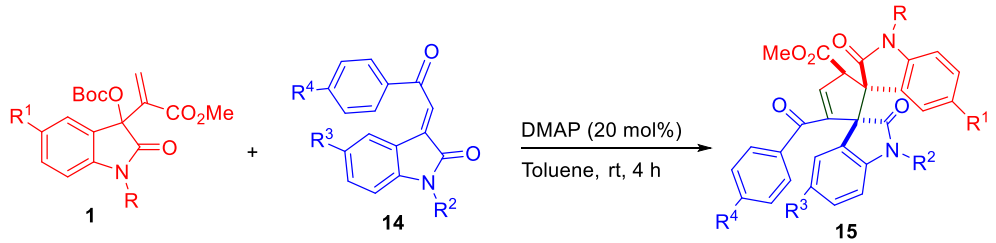
Though MBH carbonates **1** have been effectively explored in various annulations to construct spirocyclic architecture, interestingly, still there is a huge scope to employ MBH adducts to access synthetically challenging and medicinally useful spirocyclic compounds. Also, some of the available protocols involving the use of isatin based MBH adducts still have to meet the very high stereoselectivity. Moreover, novel and practical uses of MBH carbonates of isatin are highly demanding and challenging to pursue.

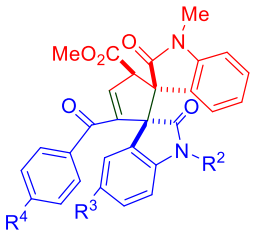
Chapter 2: *Cycloaddition of Isatin-Derived MBH Carbonates and 3-methyleneoxindoles to Construct Cyclopentenyl Bis-spirooxindoles and Cyclopropyl Spirooxindoles*

This chapter describes the development of a novel, regio- and diastereo-selective protocol for the synthesis of cyclopentenyl bis-spirooxindoles **15** and cyclopropyl spirooxindoles **16** via [3+2] annulation of MBH carbonates of isatin **1** and 3-methyleneoxindoles **14** via tertiary amine catalysis. The chapter begins with a brief account on the importance of bis-spirooxindole and cyclopropyl spirooxindole and some of the selected methods for their preparation. Spirooxindole is a versatile as well as unique scaffold. Owing to the pharmacological importance and significance of spirooxindole motif, over the years efforts have been devoted to construct different spirooxindole derivatives in regio- and stereoselective manner. However, some of the shortcomings of these methods are limited substrate scope, use of transition metal catalyst, required stoichiometric base and heating condition. In this regard, a straightforward approach has been developed for the synthesis of bis-spirooxindole **15** and cyclopropyl spirooxindole **16** starting from MBH carbonates (MBHCs) of isatin **1** and **3**-methyleneoxindoles **14** via [3 + 2] cycloaddition pathway under Lewis base organocatalysis.

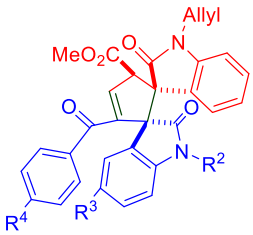
Having obtained the optimized protocol in hand, the scope of [3 + 2] annulation was investigated by the different combination of various substituted (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-ones **14a-14j** and MBH carbonates **1a-1d** to afford the corresponding bis-spirooxindole derivatives **15a-15t** (Table 2.1). All the substrates underwent facile [3 + 2] annulation to afford the desired bis-spirooxindole compounds **15a-15t** containing adjacent quaternary spirocenters in good to excellent yields with very high diastereoselectivity (81-98%, *dr* >20:1, Table 2.1). Importantly, both electron donating and weakly electron deactivating (Br, Cl) substituents on either MBH carbonates **1** or on 3-methyleneoxindoles **14** did not affect the outcome of the yield and stereoselectivity.

Table 2.1 Substrate scope of [3 + 2] annulation to access bis-spirooxindole derivatives[a-c]

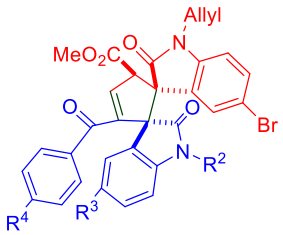




15a-15i
(***dr*** **> 20:1 in all cases)**



15j-15m
(***dr*** **> 20:1 in all cases)**

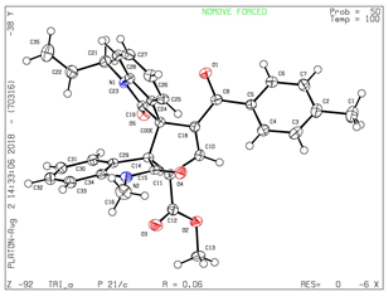


15n-15q
(***dr*** **> 20:1 in all cases)**

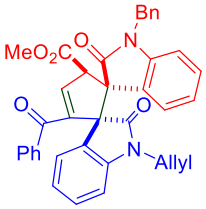
15a, R^2= Me, R^3= H, R^4= H, 97%
15b, R^2= allyl, R^3= H, R^4= Cl, 96%
15c, R^2= Bn, R^3= H, R^4= Me, 97%
15d, R^2= Me R^3= H, R^4= Cl, 95%
15e, R^2=Bn, R^3= H, R^4= Cl, 96%
15f, R^2= allyl, R^3= H, R^4= Me 98%
15g, R^2= allyl, R^3= H, R^4= H, 94%
15h, R^2= Me, R^3= Br, R^4= H, 90%
15i, R^2= Me, R^3= Cl, R^4= H, 92%

15j, R^2= allyl, R^3= H, R^4= Me, 95%
15k, R^2= allyl, R^3= H, R^4= Cl, 93%
15l, R^2=Bn, R^3= H, R^4= Me, 81%
15e, R^2= Bn, R^3= H, R^4= Cl 88%

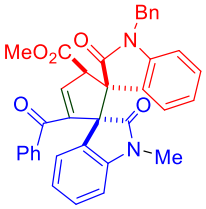
15n, R^2= Me, R^3= H, R^4= H, 91%
15o, R^2= Me, R^3= H, R^4= Cl, 88%
15p, R^2=allyl, R^3= H, R^4= Me, 95%
15r, R^2= allyl, R^3= H, R^4= H, 90%



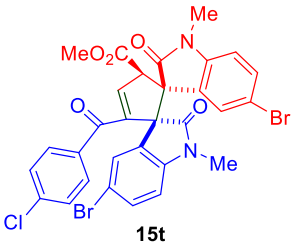
(Molecular Structure **15f**)
CCDC 1860014



15r
87%, *dr* >20:1



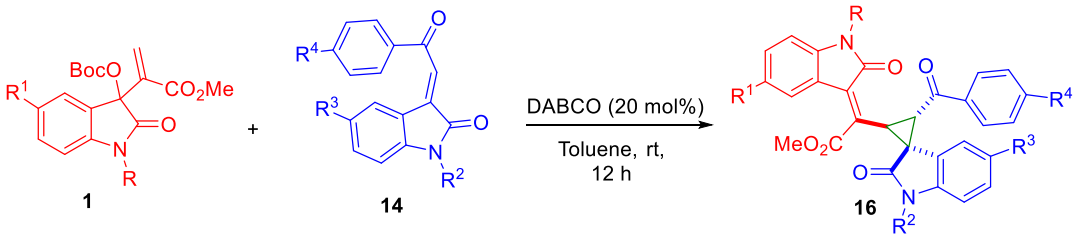
15s
86%, *dr* >20:1

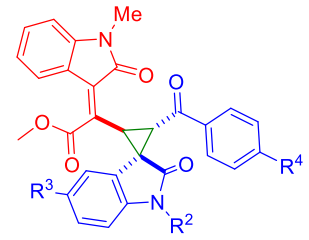


15t
81%, *dr* >20:1

[a]Optimized reaction conditions: Substituted MBH carbonate **1** (0.28 mmol) and substituted 3-methyleneoxindole **14** (0.31 mmol) with DMAP (20 mol%), in toluene (2 mL) at room temperature, 4 h. [b]Isolated yields after purification by column chromatography. [c]*dr* was calculated by ^{1}H-NMR.

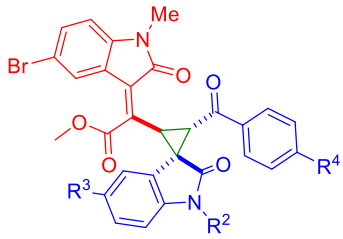
Table 2.2 Substrate scope of [2 + 1] annulation to access cyclopropyl spirooxindole derivatives[a-c]





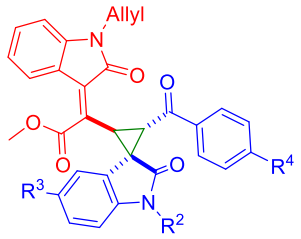
16a-16d
(***dr*** **>20:1 in all cases)**

16a, R^2= Me, R^3= H, R^4= H, 85%
16b, R^2= Me, R^3= H, R^4= Cl, 82%
16c, R^2=Me, R^3= Br, R^4= H, 79%
16d, R^2= Me, R^3= Cl, R^4= H, 83%



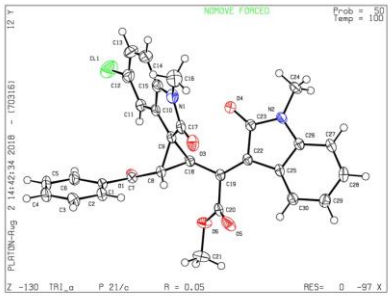
16e-16h
(***dr*** **>20:1 in all cases)**

16e, R^2= Me, R^3= H, R^4= H, 75%
16f, R^2= Me, R^3= Br, R^4= H, 72%
16g, R^2=Me, R^3= Cl, R^4= H, 70%
16h, R^2= Me, R^3= Cl, R^4= Me, 75%

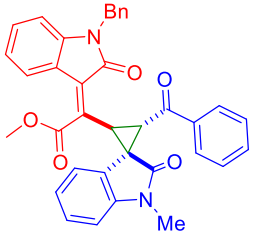


16a-16d
(***dr*** **>20:1 in all cases)**

16i, R^2= Me, R^3= H, R^4= H, 83%
16j, R^2= Me, R^3= H, R^4= Cl, 80%
16k, R^2=Me, R^3= Br, R^4= H, 72%



(Molecular structure **16d**)
CCDC 1860035



16l
70%, *dr* >20:1

[a]Optimized reaction conditions: MBH carbonate **1** (0.28 mmol) and (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-ones **14** (0.31 mmol) with DABCO (20 mol%) in toluene (2 mL) at room temperature, 12 h. [b]Isolated yields after column chromatography. [c] *dr* was determined by ^{1}H-NMR.

Similarly, the substrate scope for [2 + 1] annulation was examined under optimized reaction conditions (Table 2.2). The reaction of various MBH carbonates **1a-1d** derived from isatin with few 3-methyleneoxindoles (**14a**, **14d, 14h, 14i, 14k)** in presence of DABCO (20 mol%) in toluene

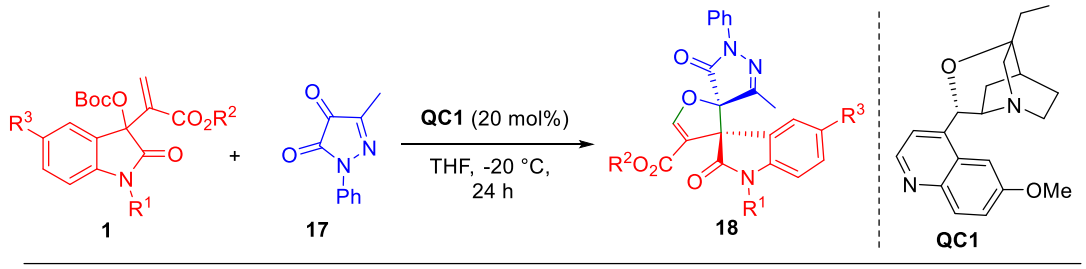
at room temperature afforded the corresponding cyclopropyl spirooxindole compounds **(16a-16l)** in very good yields with excellent diastereoselectivity (70-85%, *dr* >20:1, Table 2.2).

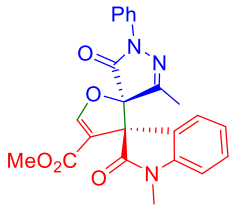
We have developed an expedient method to access structurally diverse bis-spirooxindoles and cyclopropyl spirooxindole derivatives via [3 + 2] and [2 + 1] annulations of isatin-derived Morita−Baylis−Hillman carbonate and 3-methyleneoxindoles. This catalyst-controlled protocol delivered the spirooxindole products in good to excellent yields with very high diastereoselectivity. The practicality and generality of the protocol have been demonstrated by synthesizing a total of 32 examples.

Chapter 3: *Enantioselective Synthesis of Spirooxindole Dihydrofuran Fused Pyrazolones via [3+2] Annulation of Morita-Baylis–Hillman Carbonate with Pyrazolone 4, 5-diones*

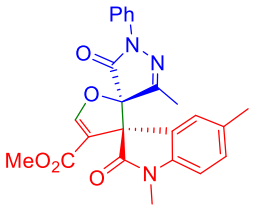
This chapter presents an expedient and straightforward method for the construction of enantiopure spirooxindole dihydrofuran fused pyrazolones via asymmetric [3 + 2] annulation process. Spirooxindole and spiropyrazolone core is an important heterocyclic skeleton found in several bioactive synthetic and naturally occurring compounds. The chapter briefly gives an overview on the importance of heterocyclic spirooxindole and spiropyrazolone derivatives and some of the selected approaches for the synthesis of spiropyrazolone fused oxindole derivatives. Considering the importance of both these scaffolds, few asymmetric methods have been reported for the synthesis of spirooxindole fused pyrazolone scaffolds. Interestingly, till date no protocol has been developed for the construction of scaffold that contains three different moieties such as pyrazolone, oxindole and dihydrofuran in an enantioselective fashion. In this regard, the development of easy, practical and one pot strategy which allow the synthesis of multifunctional spiropyrazolne fused oxindole is highly challenging and demanding in synthetic chemistry point of view. In view of this, we developed a strategy for the synthesis of spirooxindole dihydrofuran fused derivatives **18** via [3 + 2] annulation of MBH carbonate of isatin **1** and pyrazolone 4,5-dione **17** in presence of chiral quinine derived catalyst **QC1** (Table 3.1).

Table 3.1 Substrate scope of [3 + 2] annulation to access spirooxindole fused pyrazolones[a-d]

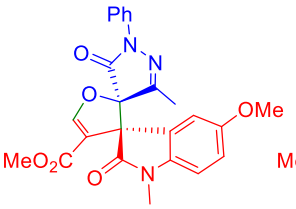




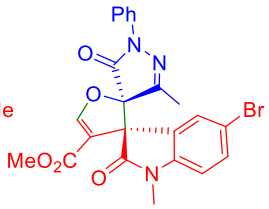
18a
(75%, 93% *ee*) (*dr* >20:1)[c]



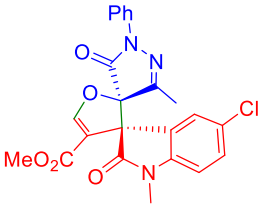
18b
(92%, 90% *ee*)



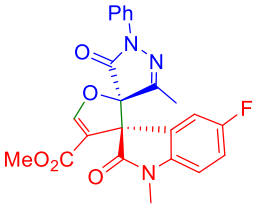
18c
(88%, 91% *ee*)



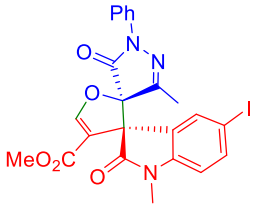
18d
(91%, 88% *ee*)



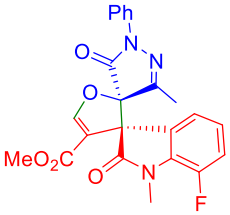
18e
(91%, 92% *ee*)



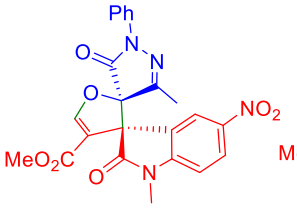
18f
(89%, 92% *ee*)



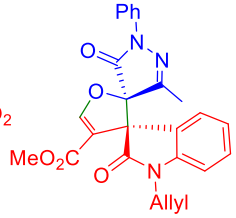
18g
(89%, 91% *ee*)



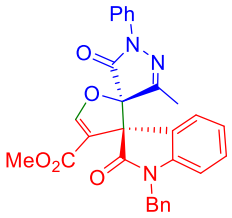
18h
(90%, 93% *ee*)



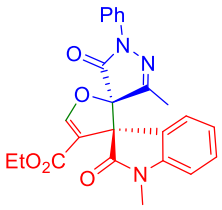
18i
(92%, 90% *ee*)



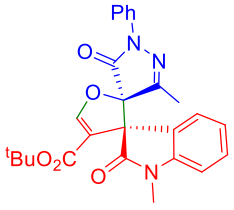
18j
(90%, 91% *ee*)



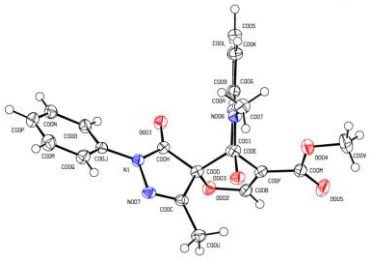
18k
(82%, 93% *ee*)



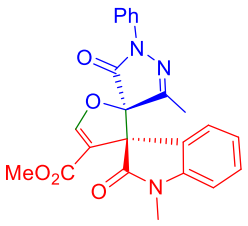
18l
(92%, 90% *ee*)
recrystallization >99% *ee*



18m
(92%, 88% *ee*)



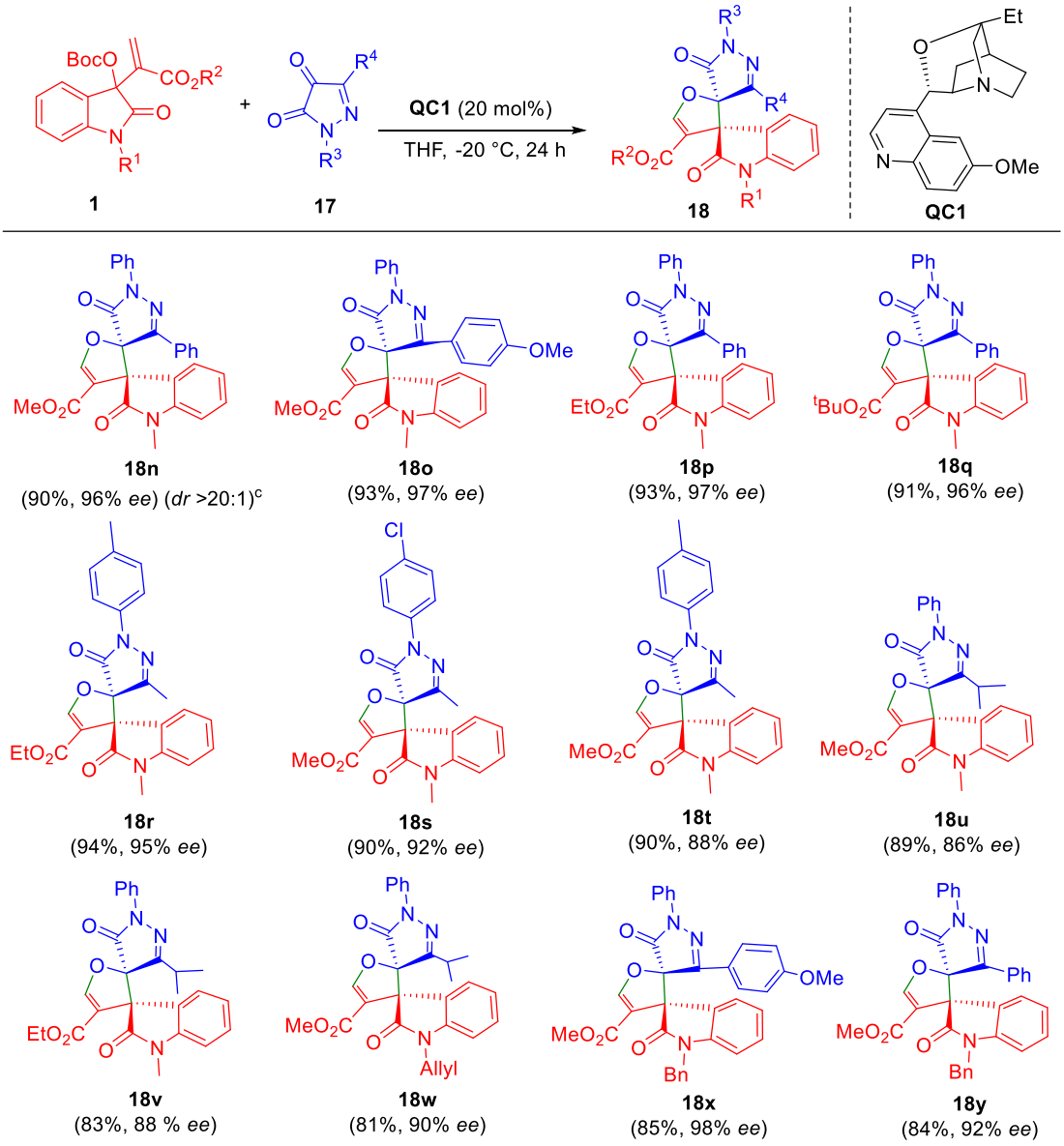
(Molecular Structure of **18a**)
CCDC 1967741



18a (2*R*, 3*S*)

[a]Optimized reaction conditions: MBHCs of isatin **1** (1.0 equiv.), Pyrazolone 4,5-dione **2** (1.0 equiv.), **QC1** (20 mol%) in THF (1.0 mL). [b]Isolated yield. [c]*dr* was calculated by ^{1}H NMR (*dr* >20:1) in all cases. [d]*ee* was determined by HPLC.

Table 3.2 Substrate scope of pyrazolone 4, 5-dione derivatives[a-d]

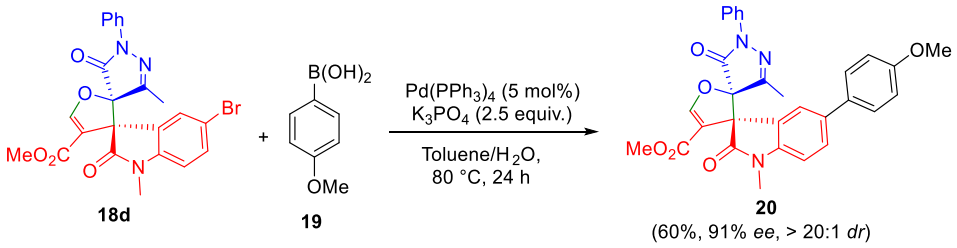


[a]Optimized reaction conditions: MBHCs of isatin **1**(1.0 equiv.), Pyrazolone 4,5-diones **2** (1.0 equiv.), **QC1** (20 mol%) in tetrahydrofuran (1.0 mL) at -20 °C, 24 h. [b]Isolated yield of products after colum chromatography. [c]*dr* was calculated by ^{1}H NMR and >20:1 in all cases. [d]ee was determined by HPLC on chiral stationary phase.

Different combinations of substituted MBH carbonates of isatin (**1a-1m**) and various pyrazole-4,5-diones (**17a-17f**) underwent a facile [3 + 2] cyclization to afford corresponding spirooxindole dihydrofuran pyrazolone derivatives (**18a-18y**) in good to excellent yields (75-84%)

with very high stereoselectivitties under the optimized reaction conditions (Table 3.1 and 3.2, *dr* >20:1, 88-98% *ee*). Further, the absolute configuration of spirooxindole **18a** was unambiguously determined by single-crystal X-ray diffraction analysis (Table 3.1).

Further, we demonstrated the synthetic utility of this protocol by employing the bromo derivative of spirooxindole dihydrofuran fused pyrazolone **18d** as a substrate to explore the Suzuki coupling. The cross coupling of **18d** with **19** in presence of $Pd(PPh_3)_4$ delivered the spirooxindole derivative **20** in moderate yield with high enantioselectivity (Scheme 3.1).



Scheme 3.1 Cross-coupling (Suzuki) reaction

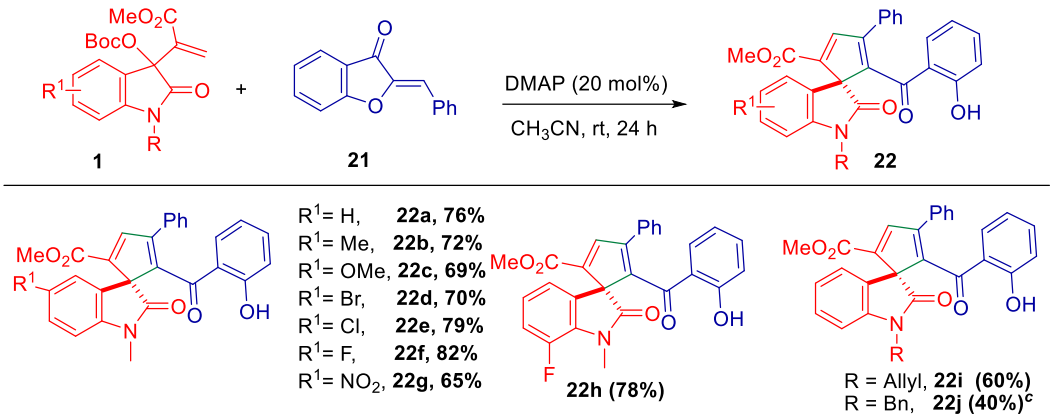
We have developed robust and practical method to access highly enantiopure spirooxindole fused pyrazolones via organocatalytic cycloaddition strategy. A series of structurally diverse functionalized spirooxindoles dihydrofuran fused pyrazolone derivatives with two contiguous quaternary spirocenters were synthesized in good to excellent yields with excellent stereoselectivity in presence of chiral tertiary amine catalyst.

Chapter 4: *An Easy and Practical Approach to Access Multifunctional Cylcopentadiene- and Cyclopentene-Spirooxindoles via [3 + 2] Annulation*

This chapter presents a practical, easy, and one-pot transition-metal-free approach for synthesizing spirooxindole compounds via the organocatalytic cycloaddition process. A brief overview on the importance of spirooxindoles and spirocyclic benzofuranones scaffolds has been presented. These scaffolds are found in a variety of synthetic as well as natural products and they are known to exhibit potential biological activity. Owing to the importance of these scaffolds, many elegant protocols have been reported for their synthesis. However, some of these methods had narrow utility in organic synthesis due to the limited substrate scope and the use of transition

metals. The development of novel, efficient and mild protocol to access these scaffolds is highly demanding and challenging. In order to overcome some of these limitations, we explored organocatalytic approach for the synthesis of spirooxindole derivatives **22** via formal [3 + 2] cycloaddition of MBH carbonates of isatin **1** and aurone [(*Z*)-2-benzylidenebenzofuran-3(2*H*)-one] **21** in presence of Lewis base catalyst such as DMAP (20 mol%) at room temperature (Table 4.1).

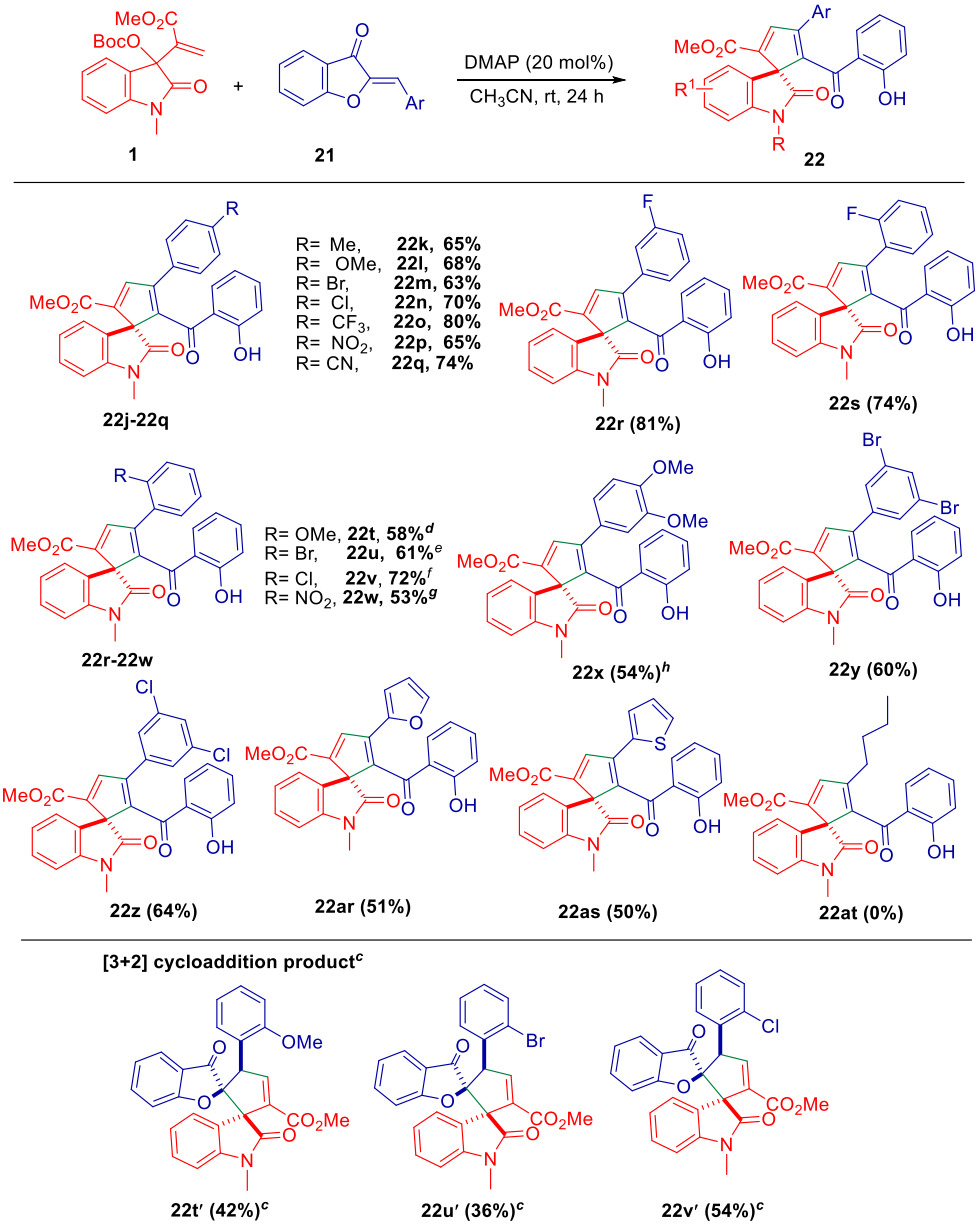
Table 4.1 Substrate scope of substituted MBH carbonate[a-c]



[a]Optimized reaction condition: MBH carbonate of isatin **1** (0.115 mmol), (*Z*)-2-benzylidenebenzofuran-3(2*H*)-one **21** (0.138 mmol), DMAP (20 mol%), ACN (2.0 mL) at room temperature; [b]Isolated yield after column chromatography. [c]DMAP (50 mol%).

For the generality of the protocol and for the wider substrate scope, [3 + 2] annulation ring opening reaction was explored using various isatin-derived MBH carbonates (**1a-1j**) and substituted aurones (**21a-21t**) under the optimized reaction conditions. Gratifyingly, all the substrates underwent 1,3 dipolar cycloaddition efficiently to afford corresponding cyclopentadiene oxindole derivatives (**22a-22as)** in satisfactory to good yields (40-82%, Table 4.1 and 4.2). It is important to note that, in case of *ortho* substituted aurones, the bis-spirocyclic compounds (**22t'-22v'**) were obtained in satisfactory yields (up to 54%, Table 4.2). The reaction of *ortho*-substituted aurones with MBH carbonates at higher temperature (up to 70 °C) delivered the cyclopentadiene oxindole compounds **22t-22w** in moderate to good yields (up to 72%, Table 4.2). In order to have

Table 4.2 Substrate scope of substituted aurone[a-h]

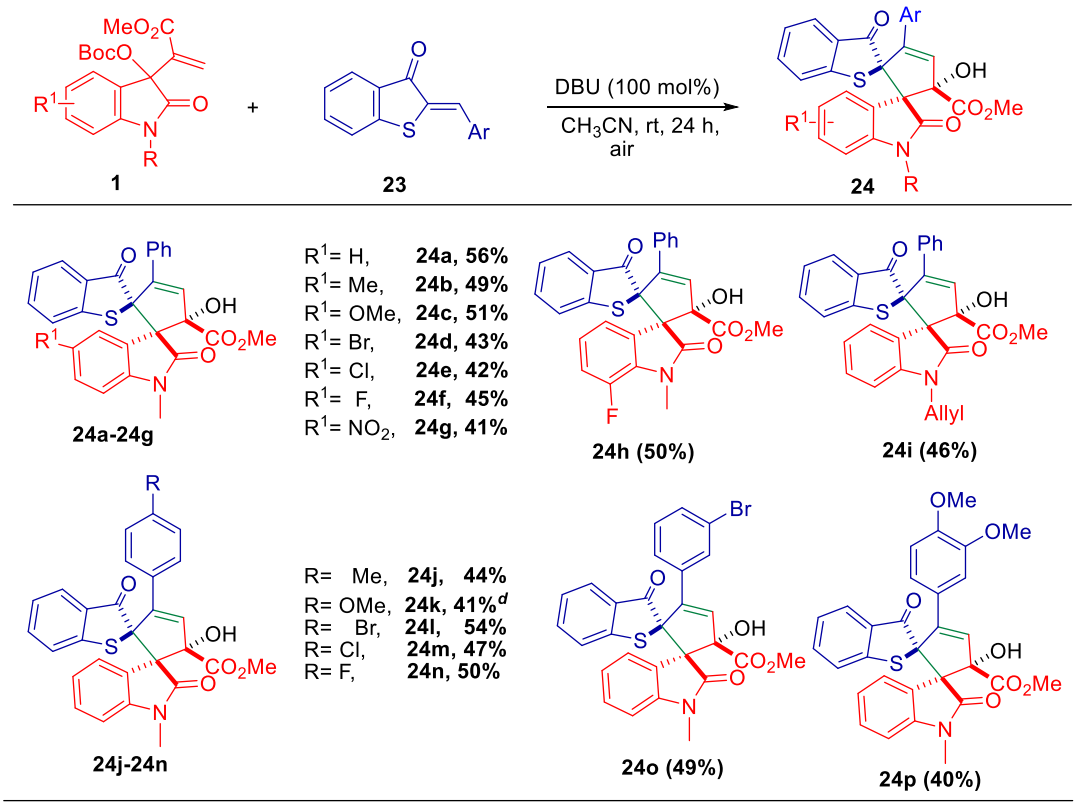


[a]Optimized reaction condition: Substituted MBH carbonate of isatin **1a** (0.115 mmol), (*Z*)-2-benzylidenebenzofuran-3(2*H*)-ones **21** (0.138 mmol), DMAP (20 mol%), acetonitrile (2.0 mL) at room temperature; [b]Isolated yield after column chromatography; [c]Spirocyclopentene compounds were obtained at room temperature; [d]DMAP (20 mol% at 50 °C) or DMAP (1.0 equiv.); [e]DMAP (1.0 equiv. at 70 °C); [f] DMAP (50 mol% at 70 °C); [g]DMAP (30 mol% at 70 °C); [h]DMAP (1.0 equiv.).

mechanistic insights of the transformations and to understand the different reactivity of *ortho* and *para* substituted aurones, we further performed the computational (DFT) calculations.

Later, our initial attempts to synthesize cycloaddition products derived from structurally similar sulphur analogue of aurones were unsuccessful under the standard conditions. After the exhaustive screening, reaction of MBH carbonate **1** (1.0 equiv.), thioaurone [(*Z*)-2-benzylidenebenzo[*b*]thiophen-3(2*H*)-one] **23** worked efficiently in presence of DBU in acetonitrile at room temperature to afford the corresponding spirooxindole fused benzo[*b*]thiophen-3(*2H*)-one **24** derivative (Table 4.3).

Table 4.3 Substrate scope of substituted MBH carbonate and thioaurones[a-d]



[a]Optimised reaction condition: MBH carbonate **1** (0.115 mmol), Substituted thioaurone **23** (0.138 mmol), DBU (0.115 mmol), CH_3CN (2.0 mL) at room temperature, 24 h. [b]Isolated yield after column chromatography. [c]diastereomeric ratio (*dr* >20:1 in all cases) was determined by ^1H NMR. [d]DBU (2.0 equiv.).

The treatment of substituted isatin based MBH carbonates (**1a-1i**) with various (*Z*)-2-benzylidenebenzo[*b*]thiophen-3(2*H*)-one (**23a-23h,** thioaurones) under the optimized reaction

conditions furnished the corresponding spirooxindole products (**24a-24p**) in moderate yields (40-56%) with high diastereoselectivity (*dr* >20:1) via [3 + 2] annulation-hydroxylation pathway (Table 4.3). It is important to note that the *ortho*-substituted and heteroaryl thioaurone substrates did not react under the standard reaction condition. To understand the reaction pathways of [3 + 2] annulation-hydroxylation, control experiments and DFT calculations were performed. Radical scavengers such as TEMPO and BHT did not inhibit the formation of hydroxylated spirooxindole compound and thus eliminated the possibility of radical intermediate formation during the course of the reaction.

We have developed highly practical, facile and straightforward protocol for the construction of molecules bearing cyclopentadiene and cyclopentene oxindole scaffolds. The α-regioselective [3 + 2] cycloaddition of thioaurone and aurone with MBH carbonates of isatin furnished the spiroheterocyles in moderate to good yields with high stereoselectivity.

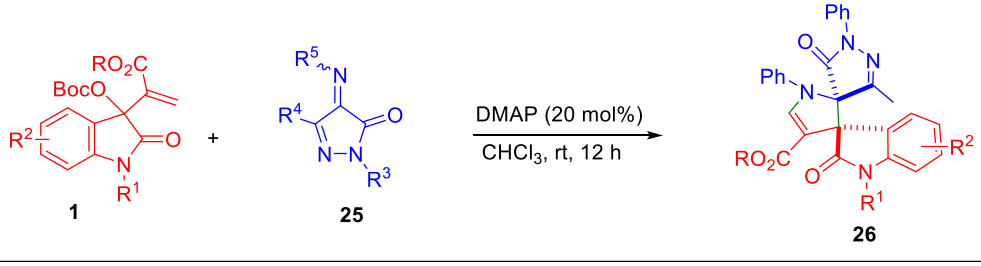
Chapter 5: *Direct Access to Spirooxindole Dihydropyrrole Fused Pyrazolone and Bis-Spiropyrazolone Derivatives*

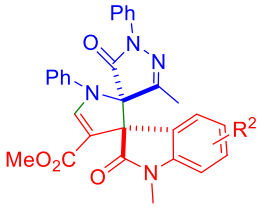
This chapter discloses a facile and robust approach to access spirooxindole dihydropyrrole fused pyrazolone and bis-spiropyrazolone derivatives via Lewis base catalyzed [3 + 2] cycloaddition. The chapter begins with a brief account on the importance of hybrid spirooxindoles and spiropyrazolone scaffolds, and some of the selected methods for the synthesis of spiropyrazolone fused oxindole have been highlighted.

The heterocyclic scaffolds such as spirooxindole and spiropyrazolone are prevalent in numerous natural alkaloids as well as in clinical pharmaceuticals. Due to the importance of these scaffolds, some efficient strategies for the synthesis of diverse heterocycle-containing 3,3′-spirooxindoles have been developed. However, interestingly, the stereoselective synthesis of oxindole fused spiro-pyrazolones derivatives has rarely been explored in the literature. In this regard, the development of an efficient one pot strategy for the synthesis of motif containing pyrazolones, dihydropyrroles and oxindoles core is highly desirable. In this regard, we successfully developed the protocol for the synthesis of dihydropyrrole fused oxindole derivatives **26** via the cycloaddition of MBH carbonates of isatin **1** and pyrazolone derived ketimines **25** in presence of

nucleophilic Lewis base catalyst such as DMAP (20 mol%) in chloroform at room temperature (Table 5.1). The substrate scope for the γ-regioselective [3 + 2] cycloaddition was evaluated under the optimized reaction conditions.

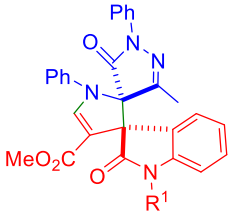
Table 5.1 Substrate scope for substituted MBH carbonates and pyrazolone ketimines[a-c]



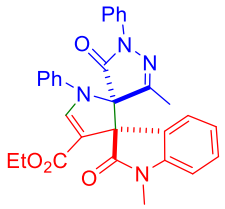


26a-26i

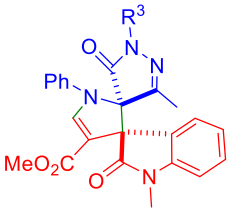
R^2= H, **26a,** (92%, >20:1 *dr*)
R^2= 5-Me, **26b,** (86%, >20:1 *dr*)
R^2= 5-OMe, **26c,** (92%, >20:1 *dr*)
R^2= 5-Br, **26d,** (89%, 95:5 *dr*)
R^2= 5-Cl, **26e,** (91%, >20:1 *dr*)
R^2= 5-F, **26f,** (94%, >20:1 *dr*)
R^2= 5-I, **26g,** (82%, >20:1 *dr*)
R^2= 5-NO_2, **26h,** (78%, >20:1 *dr*)
R^2= 7-F, **26i,** (83%, >20:1 *dr*)



R^1 = Allyl, **26j** (86%, >20:1 *dr*)
R^1 = Bn, **26k** (84%, >20:1 *dr*)

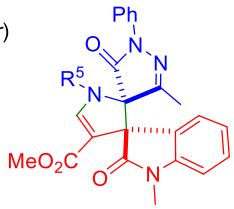


26l (89%, >20:1 *dr*)

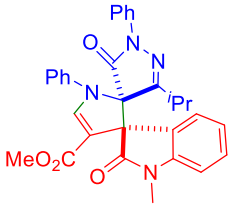


26m-26p

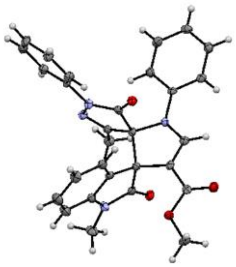
R^3= 4-MeC_6H_4, **26m,** (70%, >20:1 *dr*)
R^3= 4-BrC_6H_4, **26n,** (82%, >20:1 *dr*)
R^3= 4-ClC_6H_4, **26o,** (79%, >20:1 *dr*)
R^3= Me, **26p,** (77%, >20:1 *dr*)



R^5= 2-ClC_6H_4, **26q,** (61%, >20:1 *dr*)
R^5= 2-FC_6H_4, **26r,** (68%, >20:1 *dr*)
R^5= 3-BrC_6H_4, **26s,** (73%, >20:1 *dr*)
R^5= 4-BrC_6H_4, **26t,** (75%, >20:1 *dr*)
R^5= 4-ClC_6H_4, **26u,** (89%, >20:1 *dr*)
R^5= 4-IC_6H_4, **26v,** (70%, >20:1 *dr*)



26w, (70%, >20:1 *dr*)

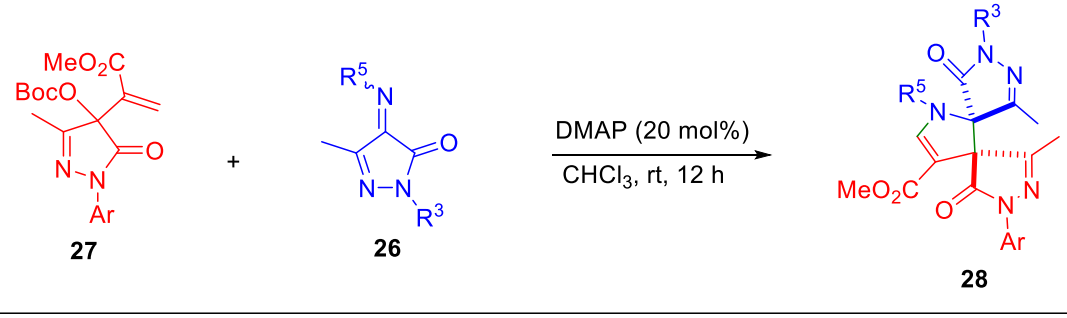


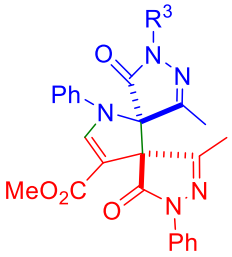
Molecular structure of **26a**
CCDC 2092026

[a]Optimized reaction conditions: MBH carbonate **1** (1.0 equiv.), Pyrazolone derived ketimine **25** (1.1 equiv.), DMAP (20 mol%) in $CHCl_3$ (2.0 mL) at room temperature, 12 h; [b]Isolated yield after column chromatography separation. [c]*dr* was determined by proton NMR.

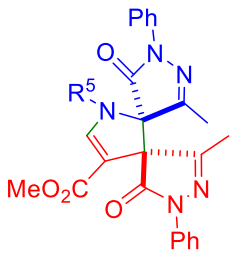
A wide range of substituted isatin derived MBH carbonates (**1a-1l**) reacted efficiently with the different pyrazolone derived ketimines (**25a-25j**) to afford corresponding dihydropyrrole fused oxindole derivatives (**26a-26w**) in moderate to excellent yields (61-94%) with very high diastereoseletivity (*dr* >20:1, Table 5.1). Later, we employed the MBH carbonates of pyrazolone **27** to synthesize novel bis-spiropyrazolone **28** scaffolds via γ-regioselective [3 + 2] cycloaddition. To the best of our knowledge, the synthesis of bis-spiropyrazolone compounds bearing vicinal quaternary spirocenters has not been achieved yet. In this regard, we treated the MBH carbonates of pyrazolone (**27a-27b)** with different pyrazolone derived ketimine (**25a, 25d, 25e, 25g-j**) under similar reaction conditions (Table 5.2). To our delight, all the reactions underwent facile [3 + 2] annulation to afford the corresponding bis-spiropyrazolone dihydropyrrole (**28a-28i)** derivatives in moderate to excellent yields with excellent diastereoselectivity (69-90%, >20:1 *dr*, Table 5.2).

Table 5.2 Substrate scope for the synthesis of bis-spiropyrazolone derivatives[a-c]

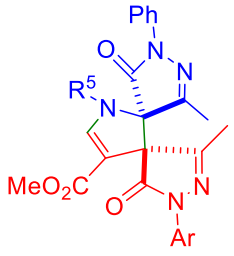




R^3= Ph, **28a,** (88%, >20:1 *dr*)
R^3= 4-ClC_6H_4, **28b,** (81%, >20:1 *dr*)
R^3= Me, **28c,** (70%, >20:1 *dr*)



R^5= 2-FC_6H_4, **28d,** (80%, >20:1 *dr*)
R^5= 3-BrC_6H_4, **28e,** (90%, >20:1 *dr*)
R^5= 4-BrC_6H_4, **28f,** (69%, >20:1 *dr*)
R^5= 4-ClC_6H_4, **28g,** (73%, >20:1 *dr*)



Ar = 4-ClC_6H_4, R^5= Ph, **28h** = (85%, >20:1 *dr*)
Ar = 4-ClC_6H_4, R^5= 4-ClC_6H_4 **28i** = (77%, >20:1 *dr*)

[a]Optimized reaction conditions: Pyrazolone derived MBH carbonate **27** (0.107 mmol), Pyrazolone derived ketimine **25** (0.117 mmol), DMAP (20 mol%) in $CHCl_3$ (2.0 mL) at room temperature, 12 h; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was determined by ^1H NMR.

We have developed a facile and highly regio-selective [3 + 2] annulation of MBH carbonates of isatin/pyrazolones and pyrazolone derived ketimines to construct biologically relevant dihydropyrrole fused oxindole and bis-spiropyrazolone derivatives. A range of dihydropyrrole fused pyrazolone-oxindole and bis-spiropyrazolone dihydropyrrole derivatives have been synthesized in presence of DMAP as a catalyst (20 mol%) in high yields with excellent diastereoselectivity under mild reaction condition.

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(*Numbers of substrates and products in the synopsis are different from those in thesis. Please note that compound numbers have been assigned for the convenience in every chapter and number of few compounds may vary from chapter to chapter*)

List of Publications

Included in the thesis

1. **Prakash K. Warghude**, Pankaj D. Dharpure, Ramakrishna G. Bhat* "Cycloaddition of isatin-derived MBH carbonates and 3-methyleneoxindoles to construct diastereoselective cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles: Catalyst controlled [3 + 2] and [2 + 1] annulations". *Tetrahedron Lett*. **2018**, *59*, 4076.

2. **Prakash K. Warghude**, Abhijeet S. Sabale, Ramakrishna G. Bhat* "Access to highly enantioselective and diastereoselective spirooxindole dihydrofuran fused pyrazolones''. *Org. Biomol. Chem.* **2020,** *18*, 1794.

3. **Prakash K. Warghude**, Abhijeet S. Sabale, Ruchi Dixit, Kumar Vanka, Ramakrishna G. Bhat* "An easy and practical approach to access multifunctional cylcopentadiene- and cyclopentene-spirooxindoles via [3 + 2] annulation". *Org. Biomol. Chem.* **2021**, *19*, 4338.

4. **Prakash K. Warghude**, Anindita Bhowmick, Ramakrishna G. Bhat* "Direct Access to Spirooxindole Dihydropyrrole Fused Pyrazolone and Bis-Spiropyrazolone Derivatives" *Tetrahedron Lett*ers, https://doi.org/10.1016/j.tetlet.2022.153791

Not included in the thesis

5. Tushar M. Khopade, **Prakash K. Warghude**, Amol D. Sonawane, Ramakrishna G. Bhat* "Multicomponent synthesis of pyroglutamic acid derivatives via Knoevenagel–Michael-hydrolysis-lactamization-decarboxylation (KMHL-D) sequence". *Org. Biomol. Chem.* **2019**, *17*, 561.

6. Tushar M. Khopade, **Prakash K. Warghude**, Trimbak B. Mete, Ramakrishna G. Bhat* "Acyl/aroyl Meldrum's acid as an enol surrogate for the direct organocatalytic synthesis of α, β-unsaturated ketones". *Tetrahedron Lett*. **2019**, *60*, 197.

7. L V. R. Babu syamala, Tushar M. Khopade, **Prakash K. Warghude**, Ramakrishna G. Bhat* "An access to α, β-unsaturated ketones via dual cooperative catalysis''. *Tetrahedron Lett*. **2019**, *60*, 88.

8. Pankaj D. Dharpure, Anindita Bhowmick, **Prakash K. Warghude**, Ramakrishna G. Bhat* "Visible-light mediated facile dithiane deprotection under metal free conditions". *Tetrahedron Lett.* **2020**, *61*, 1514073.

9. Anindita Bhowmick, **Prakash K. Warghude**, Pankaj D. Dharpure, Ramakrishna G. Bhat* "Direct access to α-acyloxycarbonyl compounds and esters via oxidative esterification of aldehydes under visible light". *Org. Chem. Front*. **2021**, *8*, 4777.

10. Vikas V. Khade, Archana S. Thube, **Prakash K. Warghude**, Ramakrishna G. Bhat* "DABCO mediated one pot synthesis of sulfoxonium ylides under blue LED". *Tetrahedron Lett*. **2021,** *77*, 153258.

11. Anindita Bhowmick, **Prakash K. Warghude**, Ramakrishna G. Bhat* "Visible Light Promoted Metal Free Sustainable Reduction of Activated Carbon-Carbon Double Bonds Without Any External Reductant". https://doi.org/10.26434/chemrxiv-2021-qrzf1.

1 Regio-divergent Organocatalytic reactions of Morita-Baylis-Hillman (MBH) adducts to access spirocarbocyclic compounds

Abstracts

The carbon−carbon bond forming reactions have always remained as one of the most indispensable reactions in organic synthesis. Among various carbon−carbon bond forming reactions, the Morita−Baylis−Hillman (MBH) reaction is one of the very useful and potential reactions with enormous synthetic utility. A brief account on the classical MBH reaction, the utility of MBH adducts in the synthesis of various important and useful scaffolds has been given in this chapter. The utility of Morita-Baylis-Hillman (MBH) adducts as versatile precursors to construct various spirooxindole frameworks has also been in described.

1 Regio-divergent Organocatalytic reactions of Morita-Baylis-Hillman (MBH) adducts to access spirocarbocyclic compounds

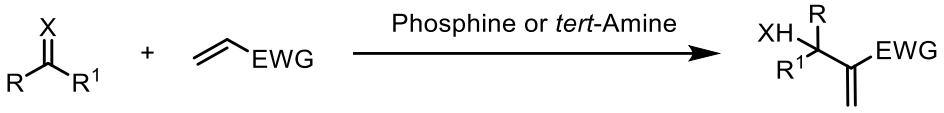
1.1 Introduction

Potent small molecules with varied activities are of great significance and some of these molecules can be designed and developed relying on the art of organic synthesis. In this regard, synthetic organic chemists have always been looking for developing newer as well as alternative methodologies that would allow the product formation in a simple, practical, highly chemo-, regio- and stereo-selective manner. The construction of a complex molecular framework or even a small organic molecule involves a functional group transformation or carbon-carbon/hetero atom bond formation process. To achieve some of these goals, the synthetic organic community from around the globe has been working on various research areas to develop more efficient methods to construct selective carbon-carbon (C-C) or carbon-hetero (C-X) bonds. The construction of a carbon-carbon (C-C) bond is one of the important and fundamental reactions in organic chemistry. The C-C bond forms the backbone of almost all the organic molecules, and its formation remains a fascinating area of research in the organic synthesis. The carbon-carbon (C-C) bond forming reactions including aldol reaction, Morita-Baylis-Hillman reaction, Claisen reaction, Diels-Alder reaction, Grignard reaction, Reformatsky reaction, Wittig reaction, Grubb's metathesis, Heck reaction and many more have been well documented in the literature. Among these, the Morita-Baylis-Hillman (MBH) reaction has become one of the most important, popular and versatile methods with enormous synthetic potential to construct C-C and C-X bonds efficiently.[1-2]

1.2 The Morita-Baylis-Hillman (MBH) reaction

The Morita-Baylis-Hillman (MBH) reaction is known for the formation of α-methylene-β-hydroxy carbonyl compounds by coupling an activated alkene at α-position with an aldehyde under the phosphine catalysis (Morita-1968)[3] or tertiary amine catalysis (Baylis and Hillman-1972)[4] (Scheme 1.1). In place of aldehydes, an appropriately activated imine can

also be used as a substrate in the reaction, providing α-methylene-β-amino carbonyl compounds, and in this case, the process is referred to as aza-Morita-Baylis-Hillman (aza-MBH) reaction.



R = aryl, alkyl, heteroaryl; R^1 = H, alkyl, aryl, CO_2R^3, COR^3
X = O, NR^2
EWG = CO_2R^3, CHO, NO_2, CN, COR^3, SO_2Ph, *etc.*

Scheme 1.1 Representative example of Morita-Baylis-Hillman reaction

Though the MBH reaction is very promising and fascinating, unfortunately, it did not receive enough attention from the synthetic organic chemists in the initial years after its discovery. Gratifyingly, 1980s onwards, this reaction and its applications have received significant and growing interest and attention in organic synthesis.

The MBH reaction has been employed for a wide variety of transformations to access many useful compounds and synthetic precursors due to its inherent advantages and potential reactivity for various applications. Some of the merits of MBH reaction are listed below.

1) It is an atom-economic coupling of commercially available or readily prepared starting materials.

2) It affords a chiral center from a pro-chiral electrophile and provides an opportunity for the asymmetric synthesis.

3) The MBH adducts are usually densely functionalized and due to this reason, they have been utilized as valuable synthons in various synthetic transformations.

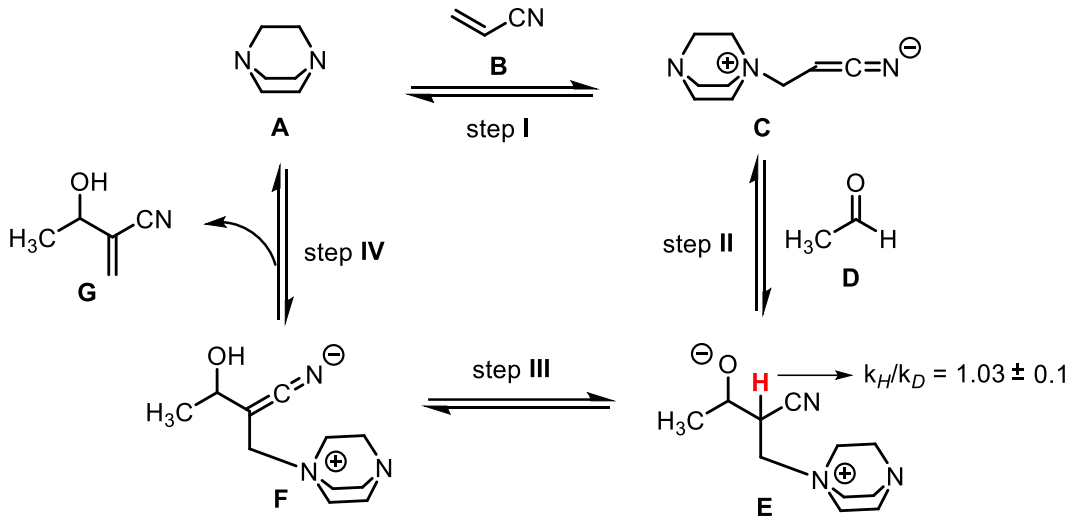
4) The reaction generally involves a nucleophilic organocatalytic system under mild reaction conditions without relying on any heavy metal reagents/catalysts.

1.3 MBH reaction mechanism

In the year 1983, for the first time Hoffmann[5] proposed the reaction mechanism for the Morita-Baylis-Hillman (MBH) reaction. Subsequently, Hill and Isaacs[6] and other research groups further redefined the mechanism of MBH reaction.[7] The proposed reaction mechanism

for the MBH reaction is depicted in Scheme 1.2. In the first step, the tertiary amine catalyst **A** (DABCO) reacts with the activated (electron deficient) alkene **B** (α, β-unsaturated carbonyl compounds, acrolein, methyl acrylate, methyl vinyl ketone, *etc*.) via 1, 4-conjugate addition (Michael addition) to generate zwitterionic aza-enolate intermediate **C**. In the second step, the intermediate **C** undergoes an aldol type reaction with an aldehyde **D** (acetaldehyde, benzaldehyde, *etc*.) to form an intermediate **E**. In the third step, this intermediate **E** further undergoes intramolecular proton shift to generate intermediate **F**. Finally, intermediate **F** furnishes the MBH adduct **G** via E2 or E1cb elimination and releases the catalyst **A** to complete the catalytic cycle.

In order to have further insight into the reaction mechanism, Hill and Isaacs performed the kinetic isotopic effect (KIE) measurement between acrolein, acetaldehyde and DABCO. The kinetic isotopic effect (KIE=1.03 ± 0.1) was not observed when α-deuterated acrylonitrile was used as a substrate in the reaction. Based on these observations, it was proposed that the aldol addition step (carbon-carbon bond formation) is the rate determining step (RDS), as it involves all three reactants (**A**, **B** and **D**, Scheme 1.2).



Scheme 1.2 Plausible mechanism of MBH reaction as proposed by Hoffman/Hill and Isaacs

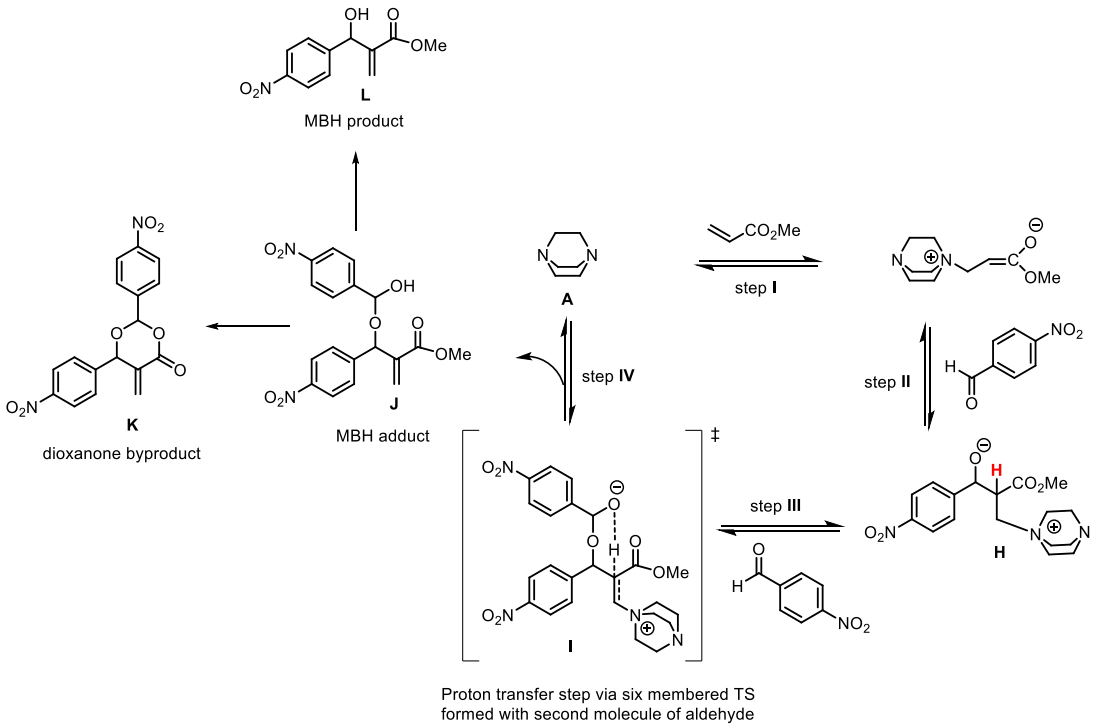
However, the mechanism initially proposed by Hoffmann, Hill and Isaacs led to many queries and failed to explain some of the following points.

1. It could not explain the autocatalytic effect (acceleration of rate of reaction by the build-up of product).

2. The mechanism also failed to explain the formation of unusual dioxanone by-product in considerable amount, when reaction was carried out using aryl aldehydes and acrylates.

In order to have further insights into MBH reaction mechanism, recently research groups of McQuade et al.[8] and Aggarwal et al.[9] have independently reinvestigated the mechanism of MBH reaction systematically. They have studied the both kinetic as well as theoretical aspect of the reaction by focusing on the proton transfer step.

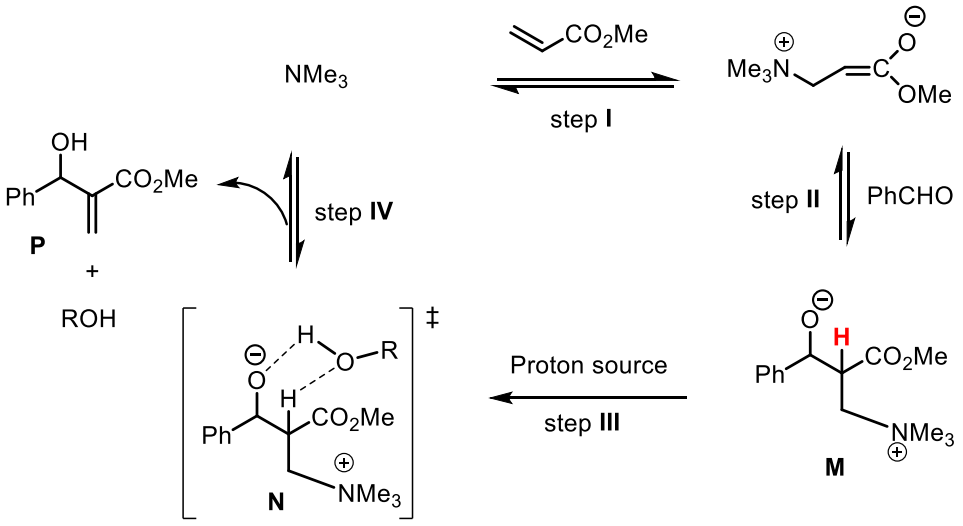
According to McQuade, the MBH reaction is first order with respect to DABCO and methyl acrylate and second order with respect to aldehyde (*p*-nitrobenzaldehyde) and the reaction exhibited a significant kinetic isotopic effect (KIE: $k_H/k_D = 5.2 \pm 0.6$ in DMSO). They observed that regardless of the solvents (chloroform, acetonitrile, tetrahydrofuran, dimethylformamide), the kinetic isotopic effect was greater than 2, indicating the involvement of abstraction of the proton in the rate-determining step. Based on these kinetic data, McQuade proposed a new revised mechanism where in step I and II are similar to the earlier mechanism that was proposed by Hill and Isaacs (Scheme 1.3)



Scheme 1.3 Plausible mechanism for MBH reaction as proposed by McQuade and co-workers

However, it was proposed that after the first aldol addition (step II), the addition of second molecule of aldehyde occurs to give hemiacetal alkoxide intermediate (**I**) (Scheme 1.3). This intermediate further undergoes proton transfer (RDS) via six-membered transition state to give MBH adduct **J**. Finally, this adducts **J** releases the MBH product **L** or dioxanone by-product **K** (Scheme 1.3).

While, the Aggarwal and co-workers proposed that the proton transfer is the rate-determining step. The proton transfer is the RDS only at the beginning of reaction (≤ 20% of conversion); after that, step II turns out to be the RDS when the concentration of product builds-up and thereby it enhances the proton transfer and making it much more efficient. They suggested that the Morita-Baylis-Hillman (MBH) adduct **P** may act as a proton donor and thereby assisting the proton-transfer step via a six-membered intermediate effectively (Scheme 1.4).



Proton transfer step via six membered TS intermediate formed by autocatalysis

Scheme 1.4 Plausible mechanism for MBH reaction by Aggarwal and coworkers

Finally, based on all the recent mechanistic investigations, it has been concluded that rate-determining step (RDS) is the 1,3- proton shift.

1.4 Morita-Baylis-Hillman (MBH) adducts

Due to the dense functionalities of MBH adducts, over the past few decades there has been a considerable growth in its application in organic synthesis. The MBH adduct contains

different functional groups such as allylic alcohols or amine, activated alkenes (act as Michael acceptors) and electron withdrawing groups (Figure 1.1).

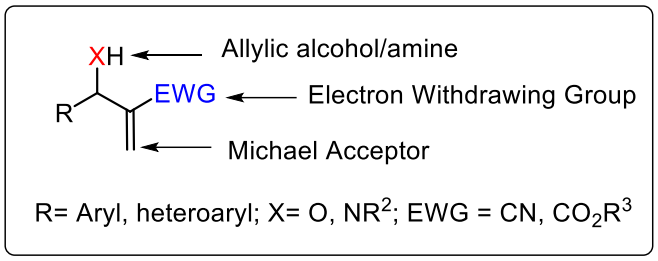


Figure 1.1 Densely functionalized MBH adducts

1.4.1 Transformations of functional groups in Morita-Baylis-Hillman adducts

The MBH adducts contain different functional groups in close proximity and make them important and useful substrates for various types of synthetic transformations such as Claisen rearrangement, Friedel-Crafts reaction, Heck reaction, Diels-Alder reaction, hydrogenation, Michael addition, *etc.* (Figure 1.2).[10]

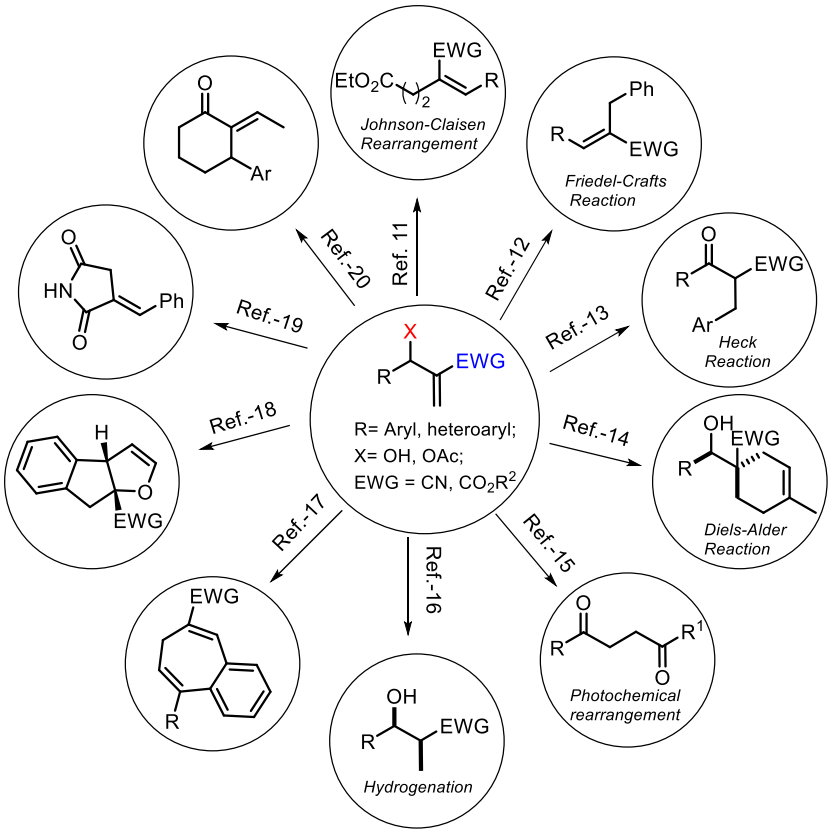


Figure 1.2 Useful transformation of Morita-Baylis-Hillman (MBH) adducts

1.4.2 Application of Morita-Baylis-Hillman adducts in the synthesis of natural products

Apart from the synthetic transformations, Morita-Baylis-Hillman (MBH) adducts have also been used as important intermediates or starting materials for the synthesis of bioactive compounds, drug molecules and natural products (Figure 1.3).

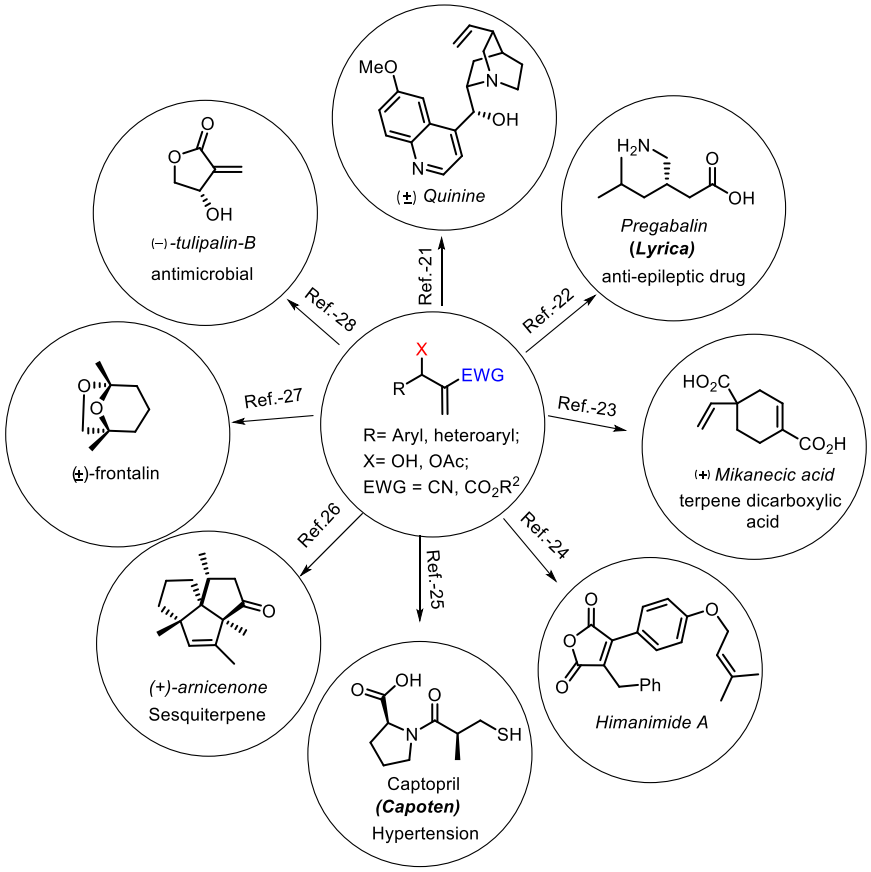


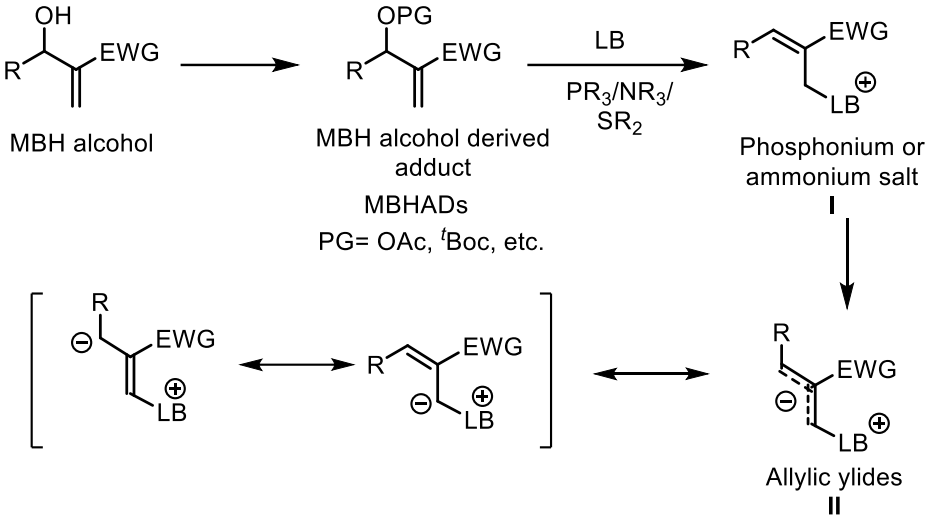
Figure 1.3 Useful transformations of Morita-Baylis-Hillman (MBH) adducts: Accessing bio-active and natural products

1.4.3 Application of Morita-Baylis-Hillman adducts for the construction of cyclic frameworks

The carbocyclic and heterocyclic architecture have gained a considerable attention from the synthetic organic chemists due to their potential biological activity and significant applications in the research field of fine chemicals.[29] As a result, enormous efforts have been devoted for developing effective methods for the construction of these types of cyclic frameworks. Over the past few decades, cyclo-forming reactions such as Diels-Alder reaction, ring-closing

metathesis (RCM), and cyclo-isomerization have emerged as powerful tools for constructing ring systems.[30]

Along with the development of these reactions, the Morita-Baylis-Hillman reaction has emerged as one of the important and useful reactions for the synthesis of useful compounds of relevance. In recent years, the Morita-Baylis-Hillman alcohol derivatives have emerged as versatile and valuable building blocks in Lewis base mediated annulation reactions for the construction of cyclic compounds.[31] The Morita–Baylis–Hillman alcohol derivatives (MBHADs) are usually prepared from Morita-Baylis-Hillman (MBH) alcohols by converting the hydroxyl group into *tert*-butoxycarbonyloxy or acetoxy leaving group. Thus, the electrophilicity at the allylic position as well as terminal double bond is retained or enhanced after converting the hydroxyl group into *tert*-butoxycarbonyloxy or acetoxy group. The general mode of reactivates of modified MBHADs in presence of Lewis base is depicted in scheme 1.5.



Scheme 1.5 General reactivity of MBHADs in presence of Lewis base

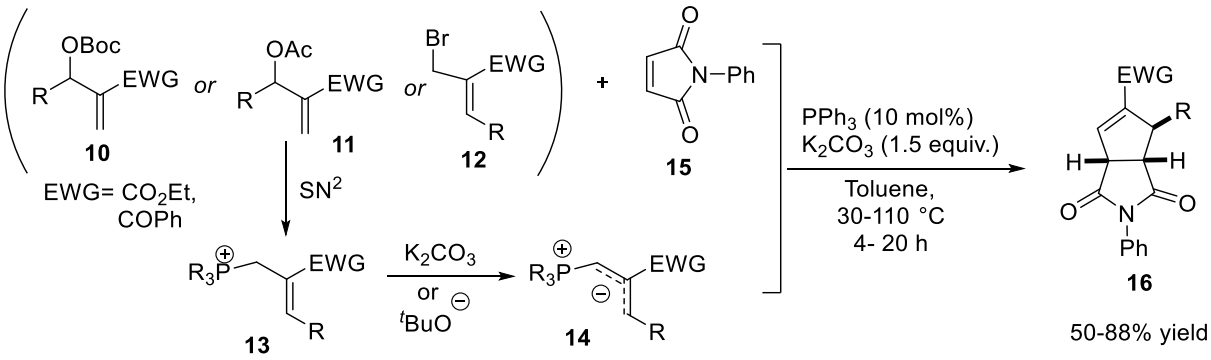
Initially, a Lewis base catalyst (PR_3, NR_3, SR_2) attacks the MBHADs via S_N2' mechanism, to generate the phosphonium/ammonium salt intermediate **I** by the elimination of a leaving group. This intermediate **I** further easily undergoes the second S_N2' reaction when treated with suitable nucleophiles (Scheme 1.5). The phosphonium/ammonium salt intermediate **I** generated during the course of the reaction can be further deprotonated either by the in situ generated Brønsted base (*tert*-butoxide or acetate) or by the addition of external base to give allylic phosphorus/amine ylide **II** intermediate. This ylide intermediate **II** serves as C1 or C3 synthon

to complete the cycloaddition by reacting with suitable dipolarophiles to give three, five or seven membered cyclic products (Scheme 1.5).[32]

1.5 Lewis base mediated [3 + n] annulation of MBH adduct

1.5.1 [3 + 2] cycloadditions of MBH adducts

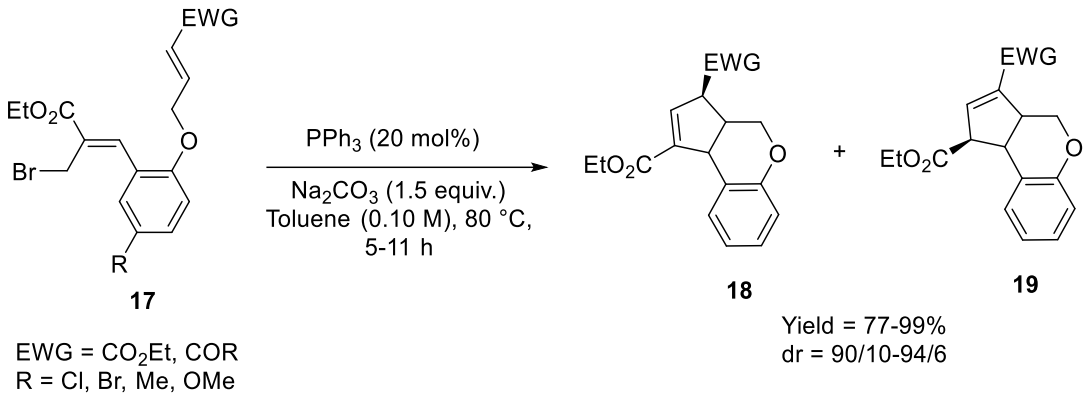
In 2003, Lu and coworkers[33] have reported the first phosphine-catalyzed [3 + 2] annulation of MBH adducts. The reaction of MBH adducts (bromides, acetate or *tert*-butyl carbonates of MBH alcohol) with *N*-phenylmaleimide in the presence of phosphine catalyst delivered the cyclopentene products in moderate to high yields with excellent stereoselectivities (Scheme 1.6). In this annulation reaction, MBH adduct acts as an excellent C3 synthon. It has been proposed that the reaction proceeds through the formation of phosphonium salt **13** either by the attack of triphenylphosphine (PPh_3) on MBH carbonate **10**, or on acetate **11** or on bromide **12**. Then the phosphonium salt **13** undergoes deprotonation by the in situ generated Brønsted base (*tert*-butoxide or acetate) or additional base (K_2CO_3) to give the P-ylide intermediate **14**. Subsequently, the nucleophilic addition of P-ylide intermediate **14** to the electron deficient olefin (such as maleimide **15**) affords the zwitterionic intermediate. Finally, the intramolecular cyclization of zwitterionic intermediate furnishes the cyclopentene derivative **16** by the elimination of phosphine catalyst. This reaction gave an access to both α- and γ-regioselective annulation products with specific substrates (Scheme 1.6).



Scheme 1.6 Phosphine catalyzed [3 + 2] annulation by Lu and coworkers

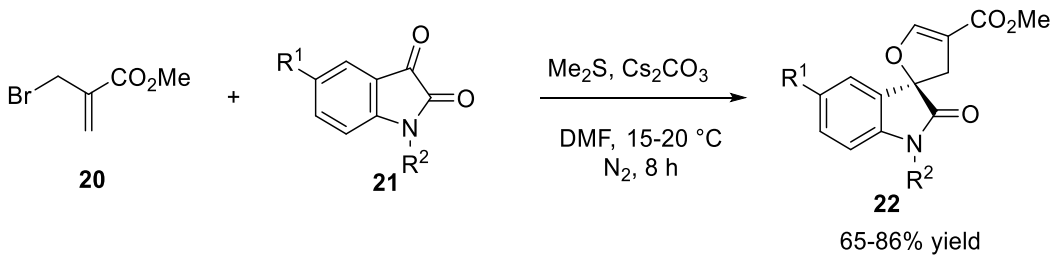
In the year 2007, Tang and coworkers have described the phosphine catalyzed intramolecular formal [3 + 2] cycloaddition.[34] The reaction of preorganized acyclic (allylic) bromide **17** in the presence of triphenylphosphine (20 mol%) and sodium carbonate (1.5 equiv.)

in toluene (0.1 M) at an elevated temperature (80 °C) furnished the benzobicyclo[4.3.0] compounds **18** and **19** in good to excellent yields with excellent diastereoselectivities (Scheme 1.7).



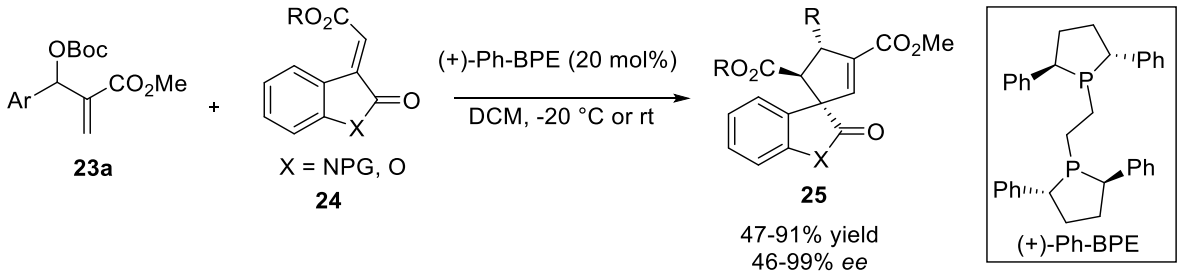
Scheme 1.7 Phosphine catalyzed intramolecular [3 + 2] annulation

In 2007, Basavaiah and coworkers[35] first reported the synthesis of oxindole fused spirodihydrofuran derivatives **22** starting from allyl bromide derived MBH adduct **20** with isatins **21** via Me_2S mediated [3 + 2] annulation strategy in very good yields (up to 86%) (Scheme 1.8).



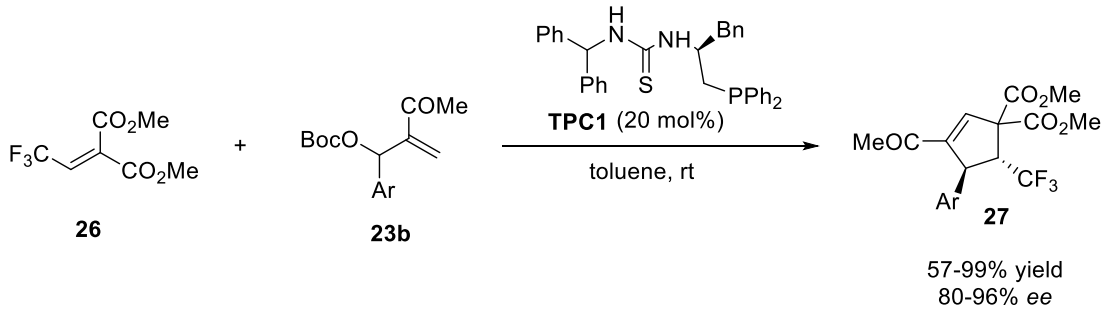
Scheme 1.8 Me_2S mediated [3 + 2] annualtion of MBH bromide with isatins

In 2011, Barbas and coworkers[36] have developed the first intermolecular [3 + 2] annulation of MBH adducts using a chiral phosphine as a nucleophilic organocatalyst. The reaction of MBH carbonates **23a** with *N*-Boc-methyleneindolinone **24** in the presence of the (+)-Ph-BPE [(+)-1,2-Bis ((2*S*, 5*S*)-2,5-diphenylphospholano)ethane], delivered the 3-spiro cyclopenteneoxindole derivatives **25** in good to excellent yields with very good enantioselectivities (Scheme 1.9).



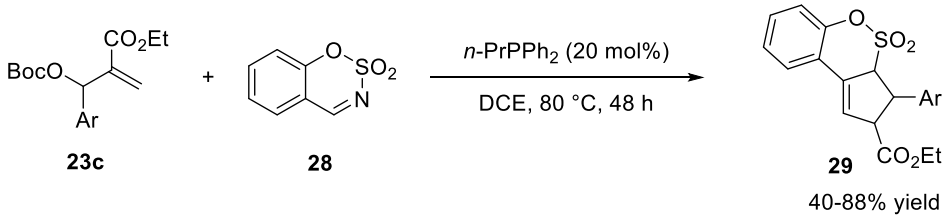
Scheme 1.9 (+)-Ph-BPE catalyzed asymmetric [3 + 2] annulation of MBH adducts

In 2012, Shi and coworkers[37] have disclosed a natural amino acid based thiourea-phosphines catalyst **TPC1** to carry out the asymmetric [3+2] cycloaddition. The reaction of trifluoroethylidenemalonates **26** and MBH carbonates **23b** in presence of catalyst **TPC1** (20 mol%) led to the formation of multi-functional trifluoromethyl- or pentafluoroethyl-bearing cyclopentene products **27** in moderate to excellent yields with very high enantioselectivities (Scheme 1.10).



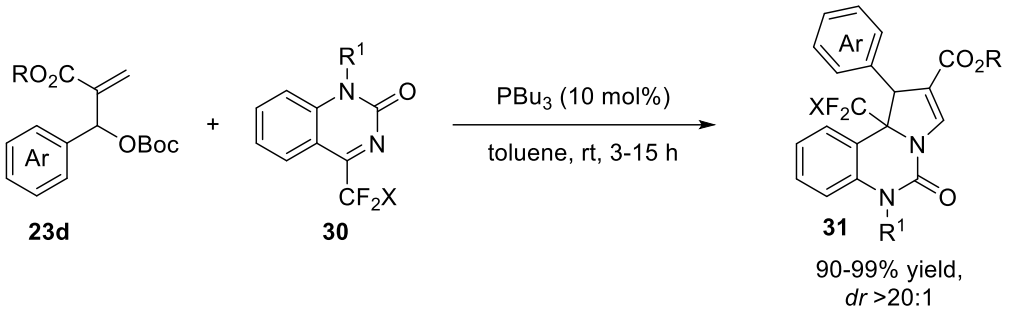
Scheme 1.10 Chiral thiourea-phosphine-catalyzed asymmetric [3 + 2] cycloaddition

In 2013, Guo and coworkers[38] have reported the [3 + 2] cycloaddition of Morita–Baylis–Hillman (MBH) carbonates **23c** with sulfamate-derived cyclic imines **28** in the presence of *n*-propyldiphenylphosphine (*n*-PrPPh$_2$) at an elevated temperature (80 ^{o}C) to afford the corresponding sulfamate-fused dihydropyrrole derivatives **29** in moderate to high yields (Scheme 1.11)



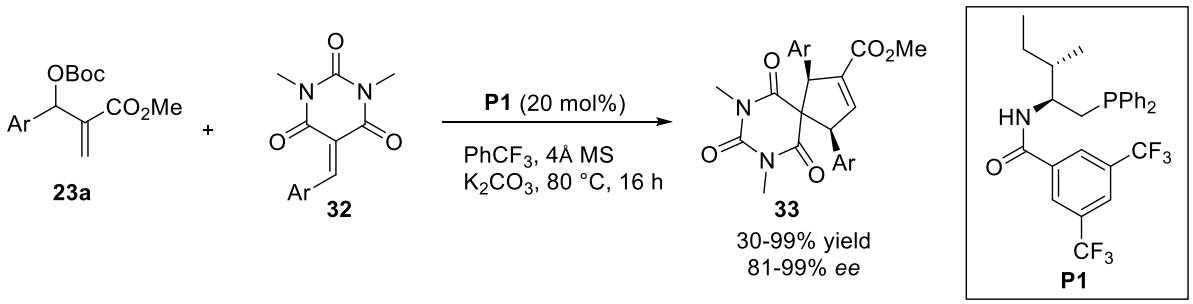
Scheme 1.11 Phosphine-catalyzed [3 + 2] cycloaddition of MBH carbonates and cyclic imine

In same year, Ma research group[39] has reported the γ-regioselective [3 + 2] annulation of Morita–Baylis–Hillman (MBH) carbonates **23d** with cyclic *N*-acyl-substituted ketimines **30** in the presence of tributylphosphine (PBu_3, 10 mol%) as a catalyst. This γ- regioselective [3+2] annulation delivered the *N*-fused tricyclic products **31** in excellent yields with very high diastereoselectivities (>20:1 *dr*). The presence of strong electron-withdrawing character of difluoro- and trifluoromethyl groups in cyclic *N*-acyl ketimines has been found to be very crucial for this transformation (Scheme 1.12).



Scheme 1.12 Phosphine-catalyzed [3 + 2] cycloaddition of MBH carbonates and cyclic imine

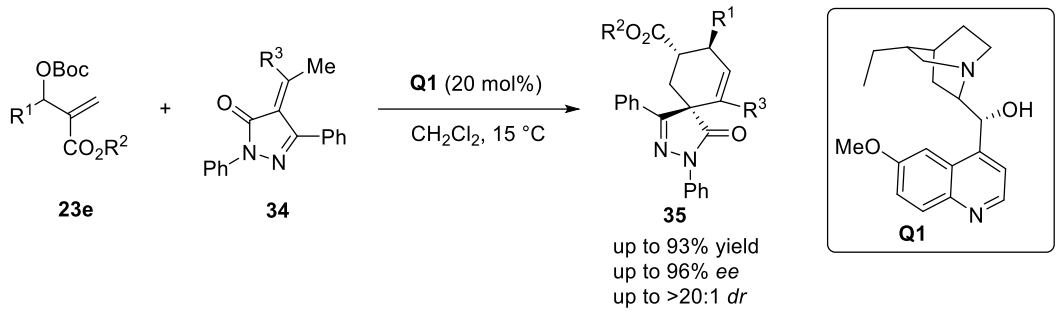
In 2016, Gao research group[40] has demonstrated the chiral phosphine **P1** catalyzed enantioselective [3 + 2] annulation of MBH carbonates **23** with barbiturate-derived alkenes **32** to synthesize the chiral spirobarbiturate-cyclopentene derivatives **33** in moderate to excellent yields with good to excellent stereoselectivities (81–99% *ee*) (Scheme 1.13).



Scheme 1.13 Asymmetric [3 + 2] annulation of MBH adducts using phosphine–amide catalyst

In the year 2017, Yang et al.[41] have reported an organocatalytic asymmetric [3 + 3] cycloaddition of MBH carbonates **23e** with α-arylidene pyrazolinone **34** to afford the spiropyrazolones **35**. The Lewis base such as hydroquinidine **Q1** catalyzed the reaction to afford the cyclohexene-fused spiropyrazolones **35** bearing an all-carbon quaternary

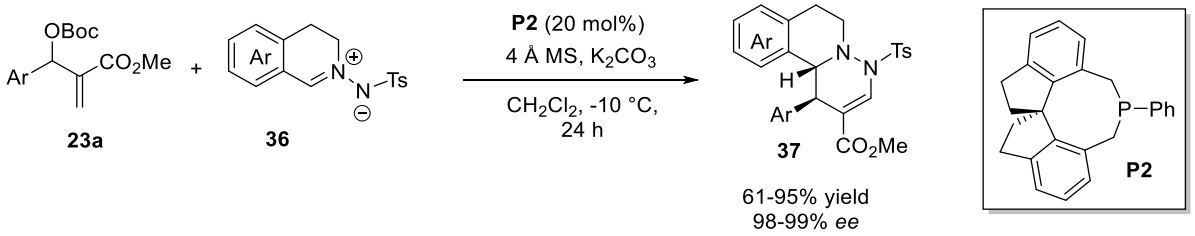
stereocenter in high yields (up to 93%) with good to excellent stereoselectivities (up to >20:1 *dr* and 96% *ee*) (Scheme 1.14).



Scheme 1.14 Synthesis of spiropyrazolones from MBH carbonates and vinylogous pyrazolones

1.5.2 [3 + 3] annulation of MBH adducts

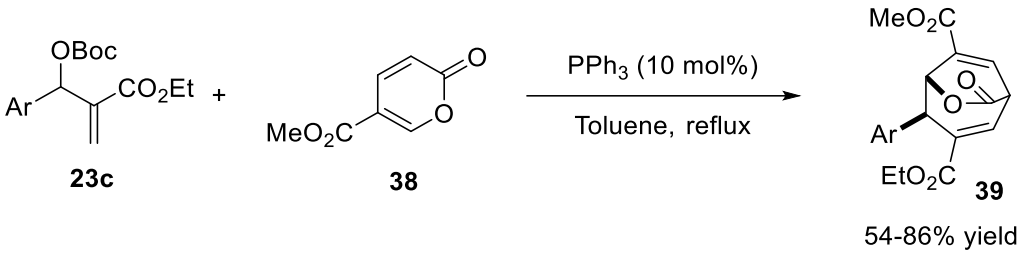
In 2015, Guo research group[42] has for the first time developed an enantioselective [3 + 3] cycloaddition of Morita−Baylis−Hillman (MBH) carbonates **23a** with *C*, *N*-cyclic azomethine imines **36** in the presence of chiral spirocyclic phosphine catalyst **P2** (20 mol%). This protocol gave an access to structurally diverse 4,6,7,11*b*-tetrahydro-1*H*-pyridazino[6,1-a]iso-quinoline **37** derivatives in high yields with good to excellent enantioselectivities (> 98-99% *ee*) (Scheme 1.15).



Scheme 1.15 Phosphine-catalyzed [3 + 3] annulation of MBH carbonate

1.5.3 [4 + 3] annulation of MBH adducts

In 2009, Lu and Zheng[43] have reported the phosphine catalyzed [4 + 3] annulation to synthesize bicyclo[3.2.2]nonadiene **39**. The reaction of MBH carbonates **23c** with conjugated dienes such as methyl coumalate **38** in the presence of triphenylphosphine catalyst (10 mol%) delivered the oxabicyclo[3.2.2]nonanones **39** compounds in good yields with exclusive γ-regioselectivity (Scheme 1.16).



Scheme 1.16 Phosphine-catalyzed [4 + 3] annulation of MBH carbonate

1.6 Spirooxindoles

2-Oxindoles when spirofused with the other cyclic frameworks at C-3 position are commonly known as 'spirooxindoles'. The spirocyclic oxindole scaffold has drawn an enormous attention from the synthetic organic chemists as well as medicinal chemists of worldwide due to their occurrence in many natural products such as horsfiline, spindomycin B, gelsemine, elacomine, spirotryprostatins, citrinadin B, Notoamide A and synthetic compounds like CFI-400945 (antitumour agent), SAR-405838 (Figure 1.4). These types of scaffolds exhibited various potent bioactivities such anticancer, antiparasitic and some of these compounds are under phase I clinical trial for their potent anticancer activities (Figure 1.4).[44]

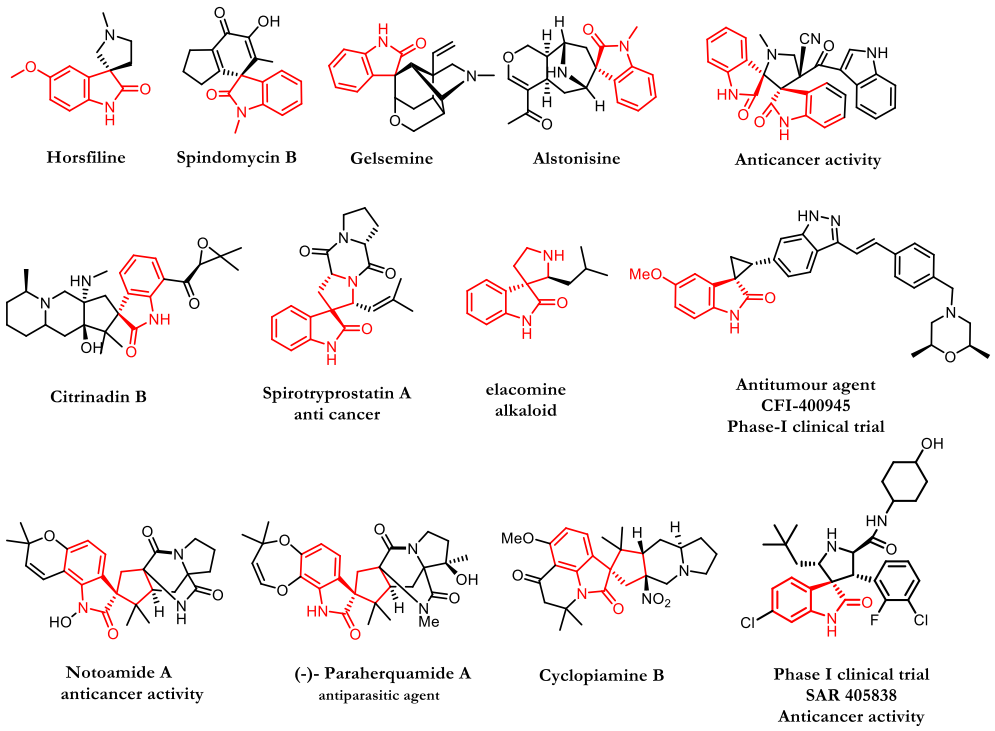
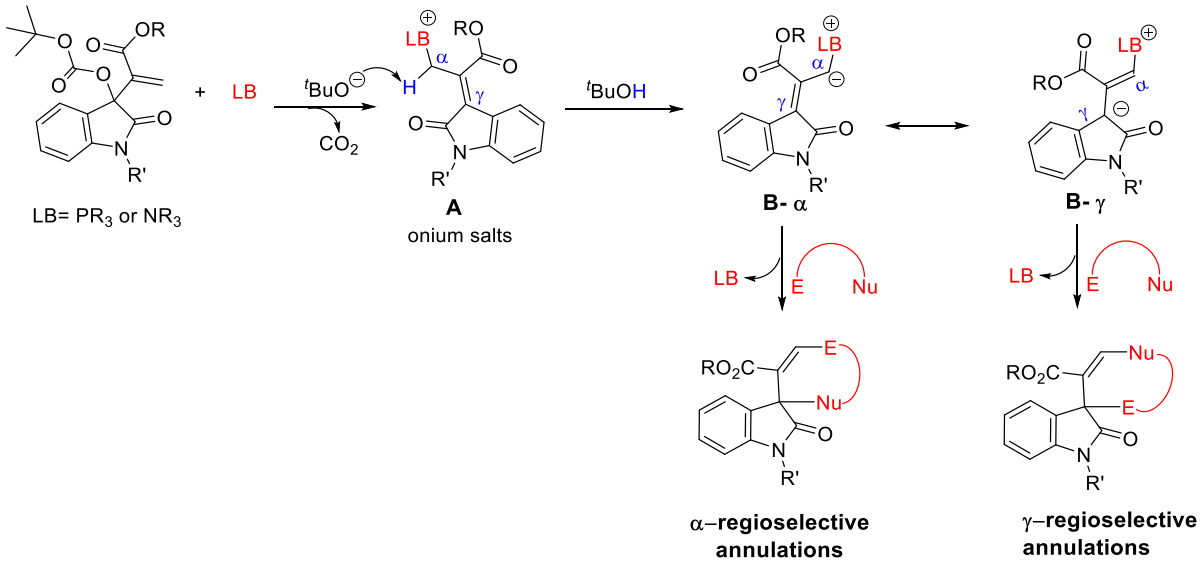


Figure 1.4 Representative examples of spirooxindoles

Due to the diverse biological activities of spirooxindoles and owing to the importance of this useful scaffold, considerable efforts have been devoted towards the development of newer efficient strategies for the construction of different spirooxindole scaffolds in a stereoselective manner.[45] Some of the strategies include metal-mediated cyclization, radical cyclization and cycloaddition reaction. This section will specifically focus on the cycloaddition reaction of Morita-Baylis-Hillman adducts of isatin for the synthesis of spirooxindoles to have direct connection with the thesis work.

1.6.1 Synthesis of spirooxindoles utilizing Morita-Baylis-Hillman adducts of isatin

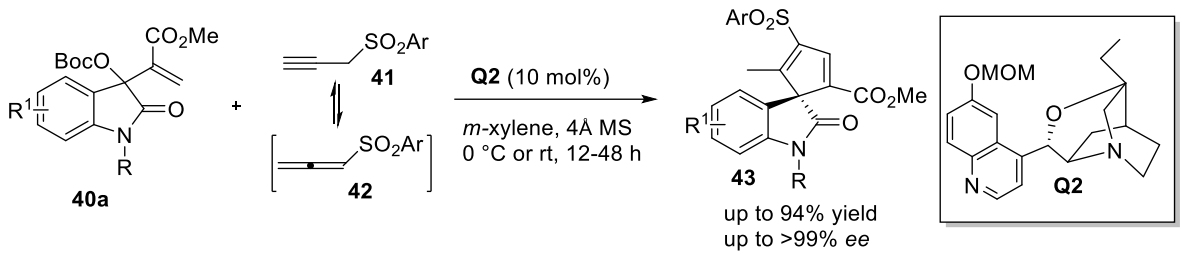
In recent years, isatin derived Morita-Baylis-Hillman adducts have emerged as versatile and excellent precursors for the construction of structurally diverse spirooxindole scaffolds.[46] The general reactivity of isatin derived Morita-Baylis-Hillman adducts has been depicted in scheme 1.17. Initially, Lewis base catalyst **LB** (PR_3, NR_3, SR_2) attacks on the Morita-Baylis-Hillman (MBH) carbonate of isatin via S_N2' mechanism, generating the phosphonium/ammonium salt intermediate **A** along with the elimination of carbon dioxide and *tert*-butoxide. Subsequently, this phosphonium/ammonium salt intermediate **A** gets deprotonated by the *in situ* generated Brønsted base (*tert*-butoxide) to give allylic phosphorus/amine ylide **B** intermediate. This ylide intermediate **B** would further react with the suitable dipolarophiles via **B**-α or **B**-γ position to afford α-annulation or γ-annulation products respectively by the elimination of the Lewis base catalyst **LB** (Scheme 1.17).[46]



Scheme 1.17 Cycloaddition of isatin-derived MBH carbonates via allylic ylides

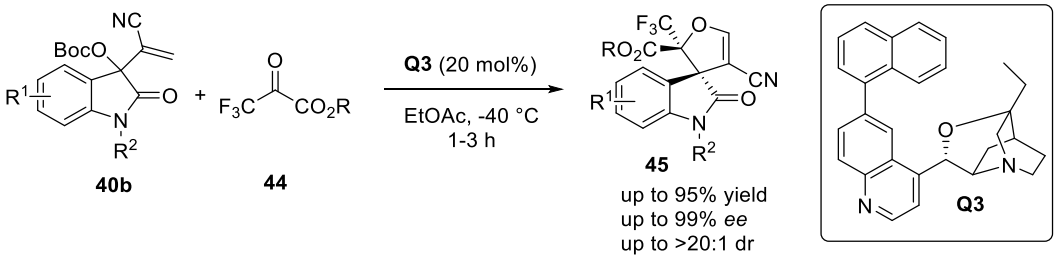
1.6.2 [3 + 2] cycloadditions of MBH adducts of isatin

In 2011, Chen and coworkers[47] have reported the asymmetric [3 + 2] annulation of Morita-Baylis-Hillman carbonates of isatins **40a** with propargyl sulfones **41** under cinchona alkaloid derivative *β*-ICD-*O*-MOM ether **Q2** catalysis to afford the spirocyclic 2-oxindoles appended with cyclopentadiene derivatives **44** in very high yields (up to 94%) with excellent enantioselectivities (up to > 99% *ee*). This transformation believed to proceed via the formal dipolar cycloaddition of in situ generated allylic *N*-ylides and allenyl sulfones **42** followed by the carbon-carbon bond isomerization sequence (Scheme 1.18).



Scheme 1.18 Asymmetric [3 + 2] annulation of MBH carbonates with propargyl sulfones

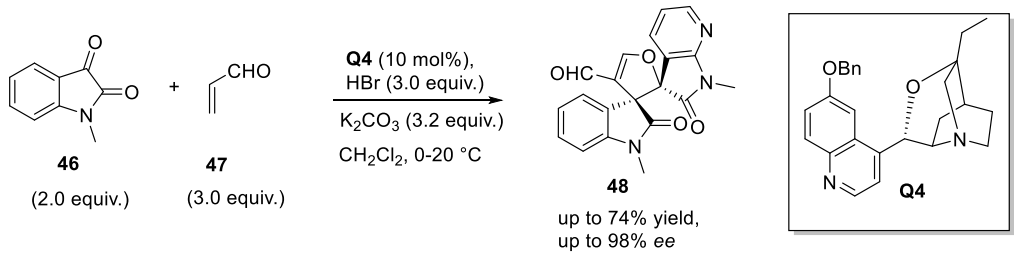
In 2013, Liu and coworkers[48] have developed an organocatalytic asymmetric [3 + 2] annulation of isatin derived MBH carbonates **40b** and trifluoropyruvate **44** in presence of modified β-ICD derivative **Q3** catalyst. This protocol provided an efficient and enantioselective approach for the construction of different chiral 2*H*-spiro[furan-3,3'-indolin]-2'-ones **45** as a single regio-isomer in good to excellent yields (up to 95%) with high diastereo- (up to >20:1 *dr*) and enantio-selectivities (up to 99% *ee*) (Scheme 1.19).



Scheme 1.19 Asymmetric [3 + 2] annulation of isatin derived MBH carbonates and activated ketones

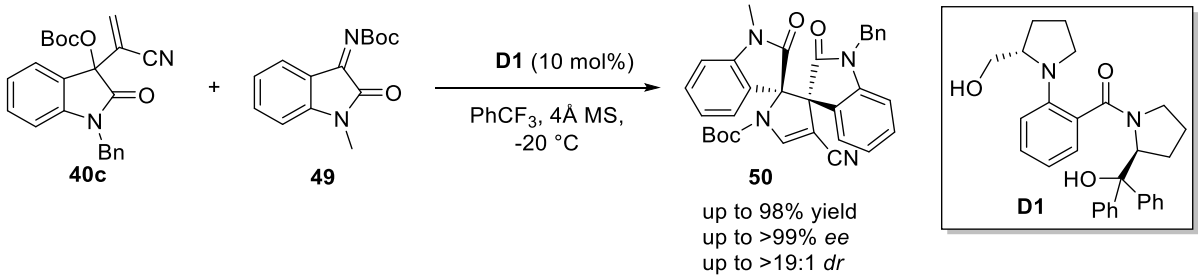
Zhou research group[49] has developed an asymmetric multi-component [3 + 2] annulation reaction of *N*-methylisatin **46** with *α, β*-unsaturated aldehyde **47** in presence of tertiary amine catalyst **Q4** to give the corresponding spirocyclic oxindole products **48**

containing two vicinal spirostereocenters in good yields with high diastereo- and enantio-selectivities. It is important to note that this transformation involving tandem MBH reaction/bromination/[3 + 2] annulation reaction takes place in one-pot (Scheme 1.20).



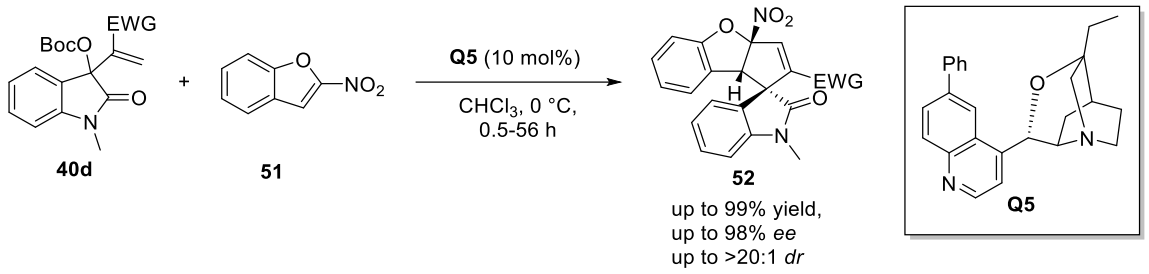
Scheme 1.20 Tertiary amine catalyzed tandem reactions

In 2017, Chen and coworkers[50] have developed an asymmetric [3 + 2] annulation of MBH carbonates of isatin **40c** with isatin derived *N*-Boc-ketimines **49** in presence of a multifunctional 4-dimethylaminopyridine type catalyst **D1** to afford bispirooxindole derivatives **50**. This *γ*-regioselectivity drove [3 + 2] annulation to furnish the highly substituted dihydropyrrolidinyl 1,2-bispirooxindole derivatives **50** in moderate to excellent yields with very high stereoselectivities (>19:1 *dr*, up to >99% *ee*) (Scheme 1.21).



Scheme 1.21 Chiral DMAP derivative catalyzed [3 + 2] annulation of MBH of adducts

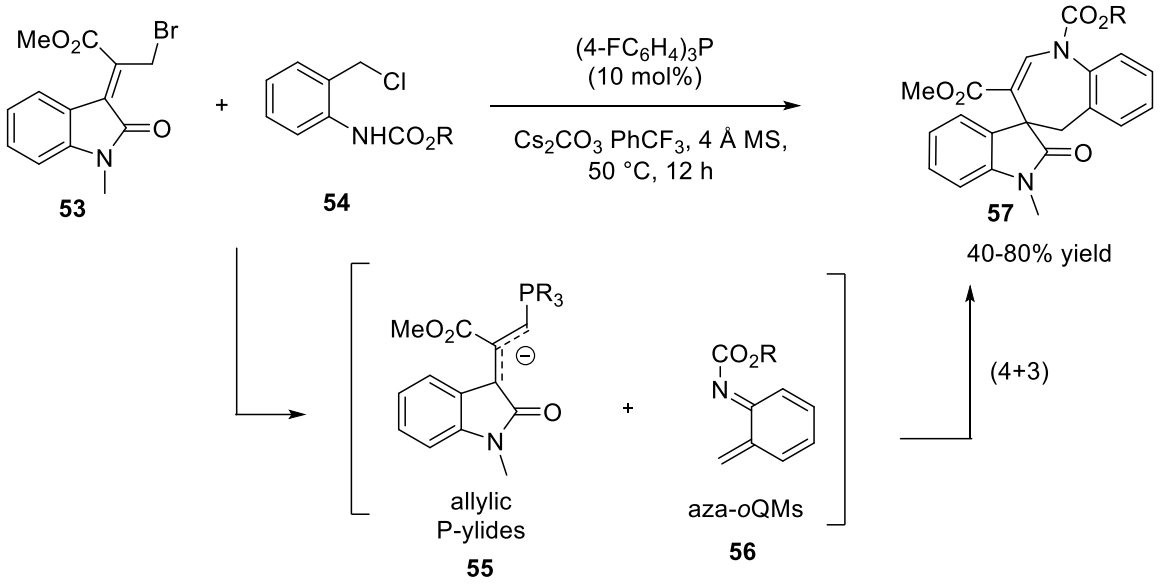
In 2019, Yuan and coworkers[51] have reported the asymmetric dearomative cycloaddition between isatin-derived Morita−Baylis−Hillman carbonates **40d** and 2-nitrobenzofurans **51** to access spiro compounds **52**. The modified cinchona alkaloid catalyst **Q5** (10 mol%) proved to be efficient by affording a series of structurally diverse cyclopenta[*b*]benzofuran derivatives **52** bearing three contiguous stereocenters in excellent yields with very high stereoselectivities (in all cases >20:1 *dr*, up to 99% yield and 98% *ee*) (Scheme 1.22).



Scheme 1.22 Chiral tertiary amine catalyzed dearomative cycloaddition

1.6.3 [4 + 3] cycloadditions of MBH adducts of isatin

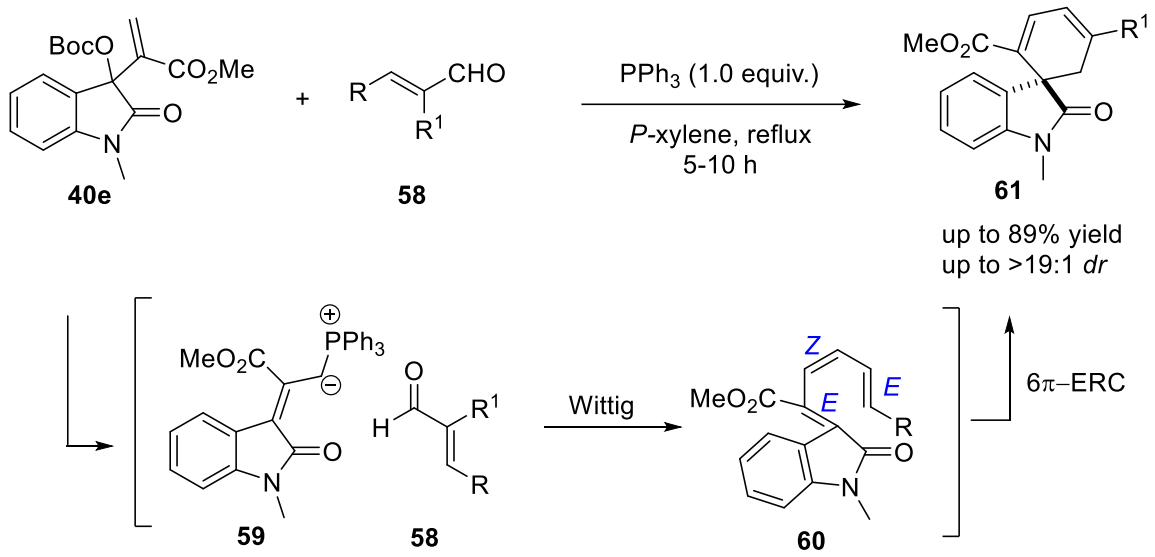
In 2015, Chen and coworkers[52] have described an efficient [4 + 3] cycloaddition protocol for the construction of aza-spirocycloheptaneoxindole derivatives **57**. The reaction of MBH bromides **53** and *N*-(*ortho*-chloromethyl) aryl amides **54** in presence of tri(4-flourophenyl)phosphine catalyst (10 mol%) and cesium carbonate (Cs_2CO_3) afforded the corresponding aza-spirocycloheptaneoxindoles **57** in good yields. The reaction pathway is believed to undergo via the reaction of *in situ* generated allylic P-ylide **55** and aza *o*-quinone methides **56** (aza-*o*QMs) (Scheme 1.23).



Scheme 1.23 Phosphine promoted [3 + 4] annulation of MBH bromides.

1.6.4 Electrocyclic reaction

In 2017, Kim research group[53] has reported the triphenyl phosphine (PPh_3) mediated coupling of MBH carbonates of isatin **40e** and *α, β*-unsaturated aldehydes **58** to afford spiro compound **61**. It is very important to note that the in situ generated triene intermediate **60** (formed by the Wittig reaction of allylic P-ylides **59** and *α, β*-unsaturated aldehydes **58**) subsequently undergoes 6π-electrocyclic ring-closure (ERC) to furnish the spirooxindoles bearing an unusual cyclohexadienyl derivative **61** (Scheme 1.24).



Scheme 1.24 6π-ERC of trienes derived from MBH carbonates and enals

1.7 Conclusions

In conclusion, easily accessible and diversely functionalized Morita-Baylis-Hillman (MBH) adducts have been proved to be very efficient and powerful synthons. In general, many MBH adducts have been explored in diverse reaction pathways to easily access structurally diverse compounds. While, Morita-Baylis-Hillman (MBH) adducts derived from isatin in particular have emerged as versatile precursors to construct various spirooxindole frameworks that are present in a large number of natural products as well as pharmacologically active compounds.

This concise introductory chapter described the history of MBH reaction and its utility in organic synthesis. A brief account on many interesting methods involving MBH adducts has been presented. There has been a plenty of applications of MBH reaction and many protocols have been explored effectively. Gratifyingly, still there is a huge scope to employ MBH adducts

to access many interesting and intriguing spirocyclic compounds of relevance. Also, some of the available methods involving MBH adducts of isatin still need to meet very high stereoselectivity. Moreover, novel and practical uses of isatin-based MBH carbonates are highly demanding and challenging to pursue.

In the remaining chapters we have explored the synthetic utility and different applications of MBH adducts for synthesizing novel spiroheterocyclic compounds via the development of newer protocols.

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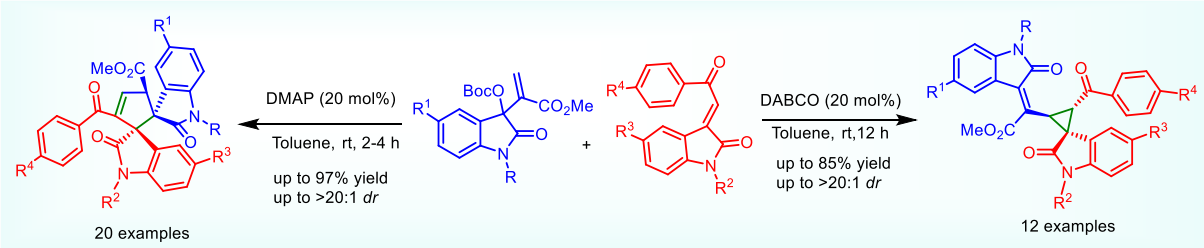
2

Cycloaddition of isatin-derived MBH carbonates and 3-methyleneoxindoles to construct cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles

Abstract

A highly regio- and diastereo-selective method for the construction of cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles has been developed. The tertiary amine catalysts have been effectively employed to tune the [3 + 2] and [2 + 1] annulations of MBH carbonates of isatin and 3-methyleneoxindoles for the outcome of two different spirooxindole frameworks. The reactions worked under mild and practical conditions to afford the spirooxindoles in good to excellent yields with very high diastereoselectvity.



Warghude, P. K.; Dharpure, P. D.; Bhat, R. G. *Tetrahedron Lett*. **2018**, *59*, 4076-4079.

2 Cycloaddition of isatin-derived MBH carbonates and 3-methyleneoxindoles to construct cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles

2.1 Introduction

The spirooxindoles are important structural motifs frequently found in a wide range of natural products and pharmacologically active compounds.[1-2] Among these, the spirocyclic oxindole scaffold bearing two adjacent quaternary spirocenters exhibit significant biological activity. Especially, the bis-spirooxindole fused with three and five membered ring are known to elicit significant bioactivities apparently due to their rigid and well defined three dimensional skeleton. For example, the bis-spirooxindole compounds **I**, **II** and **III** elicit anticancer, antimicrobial and antifungal activity respectively (Fig 2.1).[3-4]

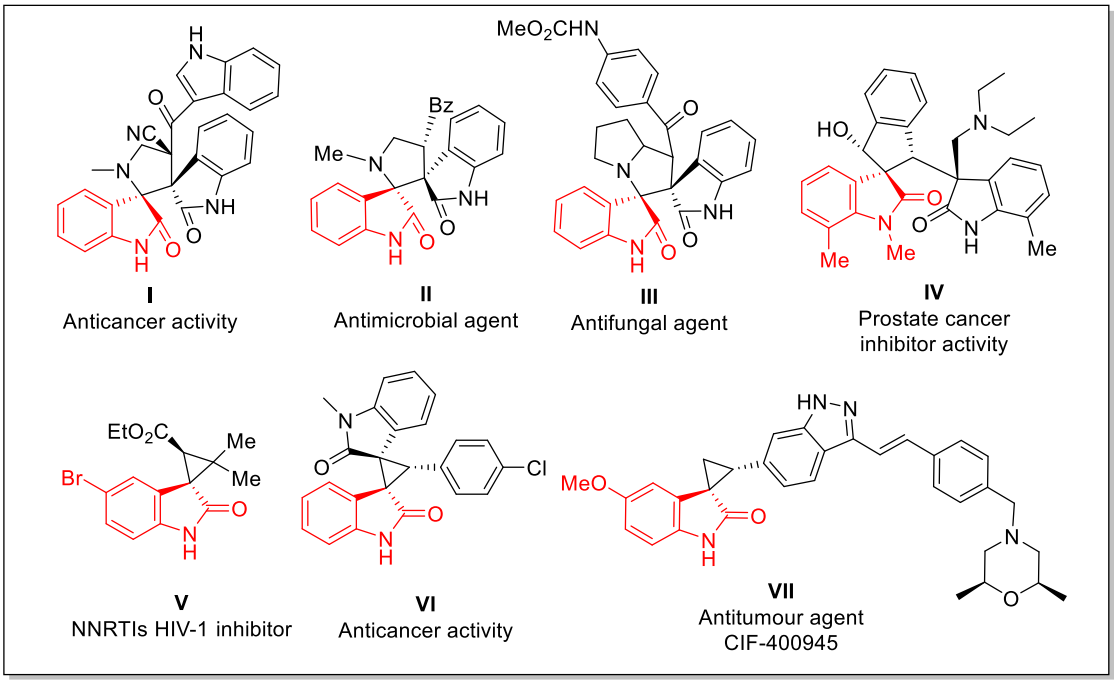


Figure 2.1 Bioactive compounds containing spirooxindoles architecture

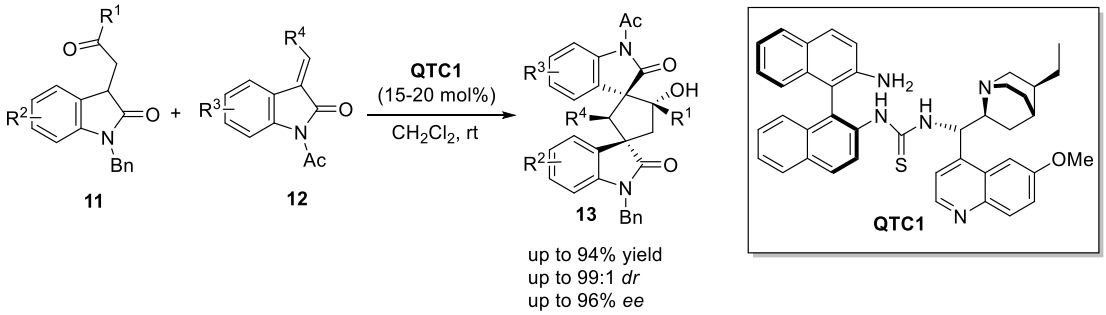
Similarly, the five membered carbocyclic di-spirooxindole compound **IV** showed inhibitory activity against the prostate cancer PC-3 cell lines. In addition, the

spirocyclopropyl oxindole **V** is known to act as an HIV-1 non-nucleoside reverse transcriptase inhibitor at nanomolar level,[3c] whereas the cyclopropane containing bis-spirooxindole **VI** displayed anticancer activity against breast cancer MDA-MB-231 cell lines.[4a] The compound **VII** (CFI-400945) exhibited significant antitumor potency and PLK4 inhibitor activity[4b] (Figure 2.1).

2.2 Recent approaches for the synthesis of bis-spirooxindoles

It is well known that synthetically and naturally occurring bis-spirooxindole and spiro-cyclopropyl oxindole scaffolds possess varied potent biological activities. Owing to the importance of these compounds, the considerable attention has been devoted towards the building of spirooxindole framework in highly regio-, distreo- and enantio-selective fashion over the last few decades. Some of the selected methods for the synthesis of bis-spirooxindoles have described.

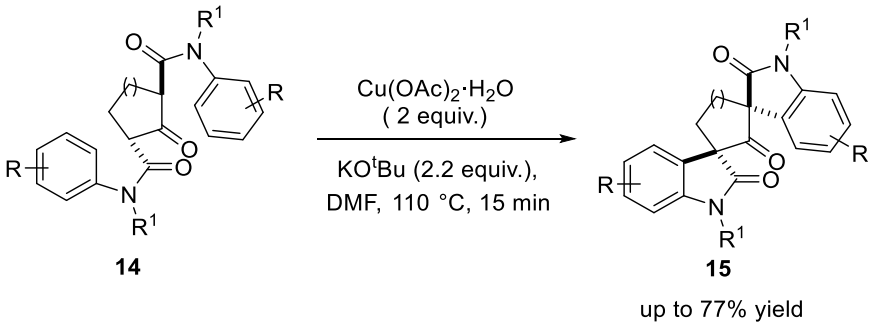
In 2011, Barbas and co-workers[5] have described the organocatalytic domino Michael/aldol cascade reaction to construct the complex molecules. The multi-functional cinchona alkaloid catalyst **QTC1** containing binaphthyl primary amine, a tertiary amine and thiourea functionalities catalyzed the domino Michael/aldol reaction between 3-substituted oxindoles **11** and methyleneindolinones **12** to furnish the bis-spirooxindole derivatives **13** containing four contagious streogenic centers, including three quaternary centers. The bis-spirooxindoles **13** were obtained in moderate to excellent yields (up to 94%) with high levels of streoselectivities (up to 99:1 *dr*, up to 96% *ee*) (Scheme 2.1).



Scheme 2.1 Synthesis of bis-spirooxindole via domino Michael/aldol cascade reaction

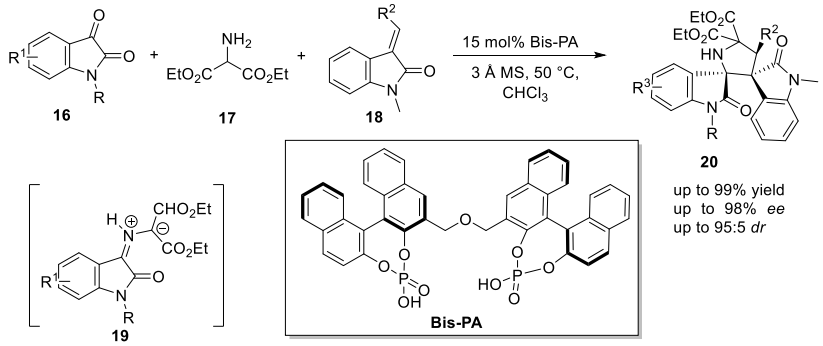
In 2014, Taylor and co-workers[6] have reported the synthesis of spirocyclic bis-oxindoles **15** starting from bis-anilides **14** through a double C-H, Ar-H coupling reaction. This protocol utilized stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ and KO^tBu as a base in DMF at an

elevated temperature (110 °C) to afford the structurally diverse bis-spirooxindoles **15** bearing two quaternary centers in moderate to good yields (up to 77%) (Scheme 2.2).



Scheme 2.2 Synthesis of bis-spirooxindoles via double C-H, Ar-H coupling process

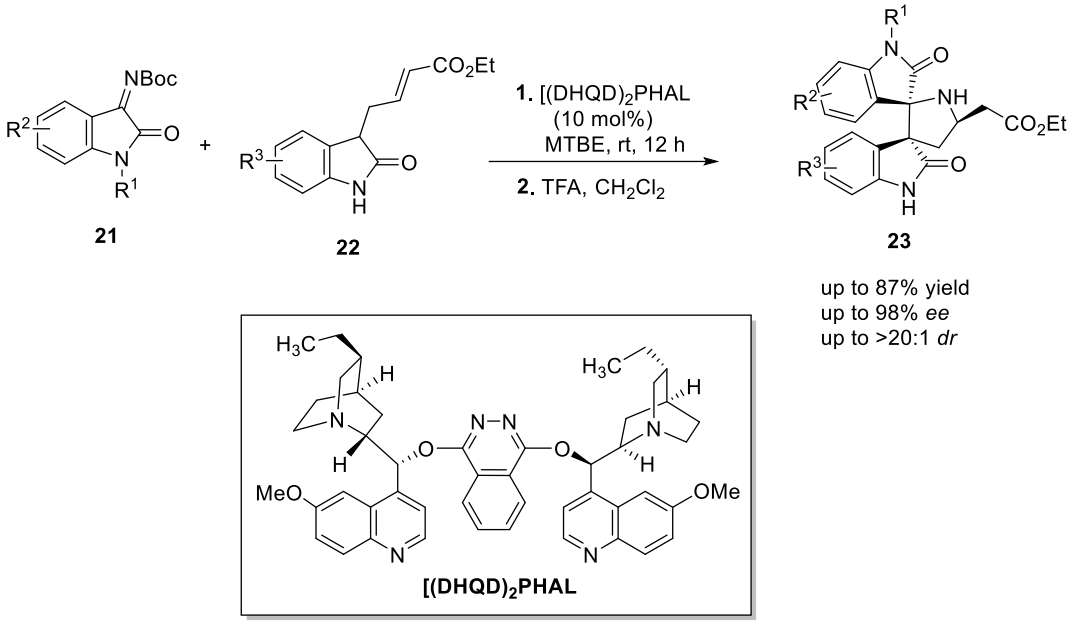
In 2015, Shi and co-workers[7] have disclosed the organocatalytic asymmetric 1, 3-dipolar cycloaddition reaction to construct the di-spirooxindoles. The azomethine ylide **19** is formed by the reaction between isatins **16** and amine **17**. This in situ generated azomethine ylide **19** underwent [3 + 2] cycloaddition with methyleneindolinones **18** in presence of chiral bis-phosphoric acid (**Bis-PA**) catalyst to afford 3, 3′-pyrrolidinyldispirooxindole **20** scaffold. This strategy enabled the synthesis of structurally complex bis-spirooxindoles **20** containing three contiguous and two quaternary spiro streocenters in high yields (up to 99%) with excellent diastereo- and enantio-selectivities (up to >95:5 *dr*, 98% *ee*) (Scheme 2.3).



Scheme 2.3 Synthesis of bis-spirooxindole via 1, 3-dipolar cycloaddition reaction

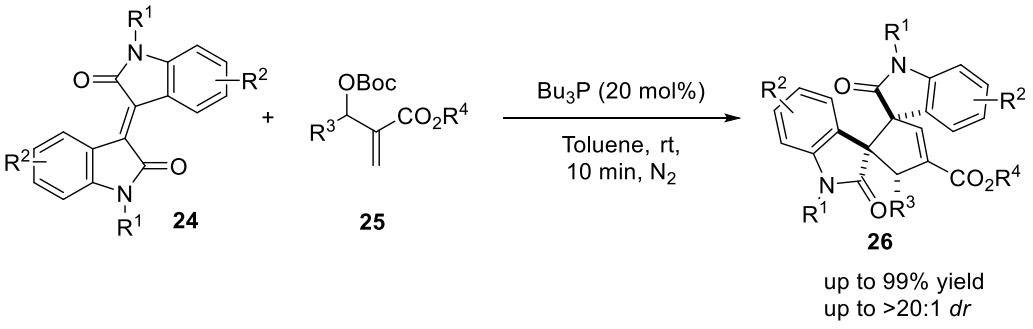
In 2016, Enders and co-workers[8] have reported the cascade reaction to construct dispirooxindoles. The treatment of *N*-Boc isatin imines **21** with oxindoles derivatives **22** in presence of cinchona derived catalyst [$(DHQD)_2PHAL$] to furnish 3,3'-pyrrolidinyl-

dispirooxindoles **23**. This cascade transformation involved Mannich/Boc-deprotection/aza-Michael reaction sequence in one-pot to afford the corresponding bis-spirooxindole derivatives **23** in moderate to good yields (up to 87%) with excellent stereoselectivities (up to 20:1 *dr* and 98% *ee*) (Scheme 2.4).



Scheme 2.4 Synthesis of bis-spirooxindole via Mannich/Boc deprotection/aza-Michael reaction sequence

In 2018, Tian and Wang[9] have reported the tributylphosphine (Bu_3P) catalyzed [3 + 2] cycloaddition of isoindigos **24** and MBH carbonates **25** to afford bis-spirooxindole **26**. This protocol enabled the synthesis of dispiro[cyclopent-3′-ene]bisoxindole **26** molecules containing vicinal spirocenters in excellent yields (up to >99%) with very high diastereoselectivities (>20 : 1 *dr*) under mild reaction conditions in a short time (Scheme 2.5).

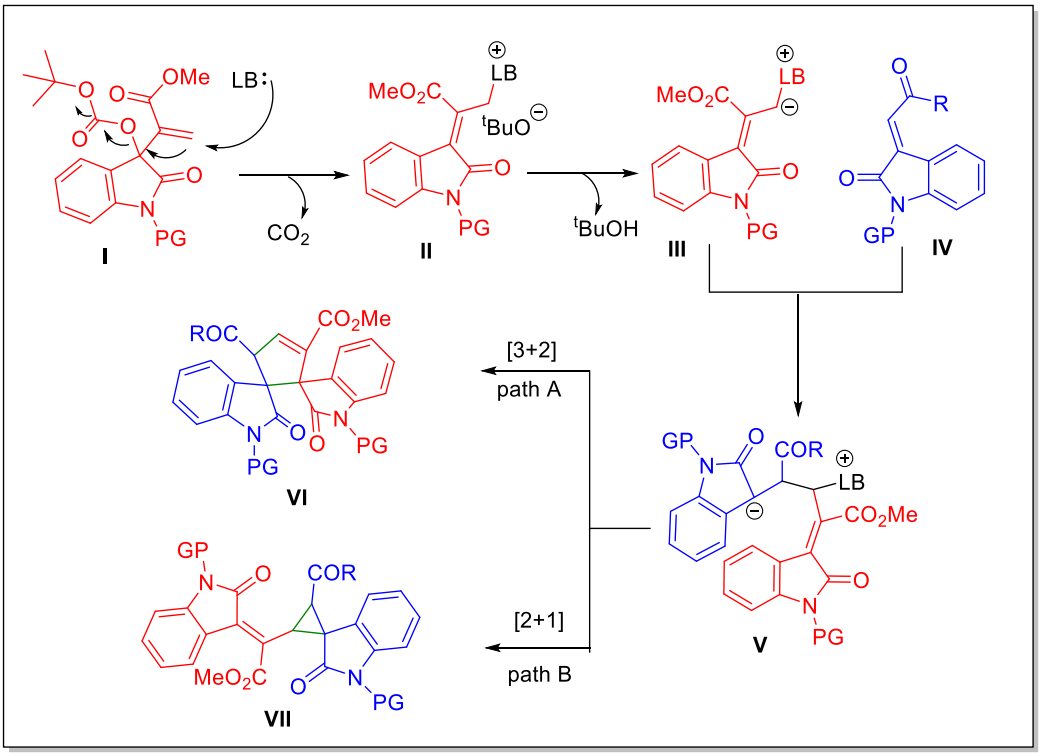


Scheme 2.5 Diastereoselective synthesis of bis-spirooxindole via [3 + 2] annulation reaction

However, some of the available protocols rely on the use of transition metal catalyst, stoichiometric base and heating condition to achieve bis-spirooxindole skeletons. In view of some of these limitations, the development of transition metal-free, highly efficient, more practical protocol for the synthesis of structurally diverse bis-spirooxindoles is highly desirable and challenging.

2.3 Our hypothesis and synthetic design

The modified oxindole derivatives have been successfully used as excellent precursors for the construction of various carbocyclic and heterocyclic spirooxindole compounds. In recent years, Morita-Baylis-Hillman (MBH) adducts of isatin have also been employed as a useful starting materials for the synthesis of enantiomerically pure multi-functional spirooxindole derivatives.[10] Similarly, 3-methylene oxindole derivatives have been also explored as dienophiles as well as Michael acceptors in various organocatalytic Diels-Alder reaction and conjugated addition (Michael reaction) reactions respectively to construct the spirooxindoles.[11] Considering the importance of spirooxindole scaffold, , we hypothesized the synthesis of di-spirooxindole and spirocyclopropyl oxindole as shown in Scheme 2.6



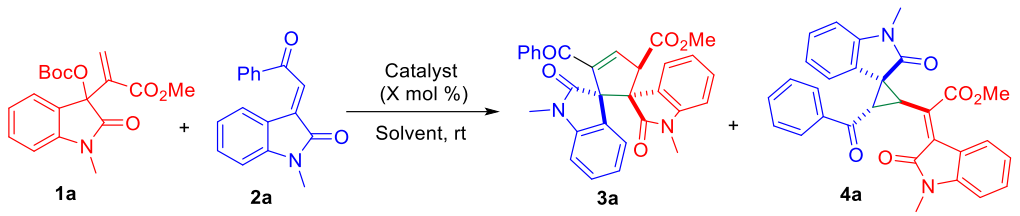
Scheme 2.6 Proposed synthesis of bis-spirocyclic oxindole

We hypothesized that a Lewis base catalyst (amine or phosphine) would initiate the S_N^2 reaction to form intermediate **II** with the elimination of CO_2 and *tert*-butoxide starting from MBH carbonate **I** (Scheme 2.6)**.** Subsequently, the in situ generated Brønsted base (*tert*-butoxide) abstracts the proton from the intermediate **II** to form a zwitterionic ylide intermediate **III.** This intermediate would further react with 3-methyleneoxindole **IV** to form the intermediate **V** containing two oxindole rings. We hypotheisized that this intermediate **V** may finally lead to the formation of different bis-spirooxindoles via [3 + 2] annulation (path A, **VI**) and/or spirocyclopropyl oxindole through [2 + 1] cycloaddition pathway (path B, **VII**).

2.4 Results and Discussion

In order to validate the feasibility of our hypothesis, we set out a model reaction between MBH carbonate of isatin **1a** and (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-one **2a** using PPh_3 (20 mol%) as a catalyst in toluene at room temperature. Gratifyingly, the reaction delivered the α-regioselective [3 + 2] annulation bis-spirooxindole product **3a** in good yield 85% with very high diastereoselectivity (>20:1 *dr*, Table 2.1, entry 1). Encouraged by this initial immediate result, we screened *R*-BINAP and *S*-BINAP as a nuleophilic catalysts. However, the reactions did not work under these chiral catalysts (Table 2.1, entries 2–3). Later, we planned to employ the tertiary amine catalysts. Intrestingly, in presence of DABCO (1,4-diazabicyclo[2.2.2]octane) catalyst an unexpected cyclopropyl spirooxindole compound **4a** was obtained in 85% with an excellent diastereoselectivity via [2 + 1] annulation (Table 2.1, entry 4). It was observed that neither N, N-Diisopropylethylamine (DIPEA) nor triethylamine (Et_3N) catalyzed the reaction (Table 2.1, entries 5-6). To our delight, the bis-spirooxindole product **3a** was obtained in excellent yield (97%) with very high diastereoselectivity when 4-dimethylaminopyridine (DMAP) was used as a catalyst (Table 2.1, entry 7). Our various attempts to achieve enantioselective [3 + 2] annulation did not succeed in spite of screening different chiral cinchona based catalysts (Table 2.1, entries 8-10). Therefore, we planned for diastereoselective construction of bis-spirooxindoles systematically. Further reduction in the catalyst loading of DMAP (15 to 5 mol%) delivered the di-spirooxindole **3a** in relatively lower yields however, the diastereoselectivity was unchanged (Table 2.1, entries 11-13). Other solvents such as DCM, chloroform, ethanol, ^tBuOH, CH_3CN, THF, DMF, and DMSO delivered the bis-spirooxindole **3a** in relatively lower yields with longer reaction times (Table 1, entries 14-21).

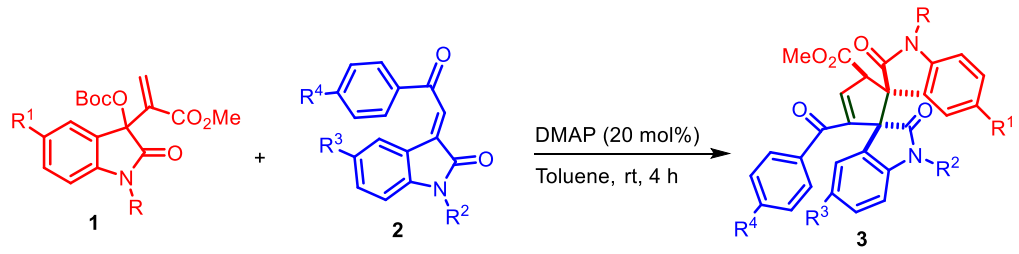
Table 2.1 Optimization of catalysts and solvents for annulation reaction[a-f]

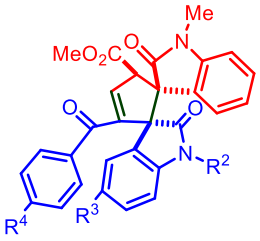


Entry	Catalysts	Solvents	Time [h]	Product & Yield[%][b]	*dr* [%][c]
1	PPh_3	Toluene	24	**3a**, 85	>20:1
2	*R*-BINAP	Toluene	120	NR	-
3	*S*-BINAP	Toluene	120	NR	-
4	DABCO	Toluene	12	**4a**, 85	>20:1
5	DIPEA	Toluene	120	NR	-
6	Et_3N	Toluene	120	NR	-
7	DMAP	Toluene	4	**3a,** 97	>20:1
8	Qunine	Toluene	120	NR	-
9	Quinidine	Toluene	120	NR	-
10	$(DHQD)_2PHAL$	Toluene	120	NR	-
11[d]	DMAP	Toluene	12	**3a**, 92	>20:1
12[e]	DMAP	Toluene	24	**3a**, 87	>20:1
13[f]	DMAP	Toluene	40	**3a**, 82	>20:1
14	DMAP	DCM	6	**3a,** 92	>20:1
15	DMAP	$CHCl_3$	7	**3a**, 90	>20:1
16	DMAP	EtOH	24	**3a**, 88	>20:1
17	DMAP	^tBuOH	24	**3a**, 90	>20:1
18	DMAP	THF	24	**3a**, 71	>20:1
19	DMAP	CH_3CN	24	**3a**, 90	>20:1
20	DMAP	DMF	30	**3a**, 74	>20:1
21	DMAP	DMSO	30	**3a**, 79	>20:1

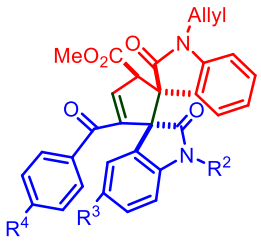
[a]**Reaction Conditions:** Unless otherwise noted, the reactions were carried out using MBH carbonate **1a** (1.0 equiv.) and (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene) indolin-2-one **2a** (1.1 equiv.) catalyst (20 mol%) in solvent (2 mL) at room temperature. [b]Isolated yield after column chromatography. [c]Determined by ^1H NMR spectroscopy. [d] DMAP (15 mol %). [e] DMAP (10 mol %). [f] DMAP (5 mol %). NR = no reaction;

Table 2.2 Substrate scope of [3 + 2] annulation[a]

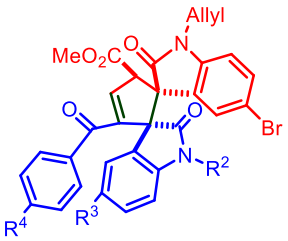




3a-3i
(***dr*** **>20:1 in all cases)**



3j-3m
(***dr*** **>20:1 in all cases)**

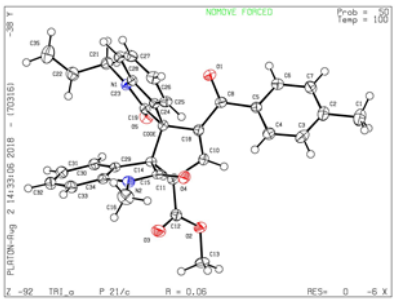


3n-3q
(***dr*** **>20:1 in all cases)**

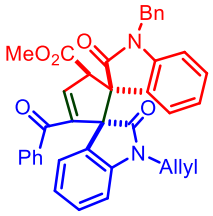
3a, R^2= Me, R^3= H, R^4= H, 97%
3b, R^2= allyl, R^3= H, R^4= Cl, 96%
3c, R^2= Bn, R^3= H, R^4= Me, 97%
3d, R^2= Me R^3= H, R^4= Cl, 95%
3e, R^2=Bn, R^3= H, R^4= Cl, 96%
3f, R^2= allyl, R^3= H, R^4= Me 98%
3g, R^2= allyl, R^3= H, R^4= H, 94%
3h, R^2= Me, R^3= Br, R^4= H, 90%
3i, R^2= Me, R^3= Cl, R^4= H, 92%

3j, R^2= allyl, R^3= H, R^4= Me, 95%
3k, R^2= allyl, R^3= H, R^4= Cl, 93%
3l, R^2=Bn, R^3= H, R^4= Me, 81%
3e, R^2= Bn, R^3= H, R^4= Cl 88%

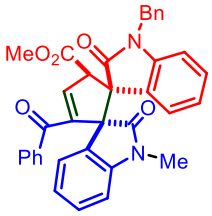
3n, R^2= Me, R^3= H, R^4= H, 91%
3o, R^2= Me, R^3= H, R^4= Cl, 88%
3p, R^2=allyl, R^3= H, R^4= Me, 95%
3r, R^2= allyl, R^3= H, R^4= H, 90%



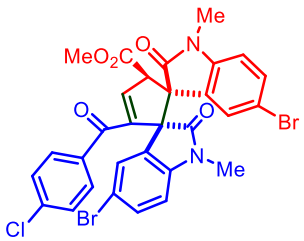
(Molecular Structure **3f**)
CCDC 1860014



3r
87%, *dr* >20:1



3s
86%, *dr* >20:1



3t
81%, *dr* >20:1

[a]**Optimized Reaction Conditons**: MBH carbonate **1** of isatin (0.28 mmol) and 3-methyleneoxindole **2** (0.31 mmol) with cat. DMAP (20 mol %) in toluene (2 mL) at room temperature. [b]Isolated yields after column chromatography. [c]*dr* was determined by ^{1}H-NMR.

Based on the catalysts and solvents screening, the optimized reaction conditions to achieve bis-spirooxindole **3a** is MBH carbonate **1a** (1 equiv.), 3-methyleneoxindole **2a** (1.1 equiv.) and DMAP (20 mol %) in toluene at room temperature.

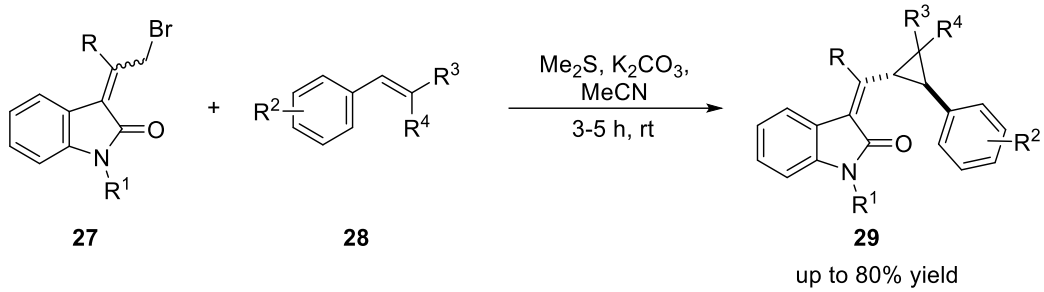
Having obtained the optimized reaction condition, we investigated the generality of the developed protocol using different MBH carbonates of isatin **1a-1d** and 3-methyleneoxindoles **2a-2j**. As depicted in Table 2.2, a wide range of bis-spirooxindole derivatives **3a-3t** were obtained in good to excellent yields with very high diastereoselectivity. All the substrates underwent facile [3 + 2] cycloaddition to afford the di-spirooxindole compounds bearing vicinal quaternary spirocenters. Importantly, we did not observe any side products emanating from [2 + 1] annulation during the course of reaction. We noticed that both weakly electron deactivating as well as electron donating substituents on either MBH carbonates **1** or (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene) indolin-2-one (3-methyleneoxindoles) **2** did not affect the yield and diastereoselectivity of the products. Further, the molecular structure of bis-spiroxindole compound **3f** was assigned by using single crystal X-ray diffraction analysis (Table 2.2).[12]

Earlier, while optimizing the reaction conditions for the synthesis of cyclopentyl bis-spirooxindole via α-regioselective [3 + 2] cyloaddition, , serendipitously we had obtained an unexpected cyclopropyl spirooxindole compound **4a** via [2 + 1] annulation (Table 2.1, entry 4). Excited by this observation, we focused our attention towards the synthesis of cyclopropane appended spirooxindole derivatives, as this type of scaffold is known for different pharmacological activities (Figure 2.1).Apart from their biological significance, the molecular framework with highly strained three membered cyclopropyl ring would be of a great importance as the ring strain makes them remarkably reactive. This would particularly invoke the easy ring opening reactions to access complex and synthetically useful compounds.[13] In this reagrd, significant efforts have been made to construct cyclopropyl spirooxindole derivatives in highly streoselective manner. However, surprisingly, only few reports are available in the literature for the synthesis of cyclopropane appended with two oxindole molecules in regioselective fashion.[14]

2.5 Methods for the synthesis of cyclopropane spirooxindole

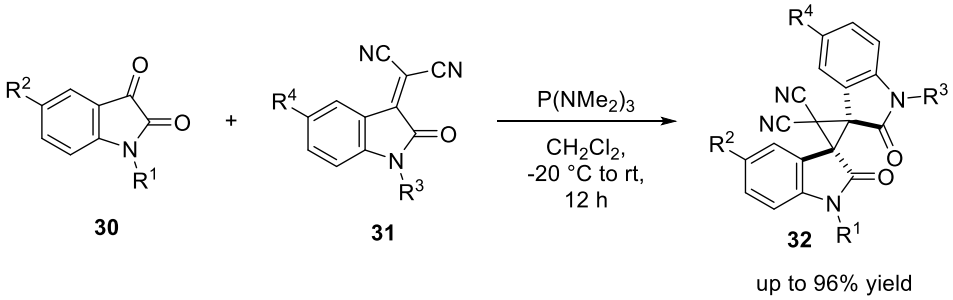
In 2012, Shanmugam and co-workers[15] have reported the diastereoselective synthesis of vinyl cyclopropane appended oxindole derivatives **29**. The reaction of bromo isomerised Morita-Baylis-Hillman adducts of isatin **27**, activated styrenes **28**, dimethyl sulphide (Me_2S)

and K_2CO_3 in acetonitrile afforded the corresponding spirooxindole appended cyclopropane **29** compounds in moderate to good yields (up to 80%). The transformation is belived to undergo via sulfur ylide intermediate to afford vinyl cyclopropane appended oxindole derivatives (Scheme 2.7).



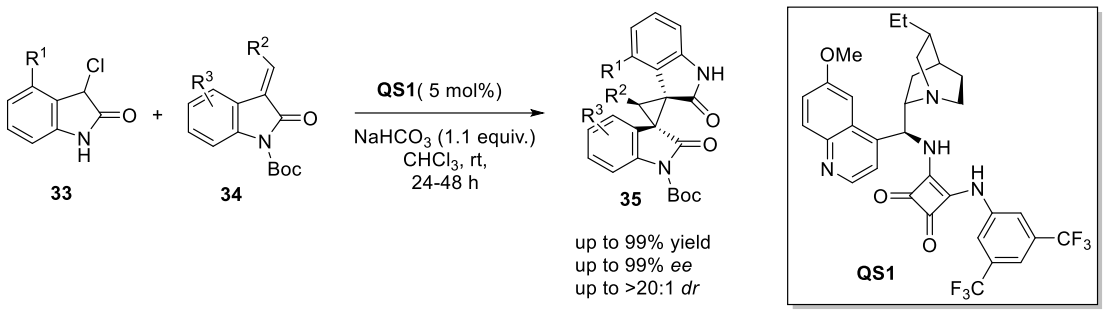
Scheme 2.7. Synthesis of vinyl cyclopropane appended oxindoles

In 2016, Han and Yan[16] have reported the diastreoselective synthesis of cyclopropane fused bis-spirooxindole derivatives. This method enabled the synthesis of spiro[indoline-3, 1'-cyclopropane-2', 3"-indolines] **32** starting from isatins **30** and isatylidene malononitriles **31** in presence of hexamethylphosphorous triamide in dry dichloromethane. The spirocyclopropyl fused oxindoles **32** were obtained in good to excellent yields with two indoline moieties in *trans*-configuration (Scheme 2.8).



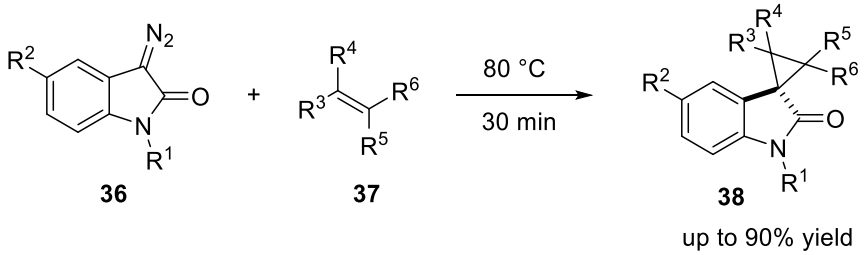
Scheme 2.8. Diastereoselective synthesis of spiro[indoline-3,1'-cyclopropane-2',3"-indolines]

In 2013, Noole et al.[17] have demonstrated the utility of bifunctional quinine derived squaramide catalyst **QS1** in the enantioselective synthesis of spirocyclopropyl oxindoles. The treatment of 3-chloro oxindoles **33** with methyleneindolinones **34** afforded the bis-spirooxindole appended cyclopropane derivatives **35** bearing three continuous chiral centres including two spiro quaternary chiral centres in good to excellent yileds (up to 99%) with high level of streocontrol (up to >20:1 *dr* and 99% *ee*) (Scheme 2.9).



Scheme 2.9 Asymmetric synthesis of cyclopropane fused bis-spirooxindoles

In 2014, Karthik et al.[18] have reported the highly effective approach for the synthesis of spirocyclopropyl oxindoles under solvent- and catalyst-free reaction condition. The reaction of 3-diazooxindole **36** and electron deficient olefins **37** at 80 °C afforded the spiro[cyclopropane-1, 3'-indolin]-2'-one derivatives **38** in good to excellent yields (up to 90%) (Scheme 2.10).



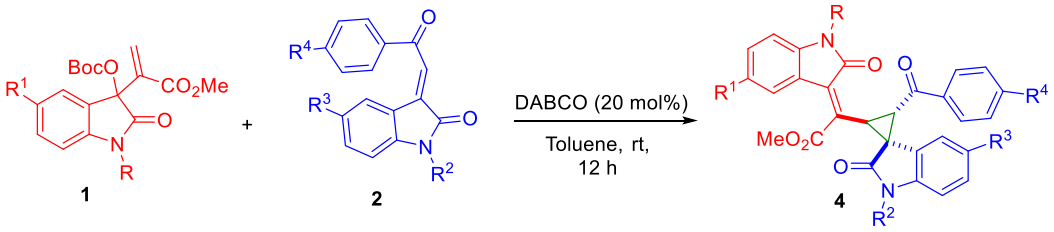
Scheme 2.10. Synthesis of spirocyclopropyl oxindoles

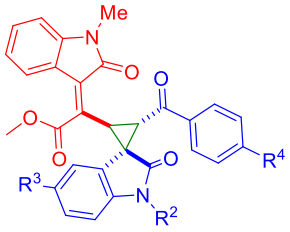
Though previous methods were interesting, they had limited applicability due to limited substrate scope, use of stoichiometric quantity of base, relying on heating conditions etc. Therefore, developing an efficient protocol for synthesizing structurally diverse cyclopropyl oxindoles under organocatalytic conditions with wider substrate scope is highly desirable.

In this regard, we planned to explore the catalytic reactivity of DABCO for the α-regioselective [2 + 1] annulation process. Based on the earlier optimized reaction conditions (table 2.1, entry 4), we set out to explore reactivity of other substrates. In order to demonstrate the generality of [2 + 1] annulation, we treated different isatin derived MBH carbonates **1a-1d** with few substituted 3-methyleneoxindoles (**2a**, **2d, 2h, 2i, 2k)** in presence of 1,4-diazabicyclo[2.2.2]octane (20 mol %) in toluene at room temperature. Pleasingly, all the reaction underwent facile [2 + 1] cycloaddition to the corresponding cyclopropyl spirooxindole derivatives **(4a-4l)** in very good yields (up to 85%) with excellent diastereoselectivity (Table 2.3). We observed that not only weakly electron deactivating but electron donating substituents

on either MBH carbonates of isatin **1** or 3-methyleneoxindoles **2** also well tolerated under optimized reaction conditions and did not affect the yield and diastereoselectivity of products. The molecular structure of cyclopropyl spirooxindole compound **4d** was assigned unambiguously using single crystal X-ray diffraction analysis.[19]

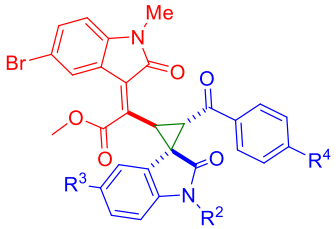
Table 2.3. Substrate scope of [2 +1] annulation[a-c]





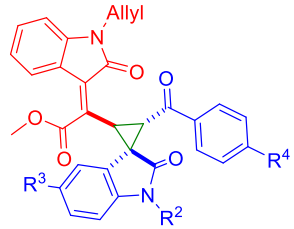
4a-4d
(***dr*** **>20:1 in all cases)**

4a, R^2= Me, R^3= H, R^4= H, 85%
4b, R^2= Me, R^3= H, R^4= Cl, 82%
4c, R^2=Me, R^3= Br, R^4= H, 79%
4d, R^2= Me, R^3= Cl, R^4= H, 83%



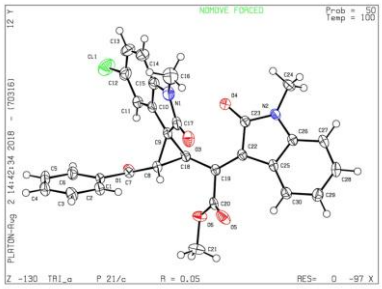
4e-4h
(***dr*** **>20:1 in all cases)**

4e, R^2= Me, R^3= H, R^4= H, 75%
4f, R^2= Me, R^3= Br, R^4= H, 72%
4g, R^2=Me, R^3= Cl, R^4= H, 70%
4h, R^2= Me, R^3= Cl, R^4= Me, 75%

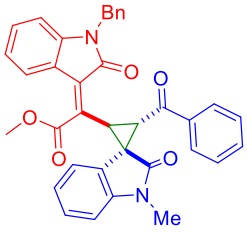


4a-4d
(***dr*** **>20:1 in all cases)**

4i, R^2= Me, R^3= H, R^4= H, 83%
4j, R^2= Me, R^3= H, R^4= Cl, 80%
4k, R^2=Me, R^3= Br, R^4= H, 72%



(Molecular structure **4d**)
CCDC 1860035

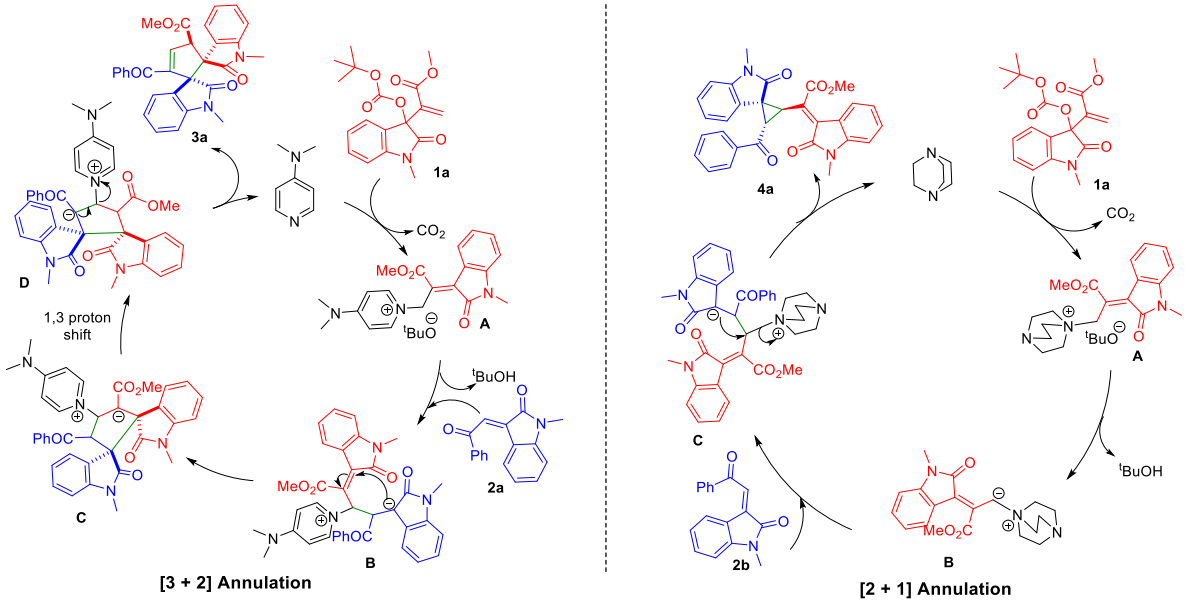


4l
70%, >20:1

[a]**Optimized Reaction Conditions**: MBH carbonate **1** (0.28 mmol) and **2** (0.31 mmol) with cat. DABCO (20 mol %) toluene (2 mL) at room temperature. [b]Isolated yields after column chromatography. [c]*dr* was calculated based on ^{1}H-NMR spectroscopy.

Based on the literature precedence on Lewis base catalyzed annulation of MBH carbonate, plausible mechanisms for [3 + 2] and [2 + 1] have been proposed (Scheme 2.11).[10] Initially, the nucleophilic attack of DMAP on MBH carbonate **1a** generate the corresponding ammonium salt intermediate **A** with the elimination of leaving group (CO_2 and *tert*-butoxide). Further, in situ generated counter anion *tert*-butoxide abstracts an acidic proton from intermediate **A** to give an allylic nitrogen-ylide. Then, this reacts with **2a** via α-position to give an intermediate **B**. Subsequently, intermediate **B** undergoes an intramolecular Michael addition to afford the corresponding cyclic intermediate **C**. Finally, the 1,3-proton shift lead to the formation of intermediate **D** which subsequently delivered bis-spirooxindole product **3a** by regenerating the catalyst (Scheme 2.11a).

Likewise, DABCO initiates the reaction by reacting with MBH carbonate **1a** to give quaternary ammonium intermediate **A** along with the carbon dioxide and *tert*-butoxide. Subsequent deprotonation of ammonium intermediate **A** by the in situ generated counter anion ($^{-}O^{t}Bu$) generates reactive nitrogen ylide intermediate **B**. Further the intermediate **B** reacts with 3-methyleneoxindole **2b** via α-postion to afford a zwitterionic intermediate **C** that subsequently undergoes [2 + 1] cycloaddtion to furnish cyclopropyl fused spirooxindole **4a** by regenerating the catalyst (Scheme 2.11b).



(a) [3 + 2] Annulation **(b) [2 +1] Annulation**

Scheme 2.11 Plausible reaction mechanism for [3 + 2] and [2 + 1] annulations

2.6 Conclusions

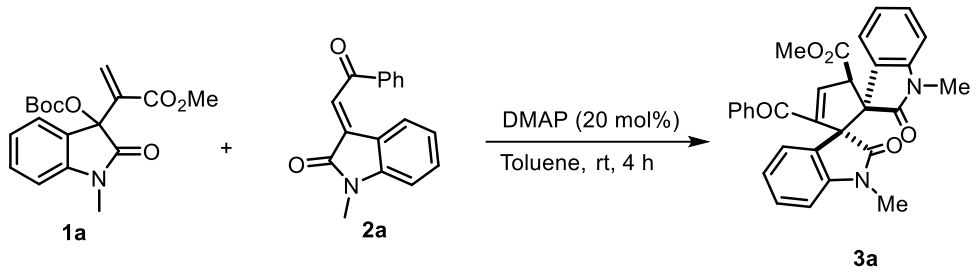
In conclusion, we have developed facile, straightforward and an efficient organocatalytic [3 + 2] and [2 + 1] annulations protocol for the synthesis of cyclopentene/cyclopropane appended bis-spirooxindole derivatives. The reaction of Morita−Baylis−Hillman carbonates of isatin with 3-methyleneoxindoles in presence of Lewis base afforded the spiorocyclic compounds overall in good to excellent yields with very high diastereoselectivity. We have demonstrated the catalyst controlled outcome of annulation to afford synthetically and biologically useful compounds.

2.7 Experimental Section

2.7.1 General

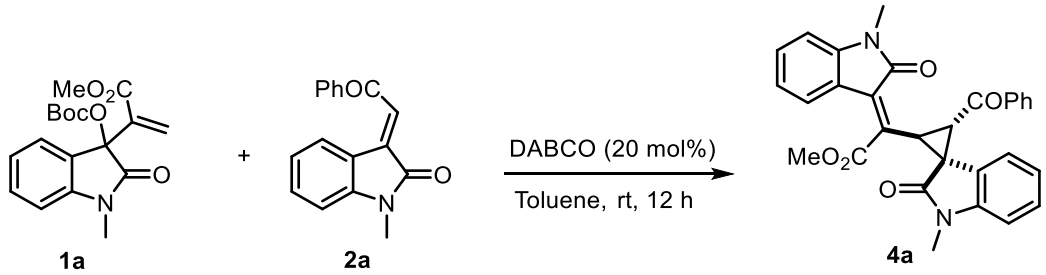
Unless otherwise stated, all the reagents were purchased from commercial suppliers (Aldrich, TCI, Alfa Aesar, and Spectrochem) and used without purification. All the reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and the solution of Phosphomolybdic Acid (PMA), $KMnO_4$ was used to stain products. The column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate. The NMR spectra were recorded using tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) are given in Hz and integration. All the samples were analyzed by high resolution mass spectrometer (HRMS) using ESI TOF. Melting points were measured using BÜCHI M-560 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Morita-Baylis-Hillman carbonates **1a-1j** were prepared according to the literature procedure.[10b,10d] Substrates **2a-2j** were prepared according to the literature procedure.[20]

2.7.2 General procedure for the synthesis of bis-spirooxindole



In an oven dried 10 mL round bottomed flask containing a mixture of methyl 2-(3-((tert-butoxycarbonyl)oxy)-1-methyl-2-oxoindolin-3-yl)acrylate **1a** (100 mg, 0.28 mmol), (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-one **2a** (83 mg, 0.31 mmol and 20 mol% DMAP (7 mg, 0.06 mmol, in 2 mL toluene was stirred at room temperature for 4 h and the reaction was monitored by TLC. Upon the completion of the reaction (monitored by TLC), the crude product was directly purified by silica gel chromatography to give the corresponding product **3a** as a white solid (138 mg, 97 % yield).

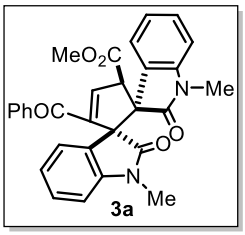
2.7.3 General procedure for the synthesis of cyclopropyl spirooxindoles



In an oven dried round bottomed flask containing a mixture of methyl 2-(3-((tert-butoxycarbonyl)oxy)-1-methyl-2-oxoindolin-3-yl)acrylate **1a** (100 mg, 0.28 mmol), (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene)indolin-2-one **2a** (83 mg, 0.31 mmol and 20 mol% DABCO (7 mg, 0.06 mmol) in 2 mL of toluene was stirred at room temperature, and the reaction was monitored by TLC. Upon the completion of the reaction (monitored by TLC), the crude product was directly purified by silica gel chromatography to give the corresponding product **4a** as a red solid (120 mg, 85 % yield, *dr* >20:1).

2.7.4 Experimental Data

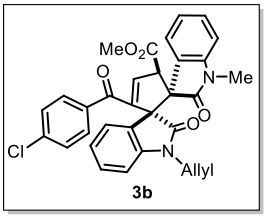
Methyl-5'-benzoyl-1,1''-dimethyl-2,2''-dioxodispiro[indoline-3,1'cyclopentane-2',3''-indolin]- 3'- ene-3'- carboxylate (3a)



White solid (138 mg, 97%, *dr* >20:1). MP: 230-232 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.98 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.30 – 7.25 (m, 1H), 7.18 (td, *J* = 3.4, 2.9, 1.2 Hz, 2H), 7.11 (d, *J* = 1.2 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.85 – 6.79 (m, 1H), 6.58 (dd, *J* = 7.7, 3.0 Hz, 2H), 5.01 (d, *J* = 2.2 Hz, 1H), 3.65 (s, 3H), 3.08 (s, 3H), 3.01 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 191.0, 176.0, 174.7, 169.6, 144.6, 144.4, 144.1, 142.7, 136.9, 132.9, 129.5, 129.0, 128.3, 124.9, 124.8, 124.2, 123.8, 122.2, 122.1, 107.7, 107.6, , 66.2, 61.9, 55.7, 52.2, 25.6; IR (neat) cm^{-1}: 3058, 2925, 2857, 1705, 1642, 1607, 1465, 1340, 1257, 1148, 1087, 995, 939, 879, 808, 737, 701; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{24}N_2O_5$ $[M + H]^+$ 493.1763, found 493.1774.

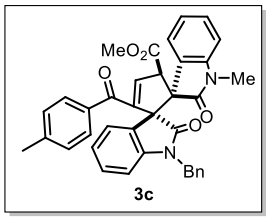
Methyl-1-allyl-5'-(4-chlorobenzoyl)-1''-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-3'-carboxylate (3b)

The compound **3b** was synthesized starting from **1a** and **2b** following the general procedure described for **3a**; The compound **3b** was obtained as a white solid (150 mg, 96 % yield, *dr* >20:1), MP: 125-128 °C; IR (neat) cm^{-1}: 3057, 2925, 1705,1647, 1607, 1466, 1343, 1235, 1185,1096,1009, 878,834, 734,697, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H), 7.59 – 7.43 (m, 3H), 7.33 – 7.25 (m, 1H), 7.23 – 7.06 (m, 3H), 6.96 (td, *J* = 7.6, 0.8 Hz, 1H), 6.82 (td, *J* = 7.6, 0.8 Hz, 1H), 6.59 (dd, *J* = 16.2, 7.8 Hz, 2H), 5.60 (ddd, *J* = 12.4, 10.5, 5.3 Hz, 1H), 5.09 – 4.99 (m, 2H), 4.97 – 4.85 (m, 1H), 4.37 (d, *J* = 4.5 Hz, 1H), 4.14 (d, *J* = 5.2 Hz, 1H), 3.66 (s, 3H), 3.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.2, 176.3, 174.7, 169.8, 145.0, 144.4, 144.1, 142.9, 139.7, 135.5, 131.2, 130.7, 129.3, 129.0, 125.1, 125.0, 124.6, 124.5, 122.7, 122.6, 117.4, 109.1, 108.1, 66.4, 62.2, 56.1, 52.6, 42.5, 25.9; HRMS (ESI TOF) *m/z* calcd for $C_{32}H_{25}ClN_2O_5$ $[M + Na]^+$ 575.1350, found 575.1350.



Methyl-1-benzyl-1''-methyl-5'-(4-methylbenzoyl)-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-3'-carboxylate (3c)

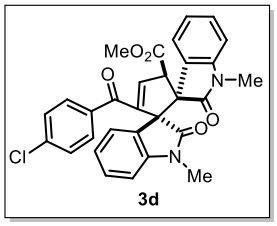
The compound **3c** was synthesized starting from **1a** and **2c,** following the general procedure described for **3a**; The compound **3c** was obtained as a white solid (172 mg, 97 % yield, *dr* >20:1), MP: 229-231 °C; IR (neat) cm^{-1}: 3060, 2933, 1705, 1652, 1609, 1469, 1343, 1241, 1148, 1091, 1005, 878.06 845.26 815.07 743, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.59 – 7.49 (m, 1H), 7.34 – 7.23 (m, 4H), 7.22 – 7.17 (m, 3H), 7.15 (d, *J* = 2.3 Hz, 1H), 7.01 – 6.89 (m, 4H), 6.84 – 6.72 (m, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 5.07 – 4.96 (m, 2H), 4.72 (d, *J* = 16.2 Hz, 1H), 3.65 (s, 3H), 3.02 (s, 3H), 2.42 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 176.4, 175.3, 170.0, 144.5, 144.2, 144.1, 143.4, 135.3, 134.7, 130.1, 129.4, 129.2, 129.2, 128.7, 127.2, 126.8, 125.5, 125.3, 124.8, 124.7, 122.9, 122.6, 109.3, 108.1, , 66.6, 62.1, 56.3, 52.5, 44.0, 26.0, 21.8; HRMS (ESI TOF) *m/z* calcd for $C_{37}H_{30}N_2O_5$ $[M + Na]^+$ 605.2052, found 605.2055.



3c

Methyl- 5'- (4-chlorobenzoyl)- 1,1''- dimethyl-2,2''- dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-3'-carboxylate, (3d)

The compound **3d** was synthesized starting from **1a** and **2d** following the general procedure described for **3a**; The compound **3d** was obtained as a white solid (144 mg, 95 % yield, *dr* >20:1), MP: 238-242 °C; IR (neat) cm^{-1}: 3059, 2925, 2855, 1707, 1652, 1610, 1467, 1348, 1261, 1182, 1153, 1091, 1007, 879, 844, 813, 731, 697 ;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.51 – 7.40 (m, 3H), 7.27 – 7.08 (m, 4H), 6.99 – 6.93 (m, 1H), 6.85 – 6.78 (m, 1H), 6.57 (dd, *J* = 7.7, 2.0 Hz, 2H), 4.99 (d, *J* = 2.2 Hz, 1H), 3.64 (s, 3H), 3.07 (s, 3H), 3.00 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.1, 176.3, 174.8, 169.8, 145.2, 144.7, 144.4, 142.8, 139.7, 135.5, 131.2, 129.4, 129.0, 125.1, 125.0, 124.5, 124.1, 122.6, 122.5, 108.1, 108.0, , 66.5, 62.2, 56.0, 52.6, 26.4, 25.9; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}N_2O_5Cl$ $[M + Na]^+$ 549.1193, found 549.1199.

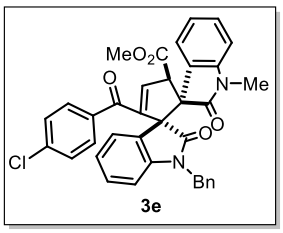


3d

Methyl-1''-benzyl-3'-(4-chlorobenzoyl)-1-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3e)

The compound **3e** was synthesized starting from **1a** and **2e** following the general procedure described for **3a**; The compound **3e** was obtained as a light yellow solid (166 mg, 96 % yield, *dr* >20:1), MP: 212-216 °C.

IR (neat) cm^{-1}: 3058, 2956, 1710, 1649, 1610, 1469, 1432, 1364, 1235, 1151, 1098, 1008, 753;

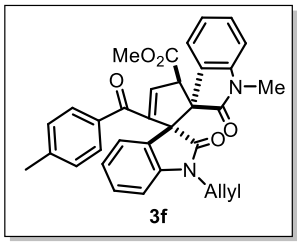


3e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.54 – 7.49 (m, 1H), 7.49 – 7.42 (m, 2H), 7.31 – 7.27 (m, 1H), 7.25 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.23 – 7.18 (m, 3H), 7.16 (d, *J* = 2.2 Hz, 1H), 7.01 – 6.89 (m, 4H), 6.79 (td, *J* = 7.6, 0.9 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 4.97 (d, *J* = 16.1 Hz, 1H), 4.74 (d, *J* = 16.2 Hz, 1H), 3.65 (s, 3H), 3.03 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.2, 176.4, 175.1, 169.8, 144.9, 144.5, 144.2, 143.1, 139.8, 135.5, 135.1, 131.3, 129.4, 129.3, 129.0, 128.7, 127.3, 126.8, 125.3, 125.1, 124.7, 123.0, 122.7, 109.4, 108.2, , 66.5, 62.2, 56.2, 52.6, 44.0, 26.0.HRMS (ESI TOF) *m/z* calcd for $C36H_{27}ClN_2O_5$ $[M + Na]^+$ 625.1506, found 625.1505.

Methyl -1''-allyl-1-methyl-3'-(4-methylbenzoyl)-2, 2''-dioxodispiro[indoline-3, 1'-cyclopentane-2', 3''-indolin]-3'-ene-5'-carboxylate (3f)

The compound **3f** was synthesized starting from **1a** and **2f** following the general procedure



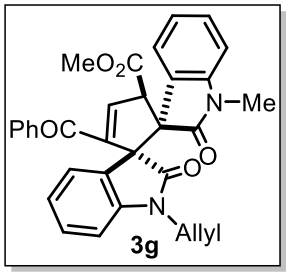
3f

described for **3a**; The compound **3f** was obtained as a white solid (150 mg, 98 % yield, *dr* >20:1), MP: 228-229 °C; IR (neat) cm^{-1}: 3063,2926, 1709, 1650, 1611, 1470, 1359, 1232, 1151, 1098, 995, 929, 876, 811, 750; ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.49 (m, 1H), 7.30 – 7.24 (m, 3H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.08 (td, *J* = 7.7, 1.2 Hz, 1H), 6.95 (td, *J* = 7.6, 1.0 Hz, 1H), 6.80 (td, *J* = 7.6, 1.0 Hz, 1H), 6.58 (dd, *J* = 17.9, 7.6 Hz, 2H), 5.59 (ddt, *J* = 17.2, 10.3, 4.9 Hz, 1H), 5.08 – 5.02 (m, 1H), 5.00 (d, *J* = 2.2 Hz, 1H), 4.93 – 4.83 (m, 1H), 4.41 (ddt, *J* = 16.6, 4.2, 1.9 Hz, 1H), 4.10 (ddt, *J* = 16.4, 5.1, 1.7 Hz, 1H), 3.65 (s, 3H), 3.01 (s, 3H), 2.42 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.4, 176.7, 175.2, 170.3, 144.8, 144.5, 144.4, 143.5, 135.1, 131.2, 130.4, 129.7, 129.6, 129.5, 125.7, 125.6, 125.0, 124.9, 123.0, 122.8, 117.7, 109.4, 108.3, 66.8, 62.5, 56.5, 52.9, 42.8, 26.3, 22.2. HRMS (ESI TOF) *m/z* calcd for $C_{33}H_{28}N_2O_5$ $[M + Na]^+$ 555.1895, found 555.1895.

Methyl-1''-allyl-3'-benzoyl-1-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3g)

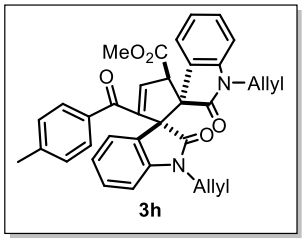
The compound **3g** was synthesized starting from **1a** and **2g** following the general procedure described for **3a**; The compound **3g** was obtained as a white solid (138 mg, 94 % yield, *dr* >20:1), MP : 224-226 °C.

IR (neat) cm^{-1}: 3059, 2921, 1706, 1647, 1608, 1468, 1432, 1360, 1234, 1183, 1105, 995, 926, 878, 832,742,694; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.61 – 7.55 (m, 1H), 7.54 – 7.45 (m, 3H), 7.30 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.08 (td, *J* = 7.7, 1.2 Hz, 1H), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H), 6.81 (td, *J* = 7.6, 1.0 Hz, 1H), 6.59 (dd, *J* = 15.7, 7.8 Hz, 2H), 5.69 – 5.51 (m, 1H), 5.09 – 5.00 (m, 2H), 4.96 – 4.82 (m, 1H), 4.47 – 4.35 (m, 1H), 4.17 – 4.05 (m, 1H), 3.65 (s, 3H), 3.02 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.7, 176.7, 175.2, 170.2, 145.1, 144.8, 144.4, 143.5, 137.6, 133.5, 131.2, 130.2, 129.6, 129.5, 129.0, 125.6, 125.5, 125.0, 124.9, 123.0, 122.8, 117.7, 109.4, 108.3, 66.8, 62.5, 56.4, 52.9, 42.8, 30.1, 26.3; HRMS (ESI TOF) *m/z* calcd for $C_{32}H_{26}N_2O_5$ $[M + H]^+$ 519.1920, found 519.1914.



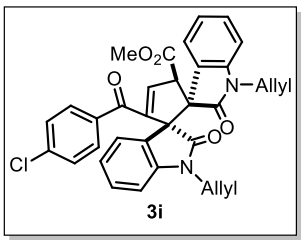
Methyl-1,1''-diallyl- 3'- (4-methylbenzoyl)- 2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate, (3h)

The compound **3h** was synthesized starting from **1b** and **2f** following the general procedure described for **3a**; The compound **3h** was obtained as a light yellow solid (142 mg, 95 % yield, *dr* >20:1), MP: 215-217 °C; IR (neat) cm^{-1}: 3059, 2921, 1706, 1647, 1608, 1468, 1432, 1360, 1234, 1183, 1105, 995, 926, 878, 832; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.62 – 7.53 (m, 1H), 7.37 – 7.26 (m, 3H), 7.23 – 7.15 (m, 2H), 7.10 (td, *J* = 7.8, 1.2 Hz, 1H), 6.98 (td, *J* = 7.6, 1.0 Hz, 1H), 6.81 (td, *J* = 7.6, 1.0 Hz, 1H), 6.61 (dd, *J* = 11.8, 7.7 Hz, 2H), 5.60 (dddd, *J* = 17.0, 12.0, 10.5, 5.3 Hz, 2H), 5.11 – 5.01 (m, 3H), 4.99 – 4.86 (m, 2H), 4.43 (ddt, *J* = 16.6, 4.2, 1.9 Hz, 1H), 4.29 (ddt, *J* = 16.4, 4.9, 1.7 Hz, 1H), 4.12 (dtq, *J* = 13.8, 5.3, 1.6 Hz, 2H), 3.67 (s, 3H), 2.44 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.4, 176.4, 175.3, 170.2, 144.5, 144.5, 144.4, 144.1, 143.5, 135.1, 131.3, 131.2, 130.4, 129.7, 129.5, 125.7, 125.6, 125.4, 125.1, 123.0, 123.0, 118.1, 117.7, 109.4, 109.3, 66.9, 62.4, 56.7, 53.9, 52.8, 42.9, 42.6, 22.2. HRMS (ESI TOF) *m/z* calcd for $C_{35}H_{35}N_2O_5$ $[M + Na]^+$ 581.2052, found 581.2051.



Methyl -1,1''-diallyl-3'-(4-chlorobenzoyl)-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3i)

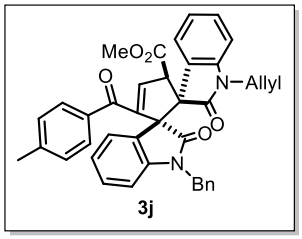
The compound **3i** was synthesized starting from **1b** and **2b** following the general procedure described for **3a**; The compound **3i** was obtained as a light yellow solid (144 mg, 93 % yield, *dr* >20:1), MP: 206-210 °C; IR (neat) cm^{-1}: 3065, 2922, 1705, 1651,1606,1476, 1432, 1359, 1232,1183, 1095, 997,878,832; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.56 – 7.50 (m, 1H), 7.48 – 7.43 (m, 2H), 7.29 – 7.25 (m, 1H), 7.19 – 7.14 (m, 2H), 7.09 (td, *J* = 7.8, 1.2 Hz, 1H), 6.96 (td, *J* = 7.6, 0.9 Hz, 1H), 6.80 (td, *J* = 7.6, 0.9 Hz, 1H), 6.62 – 6.56 (m, 2H), 5.66 – 5.50 (m, 2H), 5.06 (dt, *J* = 10.4, 1.3 Hz, 2H), 5.01 (d, *J* = 2.2 Hz, 1H), 4.97 – 4.87 (m, 2H), 4.44 – 4.35 (m, 1H), 4.24 (d, *J* = 5.0 Hz, 1H), 4.11 (dddt, *J* = 13.6, 10.1, 5.3, 1.6 Hz, 2H), 3.65 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.5, 176.4, 175.1, 170.0, 145.4, 144.5, 144.1, 143.3, 140.1, 135.9, 131.6, 131.3, 131.1, 129.7, 129.6, 129.4, 125.5, 125.4, 125.3, 125.0, 123.1, 123.0, 118.1, 117.8, 109.5, 109.4, 66.8, 62.5, 56.7, 52.9, 42.9, 42.7, 22.8, 14.5. HRMS (ESI TOF) *m/z* calcd for $C_{34}H_{27}ClN_2O_5$ $[M + Na]^+$ 601.1506, found 601.1505.



3i

Methyl-1-allyl-1''-benzyl-3'-(4-methylbenzoyl)-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3j)

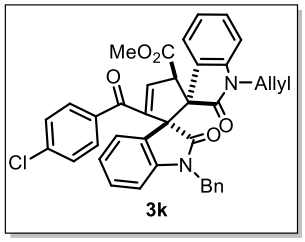
The compound **3j** was synthesized starting from **1b** and **2b** following the general procedure described for **3a**; The compound **3j** was obtained as a light yellow solid (148 mg, 91 % yield, *dr* >20:1), MP: 202-204 °C; IR (neat) cm^{-1}: 3061, 2924, 2856, 1706, 1652, 1607, 1467, 1360, 1233, 1181, 1094, 1003, 927, 877, 844, 813, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.38 – 7.16 (m, 9H), 7.07 – 6.89 (m, 4H), 6.79 (td, *J* = 7.6, 1.0 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 5.60 (ddt, *J* = 17.2, 10.3, 5.1 Hz, 1H), 5.10 – 4.90 (m, 4H), 4.76 (d, *J* = 16.2 Hz, 1H), 4.30 (ddt, *J* = 16.4, 4.9, 1.7 Hz, 1H), 4.13 (ddt, *J* = 16.5, 5.2, 1.6 Hz, 1H), 3.68 (s, 3H), 2.45 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 175.9, 175.1, 169.6, 144.0, 143.8, 143.6, 143.1, 135.0, 134.4, 130.7, 129.8, 129.1, 129.0, 128.8, 128.4, 127.0, 126.5, 125.3, 125.0, 124.9, 124.6, 122.6, 122.5, 117.5, 109.0, 108.8, 66.4, 61.8, 56.2, 52.2, 43.8, 42.1, 29.5, 21.6 ; HRMS (ESI TOF) *m/z* calcd for $C_{39}H_{32}N_2O_5$ $[M + Na]^+$ 631.2209, found 631.2203.



3j

Methyl-1-allyl-1''-benzyl-3'-(4-chlorobenzoyl)-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3k)

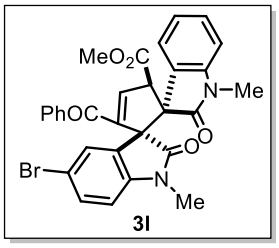
The compound **3k** was synthesized starting from **1b** and **2e** following the general procedure described for **3a**; The compound **3k** was obtained as a light yellow solid (148 mg, 88 % yield, *dr* >20:1), IR (neat) cm^{-1}: 3059, 2923, 2854, 1708, 1649, 1609, 1486, 1462, 1360, 1305, 1232, 1180, 1105, 1001, 928, 876; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.7 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.53 – 7.44 (m, 2H), 7.36 – 7.30 (m, 1H), 7.27 – 7.18 (m, 5H), 7.06 – 6.92 (m, 4H), 6.81 (td, *J* = 7.6, 1.0 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 7.6 Hz, 1H), 5.60 (ddd, *J* = 12.0, 10.4, 5.2 Hz, 1H), 5.14 – 4.90 (m, 4H), 4.79 (d, *J* = 16.1 Hz, 1H), 4.29 (ddt, *J* = 16.4, 5.0, 1.7 Hz, 1H), 4.14 (ddt, *J* = 16.5, 5.2, 1.6 Hz, 1H), 3.68 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.5, 176.5, 175.5, 170.0, 145.3, 144.5, 144.2, 143.4, 140.1, 135.9, 135.5, 131.6, 131.2, 129.7, 129.6, 129.4, 129.1, 127.6, 127.2, 125.7, 125.4, 125.4, 125.1, 123.3, 123.2, 118.2, 109.7, 109.567.0, 66.3, 62.4, 56.8, 52.9, 44.4, 42.7. HRMS (ESI TOF) *m/z* calcd for $C_{38}H_{29}ClN_2O_5$ $[M + Na]^+$ 651.1663, found 651.1660.



3k

Methyl-3'-benzoyl-5''-bromo-1,1''-dimethyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3l)

The compound **3l** was synthesized starting from **1a** and **2h** following the general procedure described for **3a**; The compound **3l** was obtained as a light yellow solid (148 mg, 90 % yield, *dr* >20:1), MP: 283-284 °C; IR (neat) cm^{-1}: 3062, 2959, 1712, 1644, 1609, 1486, 1430, 1345, 1217, 1153, 1097, 1001, 883, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.55 – 7.43 (m, 3H), 7.41 (d, *J* = 1.9 Hz, 1H), 7.29 – 7.17 (m, 4H), 6.97 (td, *J* = 7.7, 0.8 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 4.99 (d, *J* = 2.2 Hz, 1H), 3.67 (s, 3H), 3.07 (d, *J* = 0.9 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 175.7, 174.2, 169.4, 145.4, 144.0, 143.5, 142.2, 136.7, 133.1, 131.9, 129.6, 129.2, 128.5, 127.3, 124.5, 123.7, 122.3, 115.0, 109.1, 107.9, 61.9, 55.6, 52.4, 26.2, 25.7. HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}N_2O_5Br$ $[M + Na]^+$ 593.0687, found 593.0686, 595.0671.

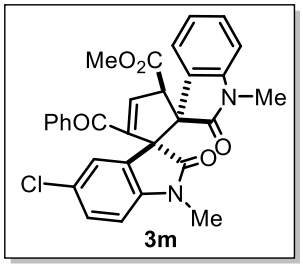


3l

Methyl-3'-benzoyl-5''-chloro-1,1''-dimethyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3m)

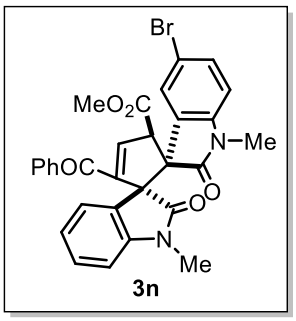
The compound **3m** was synthesized starting from **1a** and **2i** following the general procedure described for **3a**.

The compound **3m** was obtained as a light yellow solid (140 mg, 92 % yield, *dr* >20:1), MP: 290-292°C; IR (neat) cm^{-1}: 2960, 1716, 1643, 1608, 1481, 1355, 1218, 1152, 1097, 1000, 882, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.95 (m, 2H), 7.62 – 7.56 (m, 1H), 7.53 – 7.43 (m, 3H), 7.28 – 7.23 (m, 1H), 7.23 – 7.15 (m, 2H), 7.09 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 4.98 (d, *J* = 2.2 Hz, 1H), 3.65 (s, 3H), 3.05 (d, *J* = 4.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.2, 174.6, 169.7, 145.7, 144.3, 143.3, 142.6, 137.0, 133.4, 129.9, 129.5, 129.3, 128.8, 128.0, 126.9, 124.9, 124.9, 124.1, 122.6, 108.9, 108.2, 62.1, 56.0, 52.7, 29.8, 26.6, 26.0; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}ClN_2O_5$ $[M + Na]^+$ 549.1192, found 549.1196.



Methyl-3'-benzoyl-5-bromo-1,1''-dimethyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate) (3n)

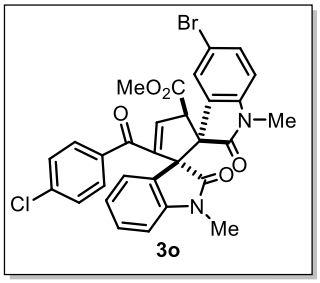
The compound **3n** was synthesized starting from **1c** and **2a** following the general procedure described for **3a**; The compound **3n** was obtained as a light yellow solid (122 mg, 91 % yield, *dr* >20:1), MP: 241-243 °C; IR (neat) cm^{-1}: 3065, 2928, 1712, 1651, 1610, 1484, 1347, 1231, 1151, 1099, 1025, 878, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.99 (m, 2H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.20 – 7.12 (m, 2H), 6.84 (td, *J* = 7.6, 0.9 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 2.2 Hz, 1H), 3.69 (s, 3H), 3.16 (s, 3H), 3.01 (s, 3H);$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1, 175.8, 174.7, 169.8, 144.7, 143.5, 142.8, 137.1, 133.3, 132.2, 129.9, 129.5, 128.7, 127.3, 124.8, 124.5, 122.6, 115.2, 109.4, 108.2, 66.5, 62.1, 56.0, 52.7, 26.5, 26.0.; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}BrN_2O_5$ $[M + Na]^+$ 593.0687, found 593.0693,595.0673.



Methyl-5-bromo-3'-(4-chlorobenzoyl)-1,1''-dimethyl-2,2''-ioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3o)

The compound **3o** was synthesized starting from **1c** and **2d** following the general procedure described for **3a**; The compound **3o** was obtained as a light yellow solid (124 mg, 88 % yield, *dr* >20:1), MP: 277-280 °C.

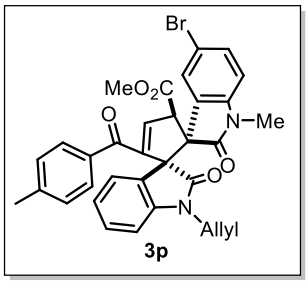
IR (neat) cm^{-1}: 3065, 2926, 1711, 1653, 1609, 1483, 1427, 1344, 1243, 1149, 1095, 1010, 877, 814; ^1H NMR (400 MHz,$CDCl_3$) δ 8.04 – 7.99 (m, 2H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.34 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.30 – 7.22 (m, 1H), 7.20 – 7.12 (m, 2H), 6.84 (td, *J* = 7.6, 0.9 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 1H), 5.00 (d, *J* = 2.2 Hz, 1H), 3.69 (s, 3H), 3.16 (s, 3H), 3.01 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.0, 175.7, 174.6, 169.7, 144.6, 143.4, 142.7, 137.0, 133.2, 132.1,129.8, 129.4, 128.6, 127.2, 124.7, 124.4, 122.5, 115.1, 109.3, 108.1, 66.4, 62.1, 55.9, 52.6, 26.3, 25.9; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{22}BrClN_2O_5$ $[M + Na]^+$ 627.0298, found 627.0306, 629.0283.



3o

Methyl-1''-allyl-5-bromo-1-methyl-3'-(4-methylbenzoyl)-2,2'' dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3p)

The compound **3p** was synthesized starting from **1c** and **2f** following the general procedure described for **3a**; The compound **3p** was obtained as a white solid (136 mg, 95 % yield, *dr* >20:1), MP: 228-230 °C; IR (neat) cm^{-1}: 2926, 1711,1647, 1608, 1481, 1429, 1353, 1232, 1151, 1103, 1046, 983, 925, 880, 821; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.38 – 7.25 (m, 4H), 7.13 (dd, *J* = 9.6, 1.7 Hz, 2H), 6.82 (td, *J* = 7.6, 0.9 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 1H), 5.71 (ddd, *J* = 12.1, 10.5, 5.2 Hz, 1H), 5.25 – 5.11 (m, 1H), 4.98 (dd, *J* = 16.1, 1.5 Hz, 2H), 4.59 – 4.44 (m, 1H), 4.20 – 4.05 (m, 1H), 3.69 (s, 3H), 3.02 (s, 3H), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 190.8, 175.9, 174.6, 169.8, 144.2, 144.1, 143.8, 143.5, 143.1, 134.6, 132.2, 130.7, 130.0, 129.4, 127.7, 127.4, 124.9, 124.6, 122.6, 117.5, 115.4, 109.4, 109.1, 66.3, 62.0, 56.2, 52.6, 42.6, 29.8, 26.0, 21.8; HRMS (ESI TOF) *m/z* calcd for $C_{33}H_{27}BrN_2O_5$ $[M + Na]^+$ 633.1001, found 633.0999.

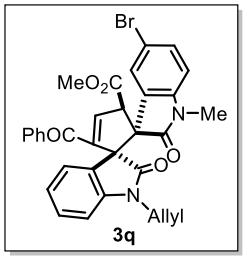


3p

Methyl-1''-allyl-3'-benzoyl-5-bromo-1-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3q)

The compound **3q** was synthesized starting from **1c** and **2g** following the general procedure described for **3a**.

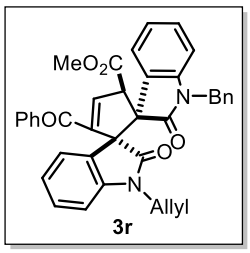
The compound **3q** was obtained as a light yellow solid (126 mg, 90 % yield, *dr* >20:1). MP: 258-260 °C. IR (neat) cm^{-1}: 3064, 2926,1709, 1649, 1608, 1484, 1431, 1346, 1232, 1152, 1102, 1059, 983, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 2H), 7.69 – 7.55 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.35 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.21 – 7.09 (m, 2H), 6.84 (td, *J* = 7.6, 1.0 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 5.71 (ddd, *J* = 12.1, 10.4, 5.2 Hz, 1H), 5.23 – 5.12 (m, 1H), 4.99 (dd, *J* = 17.8, 1.5 Hz, 2H), 4.59 – 4.43 (m, 1H), 4.14 (ddt, *J* = 16.6, 5.2, 1.6 Hz, 1H), 3.69 (s, 3H), 3.03 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.5, 176.2, 174.8, 170.1, 144.8, 144.4, 143.9, 143.4, 137.5, 133.6, 132.5, 131.0, 130.2, 129.7, 129.0, 128.1, 127.7, 125.2, 125.0, 122.9, 117.9, 115.8, 109.8, 109.5, 66.7, 62.4, 56.5, 53.0, 42.9, 30.1, 26.4; HRMS (ESI TOF) *m/z* calcd for $C_{32}H_{25}BrN_2O_5$ $[M + Na]^+$ 619.0845, found 619.0844.



3q

Methyl- 1''- allyl-3'-benzoyl-1-benzyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3r)

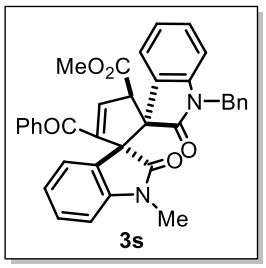
The compound **3r** was synthesized starting from **1d** and **2g** following the general procedure described for **3a**; The compound **3r** was obtained as a white solid (122 mg, 87 % yield, *dr* >20:1), 202-206 °C; IR (neat) cm^{-1}: 3059, 2923, 2854, 1708, 1649, 1609, 1486, 1462, 1360, 1305, 1232, 1180, 1105, 1001, 928, 876. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.62 – 7.54 (m, 2H), 7.53 – 7.44 (m, 2H), 7.34 – 7.30 (m, 1H), 7.22 – 7.16 (m, 4H), 7.10 (dtd, *J* = 20.8, 7.8, 1.2 Hz, 2H), 7.02 – 6.91 (m, 3H), 6.75 (td, *J* = 7.6, 0.9 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H), 5.60 (ddt, *J* = 17.2, 10.3, 4.8 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.95 – 4.87 (m, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.46 – 4.35 (m, 1H), 4.18 – 4.08 (m, 1H), 3.62 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 191.7, 176.8, 175.2, 170.1, 145.2, 144.5, 144.2, 143.5, 137.5, 135.7, 133.6, 131.1, 130.2, 129.6, 129.5, 129.0, 127.7, 127.5, 125.7, 125.7, 125.5, 125.1, 123.3, 123.1, 117.8, 109.6, 109.5, 66.9, 62.5, 56.9, 52.9, 44.2, 42.8, 30.1. HRMS (ESI TOF) *m/z* calcd for $C_{38}H_{30}N_2O_5$ $[M + Na]^+$ 617.2052, found 617.2050.



3r

Methyl-3'-benzoyl-1-benzyl-1''-methyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3s)

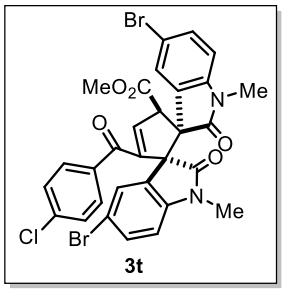
The compound **3s** was synthesized starting from **1d** and **2a** following the general procedure described for **3a**; The compound **3s** was obtained as a white solid (116 mg, 86 % yield, *dr* >20:1), IR (neat) cm^{-1}: 3062, 2954, 1710, 1653, 1609, 1488, 1463, 1362, 1233, 1179, 1094, 1006, 878. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.60 – 7.54 (m, 2H), 7.51 – 7.45 (m, 2H), 7.31 – 7.27 (m, 1H), 7.22 – 7.18 (m, 4H), 7.16 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.07 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 – 6.93 (m, 3H), 6.76 (td, *J* = 7.6, 1.0 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.44 – 6.40 (m, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 3.62 (s, 3H), 3.10 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.4, 176.4, 175.1, 169.8, 145.0, 144.8, 143.9, 143.1, 137.2, 135.4, 133.3, 129.9, 129.3, 129.3, 128.7, 127.4, 127.2, 125.4, 125.1, 124.4, 123.0, 122.6, 109.3, 108.2, 66.7, 66.0, 62.2, 56.6, 52.6, 43.8, 26.5, 15.4. HRMS (ESI TOF) *m/z* calcd for $C_{36}H_{28}N_2O_5$ $[M + Na]^+$ 591.1896, found 591.1893.



3s

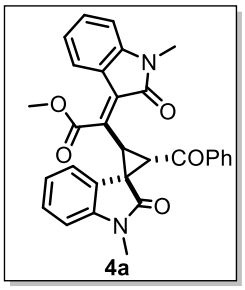
Methyl-5,5''-dibromo-3'-(4-chlorobenzoyl)-1,1''-dimethyl-2,2''-dioxodispiro[indoline-3,1'-cyclopentane-2',3''-indolin]-3'-ene-5'-carboxylate (3t)

The compound **3t** was synthesized starting from **1c** and **2j** following the general procedure described for **3a**; The compound **3t** was obtained as a light yellow solid (130 mg, 81 % yield, *dr* >20:1), IR (neat) cm^{-1}: 3059, 2952, 1708, 1650, 1609, 1465, 1356, 1229, 1093, 1008, 877, 810. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.88 (m, 2H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.26 (m, 1H), 7.17 (dd, *J* = 2.2, 0.6 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 2H), 4.96 (d, *J* = 2.2 Hz, 1H), 3.69 (s, 3H), 3.12 (s, 3H), 3.05 (s, 3H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 189.7, 175.5, 169.4, 145.6, 143.6, 142.1, 140.0, 135.2, 132.4, 131.2, 129.2, 127.5, 127.2, 126.7, 115.4, 115.3, 109.6, 66.3, 62.0, 55.8, 52.8, 26.5, 26.1; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{21}Br_2ClN_2O_5$ $[M + Na]^+$ 704.9403, found 704.9401,706.9382,708.9369.



3t

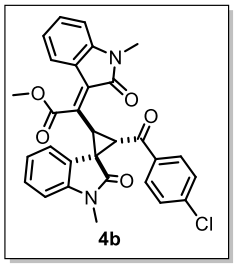
Methyl 2-2-benzoyl-1'-methyl-2'-oxospiro [cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-1-methyl-2-oxoindolin-3-ylidene)acetate (4a)



Red solid (120 mg, 85 % yield, *dr* >20:1). MP: 165-167 °C; *dr* >20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 7.55 – 7.49 (m, 2H), 7.46 – 7.37 (m, 3H), 7.26 (dtd, *J* = 14.2, 7.8, 1.2 Hz, 2H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.96 (td, *J* = 7.7, 1.1 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 4.52 (d, *J* = 8.5 Hz, 1H), 4.07 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.24 (s, 3H), 3.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 172.9, 167.5, 166.9, 144.3, 144.2, 137.4, 135.5, 133.9, 131.2, 130.9, 129.1, 128.9, 128.2, 126.1, 124.7, 123.2, 123.1, 122.5, 120.4, 108.4, 108.4, 52.9, 44.7, 42.8, 34.0, 30.1, 27.1, 26.4.; HRMS (ESI TOF) *m/z* calcd for $C_{30}H24N_2O_5$ $[M + Na]^+$ 515.1577, found 515.1578.

Methyl 2-2-(4-chlorobenzoyl)-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-1-methyl-2-oxoindolin-3-ylidene)acetate (4b)

The compound **4b** was synthesized starting from **1a** and **2d** following the general procedure described for **4a**; The compound **4b** was obtained as a yellow solid (125 mg, 82 % yield, *dr* >20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.21 (m, 3H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 6.97 (td, *J* = 7.7, 1.0 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 4.48 (d, *J* = 8.4 Hz, 1H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.25 (s, 3H), 3.08 (s, 3H): ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.5, 172.5, 167.1, 166.6, 144.0, 143.9, 140.1, 135.4, 134.9, 131.0, 130.8, 130.0, 129.1, 128.0, 125.6, 124.5, 122.8, 122.8, 122.3, 120.1, 108.2, 108.1, 52.5, 44.4, 42.4, 33.8, 26.8, 26.1; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}N_2O_5Cl$ $[M + Na]^+$ 549.1193, found 549.1199.

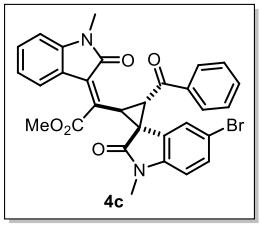


Methyl 2-2-benzoyl-5'-bromo-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-1-methyl-2-oxoindolin-3-ylidene)acetate (4c)

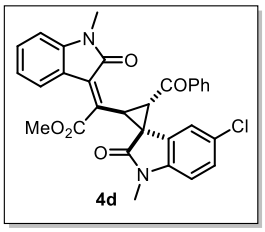
The compound **4c** was synthesized starting from **1a** and **2h** following the general procedure described for **4a**; The compound **4c** was obtained as a yellow solid (130 mg, 79 % yield, *dr* >20:1), MP: 228-229 °C. ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.45 – 7.39 (m, 2H), 7.35 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.28 (td, *J* =

7.7, 1.2 Hz, 1H), 6.96 (td, *J* = 7.7, 1.0 Hz, 1H), 6.71 (dd, *J* = 9.8, 8.2 Hz, 2H), 4.34 (d, *J* = 8.5 Hz, 1H), 4.05 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H), 3.21 (s, 3H), 3.07 (s, 3H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ 191.9, 171.8, 166.8, 166.1, 143.8, 142.8, 136.7, 133.9, 133.4, 130.7, 130.5, 130.4, 128.5, 128.3, 127.5, 125.8, 124.1, 121.9, 119.7, 115.2, 109.1, 107.8, 52.3, 43.7, 42.1, 33.7, 26.5, 25.7. HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}N_2O_5Br$ $[M + Na]^+$ 593.0687, found 593.0686, 595.0671.



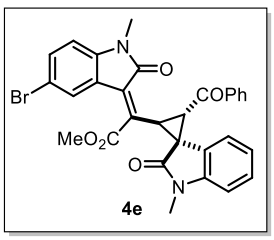
Methyl 2-2-benzoyl-5'-chloro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-1-methyl-2-oxoindolin-3-ylidene)acetate (4d)



The compound **4d** was synthesized starting from **1a** and **2i** following the general procedure described for **4a**; The compound **4d** was obtained as a red solid (126 mg, 83 % yield, *dr* >20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.60 – 7.50 (m, 2H), 7.49 – 7.38 (m, 3H), 7.33 – 7.26 (m, 1H), 7.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.96 (td, *J* = 7.7, 1.0 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 2H), 4.36 (d, *J* = 8.5 Hz, 1H), 4.05 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.22 (s, 3H), 3.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.6, 172.5, 167.4, 166.8, 144.4, 142.9, 137.3, 134.7, 134.0, 131.4, 131.2, 129.1, 128.9, 128.4, 128.2, 127.8, 124.8, 123.8, 122.6, 120.3, 109.2, 108.5, 52.9, 44.5, 42.7, 34.3, 27.2, 26.4; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}ClN_2O_5$ $[M + Na]^+$ 549.1192, found 549.1196.

Methyl-2-2-benzoyl-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-5-bromo-1-methyl-2-oxoindolin-3-ylidene)acetate (4e)

The compound **4e** was synthesized starting from **1c** and **2a** following the general procedure



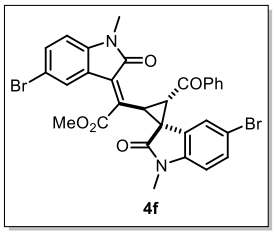
described for **4a**; The compound **4e** was obtained as a yellow solid (100 mg, 75 % yield, *dr* >20:1). ^{1}H NMR (400 MHz , $CDCl_3$) δ 8.00 – 7.89 (m, 2H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.52 (tt, *J* = 6.9, 1.2 Hz, 1H), 7.45 – 7.37 (m, 4H), 7.25 (td, *J* = 7.7, 1.2 Hz, 1H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 4.49 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.25 (s, 3H), 3.07 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.4, 172.6, 166.7, 166.0, 143.9, 142.9, 137.1, 137.1, 133.6, 133.4, 129.7, 128.8, 128.6, 128.0, 127.8, 125.6, 122.9, 122.8, 121.8, 52.7, 44.53, 42.6,

33.6, 26.8, 26.2; HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{23}BrN_2O_5$ $[M + Na]^+$ 593.0687, found 593.0693.

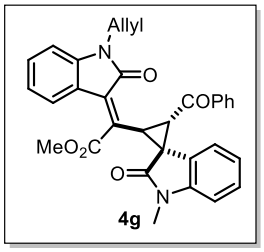
Methyl 2-2-benzoyl-5'-bromo-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-5-bromo-1-methyl-2-oxoindolin-3-ylidene)acetate (4f)

The compound **4f** was synthesized starting from **1c** and **2h** following the general procedure described for **4a**; The compound **4e** was obtained as a yellow solid (110 mg, 72 % yield, *dr* >20:1). ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.94 (dd, J = 8.4, 1.2 Hz, 2H), 7.69 (d, J = 1.9 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.47 – 7.36 (m, 4H), 6.72 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 4.31 (d, J = 8.4 Hz, 1H), 4.03 (d, J = 8.5 Hz, 1H), 3.91 (s, 3H), 3.22 (s, 3H), 3.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.5, 172.5, 167.0, 166.3, 143.4, 137.3, 136.5, 134.1, 133.9, 131.2, 130.4, 129.2, 129.0, 128.2, 128.1, 126.6, 122.0, 116.0, 115.3, 109.8, 109.8, 53.1, 44.5, 42.9, 34.3, 27.2, 26.6. HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{22}Br_2N_2O_5$ $[M + Na]^+$ 670.9793, found 670.9797, 672.9756.



Methyl- 2- ((*E*)-1- allyl-2- oxoindolin-3- ylidene)-2- 2-benzoyl-1'-methyl-2 '-oxospiro [cyclopropane-1, 3'-indolin]-3-yl)acetate (4g)

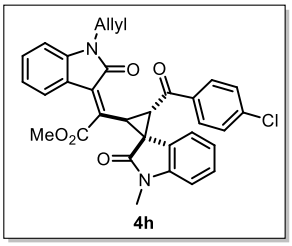
The compound **4g** was synthesized starting from **1b** and **2a** following the general procedure described for **4a**; The compound **4g** was obtained as a yellow solid (115 mg, 83 % yield, *dr* >20:1). ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 7.55 – 7.46 (m, 2H), 7.45 – 7.37 (m, 3H), 7.24 (td, *J* = 7.9, 1.2 Hz, 2H), 7.06 – 7.00 (m, 1H), 6.96 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.71 (ddd, *J* = 11.6, 10.6, 5.3 Hz, 1H), 5.18 – 5.06 (m, 2H), 4.52 (d, *J* = 8.4 Hz, 1H), 4.23 (dt, *J* = 3.5, 1.6 Hz, 2H), 4.08 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.23 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.2, 172.2, 166.9, 165.9, 143.7, 142.9, 136.8, 134.9, 133.3, 131.2, 130.5, 130.1, 128.4, 128.3, 127.5, 125.5, 124.0, 122.6, 122.4, 121.9, 119.9, 117.1, 108.7, 107.7, 52.3, 44.1, 42.1, 41.7, 33.3, 26.4. HRMS (ESI TOF) *m/z* calcd for $C_{32}H_{26}N_2O_5$ $[M + Na]^+$ 541.1739, found 539.1742.



Methyl 2-((*E*)-1-allyl-2-oxoindolin-3-ylidene)-2-2-(4-chlorobenzoyl)-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)acetate (4h)

The compound **4h** was synthesized starting from **1b** and **2a** following the general procedure described for **4a**; The compound **4g** was obtained as a yellow solid (118 mg, 80 % yield, *dr*

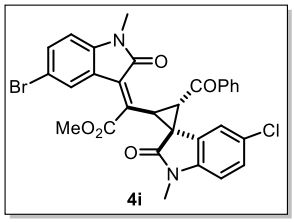
>20:1). ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.89 – 7.84 (m, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.27 – 7.22 (m, 2H), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H), 6.96 (td, *J* = 7.8, 1.0 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.71 (ddt, *J* = 16.9, 10.4, 5.1 Hz, 1H), 5.18 – 5.09 (m, 2H), 4.48 (d, *J* = 8.4 Hz, 1H), 4.24 (dt, *J* = 5.0, 2.1 Hz, 2H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.24 (s, 3H);



^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.2, 172.2, 166.9, 165.9, 143.7, 143.0, 139.8, 135.1, 134.7, 131.2, 130.6, 130.3, 129.7, 128.8, 127.7, 125.3, 124.2, 122.6, 122.5, 121.9, 119.9, 117.2, 108.8, 107.9, 52.3, 44.1, 42.1, 41.8, 33.4, 26.5. HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{25}ClN_2O_5$ $[M + Na]^+$ 575.1350, found 575.1352.

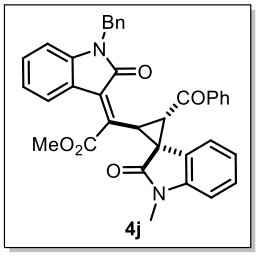
Methyl 2-2-benzoyl-5'-chloro-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-5-bromo-1-methyl-2-oxoindolin-3-ylidene)acetate (4i)

The compound **4i** was synthesized starting from **1c** and **2i** following the general procedure described for **4a**; The compound **4i** was obtained as a red solid (100 mg, 70 % yield, *dr* >20:1). ^{1}H NMR (400 MHz , $CDCl_3$) δ 7.94 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.47 – 7.40 (m, 4H), 7.23 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 4.33 (d, *J* = 8.4 Hz, 1H), 4.04 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.23 (s, 3H), 3.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.2, 172.2, 166.7, 166.0, 143.0, 142.6, 137.0, 136.3, 133.8, 133.6, 130.0, 128.9, 128.7, 128.3, 128.0, 127.9, 127.4, 123.6, 121.7, 115.0, 109.5, 109.0, 52.8, 44.3, 42.5, 34.0, 26.9, 26.2. HRMS (ESI TOF) *m/z* calcd for $C_{30}H_{22}BrClN_2O_5$ $[M + Na]^+$ 627.0298, found 627.0294, 629.0270.



Methyl 2-2-benzoyl-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)-2-((*E*)-1-benzyl-2-oxoindolin-3-ylidene)acetate (4j)

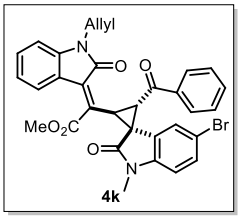
The compound **4j** was synthesized starting from **1d** and **2a** following the general procedure described for **4a**; The compound **4j** was obtained as a Yellow solid (95 mg, 70 % yield, *dr* >20:1).,^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 2H), 7.55 – 7.48 (m, 2H), 7.45 – 7.37 (m, 3H), 7.28 – 7.25 (m, 2H), 7.24 (dd, *J* = 1.9, 0.8 Hz, 2H), 7.15 (dd, *J* = 5.4, 2.7 Hz, 3H), 7.07 – 7.01 (m, 1H), 6.97 – 6.90 (m, 1H), 6.85 – 6.80 (m, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 4.74 (d, *J* = 15.9 Hz, 1H), 4.50 (d, *J* = 8.4 Hz, 1H), 4.08 (d,



J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.21 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.6, 172.6, 167.3, 166.6, 144.0, 143.1, 137.1, 135.7, 135.3, 133.6, 130.8, 130.3, 128.8, 128.6, 127.9, 127.6, 127.1, 125.9, 124.4, 122.9, 122.8, 122.3, 120.3, 109.2, 108.1, 52.6, 44.4, 43.4, 42.4, 33.6, 26.7. HRMS (ESI TOF) *m/z* calcd for $C_{36}H_{28}N_2O_5$ $[M + Na]^+$ 591.1896, found 591.1895.

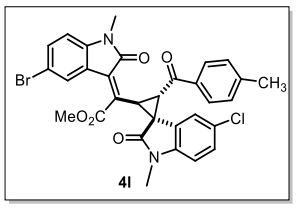
Methyl 2-((*E*)-1-allyl-2-oxoindolin-3-ylidene)-2--2-benzoyl-5'-bromo-1'-methyl-2'-oxospiro[cyclopropane-1,3'-indolin]-3-yl)acetate (4k)

The compound **4k** was synthesized starting from **1b** and **2h** following the general procedure described for **4a**; The compound **4k** was obtained as a yellow solid (115 mg, 72 % yield, *dr* >20:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.57 – 7.48 (m, 3H), 7.45 – 7.40 (m, 2H), 7.36 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.25 (td, *J* = 7.8, 1.1 Hz, 2H), 6.96 (td, *J* = 7.7, 1.0 Hz, 1H), 6.72 (dd, *J* = 13.6, 8.0 Hz, 2H), 5.72 (ddt, *J* = 17.1, 10.3, 5.1 Hz, 1H), 5.17 – 5.09 (m, 2H), 4.32 (d, *J* = 8.4 Hz, 1H), 4.23 (tt, *J* = 5.0, 1.7 Hz, 2H), 4.04 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 192.3, 172.1, 167.2, 166.1, 143.4, 143.2, 137.0, 134.3, 133.7, 131.4, 131.0, 130.8, 130.7, 128.8, 128.7, 127.9, 126.2, 124.5, 122.3, 120.1, 117.4, 115.5, 109.4, 109.1, 52.7, 44.0, 42.4, 42.0, 34.0, 26.8. HRMS (ESI TOF) *m/z* calcd for $C_{32}H_{25}BrN_2O_5$ $[M + Na]^+$ 619.0845, found 619.0844.



Methyl 2-((*E*)-5-bromo-1-methyl-2-oxoindolin-3-ylidene)-2--5'-chloro-1'-methyl-2-(4-methylbenzoyl)-2'-oxospiro [cyclopropane-1, 3'-indolin]-3-yl)acetate (4l)

The compound **4l** was synthesized starting from **1b** and **2k** following the general procedure described for **4a**; The compound **4l** was obtained as a red solid (130 mg, 75 % yield, *dr* >20:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.21 (td, *J* = 6.1, 3.0 Hz, 3H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 4.32 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.22 (s, 3H), 3.07 (s, 3H), 2.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 191.6, 172.3, 166.7, 165.9, 144.8, 143.0, 142.6, 136.4, 134.5, 133.5, 129.9, 129.5, 128.8, 128.2, 127.9, 127.8, 127.5, 123.5, 121.7, 114.9, 109.5, 108.9, 52.7, 44.2, 42.4, 33.9, 26.9, 26.2, 21.8; HRMS (ESI TOF) *m/z* calcd for $C_{31}H_{24}BrClN_2O_5$ $[M + Na]^+$ 641.0455, found 641.0454.



2.8 Appendix II ^{1}H, ^{13}C spectral data of representative compounds

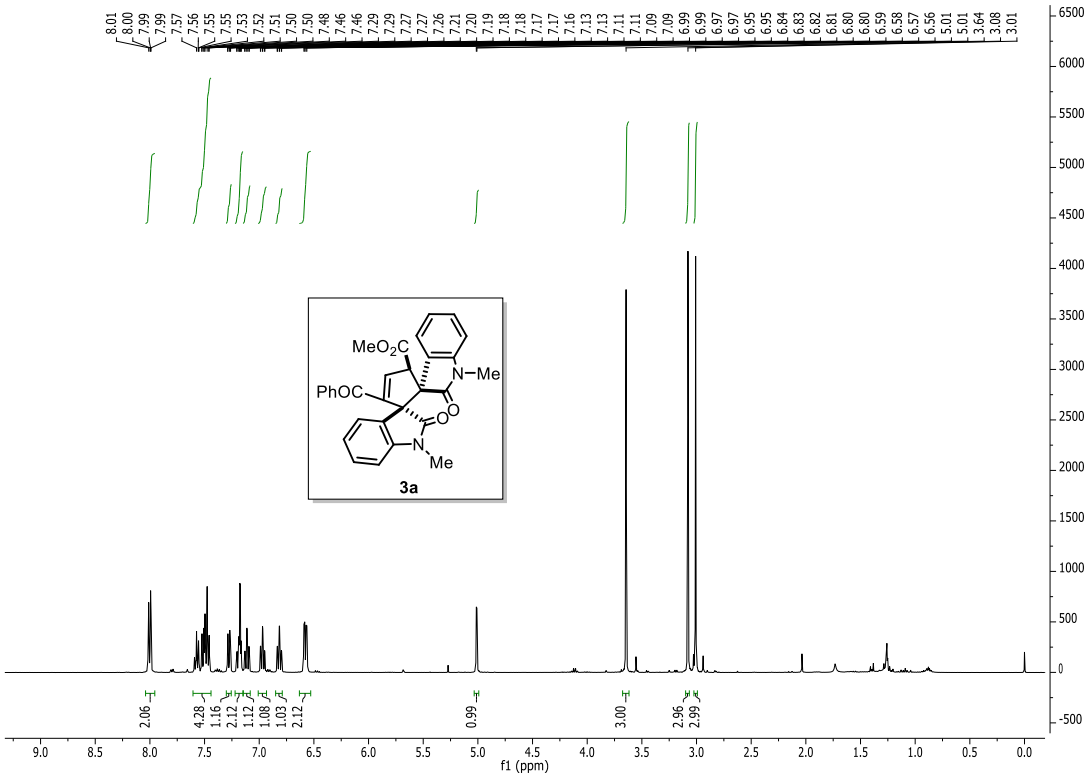


Figure AII.1 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

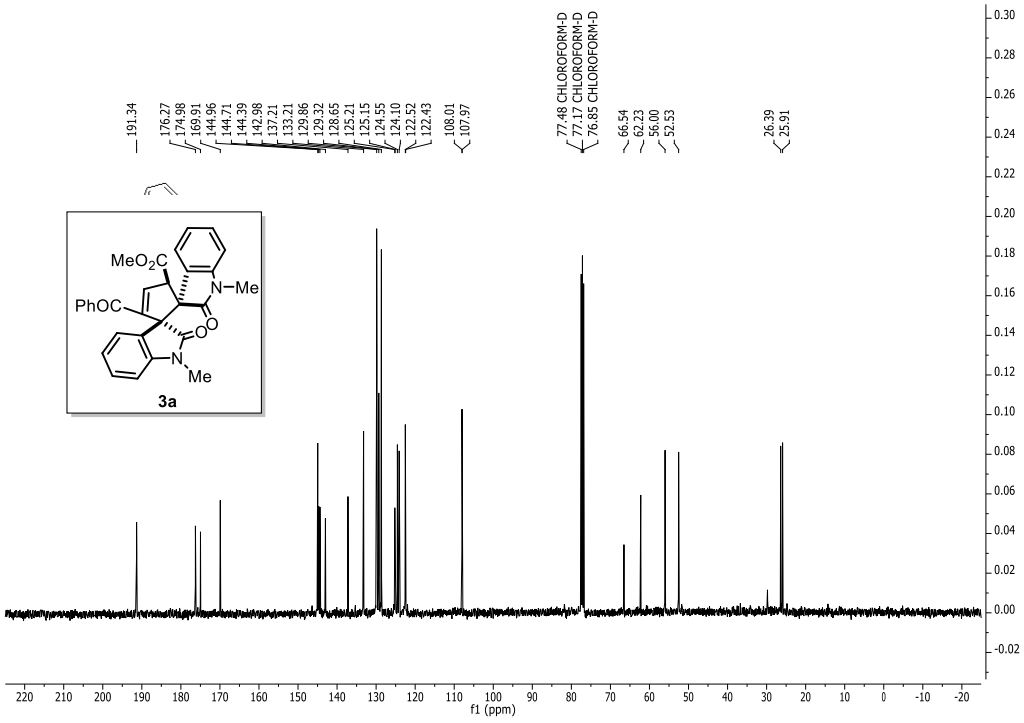


Figure AII.2 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

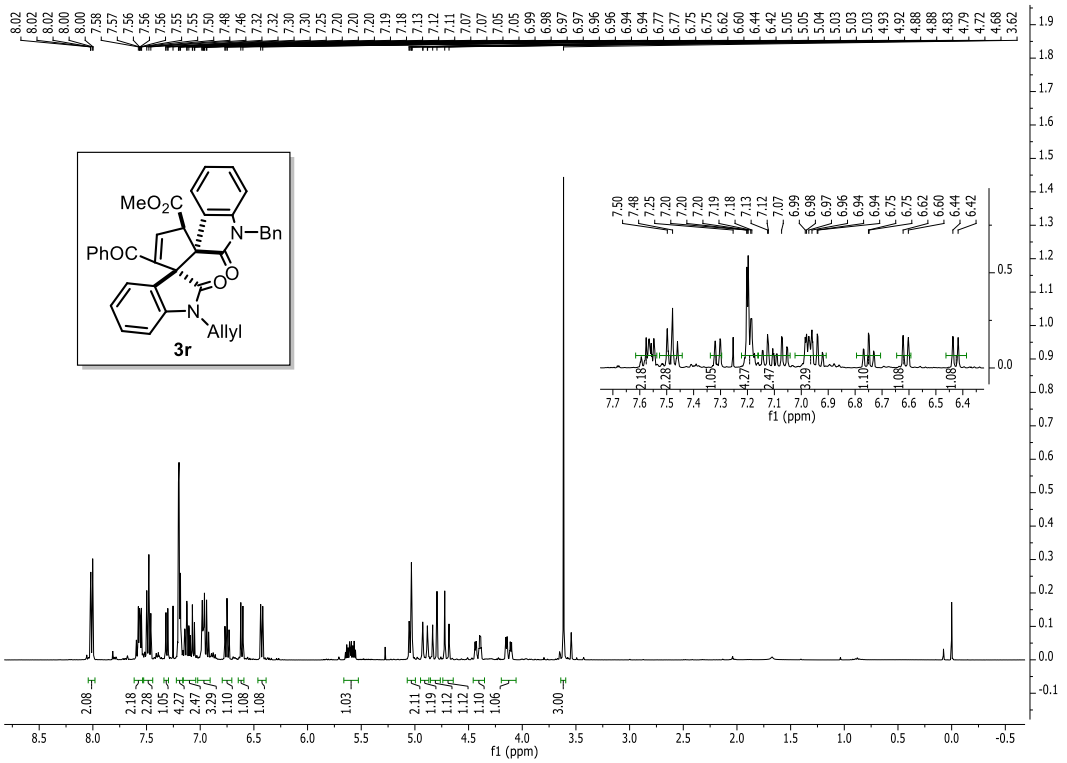


Figure AII.3 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3r**

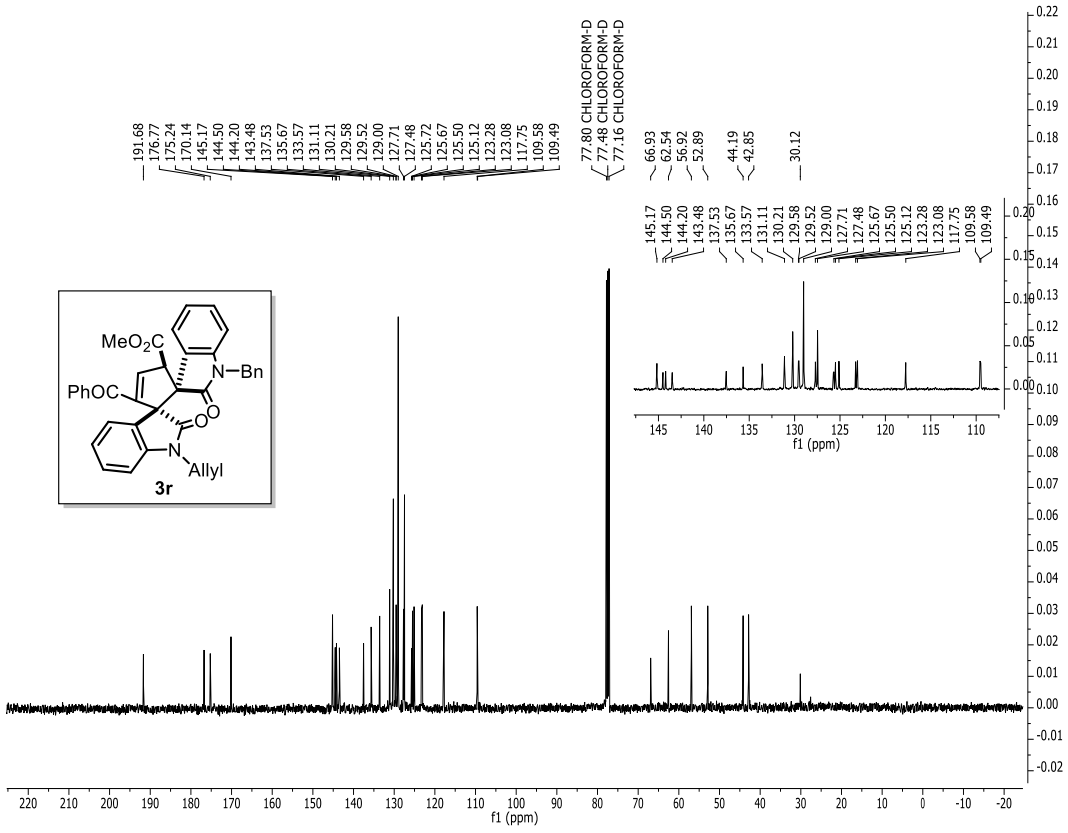


Figure AII.4 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3r**

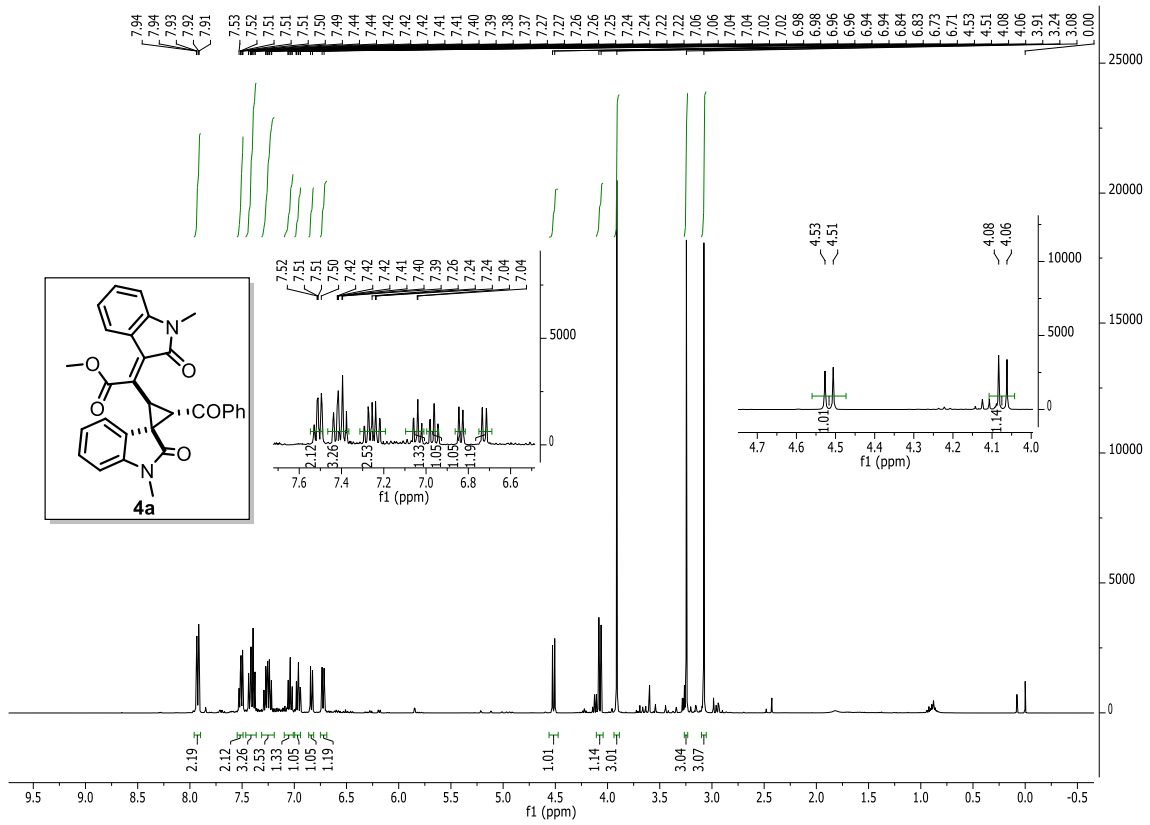


Figure AII.5 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

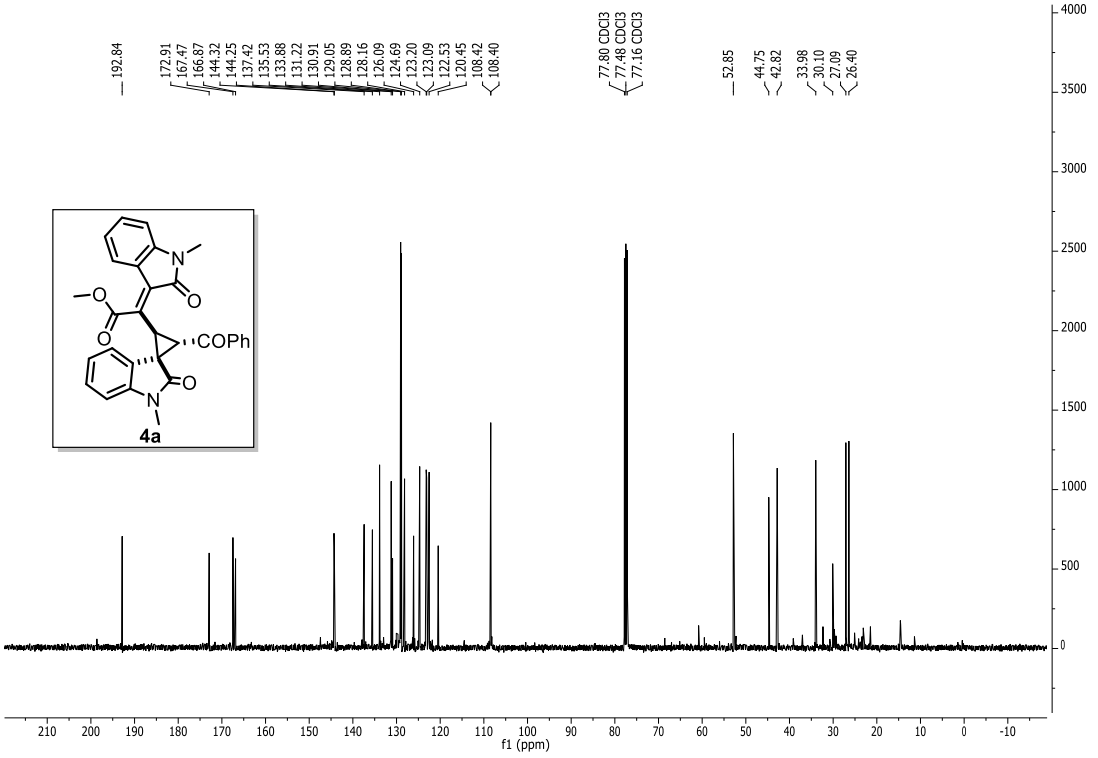


Figure AII.6 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**

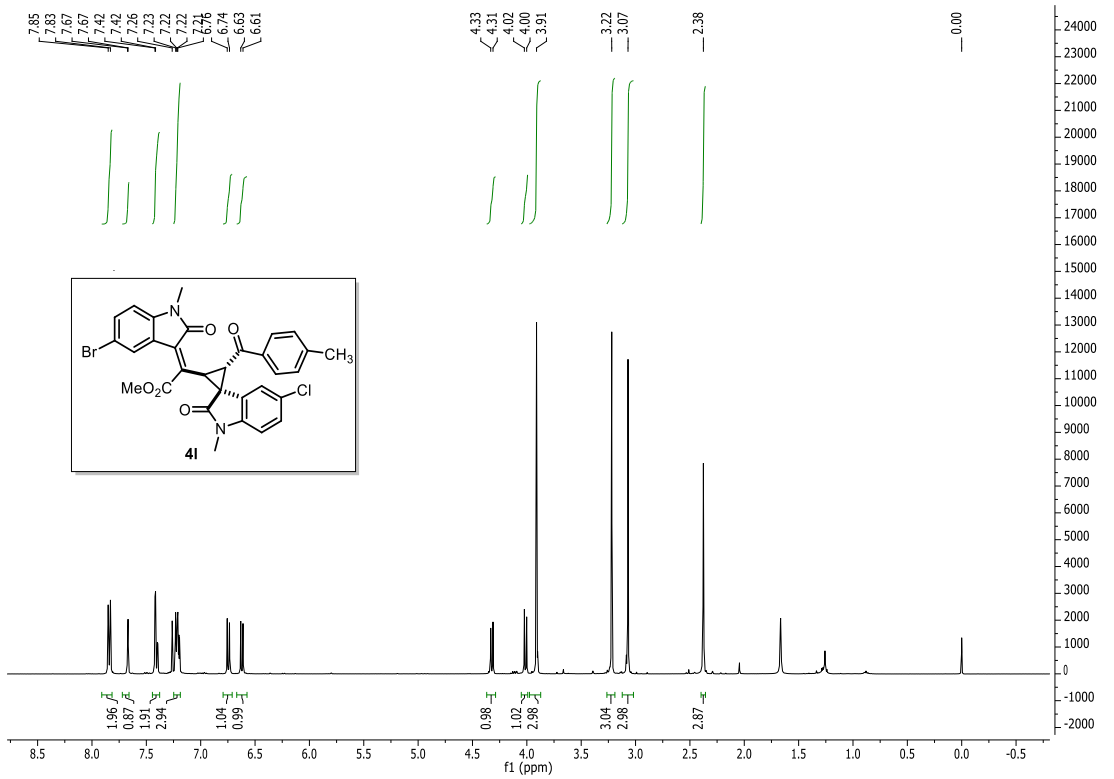


Figure AII.7 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4l**

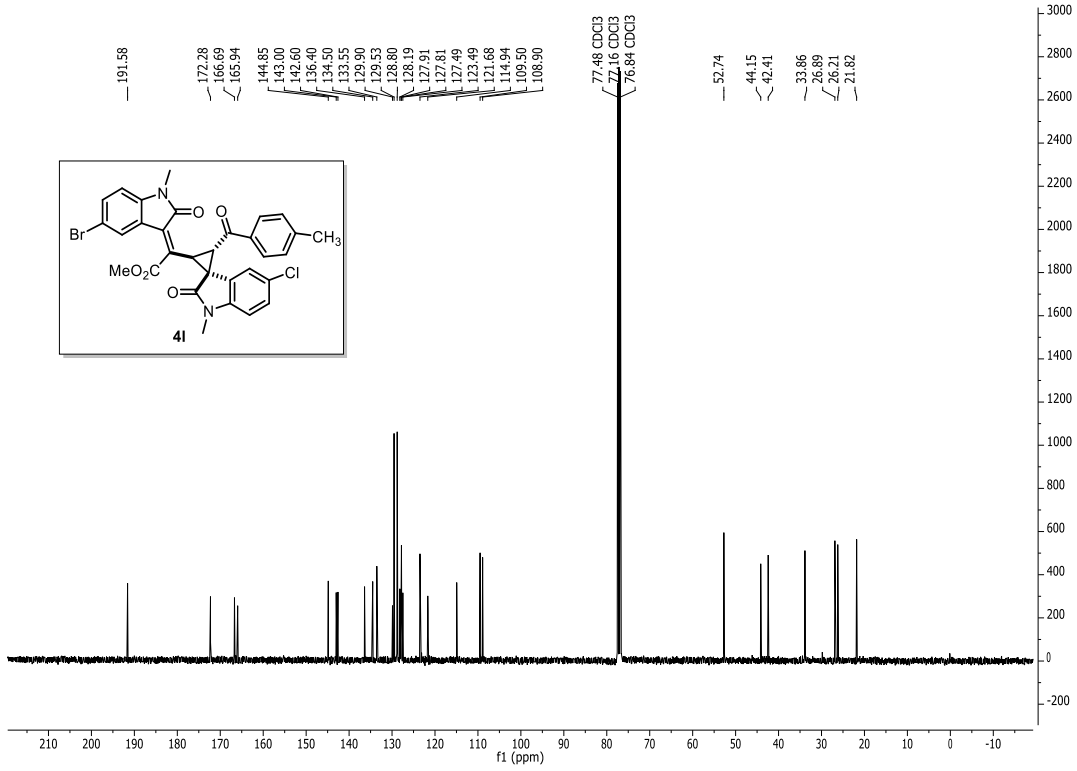


Figure AII.8 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4l**

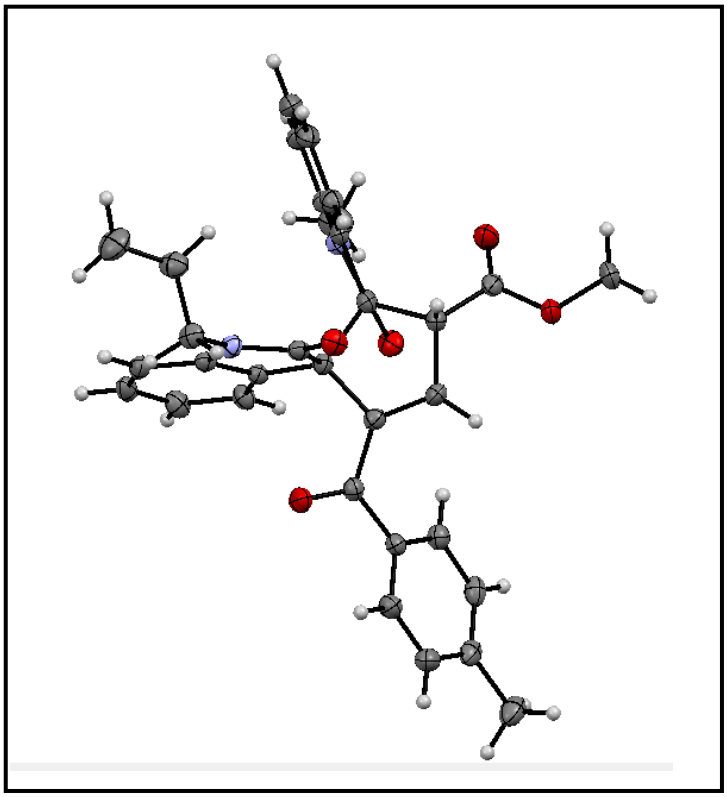


Figure AII.9 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3f**

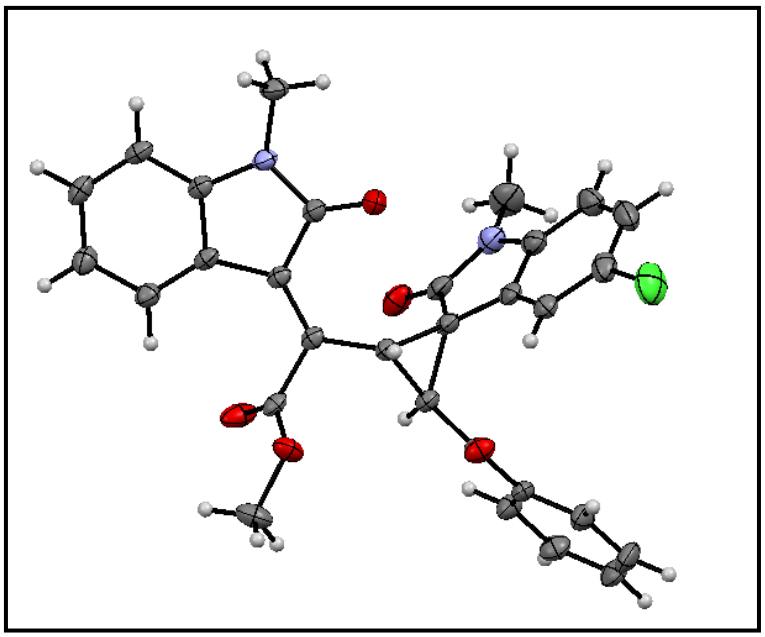


Figure AII.10 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **4d**

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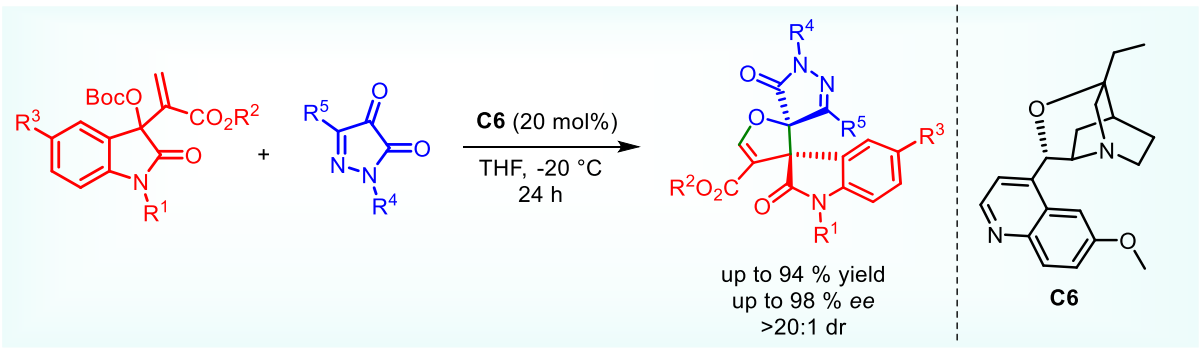
3

Enantioselective Synthesis of Spirooxindole Dihydrofuran Fused Pyrazolones via [3+2] annulation of Morita-Baylis–Hillman Carbonate with Pyrazolone 4, 5-diones

Abstract

A Lewis base catalyzed enantioselective [3 + 2] annulation between istain based Morita-Baylis-Hillman (MBH) carbonate and pyrazolone 4, 5-dione has been developed. A wide range of multifunctional and structurally diverse spirooxindole derivatives with two adjacent quaternary spirocenters has been achieved in excellent yields with good to excellent stereoselectivity. Furthermore the synthetic application of this method has been successfully demonstrated by performing Suzuki coupling reaction.



Warghude, P. K.; Sabale, A. S.; Bhat, R. G. *Org. Biomol. Chem.* **2020**, *18*, 1794-1799.

THREE

3 Enantioselective Synthesis of Spirooxindole Dihydrofuran Fused Pyrazolones via [3+2] annulation of Morita-Baylis–Hillmann Carbonate with Pyrazolone 4, 5-diones

3.1 Introduction

Among the various heterocyclic compounds,[1] spirooxindole core scaffolds are found in a wide range of clinical pharmaceuticals as well as in numerous natural products. The molecules with this scaffold exhibit remarkable biological activities.[2] Especially, the spirooxindole compounds bearing two adjacent quaternary spirocenters exhibited range of bioactivities.[3] In this regard, a great attention has been paid on the development of robust, effective and practical methods to construct different carbocyclic and heterocyclic spirooxindole frameworks.[4] Among the various heterocyclic spirooxindoles, the spirooxindole fused with five-membered oxaheterocycles have drawn the attention of synthetic chemists, due to their occurance in variety of synthetic as well as natural products (Figure 3.1).[5]

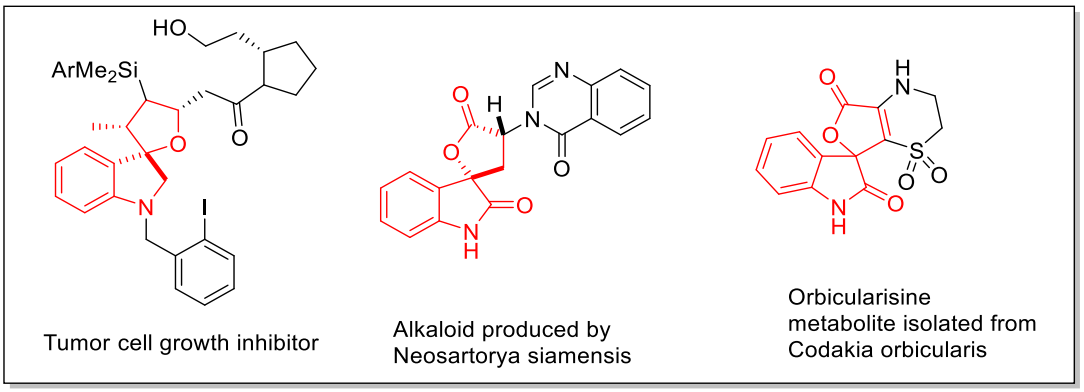


Figure 3.1 Bioactive compounds containing spirooxindole core

The distinctive structure of spirooxindole scaffold makes them very attractive tragets in the modern synthetic chemistry. As consequence a plethora of protocols has been well documented in the litereature to construct spirooxindole-dihydrofurans

architecture.[6] Some of the methods include transition-metal catalyzed cycloaddition reaction,[6a-c] oxidative [3 + 2] cycloaddition catalyzed by ceric ammonium nitrate,[6d] intramolecular Friedel–Crafts reaction,[6e] dimethyl sulfide promoted Baylis-Hillman cycloaddition,[6f] reductive [1 + 4] annulation process,[6g] asymmetric [3 + 2] annulation,[6h] iodide-mediated reaction,[6i] and domino Knoevenagel-Michael-Pinner cyclization.[6j]

In the recent years, pyrazolones and their derivatives have attracted the attention of synthetic organic chemists due to their potential utility as photographic coupler, pharmacologically active agents, chelating agents, and useful synthetic motifs in medicinal chemistry.[7] Particularly, spiropyrazolone compounds with contiguous stereocenters fused with different heterocyclic and carbocyclic units such as cyclohexane, cyclopentane and oxindole exhibit notable biological activity.[8] For instance, the spirocyclic pyrazolone compound **I** acts as an antibacterial agent,[8a] whereas the spiropyrazolone compounds **II** and **III** are known as inhibitors of type-4-phospodiesterase.[8b-c] In addition, the synthetic product **IV** containing both oxindole and pyrazolone framework is known for its anticancer activity (Figure 3.2).[8d]

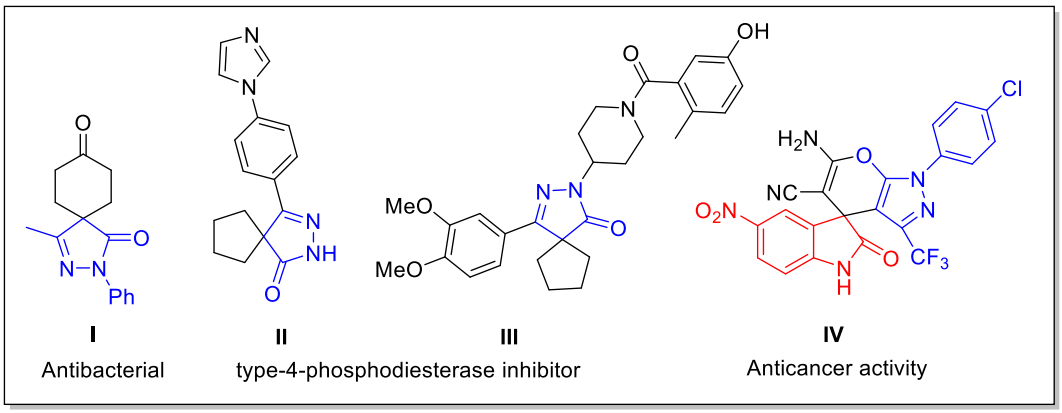
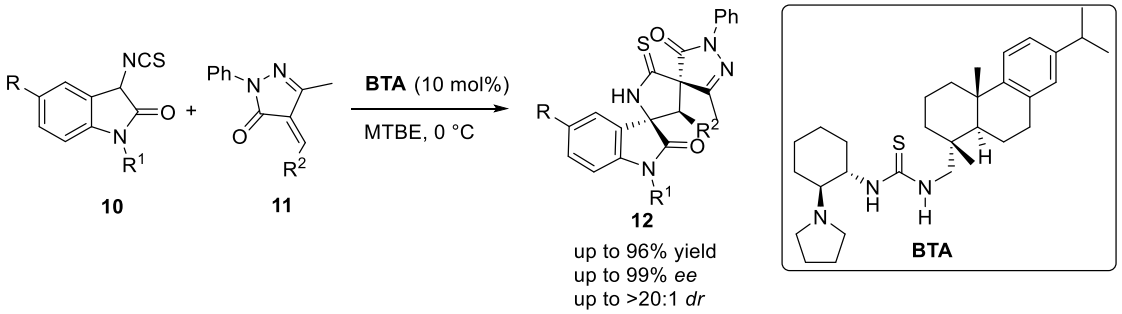


Figure 3.2 Bioactive compounds containing spiropyrazolone core scaffold

3.2 Selected methods for the synthesis of spiropyrazolone fused oxindole

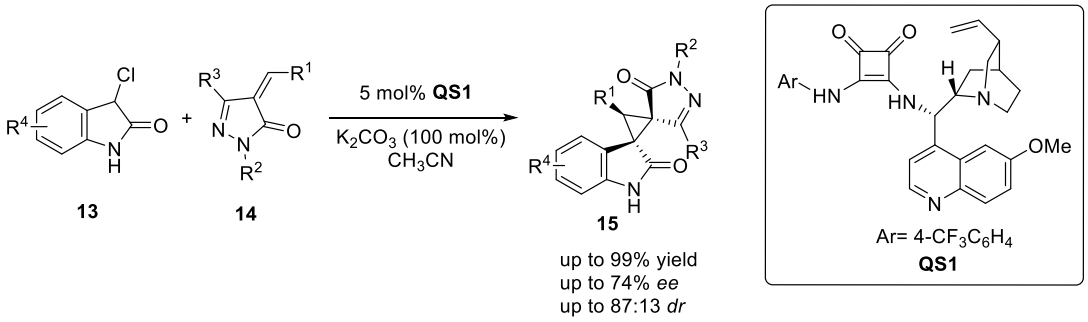
Considering the biological significance of spiropyrazolone and spirooxindole scaffold and the synthetic challenge to construct the molecule, the strategies for the stereoselective synthesis of molecules containing both pyrazolone and oxindole core is highly desirable and demanding. There are few asymmetric protocols available in the literature to construct bis-spirocyclic compounds containing pyrazolone and oxindole scaffolds. Some of the selected approaches for the preparation of spirooxindole fused pyrazolone have described.

In 2013, Chen et al.[9] have first reported the organocatalytic asymmetric Michael-cyclization cascade reaction to synthesize spiropyrazolone fused oxindole scaffold. The reaction of isothiocyanato oxindoles **10** with unsaturated pyrazolones **11** in presence of the catalytic amount of bifunctional thiourea tertiary amine catalyst **BTA** (10 mol%) furnished the multicyclic spiro[oxindole/thiobutyrolactam/pyrazolone] compounds **12** bearing three vicinal streogenic centres, including two spiro quaternary stereocenters in high yields (up to 96%) with excellent diastereo- (up to >20 : 1 *dr*) and enantio-selectivities (up to 99% *ee*) (Scheme 3.1).



Scheme 3.1 Organocatalytic asymmetric synthesis of spiropyrazolone fused oxindole

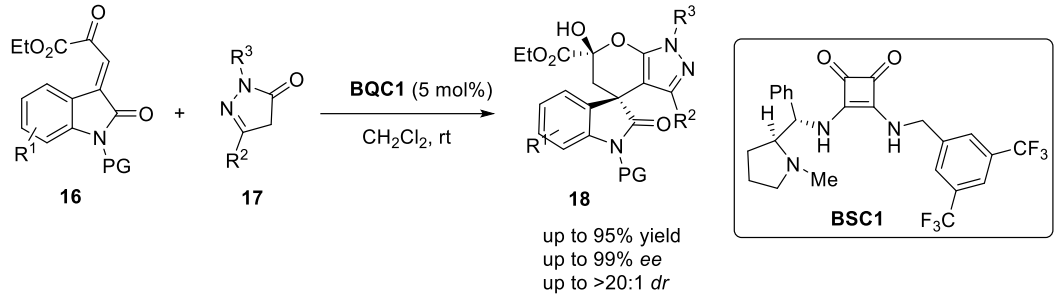
In 2015, Li et al.[10] employed the bifunctional quinine derived squaramide **QS1** catalyst for the Michael/alkylation cascade reaction to construct chiral spirocyclic scaffold. This method utilized 3-chlorooxindoles **13** and arylidenepyrazolones **14** as starting materials to achieve the highly functionalized spiro-pyrazolone-cyclopropane-oxindoles **15** in excellent yields (up to 99%) with moderate diastereoselectivities (up to 87:13 *dr*) and moderate to high enantioselectivities (up to 74% *ee*) (Scheme 3.2).



Scheme 3.2 Asymmetric synthesis of spiro-pyrazolone-cyclopropane-oxindole via Michael/Alkylation cascade reaction

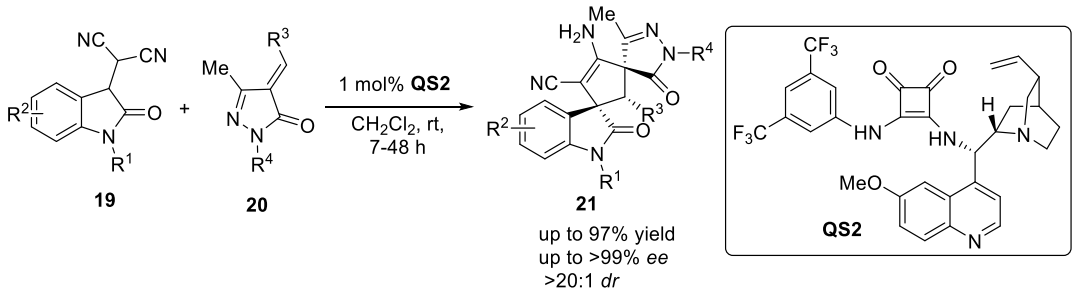
In 2016, Kesavan and co-worker[11] developed a method for the synthesis of spirooxindole fused pyranopyrazole **18** starting from isatylidine *β, γ*-unsaturated *α*-ketoester **16**

and pyrazolones **17** via Michael/hemiketalization reaction. The protocol explored the use of novel L-proline derived bifunctional squaramide catalyst (**BSC1**) to afford the corresponding chiral dihydrospiro[indoline-3,4′- pyrano[2,3-c]pyrazole] **18** derivatives in good to excellent yields (up to 95%) with very high level of stereoselectivities (up to > 20:1 *dr* and 99 % *ee*) (Scheme 3.3).



Scheme 3.3 Asymmetric synthesis of spirooxindole fused pyranopyrazole via Michael/ hemiketalization reaction

In 2019, Du and co-workers[12] reported the asymmetric [3 + 2] cycloaddition protocol to access diversely functionalized spirooxindole-fused spirocyclopentene-pyrazolones **21** starting from 2-(1-methyl-2-oxoindolin-3-yl) malononitriles **19** and unsaturated pyrazolones **20** by using chiral bifunctional quinine-derived squaramide **QS2** (1 mol%) as the catalyst. This method provided the spirooxindole-fused spirocyclopentene-pyrazolones **21** derivatives in high yields (up to 97%) with excellent streoselectivities (up to > 99% *ee* and >20:1 *dr*) at room temperature (Scheme 3.4).



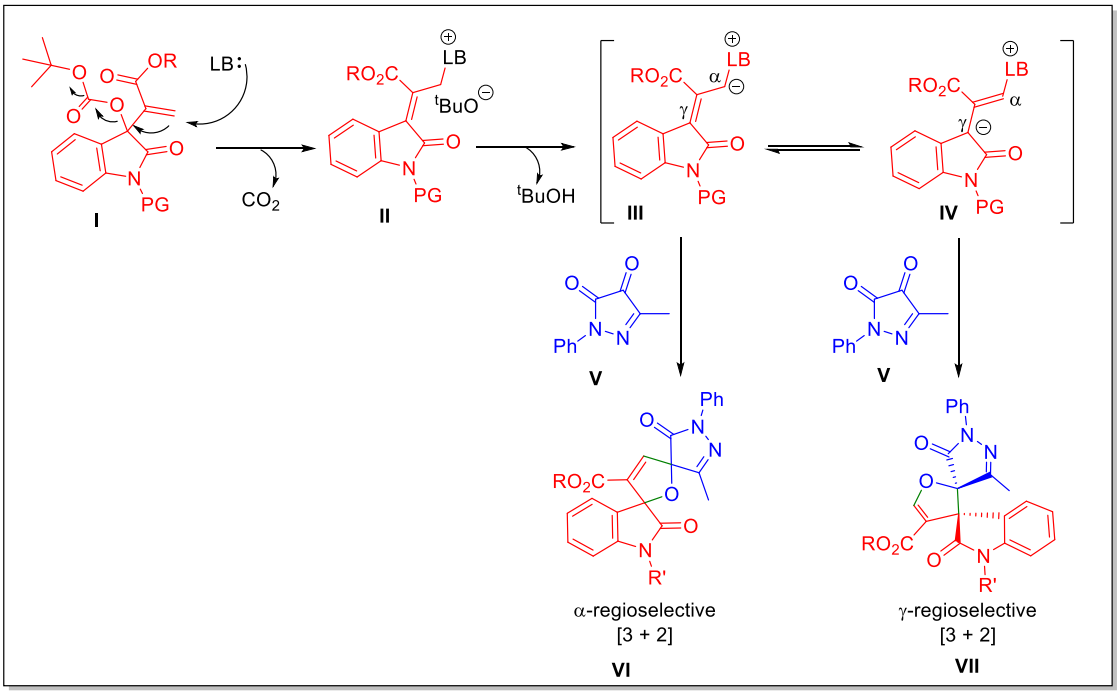
Scheme 3.4 Asymmetric synthesis of spirooxindole-fused spirocyclopentene-pyrazolones via [3 + 2] cycloaddition

Despite some of these recent advances in the synthesis of spirooxindole fused pyrazolone derivatives, there is no single protocol in the literature for the construction of scaffold

embedded with three different motifs such as oxindole, dihydrofuran and pyrazolone in an enantioselective manner. Undoubtedly, developing a more efficient, practical, catalytic and one-pot strategy to construct highly functionalized spirocyclic oxindoles and pyrazolones is highly demanding as well as challenging from the organic synthesis as well as medicinal chemistry research point of view.

3.3 Our hypothesis and synthetic design

Literature survey reveals the biological and pharmacological importance of spirooxindoles, spiropyrazolones and spiro-oxindole pyrazolone scaffolds in synthetic and medicinal chemistry. In recent years, the Morita-Baylis-Hillman (MBH) adducts of isatin have emerged as valuable and efficient precursors to construct enantiomerically pure spirooxindole derivatives.[13] Likewise, the pyrazolone 4, 5-diones have been used in various organocatalytic transformation to synthesize synthetically useful compounds.[14] In spite of these advances, the cycloaddition of pyrazolone 4, 5-dione at electrophilic C-4 position has not been achieved till date to the best of our knowledge.



Scheme 3.5 Proposed synthesis of spirooxindole dihydrofuran pyrazolones

In this regard, we hypothesized the synthesis of spirooxindole dihydrofuran fused pyrazolone compounds under organocatalytic conditions as depicted in scheme 3.5. An initial

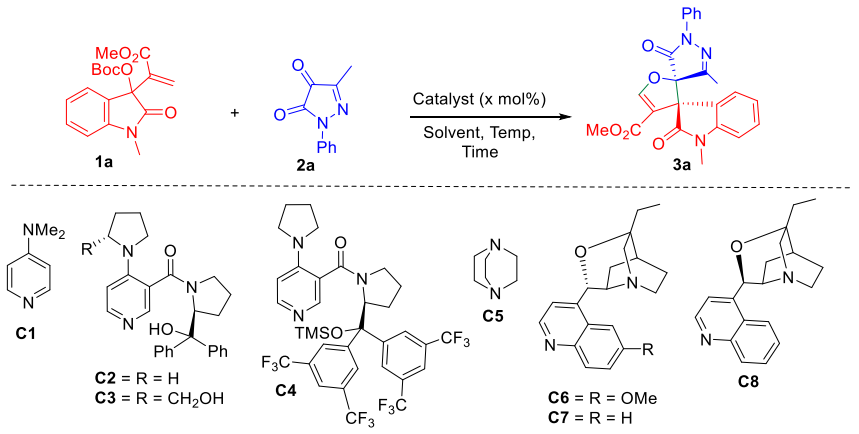
S_N2' attack of a Lewis base catalyst **LB** (phosphine or amine) on MBH carbonate **I** will give the intermediate **II** with the elimination of the leaving group. The intermediate **II**, further reacts with the in situ generated Brønsted base (*tert*-butoxide) to give a zwitterionic ylide intermediate **III** or **IV**. Then, these intermediates further react with pyrazolone 4, 5-dione **V** to give either α- or γ- regioselective **VI** or **VII** annulation products respectively (Scheme 3.5).

3.4 Results and Discussion

To validate our hypothesis, we began our study by performing a model reaction between MBH carbonate of isatin **1a** and pyrazolone 4, 5-dione **2a** in presence of DMAP (20 mol%) **C1** in CH_2Cl_2 at room temperature. Gratifyingly, the corresponding γ-regioselective [3 + 2] cycloaddition product **3a** was obtained in 95% yield with an excellent diastereoselectivity (> 20:1 *dr*, Table 3.1, entry 1). Encouraged by this result, we focused our attention to achieve asymmetric version of this reaction. The reaction of **1a** and **2a** with different chiral DMAP catalysts **C2**, **C3** and **C4** proceeded smoothly to afford the corresponding [3 + 2] cycloaddition product **3a** in high yields (75-95%) with excellent diastereoselectivity (*dr* >20:1), however, the enantioselectivity was found to be poor (up to 42% *ee*, Table 3.1, entries 2-4). We did not observe any significant change in the enantioselectivity at lower temperature (-20 °C) (40% *ee*, Table 3.1, entry 5). We surmised that the lack of enantioselectivity was probably due to the insufficient spatial interaction between chiral DMAP derived organocatalyst with either the pyrazolone 4, 5-dione or with MBH carbonate. In order to validate this and to establish better stereo-interaction, we planned to explore quinine based organocatalysts. At first, we explored the reaction **1a** and **2a** using DABCO (20 mol%) **C5** as a catalyst in dichloromethane at room temperature (racemic synthesis). Pleasingly, the expected [3 + 2] annulation product **3a** was formed in 62% yield with very high diastereoselectivity (Table 3.1, entry 6). Inspired by this initial result, we screened few quinine-based organocatalysts such as β-isoquinidine **C6**, β-isocinchonine **C7** and α-isocinchonidine **C8** to optimize the reaction. Among the screened catalysts, the [3 + 2] annulation in presence of chiral catalyst **C6** at room temperature underwent smoothly to afford the desired product **3a** in 58% yield with 70% enantiomeric excess (Table 3.1, entry 7). While, the catalysts **C7** and **C8** afforded the desired product albeit in lower enantioselectivity. (Table 3.1, entries 8-9). Therefore, we selected catalyst **C6** to optimize the reaction further. The reaction of **1a** and **2a** in presence of **C6** at 0 °C resulted in marginal increase in yield and enantioselectivity of spirooxindole **3a** (Table 3.1, entry 10). It is noteworthy that, at lower

temperature (-20 °C) the corresponding [3 + 2] annulation product **3a** was formed in 66% yield with very high stereoselectivity (>89% *ee*, Table 3.1, entry 11).

Table 3.1 Optimization of the reaction conditions[a-f]



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	*dr*[c]	*ee* (%)[d]
1	**C1**	CH_2Cl_2	rt	2	95	>20:1	-
2	**C2**	CH_2Cl_2	rt	12	95	>20:1	36
3	**C3**	CH_2Cl_2	rt	12	88	>20:1	42
4	**C4**	CH_2Cl_2	rt	12	75	>20:1	40
5	**C3**	CH_2Cl_2	-20	16	86	>20:1	40
6	**C5**	CH_2Cl_2	rt	12	62	>20:1	-
7	**C6**	CH_2Cl_2	rt	30	58	>20:1	70
8	**C7**	CH_2Cl_2	rt	30	50	>20:1	30
9	**C8**	CH_2Cl_2	rt	30	48	>20:1	20
10	**C6**	CH_2Cl_2	0	30	60	>20:1	79
11	**C6**	CH_2Cl_2	-20	36	66	>20:1	89
12	**C6**	CH_2Cl_2	-40	72	60	>20:1	95
13	**C6**	Toluene	-20	30	58	>20:1	86
14	**C6**	$CHCl_3$	-20	36	52	>20:1	75
15	**C6**	CH_3CN	-20	24	60	>20:1	78
16	**C6**	THF	-20	20	75	>20:1	93
17[e]	**C6**	THF	-20	50	58	>20:1	90
18[f]	**C6**	THF	-20	72	50	>20:1	84

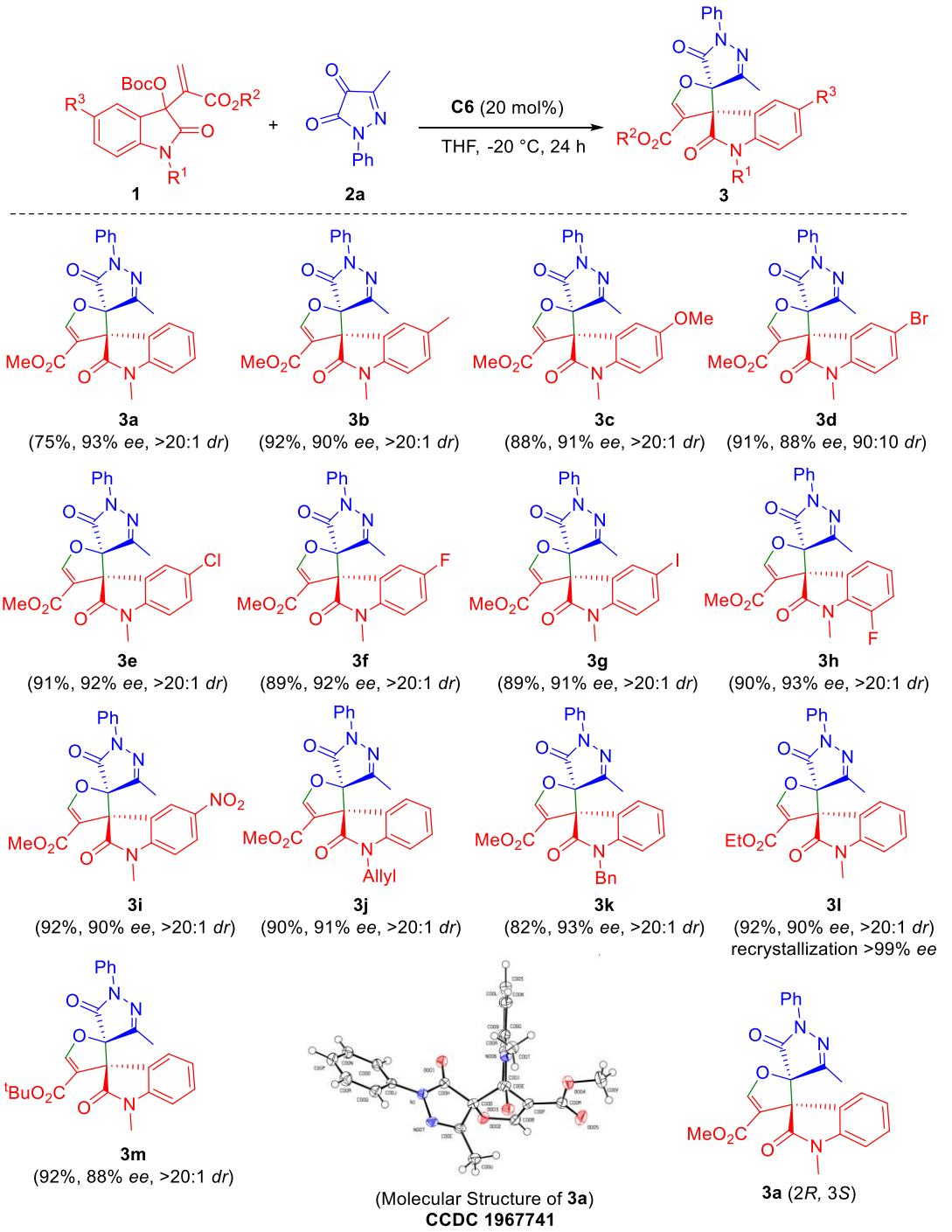
[a]**Reaction condition:** MBH carbonate **1a** (0.15 mmol, 50 mg), pyrazolone 4, 5 dione **2a** (0.15 mmol, 22 mg), Cat. (20 mol%) in 1.0 mL of solvent at specified temperature for the specified time. [b]Isolated yield after column chromatography. [c]*dr* was determined by ^{1}H NMR analysis. [d]*ee* was determined by HPLC using chiral stationary phase. [e]**C6** (15 mol%). [f]**C6** (10 mol%).

However, we observed that further lowering of the reaction temperature (- 40 °C) proved to be not beneficial as the reaction proceeded sluggishly (Table 3.1, entry 12) Subsequently, we screened different solvents such as toluene, chloroform, ($CHCl_3$) acetonitrile (CH_3CN) and tetrahydrofuran (THF) to achieve better yield and stereoselectivity (Table 3.1, entries 13-16). Among all, THF was found to be an optimal solvent to afford the desired product **3a** in good yield (75%) with excellent enantioselectivity (93% *ee*) (Table 3.1, entry 16). Further lowering of the catalyst (**C6**) loading (15 to 10 mol%) resulted in the significant reduction of yield **3a** with marginal reduction in enantioselectivity (Table 3.1, entries 17-18). Based on the extensive and exhaustive screening, pyrazolone 4, 5-dione **2a** (1.0 equiv.), MBH carbonate of isatin **1a** (1.0 equiv.), and methylated *β*-isoquinidine **C6** (20 mol%) in THF (1.0 mL) at -20 °C proved to be the optimum reaction condition to afford the corresponding spirooxindole dihydofuran fused pyrazolone derivatives.

After establishing the optimum reaction conditions, the substrate scope for asymmetric [3 + 2] cycloaddition was examined to construct novel spirooxindole dihydrofuran pyrazolone derivatives. To begin with we synthesized different MBH carbonates of isatin **(1a-1m)** and substituted pyrazolone 4, 5-diones (**2a-2f**) using reported literature procedure.[14]

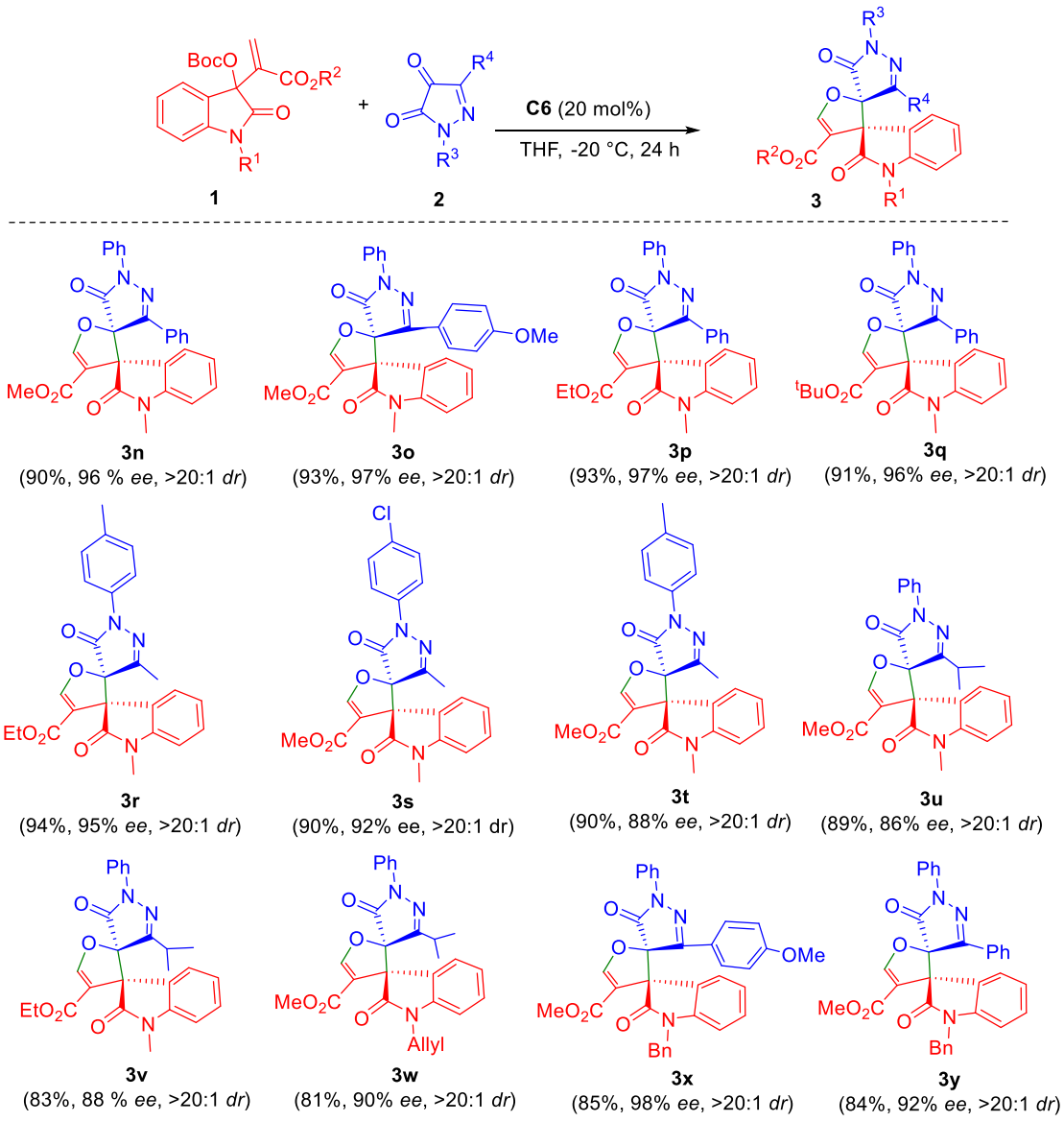
Having different substrates in hand, initially we evaluated the substrate scope of various isatin derived MBH carbonates **(1a-1m)** with pyrazolone 4, 5-dione **2a** under the standard reaction conditions to explore the generality of theprotocol. Gratifyingly, all the MBH carbonates **(1a-1m)** reacted smoothly with pyrazlone 4, 5-dione **2a** to afford the corresponding dihydrofuran fused with oxindole derivatives (**3a-3m)** in excellent yields (up to 96%) with excellent stereoselectivities (>20:1 *dr*, up to 92% *ee*; Table 3.2). We observed that, even the Morita-Baylis-Hillman carbonates bearing different esters groups underwent facile [3 + 2] cycloaddition to afford the corresponding spirooxindole dihydrofuran products (**3l, 3m**) in 92% yields with high stereoselectivity (Table 3.2). It is important to note that after recrystallization, the optical purity of the spirooxindole compound **3l** has been further enhanced (> 99% *ee* from 90% *ee* , Table 3.2). We also noticed that, electron-withdrawing (Br, Cl, F, I, NO_2) and electron-donating (CH_3, OCH_3) substituents at different positions (5 and 7 position) on the aryl ring of MBH carbonates were compatible under the optimum reaction conditions. Moreover, MBH carbonates with *N*-protected allyl and benzyl groups furnished the corresponding dihydrofuran oxindole products **3j, 3k** in excellent yields with high diastereoselectivity and enantioselectivity (Table 3.2). The absolute configuration of compound **3a** was established unambiguously using single-crystal X-ray diffraction analysis as *2R*, *3S* (Table 3.2).[15]

Table 3.2 Substrate scope for isatin derived MBH-carbonates[a-d]



[a]**Reaction conditions**: MBH carbonate **1** (1.0 equiv.), pyrazolone 4,5 dione **2** (1.0 equiv.), Cat. **C6** (20 mol%) in THF (1.0 mL) for 24 h, [b]Isolated yield after column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR. [d]Enantiomeric excess was determined by HPLC using chiral stationary phase.

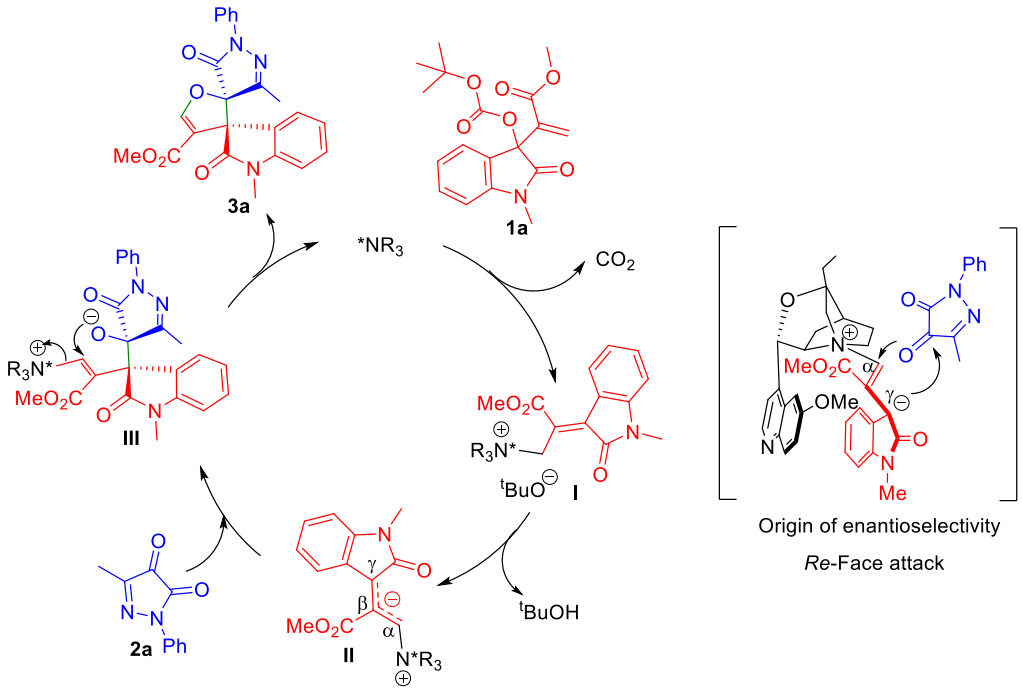
Table 3.3 Substrate scope for pyrazolone 4, 5-diones[a-d]



Reaction conditions: [a]Unless otherwise mentioned, all the reactions were carried out with **1**(1 equiv.), **2** (1 equiv.), Cat. **C6** (20 mol %) in 1.0 mL of solvent at specified temperature for the specified time. [b]Isolated yield after column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR. [d]Enantiomeric excess was determined by HPLC using chiral stationary phase.

Next, in order to further explore the substrate scope, we tretated a series of pyrazolone 4,5-diones (**2b-2f**) with few MBH carbonates of isatin (**1a, 1j, 1k, 1l, 1m**) under the optimum reaction conditions (Table 3.3). To our delight, the γ-regioselective [3 + 2] cycloaddition proceeded smoothly to afford the corresponding desired spirooxindole products **3n-3y** in very good to excellent yields (88-94%) with very high stereoselectivities (>20:1 *dr,* 88-98% *ee,*

Table 3.3). Importantly, we observed that the C-3 aryl substituted pyrazolone 4, 5-diones (**2b** and **2c)** were compatible under the optimized reaction conditions to afford the corresponding spirooxindole fused pyrazolone derivatives (**3n**, **3o**, **3p** and **3q)** in excellent yields (up to 93%) with very high enantioselectivity (up to 97% *ee*). The reaction of pyrazolone 4, 5-dione **2f** with MBH carbonate (**1a, 1j, 1l**) furnished the dihydrofuran pyrazolone products (**3u, 3v, 3w**) in very good yields (up to 90%) with very high stereoselectivities (>20:1 *dr*, up to 88% *ee*). It is significant to note that, when C-3 position of pyrazolone 4, 5-diones is substituted with aryl moiety, the desired products are formed in higher stereoselectivity as compared to aliphatic groups at C-3 position. We also found that, the *N*-alkyl substituted pyrazolone 4, 5-dione derivatives were unsuccessful under the optimized reaction condition.

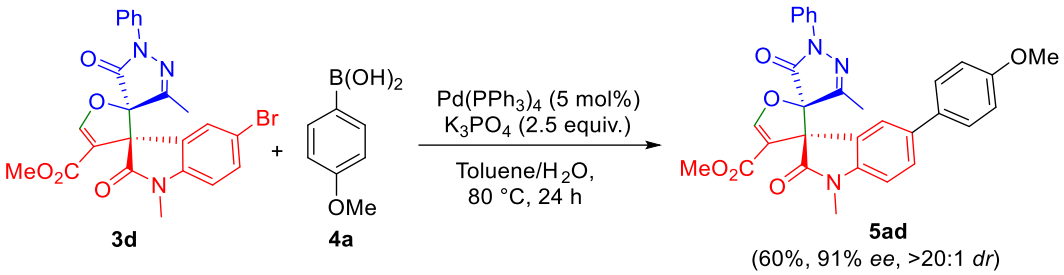


Scheme 3.6 Proposed catalytic cycle for the asymmetric [3 + 2] cycloaddition reaction

Based on our experimental observation and preceding literature reports[13] the plausible catalytic cycle for the Lewis base catalyzed cycloaddition reaction has been depicted in Scheme 3.6. Initially, the MBH carbonate **1a** is attacked by the the nucleophilic chiral Lewis base (tertiary amine) catalyst to form the quaternary ammonium salt **I** along with the elimination of *tert*-butoxide and carbon dioxide. Then the in situ generated *tert*-butoxide abstracts the acidic prtoton from ammonium salt intermediate **I** to form reactive allylic nitrogen ylide intermediate

II. Then the electrophilic C-4 position of pyrazolone 4, 5-dione **2a** was attacked by the nucleophilic intermediate **II** via γ-position to give the intermediate **III**. Subsequently, the intramolecular cyclization of intermediate **III** delivers compound **3a** with the regeneration of the tertiary amine catalyst .

In order to demonstrate the applicability of this method, the cross-coupling reaction was performed on the spirooxindole derivative **3d** (Scheme 3.7). The reaction of bromo substituted spirooxindole **3d** and methoxyphenyl boronic acid **4a** in the presence of $Pd(PPh_3)_4$ afforded the corresponding cross coupled spirooxindole product **5ad** in 60% yield with high enantioselectivity and diastereoselectivity (91% *ee*, *dr* >20:1).



Scheme 3.7 Suzuki coupling reaction

3.5 Conclusions

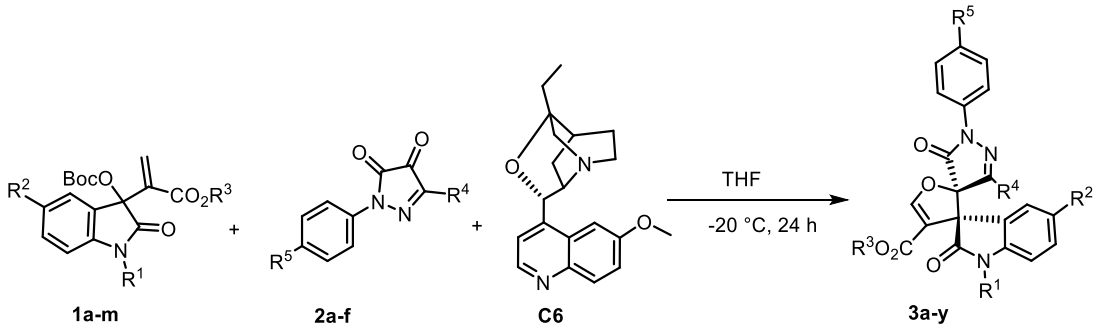
In summary, we have developed a chiral Lewis base catalyzed highly regioselective [3 + 2] cycloaddtion of isatin-derived Morita−Baylis−Hillman carbonates and pyrazolone 4, 5-diones. A series of highly functionalized dihydrofuran oxindole fused pyrazolones bearing two adjacent spiro-quaternary chiral centers has been successfully synthesized in excellent stereoselectivity under mild reaction conditions.

3.6 Experimental Section

3.6.1 General

Unless otherwise stated, all the reagents were purchased from commercial suppliers and used without purification. Isatins and pyrazolones were purchased from Aldrich, TCI chemicals and Alfa-Aeser. HPLC grade solvents were purchased from RANKEM. All the reactions were carried out in an oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and the solution of Phosphomolybdic Acid (PMA) was used to stain products. The column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate. The NMR spectra were recorded using tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) are given in Hz and integration. IR spectra were obtained using FT-IR spectrophotometer as neat and are reported in cm^{-1}. All the samples were analyzed by High-resolution mass spectrometer (HRMS) using ESI TOF. Optical rotations were measured at 589 nm at 25 °C. Optical rotation was measured in $CHCl_3$ solution. HPLC analysis was performed using an Agilent 1200 infinity series HPLC System with a diode array detector. Enantiomeric excess was determined by HPLC analysis on Chiralpak IC (4.6 mm × 250 mm) and Chiralpak IA (4.6 mm × 250 mm) columns in comparison with authentic racemic materials using *n*-hexane and isopropanol as eluents. Data were analyzed by using Agilent OpenLAB software. Melting points were measured using BUCHI M-560 melting point instrument. All melting points were measured in open glass capillary and values are uncorrected. Catalysts **C2, C3, C4, C6, C7, C8** were synthesized according to the literature procedures.[16] Morita-Baylis-Hillman carbonates **1a-1m** were prepared according to the literature procedure.[17] Substituted pyrazonlone 4, 5-diones were synthesized according to the literature procedure.[14]

3.6.2 General procedure for the enantioselective synthesis of spiro-oxindole-pyrazolone dihydrofuran

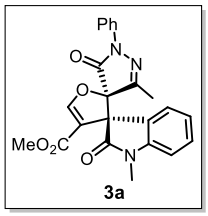


To a solution of Morita-Baylis-Hillman carbonate **1a** (50 mg, 1.0 equiv.) in 1 mL of THF, pyrazole-4, 5-dione **2a** (27 mg, 1.0 equiv.) and catalyst **C6,** (9.3 mg, 0.2 equiv.) were added at -20 °C. The resulting mixture was stirred for 24 h. After completion of the reaction (monitored by TLC) the solvent was evaporated under reduced pressure and the residue was purified by silica gel (100-200 mesh) using column chromatography (petroleum ether/ethyl acetate 70:30) to obtain desired product **3a** as white solid in 75% yield (45 mg).

[All the racemic compounds were synthesized using DMAP as catalyst]

3.6.3 Experimental Data

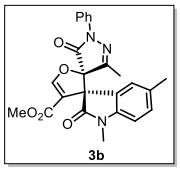
Methyl (2'*R*, 3*S*)-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3a)



The compound **3a** was obtained following the general procedure, starting from **1a**, **2a** and catalyst **C6**. The compound **3a** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as white solid (45 mg, 75%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.3, MP: 127-130 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 24.68 min, tR(minor) = 33.08 min, 93% *ee*. $[a]_D^{25}$= +374.2 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.50 (dd, *J* = 8.8, 1.0 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.16 – 7.10 (m, 1H), 7.04 (td, *J* = 7.7, 0.7 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 3H), 3.22 (s, 3H), 2.35 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 167.1, 162.3, 159.3, 157.6, 143.9, 137.0, 130.3, 128.9, 127.0, 125.7, 123.3, 122.9, 119.1, 113.8, 108.5, 93.2, 63.2, 51.8, 27.1, 16.1. FTIR (cm$^-$

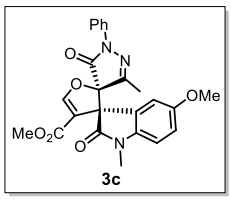
[1]): 3099, 2950, 1713, 1615, 1490, 1350, 1277, 1196, 1120, 1040, 991, 922, 746, 689, 643, 605. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{20}N_3O_5$ $[M + H]^+$ 418.1403, found 418.1403.

Methyl (2'*R*, 3*S*)-1,3'',4-trimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3b)



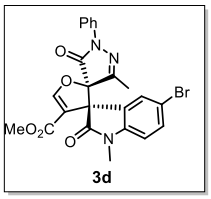
The compound **3b** was obtained following the general procedure, starting from **1b**, **2a** and catalyst **C6**. The compound **3b** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as light brown solid (55 mg, 92%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.35, MP: 189-191 °C, HPLC: CHIRAPAK IC column, n-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 35.89 min, tR(minor) = 49.68 min, 90% *ee*. $[a]_D^{25}$ = +308.04 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.50 (dt, *J* = 8.9, 1.7 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.17 – 7.09 (m, 1H), 7.07 – 7.01 (m, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 3.59 (s, 3H), 3.18 (s, 3H), 2.32 (s, 3H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 167.2, 162.3, 159.4, 157.3, 141.5, 136.9, 132.3, 130.5, 128.8, 127.5, 125.6, 123.0, 118.8, 113.7, 108.2, 93.2, 63.2, 51.7, 27.0, 21.2, 16.0. FTIR (cm^{-1}): 2924, 2858, 1713, 1620, 1496, 1440, 1350, 1279, 1189, 1042. 1114, 992, 925, 801, 741, 691, 639. HRMS (ESI TOF) *m/z* calcd. For $C_{24}H_{22}N_3O_5$ $[M + H]^+$ 432.1559, found 432.1551.

Methyl (2'*R*, 3*S*)-4-methoxy-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro [indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3c)



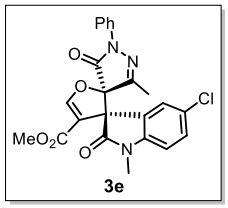
The compound **3c** was obtained following the general procedure, starting from **1c**, **2a** and catalyst **C6**. The compound **3c** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as light brown solid (52 mg, 88%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.20, MP: 164-168 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 61.75 min, tR(minor) = 68.16 min, 91% *ee*. $[a]_D^{25}$ = +285.8 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.58 – 7.51 (m, 2H), 7.34 – 7.25 (m, 2H), 7.18 – 7.09 (m, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.18 (s, 3H), 2.33 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 167.1, 162.3, 159.4, 157.3, 156.0, 137.4, 137.0, 128.9, 125.6, 124.3, 118.9, 115.4, 113.7, 108.9, 93.3, 63.4, 55.9, 51.8, 27.1, 16.0. FTIR (cm^{-1}): 3096, 2925, 2854, 1716, 1622, 1495, 1446, 1353, 1286, 1200, 1123, 1035, 923, 792, 746, 691, 638. HRMS (ESI-TOF) *m/z* calcd. For $C_{24}H_{22}N_3O_6$ $[M + H]^+$ 448.1509, found 448.1506.

Methyl (2'*R*, 3*R*)-4-bromo-1,3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3d)



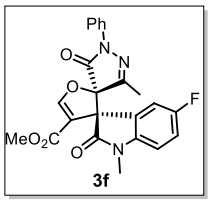
The compound **3d** was obtained following the general procedure, starting from **1d**, **2a** and catalyst **C6**. The compound **3c** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as light yellow solid (53 mg, 91%, *dr* 90:10), R_f (petroleum ether/EtOAc 70:30) = 0.32, MP: 185-188 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 24.37 min, tR(minor) = 29.65 min, 88% *ee*. $[a]_D^{25}$ = +171.0 (c 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.40 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.20 – 7.12 (m, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 3.63 (s, 3H), 3.19 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.4, 166.8, 162.2, 159.5, 159.5, 157.2, 142.9, 136.8, 133.2, 130.1, 129.0, 125.9, 125.2, 119.0, 115.7, 113.5, 109.9, 92.9, 63.0, 52.0, 51.9, 27.1, 16.1. FTIR (cm^{-1}): 3099, 2926, 1719, 1618, 1488, 1347, 1277, 1203, 1119, 990, 915, 813, 743, 689, 642. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}BrN_3O_5$ $[M + H]^+$ 496.0508, 498.0488 found 496.0517, 498.0493.

Methyl (2'R, 3R)-4-chloro-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5'' dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3e)



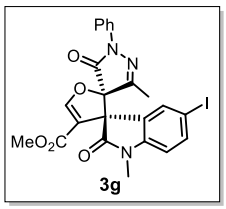
The compound **3e** was obtained following the general procedure, starting from **1e**, **2a** and catalyst **C6**. The compound **3e** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 75:25) as light brown solid (54 mg, 91%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.35, MP: 195-197 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 22.80 min, tR(minor) = 29.33 min, 92% *ee*. $[a]_D^{25}$ = +285.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 7.83 (s, 1H), 7.58 – 7.52 (m, 2H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.32 (dd, *J* = 8.5, 7.6 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 3.63 (s, 3H), 3.20 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.5, 166.7, 162.2, 159.4, 157.3, 142.4, 136.8, 130.3, 129.0, 128.4, 127.4, 125.9, 125.0, 119.0, 118.9, 118.9, 118.9, 113.6, 109.4, 92.9, 63.0, 52.0, 27.2, 16.1. FTIR (cm^{-1}): 3098, 2923, 1717, 1620, 1490, 1440, 1347, 1277, 1202, 1119, 992, 916, 815, 743, 689, 642. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}ClN_3O_5$ $[M + H]^+$ 452.1013 found 452.1011.

Methyl (2'*R*, 3*R*)-4-fluoro-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3f)



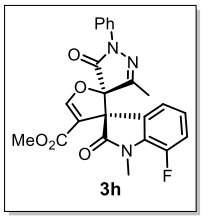
Following general procedure using **1f**, **2a** and catalyst **C6, 3f** was obtained after column chromatography (silica gel, petroleum ether/EtOAc 75:25) as light brown solid (53 mg, 89%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.25, MP: 176-178 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 23.29 min, tR(minor) = 30.66 min, 92% *ee*. $[a]_D^{25}$ = +388.9 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.58 – 7.51 (m, 2H), 7.35 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 7.18 – 7.11 (m, 1H), 6.99 (td, *J* = 8.7, 2.6 Hz, 1H), 6.71 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.62 (s, 3H), 3.20 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 166.7, 162.2, 159.4, 159.11 (d, $J_{C\text{-}F}$ = 240 Hz) , 157.4, 139.9, 136.9, 129.0, 125.01 (d, *J* = 8.6 Hz), 118.9, 116.76 (d, *J* = 23.6 Hz), 115.30 (d, *J* = 26.1 Hz), 113.7, 108.98 (d, *J* = 8.0 Hz), 93.0, 77.5, 77.2, 76.8, 63.3, 51.9, 27.2, 16.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -119.6. FTIR (cm^{-1}): 3093, 2928, 1720, 1625, 1494, 1450, 1351, 1276, 1123, 1041, 993, 919, 799, 747, 691, 640. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}FN_3O_5$ $[M + H]^+$ 436.1309 found 436.1310.

Methyl (2'R, 3R)-4-iodo-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3g)



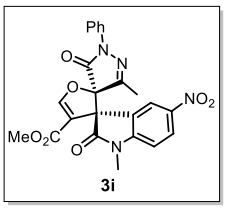
The compound **3g** was obtained following the general procedure, starting from **1g**, **2a** and catalyst **C6**. The compound **3g** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 75:25) as light brown solid (51 mg, 89%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.34, MP: 166-170 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 28.18 min, tR(minor) = 32.25 min, 91% *ee*. $[a]_D^{25}$ = +130.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.63 – 7.50 (m, 3H), 7.39 – 7.30 (m, 2H), 7.19 – 7.12 (m, 1H), 6.55 (dd, *J* = 8.2, 1.7 Hz, 1H), 3.63 (s, 3H), 3.18 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 166.8, 162.2, 159.6, 157.1, 143.6, 139.1, 136.7, 135.4, 129.0, 125.9, 125.4, 119.0, 113.4, 110.5, 93.0, 85.5, 62.8, 51.9, 27.1, 16.0. FTIR (cm^{-1}): 3100, 2923, 2857, 1717, 1623, 1487, 1346, 1277, 1199, 1121, 1040, 990, 915, 811, 746, 689, 643, 605. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}IN_3O_5$ $[M + H]^+$ 544.0369 found 544.0369.

Methyl (2'*R*, 3*S*)-7-fluoro-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3h)



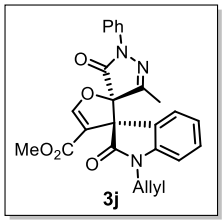
The compound **3h** was obtained following the general procedure, starting from **1h**, **2a** and catalyst **C6**. The compound **3h** was purified by column (Silica gel, petroleum ether/EtOAc 80:20) as light brown solid (54 mg, 90%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.53, MP: 165-168 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 19.88 min, tR(minor) = 30.43 min, 93% *ee*. $[\alpha]_D^{25}$ = +302.8 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.82 (s, 1H), 7.58 – 7.49 (m, 2H), 7.35 – 7.28 (m, 2H), 7.25 – 7.22 (m, 1H), 7.15 (tt, *J* = 7.0, 1.1 Hz, 1H), 7.05 – 6.93 (m, 2H), 3.62 (s, 3H), 3.42 (d, *J* = 2.8 Hz, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.6, 166.8, 162.2, 159.3, 157.4, 147.60 (d, $J_{C\text{-}F}$ = 243.8 Hz), 136.9, 130.6 (d, $J_{C\text{-}F}$ = 9 Hz), 129.0, 126.1, 125.8, 123.25 (d, $J_{C\text{-}F}$ = 6.5 Hz), 122.94 (d, *J* = 3.3 Hz), 119.0, 118.4, 118.2, 113.9, 93.1, 63.3, 51.9, 29.63 (d, $J_{C\text{-}F}$ = 6.2 Hz), 16.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -136.1. FTIR (cm^{-1}): 2922, 2859, 1718, 1626, 1486, 1349, 1281, 1243, 1188, 1122, 990, 913, 850, 740, 691, 643. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}FN_3O_5$ $[M + H]^+$ 436.1309 found 436.1313.

Methyl (2'*R*, 3*S*)-1, 3''-dimethyl-4-nitro-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro [indoline-3, 3'-furan-2',4''-pyrazole]-4'-carboxylate (3i)



The compound **3i** was obtained following the general procedure, starting from **1i**, **2a** and catalyst **C6**. The compound **3e** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as light brown solid (54 mg, 92%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.15, MP: 192-194 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 36.25 min, tR(minor) = 46.02 min, 90% *ee*. $[\alpha]_D^{25}$ = +13.0 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.37 (d, *J* = 2.3 Hz, 1H), 8.27 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.86 (s, 1H), 7.55 (dt, *J* = 8.9, 1.7 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 3.64 (s, 3H), 3.28 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 165.9, 161.9, 159.2, 157.3, 148.8, 143.5, 136.7, 128.9, 127.1, 125.8, 124.4, 123.0, 118.5, 113.6, 108.1, 92.3, 62.7, 52.0, 27.4, 16.1. FTIR (cm^{-1}): 3100, 2926, 2856, 1723, 1613, 1496, 1444, 1337, 1292, 1199, 1124, 993, 923, 831, 743, 691, 643. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{19}N_4O_7$ $[M + H]^+$ 463.1254 found 463.1253.

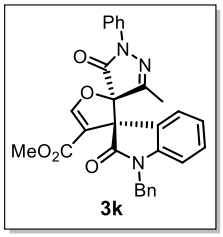
Methyl (2'*R*, 3*S*)-1-allyl-3''-methyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3j)



3j

The compound **3j** was obtained following the general procedure, starting from **1j**, **2a** and catalyst **C6**. The compound **3j** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 85:15) as light yellow solid (53 mg, 90%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.44, MP: 148-151 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 25.18 min, tR(minor) = 30.05 min, 91% *ee*. $[a]_D^{25}$ = +349.4 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.85 (s, 1H), 7.52 – 7.42 (m, 3H), 7.32 – 7.26 (m, 2H), 7.23 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 5.86 – 5.70 (m, 1H), 5.22 – 5.09 (m, 2H), 4.42 (ddt, *J* = 16.7, 5.0, 1.7 Hz, 1H), 4.24 (ddt, *J* = 16.7, 4.6, 1.8 Hz, 1H), 3.60 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.7, 167.1, 162.3, 159.4, 157.8, 143.0, 136.9, 130.6, 130.2, 128.9, 127.0, 125.7, 123.3, 122.8, 119.1, 117.5, 113.7, 109.4, 93.4, 63.4, 51.8, 42.8, 16.2. FTIR (cm^{-1}): 3094, 2923, 2857, 2314, 1719, 1618, 1490, 1356, 1285, 1237, 1187, 1124, 988, 923, 751, 687. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{22}N_3O_5$ $[M + H]^+$ 444.1559 found 444.1561.

Methyl (2'*R*, 3*S*)-1-benzyl-3''-methyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3k)

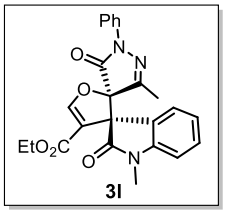


3k

The compound **3k** was obtained following the general procedure, starting from **1k**, **2a** and catalyst **C6**. The compound **3k** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 85:15) as light brown solid (48 mg, 82%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.47, MP: 139-141 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.9 mL/min, λ = 254 nm, tR(major) = 13.62 min, tR(minor) = 17.92 min, 93% *ee*. $[a]_D^{25}$ = +59.2 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (s, 1H), 7.51 – 7.45 (m, 2H), 7.43 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.16 (ddt, *J* = 7.5, 4.3, 1.7 Hz, 5H), 7.13 – 7.06 (m, 2H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.9 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 3.58 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 166.9, 162.3, 159.2, 158.5, 142.5, 137.0, 135.0, 130.3, 128.9, 128.9, 127.7, 127.1, 126.8, 125.7, 123.6, 122.8, 119.0, 114.0, 109.5, 93.4, 63.8, 51.8, 44.3,

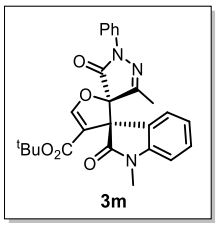
16.3. FTIR (cm^{-1}): 2923, 1718, 1607, 1492, 1357, 1281, 1234, 1178, 1126, 987, 917, 836, 743, 695, 643. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}N_3O_5$ $[M + H]^+$ 494.1716 found 494.1713.

Ethyl (2'*R*, 3*S*)-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3l)



The compound **3l** was obtained following the general procedure B, starting from **1l**, **2a** and catalyst **C6**. The compound **3l** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 80:20) as light brown solid (55 mg, 92%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.41, MP: 189-191 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(minor) = 25.51 min, tR(major) = 30.98 min, 90% *ee*. $[a]_D^{25}$ = +391 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.84 (s, 1H), 7.54 – 7.49 (m, 2H), 7.48 – 7.43 (m, 1H), 7.33 – 7.24 (m, 3H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.00 (qq, *J* = 7.4, 3.7 Hz, 2H), 3.20 (s, 3H), 2.35 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 167.1, 161.8, 159.1, 157.7, 143.9, 137.0, 130.2, 128.9, 127.0, 125.7, 123.6, 122.8, 119.0, 114.3, 108.4, 93.2, 63.2, 60.6, 27.0, 16.2, 14.0. FTIR (cm^{-1}): 2924, 1722, 1622, 1492, 1368, 1290, 1125, 1030, 950, 820,754, 690, 599. HRMS (ESI TOF) *m/z* calcd. For $C_{24}H_{22}N_3O_5$ $[M + H]^+$ 432.1559 found 432.1557.

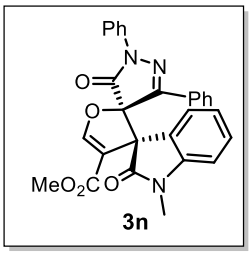
Tert-butyl (2'*R*, 3*S*)-1, 3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydrodispiro [indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3m)



The compound **3m** was obtained following the general procedure, starting from **1m**, **2a** and catalyst **C6**. The compound **3m** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 85:15 as light brown solid (54 mg, 92%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.5, MP: 65-68 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(minor) = 15.32 min, tR(major) = 15.94 min, 88% *ee*. $[a]_D^{25}$ = +345.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.79 (s, 1H), 7.54 – 7.43 (m, 3H), 7.33 – 7.23 (m, 3H), 7.17 – 7.09 (m, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 3.18 (s, 3H), 2.35 (s, 3H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 167.2, 161.0, 159.0, 157.8, 143.8, 137.0, 130.0, 128.9, 127.0, 125.6, 124.1, 122.7, 119.0, 115.5, 108.2, 93.3, 81.3, 63.3, 27.9, 26.9, 16.1. FTIR (cm^{-1}): 3093, 2928, 1720,

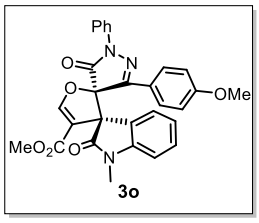
1625, 1494, 1450, 1351, 1276, 1123, 1041, 993, 919, 799, 747, 691, 640. HRMS (ESI TOF) *m/z* calcd. For $C_{26}H_{26}N_3O_5$ $[M + H]^+$ 460.1872 found 460.1871.

Methyl (2'*R*, 3*S*)-1-methyl-2, 5''-dioxo-1'', 3''-diphenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3n)



The compound **3n** was obtained following the general procedure, starting from **1a**, **2b** and catalyst **C6**. The compound **3n** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as brown solid (62 mg, 90%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.29, MP: 183-186 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 21.74 min, tR(minor) = 30.06 min, 96% *ee*. $[a]_D^{25}$ = +310.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.93 (s, 1H), 7.77 – 7.64 (m, 2H), 7.45 – 7.31 (m, 6H), 7.28 – 7.21 (m, 2H), 7.19 – 7.13 (m, 1H), 7.09 (tt, *J* = 7.0, 1.1 Hz, 1H), 6.88 (td, *J* = 7.7, 1.0 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 3.51 (s, 3H), 2.68 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.0, 167.8, 162.5, 160.5, 154.2, 144.6, 136.6, 131.1, 130.4, 130.3, 128.9, 128.0, 128.0, 126.2, 126.1, 122.7, 122.6, 119.5, 112.4, 108.4, 94.4, 63.5, 51.7, 26.4. FTIR (cm^{-1}): 3061, 2953, 1719, 1616, 1491, 1346, 1276, 1193, 1116, 987, 925, 800, 744, 684, 598. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{22}N_3O_5$ $[M + H]^+$ 480.1559 found 480.1564.

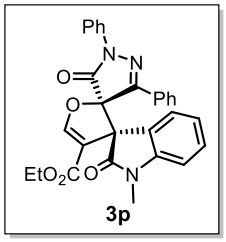
Methyl (2'*R*, 3*S*)- 3''-(4-methoxyphenyl)-1-methyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro [indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3o)



The compound **3o** was obtained following the general procedure, starting from **1a**, **2c** and catalyst **C6**. The compound **3o** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as brown solid (68 mg, 93%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.17, MP: 197-199 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 39.91 min, tR(minor) = 57.83 min, 97% *ee*. $[a]_D^{25}$ = +174.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.92 (s, 1H), 7.72 – 7.66 (m, 2H), 7.44 – 7.34 (m, 3H), 7.27 – 7.21 (m, 2H), 7.19 – 7.12 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.83 (m, 3H), 6.64 (d, *J* = 7.7 Hz, 1H), 3.80 (s, 3H), 3.51 (s, 3H), 2.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.7, 162.5, 161.9, 160.5, 153.9, 144.6, 136.7, 130.3, 129.7, 128.9, 126.2, 126.0, 123.0, 122.7, 122.7, 119.5, 113.4, 112.3, 108.3, 94.7, 63.5, 55.5, 51.7, 26.5. FTIR (cm^{-1}): 3096, 2920, 2856, 1720, 1608, 1493, 1461,

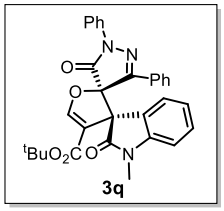
1349, 1302, 1257, 1186, 1118, 1026, 969, 924, 834, 737, 682, 612. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}N_3O_6$ $[M + H]^+$ 510.1665 found 510.1662.

Ethyl (2'R, 3S)-1-methyl-2, 5''-dioxo-1'', 3''-diphenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3p)



The compound **3p** was obtained following the general procedure, starting from **1l**, **2b** and catalyst **C6**. The compound **3p** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as brown solid (62 mg, 93%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.35, MP: 133-137 °C, HPLC: CHIRAPAK IA column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(minor) = 16.06 min, tR(major) = 25.68 min, 97% *ee*. $[a]_D^{25}$ = +270.4 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.00 (s, 1H), 7.83 – 7.76 (m, 2H), 7.53 – 7.40 (m, 6H), 7.36 – 7.28 (m, 2H), 7.26 – 7.15 (m, 2H), 6.96 (td, *J* = 7.7, 1.0 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 3.99 (qd, *J* = 7.1, 2.6 Hz, 2H), 2.77 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 167.8, 162.0, 160.3, 154.3, 144.7, 136.6, 131.1, 130.5, 130.3, 128.9, 128.0, 128.0, 126.2, 126.1, 122.9, 122.7, 119.5, 112.8, 108.3, 94.4, 63.5, 60.5, 26.4, 14.1. FTIR (cm^{-1}): 3060, 2923, 1718, 1617, 1490, 1375, 1336, 1277, 1110, 1020, 961, 810, 777, 684, 596. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}N_3O_5$ $[M + H]^+$ 494.1716 found 494.1714.

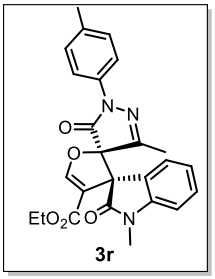
Tert-butyl (2'*R*, 3*S*)-1-methyl-2, 5''-dioxo-1'', 3''-diphenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3q)



The compound **3q** was obtained following the general procedure, starting from **1m**, **2b** and catalyst **C6**. The compound **3q** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 80:20) as brown solid (61 mg, 91%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.53, MP: 188-192 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 15.78 min, tR(minor) = 26.61min, 96% *ee*. $[a]_D^{25}$ = +111.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.94 (s, 1H), 7.83 – 7.76 (m, 2H), 7.53 – 7.38 (m, 6H), 7.36 – 7.27 (m, 2H), 7.28 – 7.19 (m, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 6.97 (td, *J* = 7.6, 1.0 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 2.77 (s, 3H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 161.1, 159.9, 154.4, 144.7, 136.6, 131.0, 130.6, 130.1, 128.9, 128.0, 128.0, 126.2, 126.0, 123.5, 122.6, 119.5, 114.3, 108.1, 94.5, 81.1, 63.5, 27.9, 26.3. FTIR (cm^{-1}): 3063, 2923, 2857, 1722, 1628, 1491, 1364, 1262, 1106, 1026,

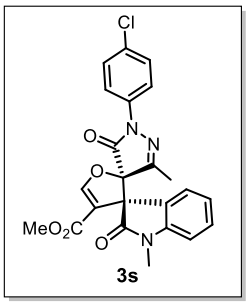
963, 922, 813, 746, 686, 596. HRMS (ESI TOF) *m/z* calcd. For $C_{31}H_{28}N_3O_5$ $[M + H]^+$ 522.2029 found 522.2040.

Ethyl (2'*R*, 3*S*)-1, 3''-dimethyl-2, 5''-dioxo-1''-(p-tolyl)-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3r)



The compound **3r** was obtained following the general procedure, starting from **1m**, **2d** and catalyst **C6**. The compound **3r** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 75:25) as brown solid (58 mg, 94%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.41, MP: 179-180 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 15.35 min, tR(minor) = 20.86 min, 95% *ee*. $[a]_D^{25}$ = +332.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (s, 1H), 7.47 – 7.43 (m, 1H), 7.39 – 7.34 (m, 2H), 7.27 (td, *J* = 7.8, 1.2 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.03 (td, *J* = 7.7, 1.0 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.00 (qq, *J* = 7.3, 3.7 Hz, 2H), 3.20 (s, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 167.0, 161.9, 159.2, 157.5, 143.9, 135.5, 134.5, 130.2, 129.4, 127.0, 123.6, 122.8, 119.1, 114.2, 108.4, 93.2, 63.2, 60.6, 27.0, 21.1, 16.1, 14.0. FTIR (cm^{-1}): 2920, 2860, 2190, 1717, 1621, 1509, 1463, 1368, 1279, 1112, 1026, 955, 897, 817, 748, 610. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{24}N_3O_5$ $[M + H]^+$ 446.1716 found 446.1723.

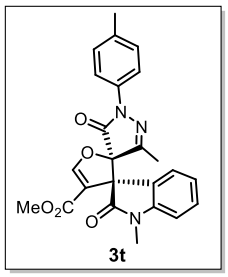
Methyl (2'*R*, 3*S*)-1''-(4-chlorophenyl)-1, 3''-dimethyl-2, 5''-dioxo-1'', 5''dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3s)



The compound **3s** was obtained following the general procedure, starting from **1a**, **2e** and catalyst **C6**. The compound **3s** was purified by column (Silica gel, petroleum ether/EtOAc 70:30) as off white solid (53mg, 90%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.34, MP: 215-218 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 31.79 min, tR(minor) = 41.26 min, 92% *ee*. $[a]_D^{25}$ = +331 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.82 (s, 1H), 7.51 – 7.46 (m, 2H), 7.43 – 7.39 (m, 1H), 7.32 – 7.22 (m, 3H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 3H), 3.21 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.7, 166.8, 162.1, 159.0, 157.9, 143.7, 135.4, 130.7,

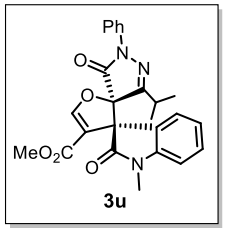
130.3, 128.9, 126.8, 123.1, 122.7, 119.9, 113.8, 108.4, 93.0, 63.2, 51.7, 26.9, 16.0. FTIR (cm^{-1}): 3102, 2923, 2856, 1717, 1619, 1489, 1351, 1278, 1194, 1123, 1036, 993, 928, 829, 747, 610. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{24}N_3O_5$ $[M + H]^+$ 452.1013 found 452.1013.

Methyl (2'*R*, 3*S*)-1,3''-dimethyl-2, 5''-dioxo-1''-(p-tolyl)-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3t)



The compound **3t** was obtained following the general procedure, starting from **1a**, **2d** and catalyst **C6**. **3t** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as off white solid (53mg, 90%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.32, MP: 201-204 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 33.60 min, tR(minor) = 48.37 min, 88% *ee*. $[a]_D^{25}$ = +201.16 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.83 (s, 1H), 7.47 – 7.42 (m, 1H), 7.39 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 3.58 (s, 3H), 3.20 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 166.8, 162.2, 159.2, 157.2, 143.8, 135.4, 134.4, 130.2, 129.3, 126.9, 123.2, 122.7, 119.0, 113.7, 108.4, 93.1, 63.0, 51.6, 26.9, 20.9, 16.0. FTIR (cm^{-1}): 2922, 2312, 1722, 1621, 1511, 1468, 1355, 1281, 1197, 1127, 1037, 991, 928, 821, 753, 695, 609. HRMS (ESI TOF) *m/z* calcd. For $C_{24}H_{22}N_3O_5$ $[M + H]^+$ 432.1559 found 432.1559.

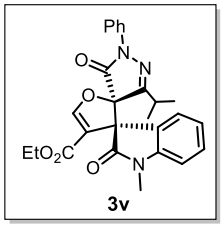
Methyl (2'*R*, 3*S*)-3''-isopropyl-1-methyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3u)



The compound **3u** was obtained following the general procedure, starting from **1a**, **2f** and catalyst **C6**. The compound **3u** was purified by column (Silica gel, petroleum ether/EtOAc 70:30) as off white solid (57mg, 89%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.36, MP: 157-159 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.9 mL/min, λ = 254 nm, tR(minor) = 8.58 min, tR(major) = 9.33 min, 86% *ee*. $[a]_D^{25}$ = +275 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (s, 1H), 7.50 – 7.40 (m, 3H), 7.32 – 7.26 (m, 2H), 7.26 – 7.23 (m, 1H), 7.15 – 7.09 (m, 1H), 7.00 (td, *J* = 7.7, 1.0 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 3.59 (s, 3H), 3.27 (p, *J* = 6.8 Hz, 1H), 3.20 (s, 3H), 1.26 (d, *J* = 6.7 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 167.7, 164.6, 162.4, 159.9, 144.1, 136.9, 130.3, 128.9, 126.7, 125.6, 123.3, 122.9, 119.1, 119.1, 119.0,

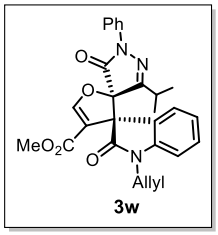
119.0, 113.1, 108.5, 94.3, 63.3, 51.8, 29.8, 27.0, 22.9, 19.3. FTIR (cm^{-1}): 3991, 2927, 1719, 1622, 1493, 1351, 1265, 1217, 1128, 991, 909, 733. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{24}N_3O_5$ $[M + H]^+$ 446.1716 found 446.1716.

Ethyl (2'*R*, 3*S*)- 3''-isopropyl-1-methyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3v)



The compound **3v** was obtained following the general procedure, starting from **1l**, **2f** and catalyst **C6**. The compound **3v** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as off white solid (53mg, 83%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.45, MP: 166-167 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.9 mL/min, λ = 254 nm, tR(minor) = 8.63 min, tR(major) = 10.43 min, 88% *ee*. $[a]_D^{25}$ = +277 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.87 (s, 1H), 7.51 – 7.41 (m, 3H), 7.32 – 7.27 (m, 2H), 7.25 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.00 (td, *J* = 7.7, 1.0 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.00 (qd, *J* = 7.1, 2.9 Hz, 2H), 3.28 (p, *J* = 6.8 Hz, 1H), 3.19 (s, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 167.6, 164.7, 161.8, 159.6, 144.0, 136.9, 130.1, 128.7, 126.7, 125.5, 123.5, 122.7, 118.9, 113.5, 108.2, 94.2, 63.2, 60.4, 29.7, 26.8, 22.8, 19.1, 13.9. FTIR (cm^{-1}): 2926, 1717, 1624, 1493, 1347, 1267, 1218, 1125, 1019, 908, 808, 736. HRMS (ESI TOF) *m/z* calcd. For $C_{26}H_{25}N_3O_5$ $[M + H]^+$ 460.1872 found 460.1872

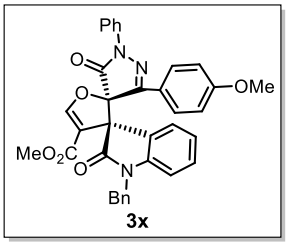
Methyl (2'*R*, 3*S*)-1-allyl-3''-isopropyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3w)



The compound **3w** was obtained following the general procedure, starting from **1j**, **2f** and catalyst **C6**. The compound **3w** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 80:20) as off white solid (51 mg, 81%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.59, MP: 169-170 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(minor) = 10.29 min, tR(major) = 10.98 min, 90% *ee*. $[a]_D^{25}$ = +175 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.49 – 7.41 (m, 3H), 7.32 – 7.26 (m, 2H), 7.22 (td, *J* = 7.8, 1.3 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.77 (ddt, *J* = 17.2, 10.3, 4.9 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.38 (ddt, *J* = 16.6, 5.0, 1.7 Hz, 1H), 4.26 (ddt, *J* = 16.6, 4.6, 1.8 Hz, 1H),

3.59 (s, 3H), 3.24 (h, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 167.7, 164.8, 162.4, 159.8, 143.2, 137.0, 130.5, 130.2, 128.9, 126.9, 125.6, 123.5, 122.8, 119.1, 117.7, 113.3, 109.4, 94.5, 63.5, 51.7, 42.8, 30.2, 22.6, 19.2. HRMS (ESI TOF) *m/z* calcd. For $C_{27}H_{26}N_3O_5$ $[M + H]^+$ 472.1872 found 472.1872.

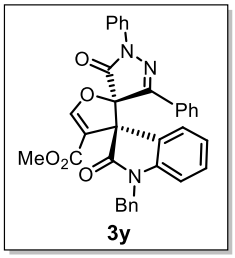
Methyl (2'*R*, 3*S*)-1-benzyl- 3''-(4-methoxyphenyl)- 2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3x)



3x

The compound **3x** was obtained following the general procedure, starting from **1k**, **2c** and catalyst **C6**. The compound **3x** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as yellow solid (59 mg, 85%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.35, MP: 172-174 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 290 nm, tR(major) = 25.45 min, tR(minor) = 37.80 min, 98% *ee*. $[a]_D^{25}$ = +60 (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.86 – 7.81 (m, 2H), 7.50 – 7.44 (m, 3H), 7.34 – 7.27 (m, 2H), 7.21 – 7.03 (m, 7H), 6.96 – 6.88 (m, 3H), 6.54 (d, *J* = 7.8 Hz, 1H), 4.60 (d, *J* = 15.9 Hz, 1H), 4.48 (d, *J* = 15.9 Hz, 1H), 3.86 (s, 3H), 3.58 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.4, 167.7, 162.3, 161.8, 160.2, 154.2, 143.6, 136.6, 135.0, 130.1, 129.6, 128.8, 128.6, 127.4, 126.9, 126.4, 125.8, 123.1, 122.9, 122.5, 119.3, 113.3, 112.9, 109.3, 94.8, 63.6, 55.3, 51.6, 44.1. HRMS (ESI TOF) *m/z* calcd. For $C_{35}H_{28}N_3O_6$ $[M + H]^+$ 586.1978 found 586.1978.

Methyl (2'*R*, 3*S*)-1-benzyl-2, 5''-dioxo-1'', 3''-diphenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (3y)

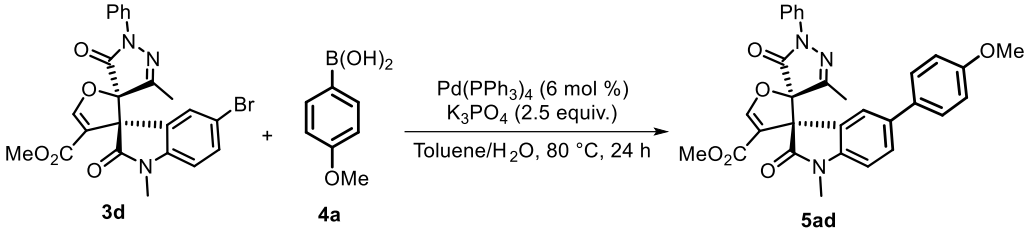


3y

The compound **3y** was obtained following the general procedure , starting from **1k**, **2b** and catalyst **C6**. The compound **3y** was purified by column chromatography (Silica gel, petroleum ether/EtOAc 70:30) as white solid (55 mg, 84%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.47, MP: 134.6-136.4 °C, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 254 nm, tR(major) = 19.18 min, tR(minor) = 22.08 min, 92% *ee*. $[a]_D^{25}$ = +158 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.89 – 7.84 (m, 2H), 7.47 (tdd, *J* = 7.2, 3.1, 1.4 Hz, 4H), 7.43 – 7.38 (m, 2H), 7.35 – 7.28 (m, 2H), 7.21 – 7.14 (m, 4H), 7.14 – 7.01 (m, 3H), 6.94 (td, *J* = 7.6, 0.9 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 15.9 Hz, 1H), 3.57 (s, 3H). $^{13}C\{^{1}H\}$

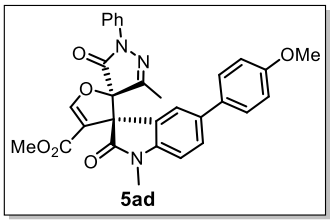
NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 167.8, 162.2, 160.2, 154.5, 143.6, 136.5, 134.9, 131.0, 130.4, 130.1, 128.8, 128.6, 127.9, 127.9, 127.4, 126.9, 126.4, 126.0, 123.0, 122.6, 119.4, 112.9, 109.4, 94.5, 63.6, 51.6, 44.0. HRMS (ESI TOF) *m/z* calcd. For $C_{34}H_{26}N_3O_5$ $[M + H]^+$ 556.1872 found 556.1872.

3.6.4 Procedure for Suzuki coupling reaction (5ad)



To a solution of **3d** (38 mg, 1.0 equiv.) in toluene/H_2O (1 mL/0.3 mL) at room temperature was added 4-methoxy phenylboronic acid **4a** (18 mg, 1.5 equiv.), $Pd(PPh_3)_4$ (5.5 mg, 0.06 equiv.) and K_3PO_4 (41 mg, 2.5 equiv.) sequentially under argon atmosphere. The reaction mixture was heated to 80 °C and maintained at this temperature for stirring 24 h. After which, the reaction mixture was cooled to room temperature and filtered through celite bed and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 100-200 mesh) to afford the desired compound **5ad** as white solid (28 mg, 60 % isolated yield).

Methyl (2'*R*, 3*S*)-5-(4-methoxyphenyl)-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydrodispiro[indoline-3, 3'-furan-2', 4''-pyrazole]-4'-carboxylate (5ad)



White solid (28 mg, 60%, *dr* >20:1), R_f (petroleum ether/EtOAc 70:30) = 0.32, HPLC: CHIRAPAK IC column, *n*-hexane/iso-propanol = 80/20, flow rate = 0.6 mL/min, λ = 290 nm, tR(minor) = 57.60 min, tR (major) = 40.59 min, 91% *ee*. $[a]_D^{25}$ = +3.00 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.45 (tt, *J* = 6.7, 2.0 Hz, 5H), 7.25 – 7.20 (m, 2H), 7.12 – 7.07 (m, 1H), 6.97 – 6.92 (m, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.59 (s, 3H), 3.24 (s, 3H), 2.36 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 167.3, 162.3, 159.4, 159.1, 157.6, 142.6, 136.9, 135.9, 133.3, 128.9, 128.5, 128.1, 125.8, 123.8, 119.1, 114.3, 113.7, 108.6, 93.4, 63.5, 55.5, 51.8, 27.2, 16.1.HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}N_3O_6$ $[M + H]^+$ 524.1822 found 524.1821.

3.7 Appendix III ^{1}H, ^{13}C and HPLC spectral data of representative compounds

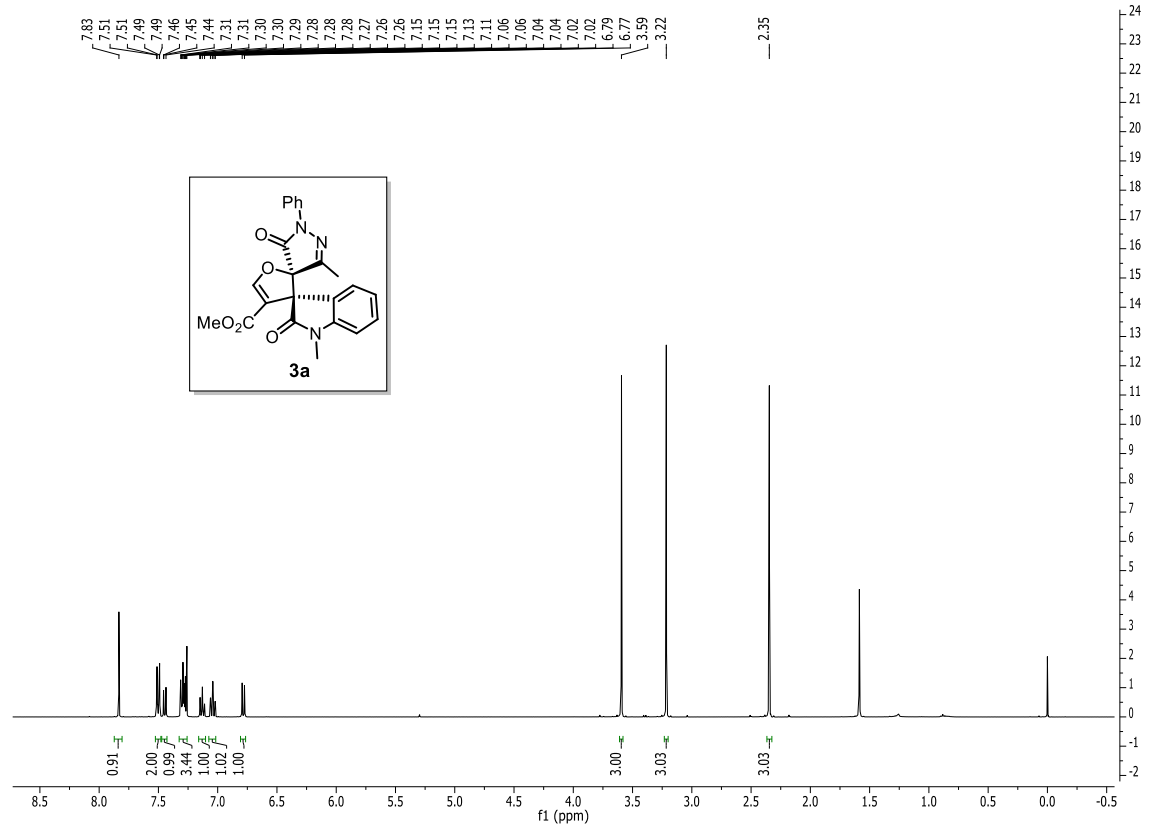


Figure AIII.1 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

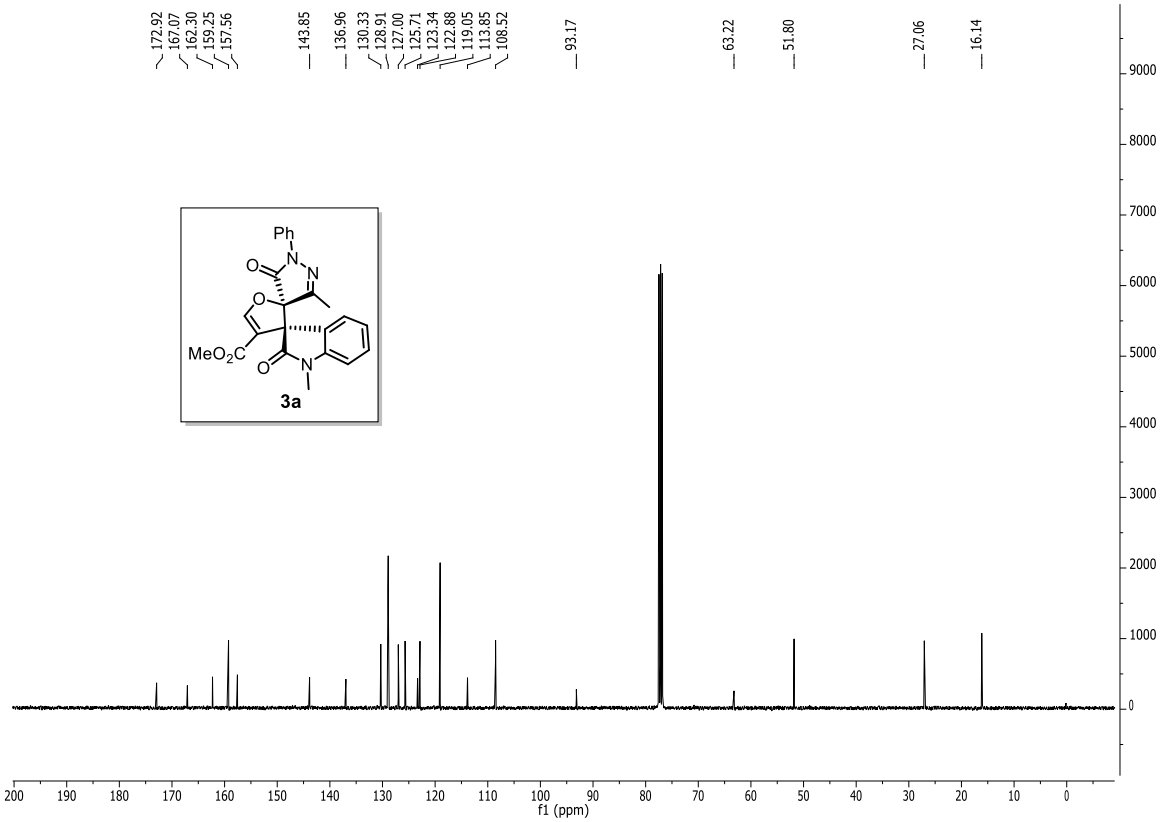
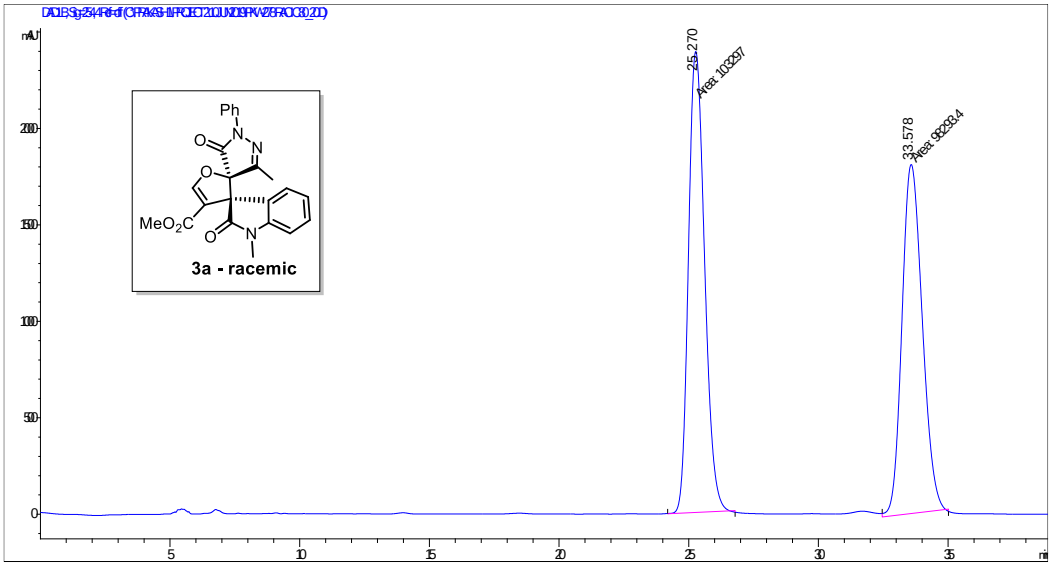
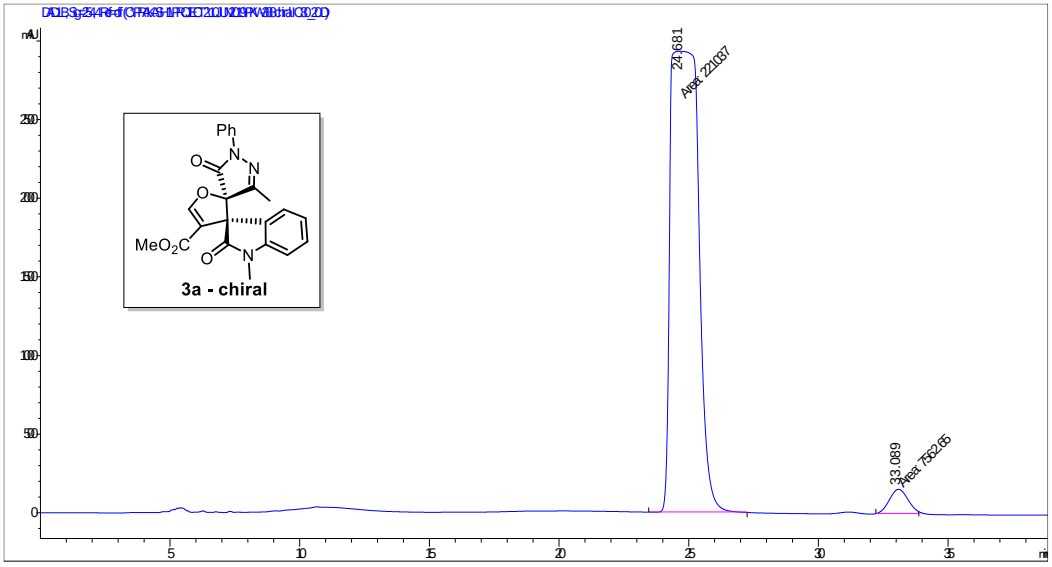


Figure AIII.2 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**



#	Time	Area	Height	Width	Area%	Symmetry
1	25.27	103296.5	2389.5	0.7205	51.241	0.784
2	33.578	98293.4	1809.3	0.9055	48.759	0.809



#	Time	Area	Height	Width	Area%	Symmetry
1	24.681	221036.5	2930.6	1.2571	96.692	0.555
2	33.089	7562.6	153.1	0.8234	3.308	0.938

Figure AIII.3 HPLC profile of compound **3a**

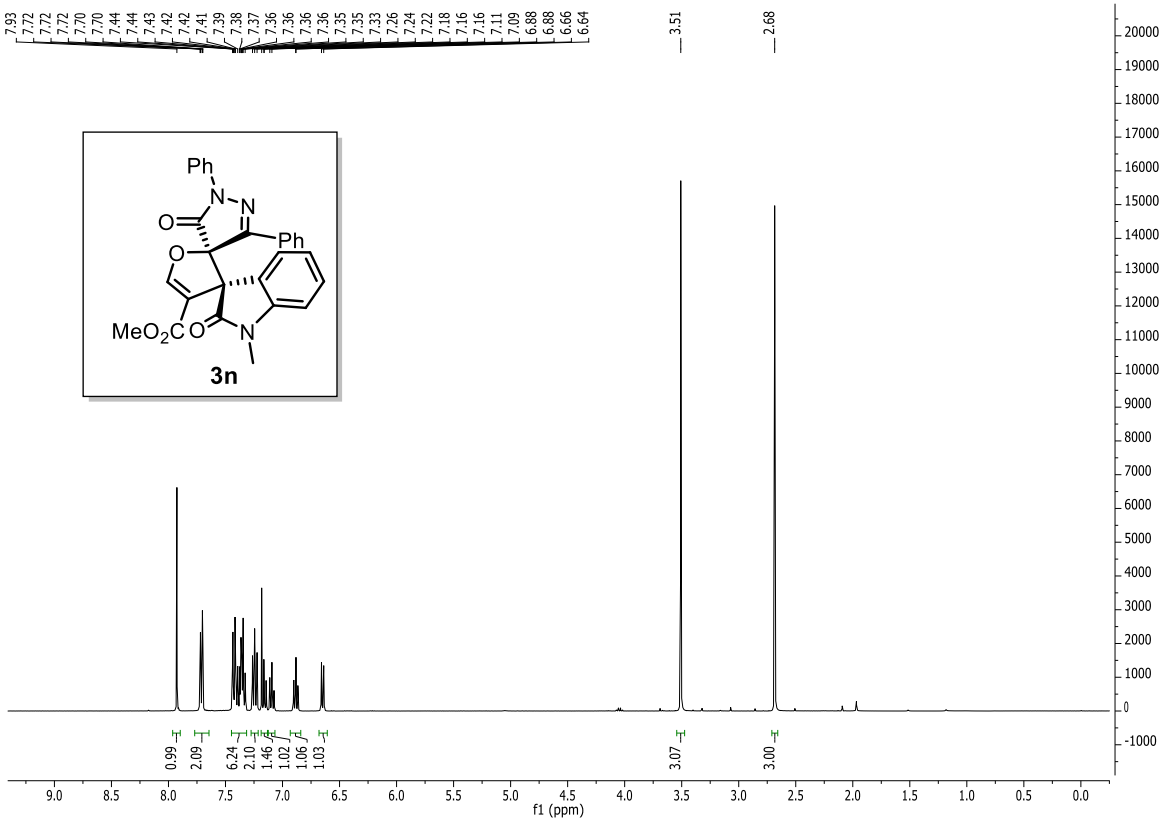


Figure AIII.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3n**

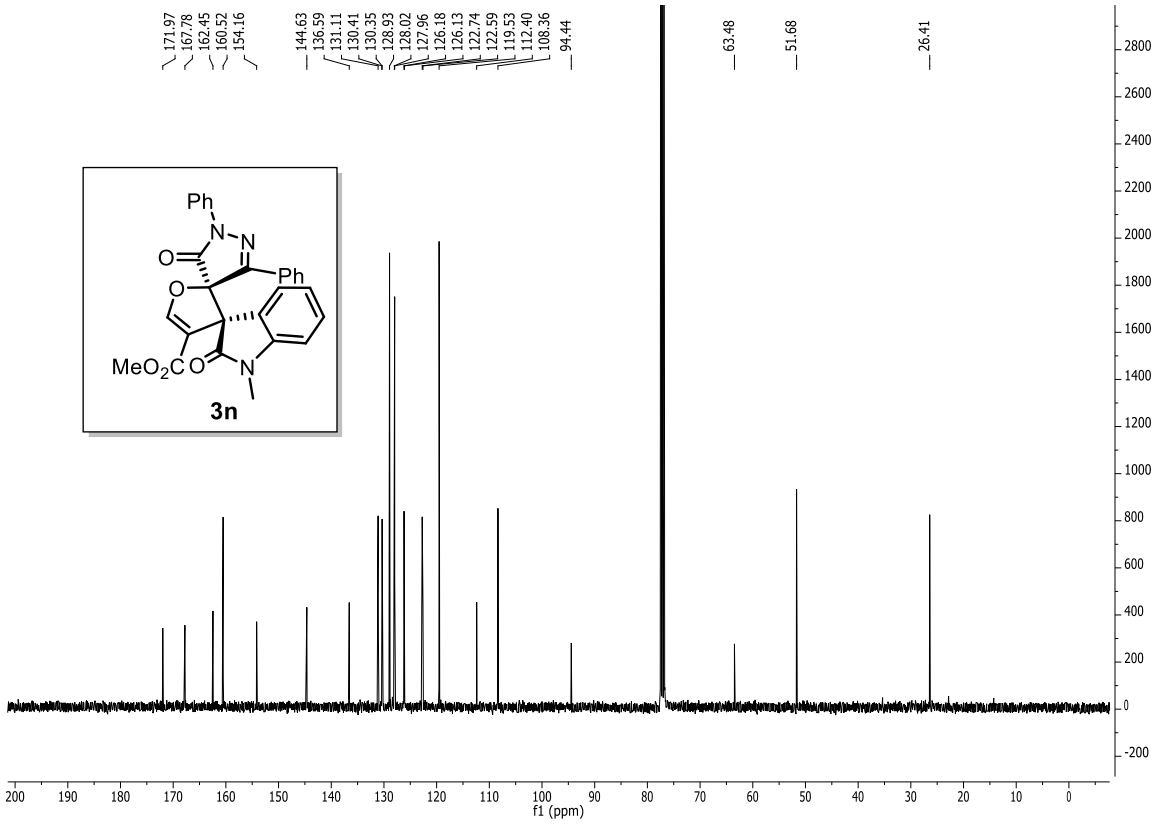
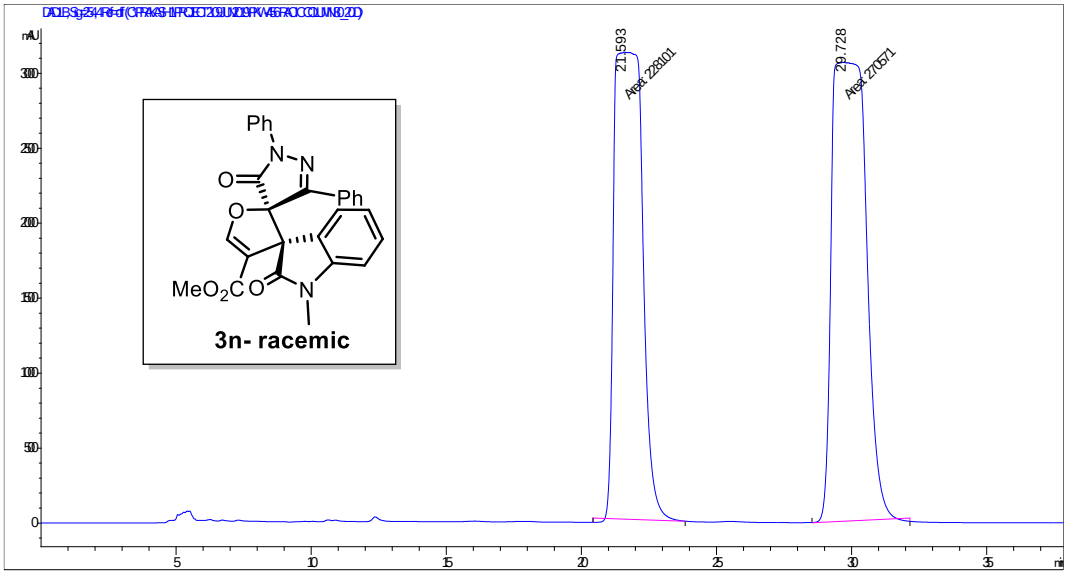
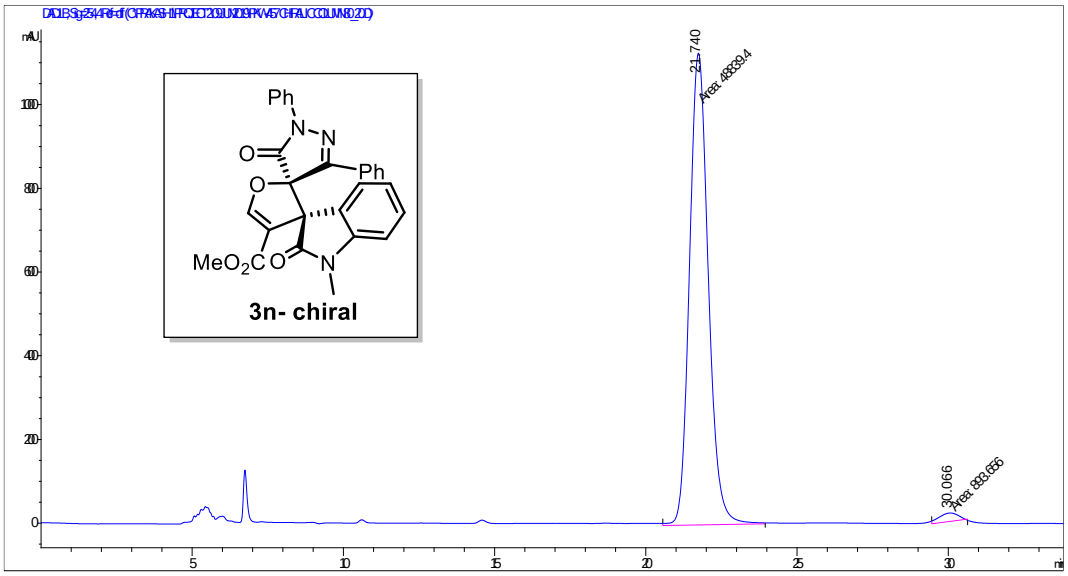


Figure AIII.5 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3n**



#	Time	Area	Height	Width	Area%	Symmetry
1	21.593	228100.6	3114.6	1.2206	45.742	0.577
2	29.728	270571.4	3061.5	1.473	54.258	0.57



#	Time	Area	Height	Width	Area%	Symmetry
1	21.74	48839.4	1127.2	0.7222	98.203	0.863
2	30.066	893.7	20.2	0.7373	1.797	1.552

Figure AIII.6 HPLC profile of compound **3n**

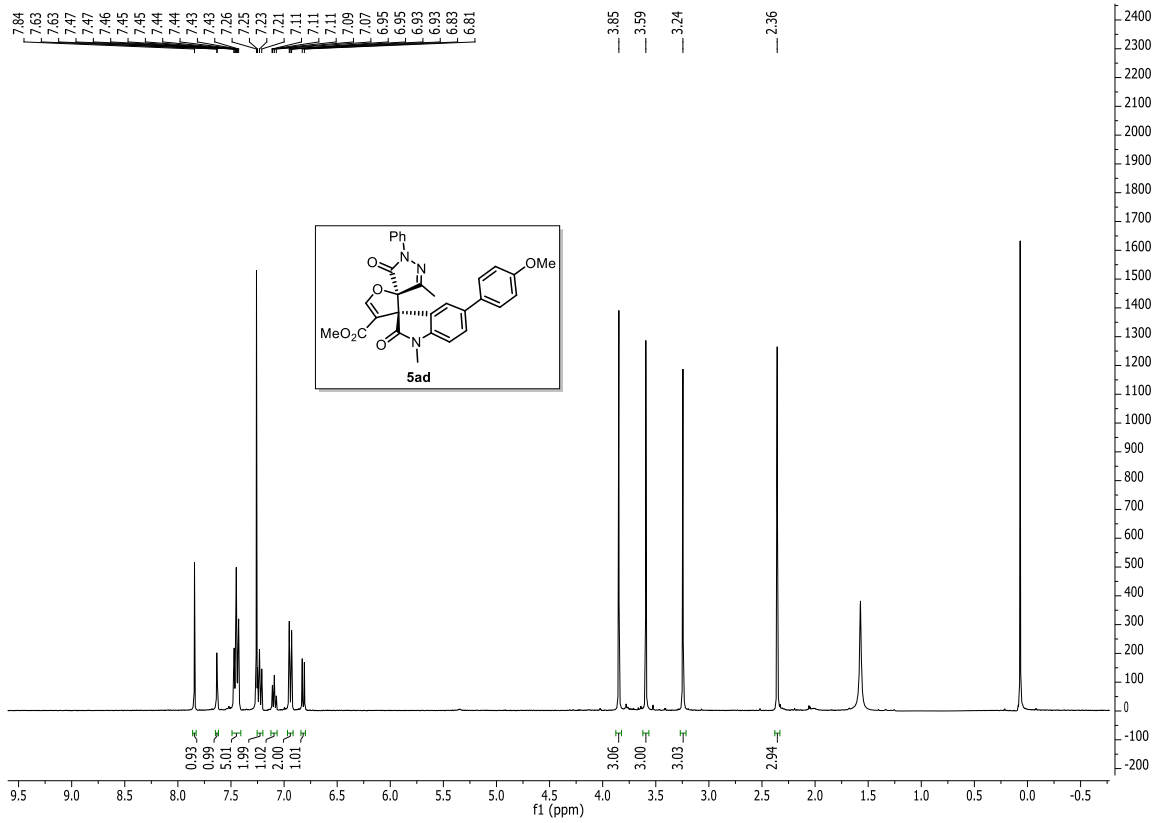


Figure AIII.7 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5ad**

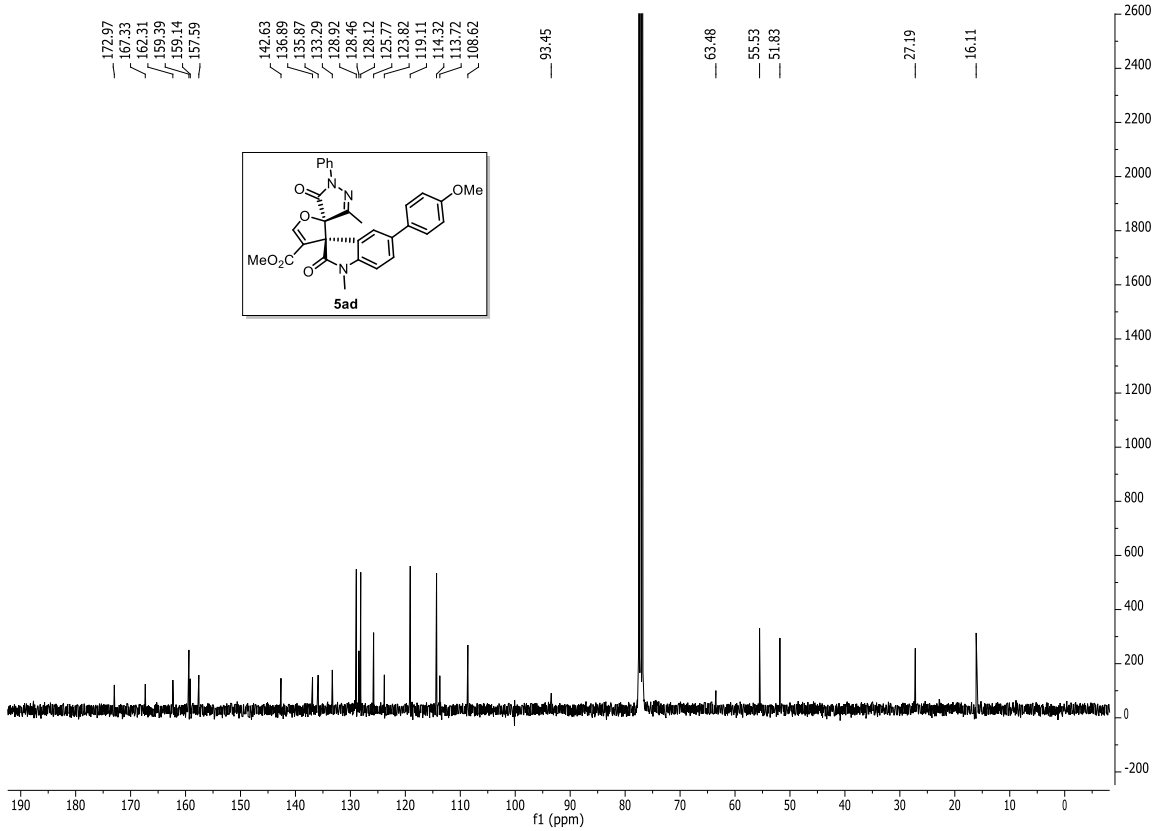
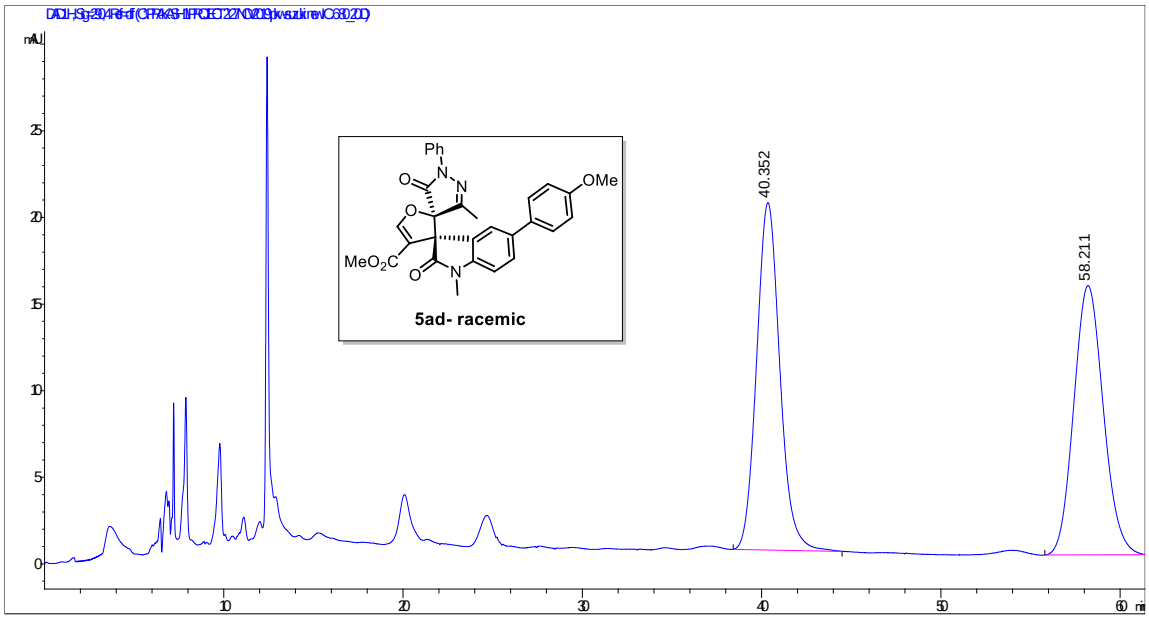
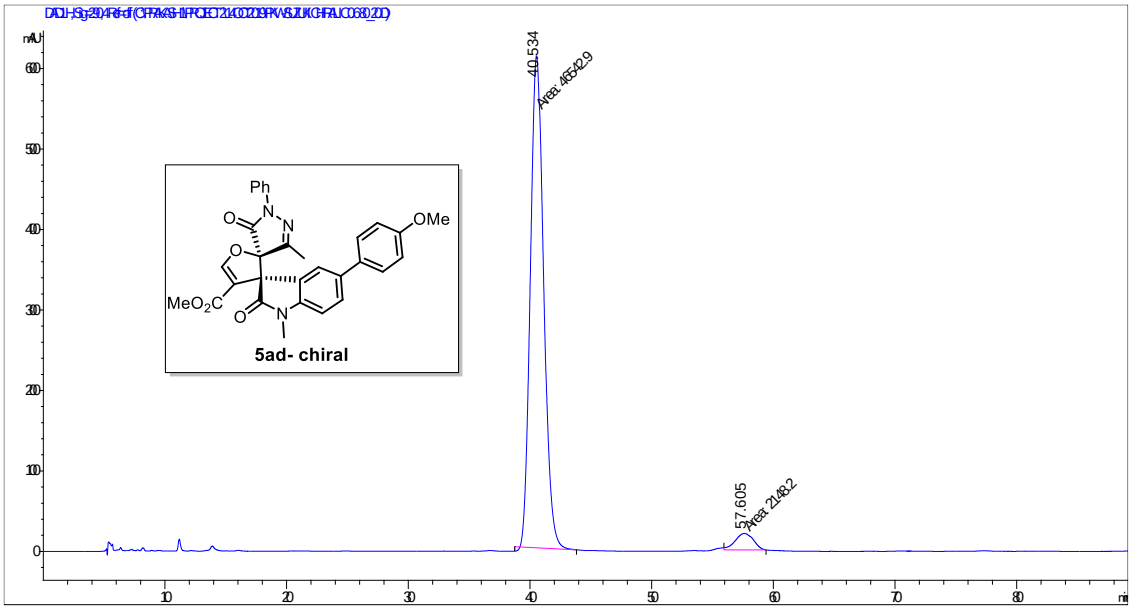


Figure AIII.8 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5ad**



#	Time	Area	Height	Width	Area%	Symmetry
1	40.352	1805.6	20	1.2067	50.358	0.9
2	58.211	1779.9	15.5	1.3417	49.642	0.909



#	Time	Area	Height	Width	Area%	Symmetry
1	40.534	46542.9	611.4	1.2688	95.588	0.823
2	57.605	2148.2	20.4	1.7512	4.412	0.996

Figure AIII.9 HPLC profile of compound **5ad**

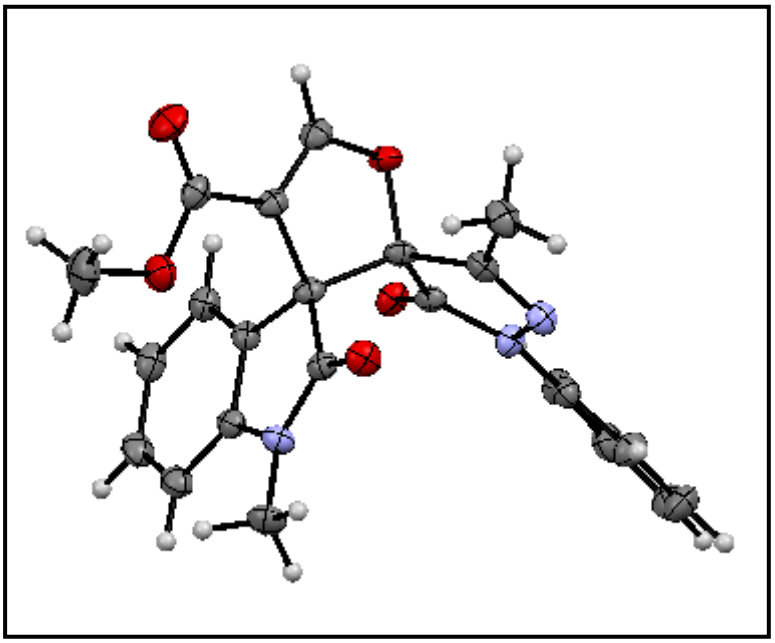


Figure AIII.10 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3a**

3.8 References

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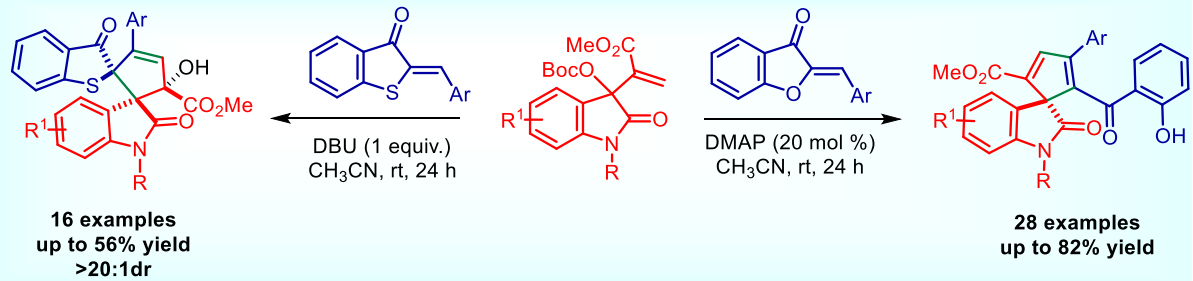
4 An Easy and Practical Approach to Access Multifunctional Cylcopentadiene- and Cyclopentene-Spirooxindoles via [3+2] Annulation

Abstract

We describe herein an efficient and regioselective [3 + 2] annulation of isatin derived Morita-Baylis-Hillman (MBH) carbonates and aurones/thioaurones in presence of Lewis base. The spiroheterocyclic moieties such as cyclopentadiene fused oxindole and hydroxy cyclopentene fused spirooxindole derivatives have been obtained in moderate to good yileds with high stereoselectivity. The combination of experimental and density functional theory (DFT) calculations offered an insight into the reaction mechanism.



Warghude, P. K.; Sabale, A. S.; Dixit, R.; Vanka, K.; Bhat. R. G. *Org. Biomol. Chem.* **2021**, *19*, 4338-4345.

FOUR

4 An Easy and Practical Approach to Access Multifunctional Cylcopentadiene- and Cyclopentene-Spirooxindoles via [3+2] Annulation

4.1 Introduction

The building of spirocyclic architecture with multiple functional groups is of great interest in asymmetric synthesis.[1] Particularly, the spirooxindole scaffold has gained considerable attention due to its occurrence in various natural products and pharmaceutically active compounds.[2,3] The unique structural features and potential pharmacological significance have paved the way for the development of an effective method to construct spirocarbocyclic/heterocyclic scaffolds.[4] Among the carbocyclic oxindoles, the spirooxindole cyclopentane skeleton is found in many naturally occurring bioactive compounds such as Notoamide A (cytotoxicity against cancer cell lines), (–)-Paraherquamide A (potent anthelmintic agent) and Cyclopiamine B (Figure 4.1).[5]

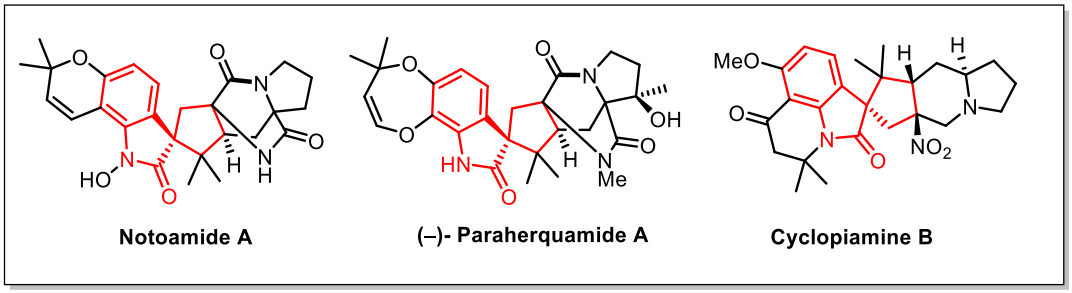


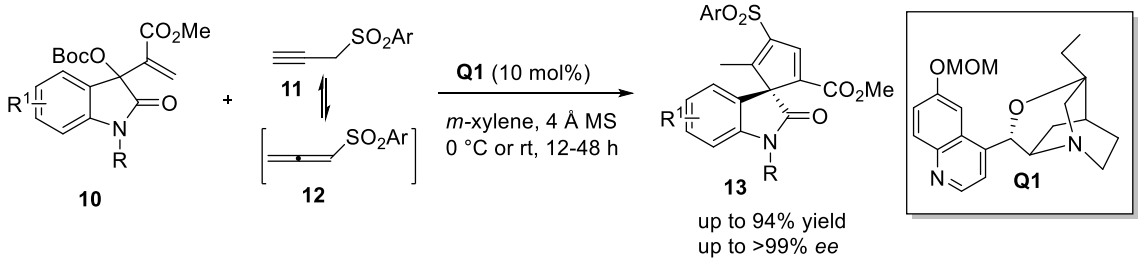
Figure 4.1 Bioactive compounds containing spirooxindoles architecture

Due to their potential biological activity and also as they are interesting pharmacophores, significant efforts have been made to construct spirocyclic architecture in racemic as well as enantioselective manner.[4] Many reports are available in the literature to construct spirocarbocylic scaffolds, however, the synthesis of densely

functionalized spiro-cyclopentadiene oxindole derivatives have been rarely been attempted.[6]

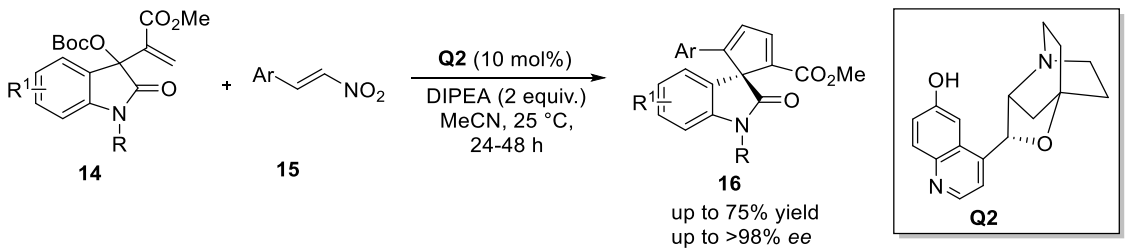
4.2 Recent approaches for the synthesis of spirooxindole fused cyclopentadiene skeletons

In 2011, Chen and co-workers[6a] have described an enantioselective [3 + 2] cycloaddition of MBH carbonates of isatins **10** and propargyl sulfones **11** under cinchona alkaloid derivative β-ICD-O-MOM ether under organocatalysis (Catalyst **Q1**) to afford the cyclopentadiene fused 2-oxindoles **13** in high yields (up to 94%) with excellent enantioselectivities (up to >99% *ee*). This transformation believed to proceed via formal dipolar cycloaddition of an in situ generated allylic *N*-ylide and allenyl sulfone **12** followed by a carbon-carbon bond isomerization sequence to furnish the desired cyclopentadiene fused 2-oxindole **13** (Scheme 4.1).



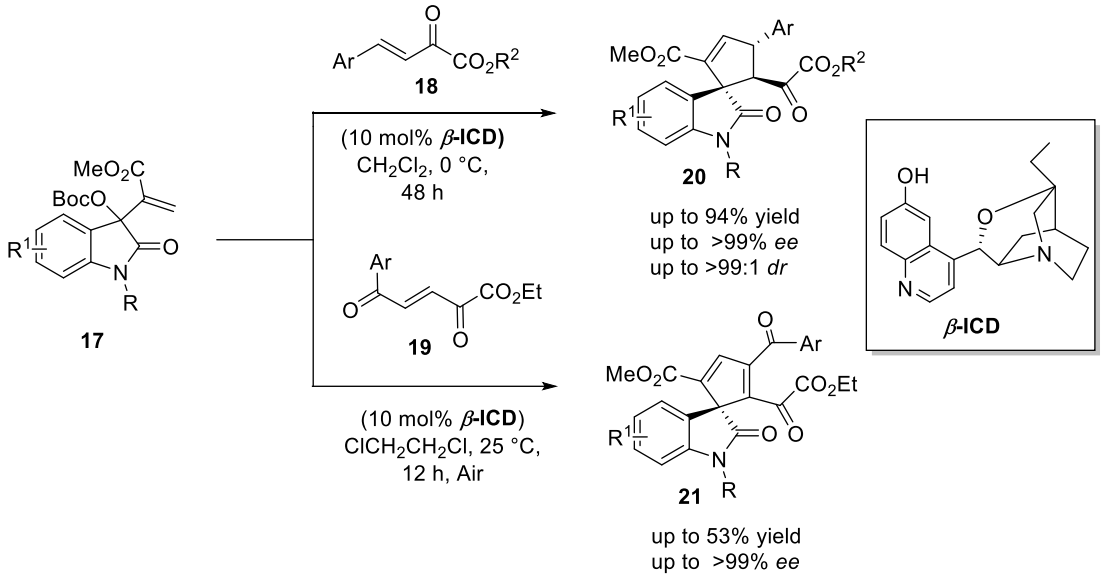
Scheme 4.1 Asymmetric synthesis of cyclopentadiene fused oxindole

In 2015, Chen's research group[6b] has reported the asymmetric [3 + 2] cycloaddition of Morita–Baylis–Hillman carbonates of isatins **14** and nitroolefins **15** in the presence of *α*-isocupreine **Q2** (10 mol%) and DIPEA (2.0 equiv.) as a base in acetonitrile. This annulation reaction delivered the enantioselective spirooxindole cyclopentadiene derivatives **16** in moderate to good yields (up to 75%) with excellent enantioselectivities (up to 98% *ee*) (Scheme 4.2).



Scheme 4.2 Enantioselective [3 + 2] annulation of MBH carbonates and nitroolefins

Recently, Cui and Chen[6c] have developed a protocol for the highly stereoselective [3 + 2] cycloaddition for the construction of chiral spiro-cyclopentene/cyclopentadiene-oxindole **20/21** frameworks. The cyclization of MBHCs of isatin **17** and β,γ-unsaturated α-keto esters **18/19** in the presence of β–isocupreidine catalyst (**β-ICD**) afforded the corresponding spirocarbocyclic oxindole derivatives **20/21** in moderate to excellent yields with an excellent diastereoselectivities and enantioselectivities (up to 99: 1 *dr*, 99% *ee*, Scheme 4.3).



Scheme 4.3 Cycloaddition of MBH carbonates with β,γ-unsaturated α-keto esters

On the other hand, spirocyclic benzofuranone is a valuable scaffold widely found in a large number of natural and synthetic compounds. Some of the compounds with this scaffold exhibit remarkable biological activities (Figure 4.2).[7] For example, Griseofulvin **I** is an orally active drug used for the treatment of skin related infections (antifungal),[7a] The bis-spirobenzofuran-dione **II** is an active agent against influenza B virus.[7b] While, the spirocyclohexane benzofuran-3-one core **III**, belongs to the polyketide leptosphaerin C class and is known to exhibit the antifungal activity (Figure 4.2).[7c] In spite of the potent biological significance of these compounds, surprisingly, very few methods have been described for the synthesis of spirocyclic benzofuranone compounds in literature.[8] Therefore, the development of alternative, highly efficient, one-pot and practical method under mild reaction conditions is highly demanding and useful.

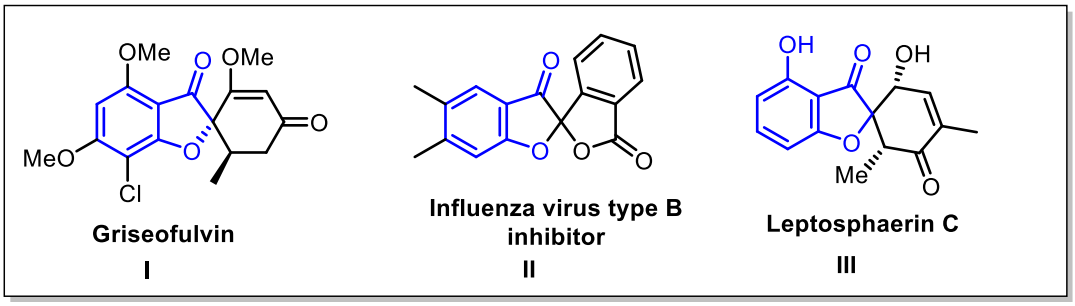
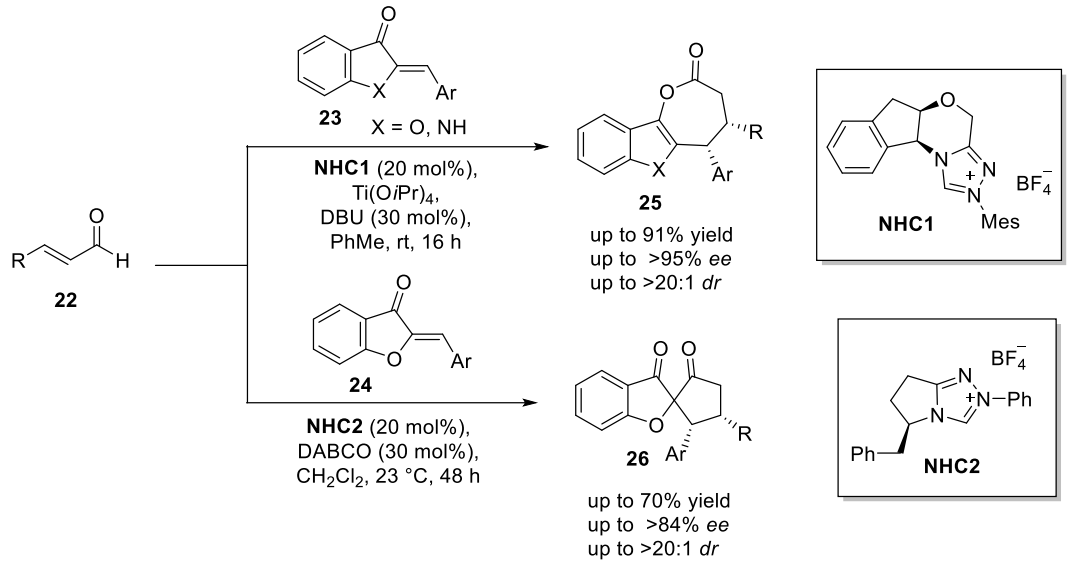


Figure 4.2 Bioactive compounds containing spirocyclic benzofuranones

4.3 Use of aurones in the synthesis of spirocyclic benzofuranones

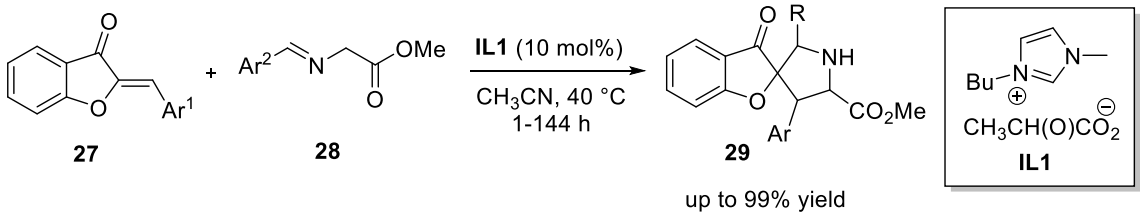
Aurone (2-benzylidenebenzofuran-3(2*H*)-one) is one of the key precursors for the synthesis of spirocyclic benzofuranones. Moreover, the aurones are also present in a different natural products and useful synthetic compounds.[9] Aurones and their derivatives have been successfully employed in various cycloaddition/annulation reactions to construct the complex spiroheterocycles.

In the year 2014, Zhao and co-workers[10] have described the *N*-heterocyclic carbene (NHC) catalyzed chemodivergent annulation reaction of enals **22** with heterocyclic enones **23/24**. The enals **22** reacted with enones **23** in presence of NHC catalyst-**NHC1** and titanium isopropoxide [$Ti(OiPr)_4$]-a co-catalyst via a formal [3 + 4] oxacyclization to deliver the corresponding ε-lactones **25** in moderate to good yields (up to 91%) with excellent streoselectivities (up to 95% *ee*). Interestingly, enals **22** when treated with enones **24** in presence of azolium **NHC2** catalyst and DABCO as a base afforded the corresponding highly enantioselective spiroheterocycles **26** via a formal [3 + 2] annulation pathway (up to 99% *ee*) (Scheme 4.4).



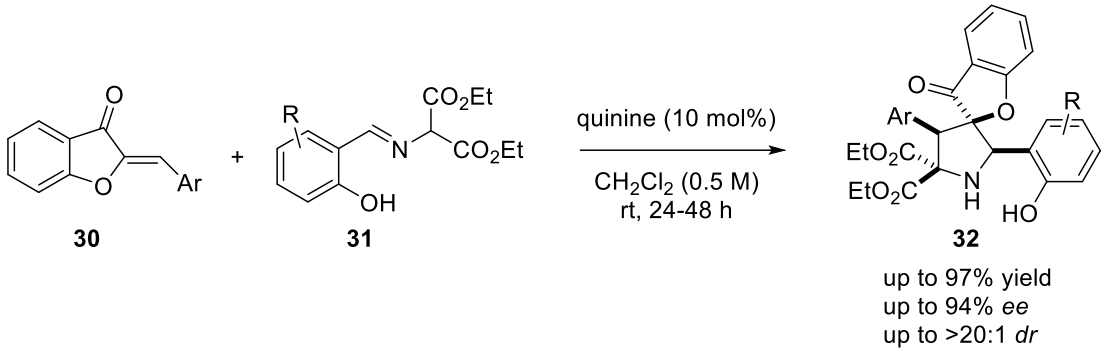
Scheme 4.4 Chemodivergent [3 + 2] annulation of enals with aurones

In 2016, Fu and Ding[11] have described the ionic liquid (**IL1**) catalyzed 1, 3-dipolar cycloaddition of 2-alkylidene-benzofuran-3-one **27** with various azomethine ylides **28** in acetonitrile at 40 °C to access the spirocyclic benzofurans **29**. This method enabled the synthesis of highly functionalized spiro[pyrrolidine-benzofuran-3-one] derivatives **29** in good to excellent yields (up to 99%) (Scheme 4.5).



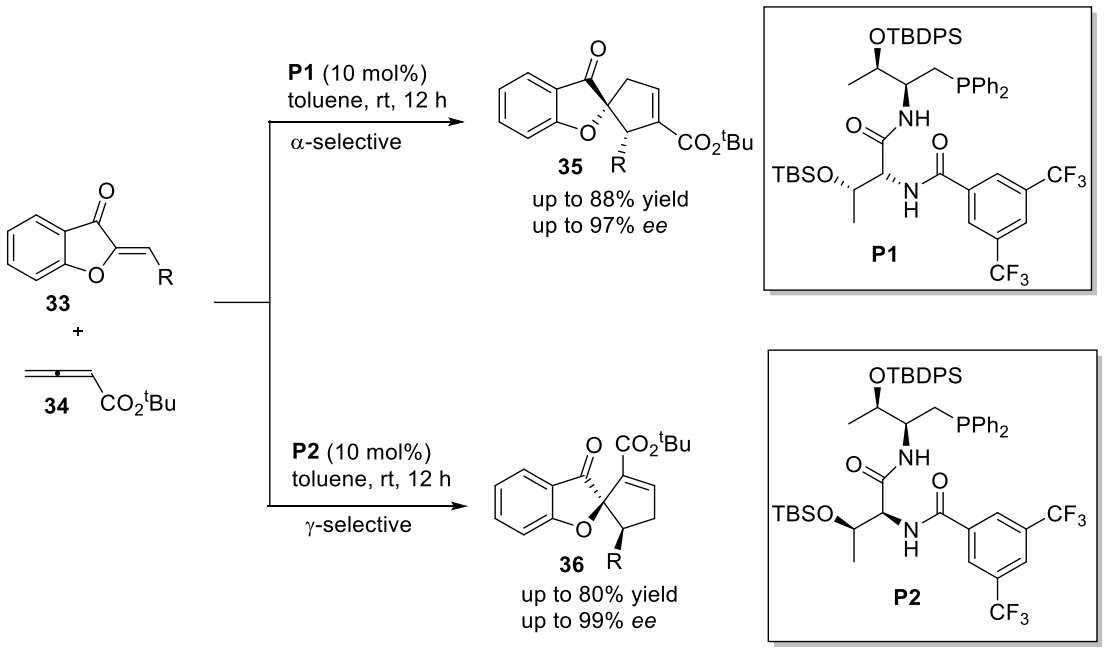
Scheme 4.5 Ionic liquid catalyzed 1, 3-dipolar cycloaddition of aurones and azomethine ylides

In 2017, Kowalczyk et al.[12] have employed [3 + 2] cycloaddition strategy for the synthesis of pyrrolidine fused benzofuran-3(2*H*)-one **32** derivatives. This reaction involved the cycloaddition of 2-arylidenebenzofuran-3(2*H*)-ones **30** and imines **31** derived from salicylaldehydes and diethyl aminomalonates under quinine catalysis. The spirocyclic benzofuranones **32** derivatives were obtained in very high yields (up to 97%) with excellent stereoselectivities (>20:1 *dr*, and 94% *ee*) (Scheme 4.6).



Scheme 4.6 Asymmetric [3 + 2] annulation of aurones with imines

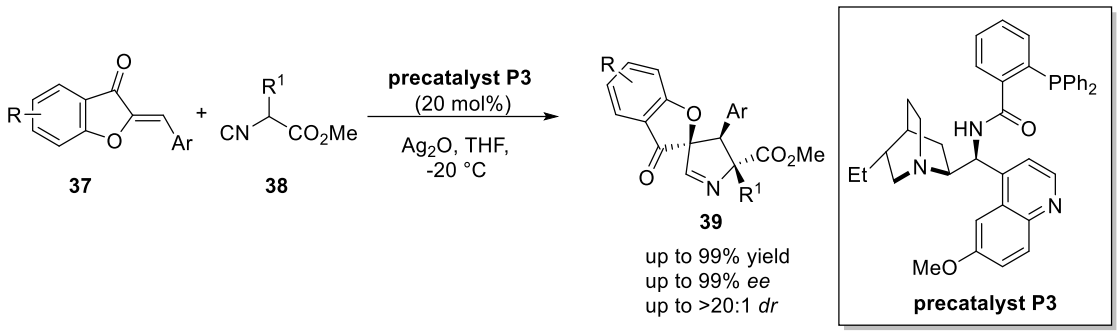
Later, Lan, Ullah and Lu[13] have developed a catalyst-controlled regio-divergent approach for the synthesis of spirocyclic benzofuranones via [3 + 2] annulation of aurones **33** and allenoate **34**. This reaction afforded different regioisomers in presence of two different dipeptide based catalysts. *α*-selective annulation products **35** were synthesized using L-Thr-D-Thr-derived dipeptide phosphine catalyst **P1** in moderate to good yields (up to 88%) with excellent enantioselectivities (up to 97% *ee*). Interestingly, the use of L-Thr-L-Thr-derived dipeptide phosphine catalyst **P2**, resulted in the formation of *γ*-selective products **36** in moderate to good yields (up to 80%) with high streoselectivities (up to 99% *ee*) (Scheme 4.7).



Scheme 4.7 Regioselective [3 + 2] annulation of aurones with allenoates

Recently, Wang et al. [14] have reported the chiral Ag-complex catalyzed enantioselective formal [3 + 2] cycloaddition of aurone **37** with isocyanoacetates **38** to access spiropyrrolines

39. The method explored the catalytic efficiency of pre-catalyst **P3** in presence of silver oxide for the enantioselective synthesis of spiropyrrolines **39** bearing three contagious chiral centers in excellent yields (up to 99%) with stereoselectivities (>20:1 *dr*, >99% *ee*) (Scheme 4.8).



Scheme 4.8 Asymmetric [3 + 2] annulation of aurones with isocyanoacetates

In spite of this recent progress on cycloaddition reactions for the elegant synthesis of spirocyclic benzofurans, yet the formal cycloaddition of aurone with MBHCs of isatin has not been achieved till date to the best of our knowledge. The sulphur analogue of aurone is called as thioaurone and it has been also utilized as an excellent Michael acceptor in various cycloaddition reactions.[15] Therefore, we believed that aurones and thioaurones could be used as suitable C2 synthons in the cycloaddition reactions to construct structurally diverse and multi-functional spiro-heterocyclic scaffolds. Herein, in this chapter we report the highly efficient one-pot synthesis of spirooxindole cyclopentadiene and hydroxy cyclopentene fused spirooxindole derivatives under mild reaction conditions.

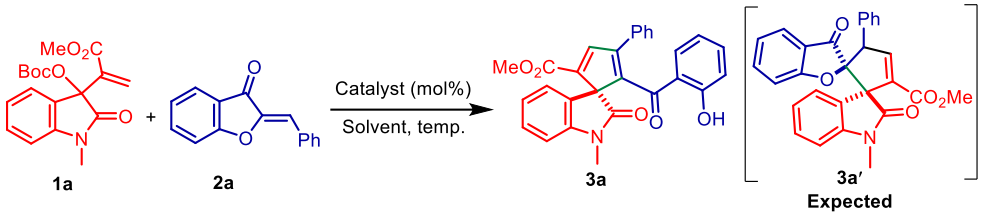
4.4 Results and Discussion

To validate our hypothesis, we performed a model reaction between MBH carbonate of isatin **1a** and aurone [(*Z*)-2-benzylidenebenzofuran-3(2*H*)-one] **2a** in presence of 4-dimethylaminopyridine (DMAP, 20 mol%) in dichloromethane (DCM) at room temperature. Surprisingly, the reaction afforded an unexpected cyclopentadiene fused oxindole **3a** in 65% yield and the anticipated bis-spirocyclic compound **3a'** did not obtain during course of the reaction (Table 4.1, entry 1). Interestingly, after gleaning through the literature it has been observed that the synthesis of spiro-cyclopentadiene scaffold has rarely been attempted.[6] In this

regard, we further planned to optimize the reaction conditions. In spite of our several attempts, the enantioselective synthesis of spiro cyclopentadiene fused oxindole **3a** starting from **1a** and **2a** in presence of different chiral catalyst such as DMAP derived catalyst as well as other chiral quinine based organocatalysts did not work under different reaction conditions and all our efforts were unsuccessful. After that, we focussed on optimizing the reaction conditions for the racemic synthesis of cyclopentadiene fused oxindole **3a**. The reaction of MBH carbonate **1a** with aurone **2a** in presence of PPh_3 (20 mol%) did not afford the desired product **3a** even after stirring for a prolonged reaction time (Table 4.1, entry 2). Later, we screened different tertiary amine catalysts for this cycloaddition ring opening transformation. The independent reactions of **1a** and **2a** in presence of DBU (1, 8-diazabicyclo[5.4.0]undec-7-ene) and DABCO (1, 4-diazabicyclo[2.2.2]octane) as a catalyst delivered the cyclopentadiene fused spirooxindole **3a** in 55% and 40% yield respectively (Table 4.1, entries 3-4). On the basis of initial results, DMAP was found to be a suitable catalyst for the desired transformation. Further, we screened different solvents such as chloroform ($CHCl_3$), toluene, EtOAc (ethyl acetate), tetrahydrofuran (THF) and acetonitrile in presence of DMAP (20 mol%) (Table 4.1, entries 5-9). Among all, acetonitrile proved to be the optimum solvent by providing the desired product **3a** in 76% yield (Table 4.1, entry 9). We observed that decrease in the catalyst loading (15 mol% DMAP) drastically lowered the yield of cyclopentadiene fused spirooxindole **3a** (40%, Table 4.1, entry 10). It was observed that lowering the reaction temperature to 0 °C significantly lowered the yield of cyclopentadiene oxindole **3a** (30%, Table 4.1, entry 11). Based on the screening, MBH carbonate **1a** (1.0 equiv.), aurone [(*Z*)-2-benzylidenebenzofuran-3(2*H*)-one]**2a** (1.2 equiv.) and DMAP (20 mol%) in acetonitrile proved to be the optimum reaction condition to achieve cyclopentadiene fused oxindoles **3a** via [3 + 2] annulation followed by ring opening reaction.

After establishing the optimum reaction conditions, in order to generalize the protocol of [3 + 2] cycloaddition and to have the wider substrate scope we planned to explore the synthesis of new cyclopentadiene oxindole derivatives. In this regard, initially, we synthesized different MBH carbonates of isatin (**1a-1j**)[18f] and substituted aurones (**2a-2t**)[14] using literature procedure. Having obtained different substrates, we investigated the substrate scope of various MBH carbonates (**1a-1j**) with aurone **2a** under the standard optimized reaction conditions. Gratifyingly, all the MBH carbonates (**1a-1j**) reacted efficiently with aurone **2a** to furnish the corresponding cyclopentadiene fused spirooxindoles (**3a-3j**) in very good yields (up to 82%, Table 4.2).

Table 4.1. Optimization of the reaction conditions[a-c]



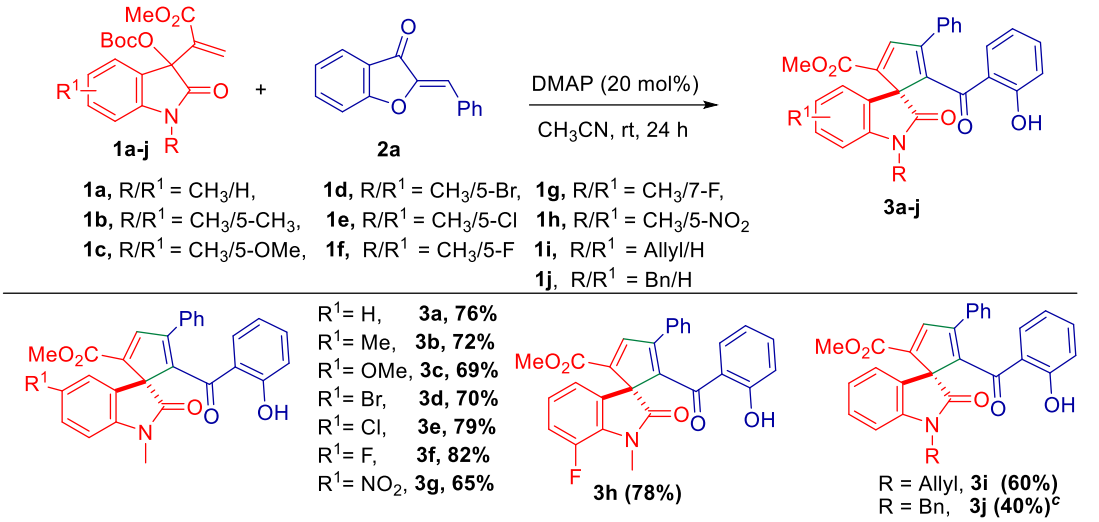
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[b]
1	DMAP (20)	DCM	24	65
2	PPh_3 (20)	DCM	48	NR
3	DBU (20)	DCM	24	55
4	DABCO (20)	DCM	24	40
5	DMAP (20)	$CHCl_3$	24	68
6	DMAP (20)	Toluene	24	70
7	DMAP (20)	EtOAc	24	72
8	DMAP (20)	THF	24	68
9	DMAP (20)	CH_3CN	24	76
10	DMAP (15)	ACN	24	40
11[c]	DMAP (20)	CH_3CN	24	30

[a]**Reaction conditions**: MBH carbonate **1a** (0.115 mmol, 40 mg), aurone **2a** (0.138 mmol, 31 mg), Cat. (20 mol %) in 2.0 mL of solvent at room temperature for the specified time. [b]Isolated yield after purification by column chromatography. [c]at 0 °C.

We found that, all the reactions proceeded smoothly regardless of the electron-donating (CH_3, OCH_3) and electron-deactivating/withdrawing (Br, Cl, F, NO_2) nature of substituents on MBH carbonates. Likewise, *N*- protected (allyl and benzyl) MBH carbonates (**1i, 1j**) reacted easily to give the cyclopentadiene oxindole **3i** and **3j** in 60% and 40% yield respectively (Table 4.2). Further, the molecular structure of cyclopentadiene fused spirooxindole derivative **3a** was established unambiguously using single-crystal X-ray diffraction analysis.[16]

Next, we examined the substrate scope of various aurones (**2b-2s**) with MBH carbonate **1a** under the optimized reaction conditions (Table 4.3). To our delight, all the reactions proceeded smoothly to furnish the corresponding [3 + 2] cycloaddition products **3j-3at** in moderate to good yields (50-81%, Table 4.3). It is noteworthy that aurones with electron deactivating/withdrawing (Br, Cl, F, CF_3, CN, NO_2) as well as electron donating (CH_3, OCH_3)

Table 4.2 Substrate scope for isatin derived MBH-carbonates[a-c]

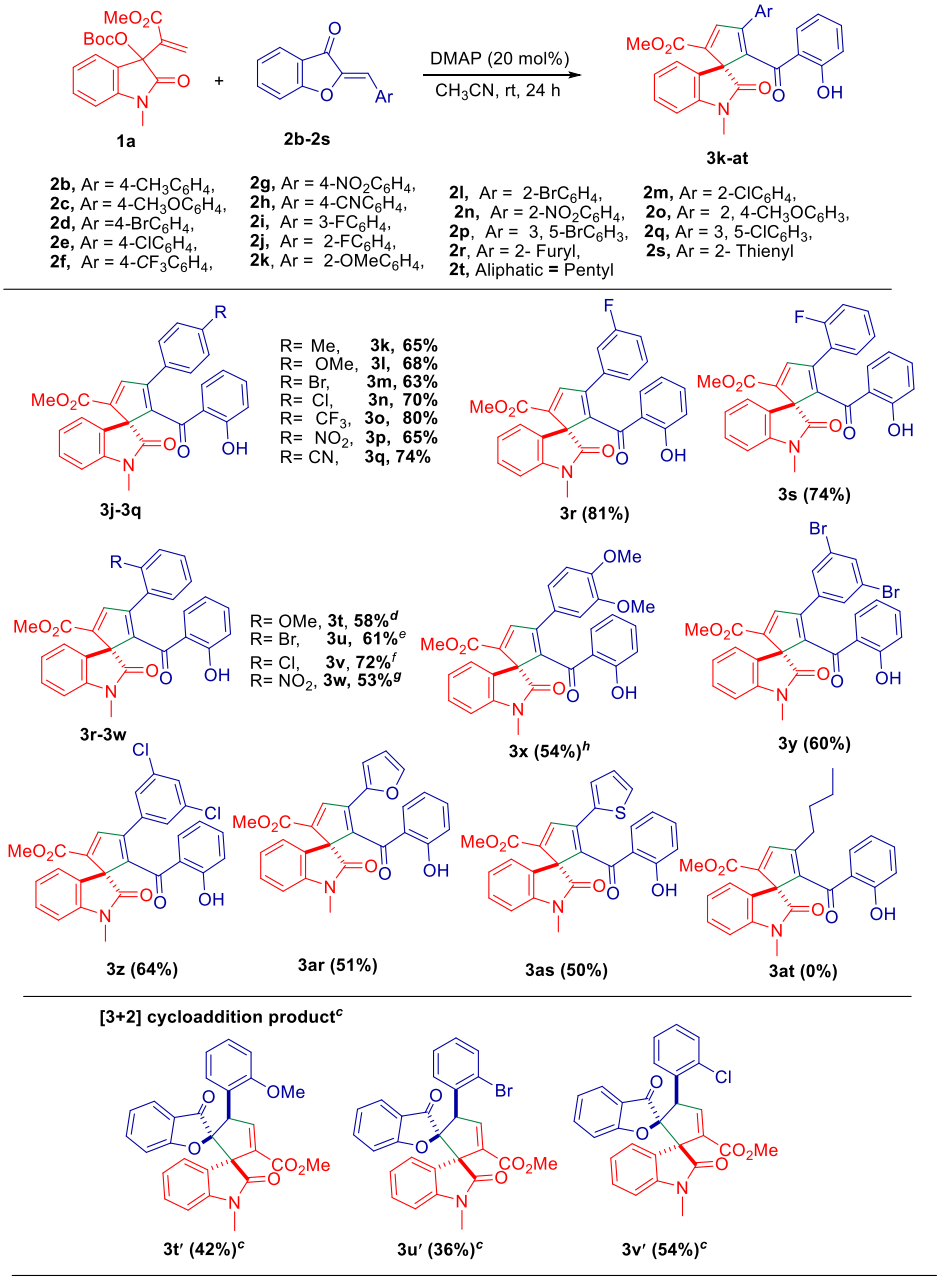


[a]**Optimized reaction conditions**: MBH carbonate of isatin **1** (0.115 mmol), Aurone **2a** (0.138 mmol), DMAP (20 mol%) in 2.0 mL of ACN at room temperature; [b]Isolated yield after column chromatography.[c]50 mol% DMAP

groups at *meta*- and *para*-positions furnished the desired products **3k-3r** in moderate to good yields (63-81%, Table 4.3). Surprisingly, *ortho*-substituted aurones (**2k-2m**) did not afford the expected cyclopentadiene fused spirooxindole products. However, the bis-spirocyclic compounds **3t'-3v'** [with benzofuran-3(*2*H)-one ring intact] were obtained starting from *ortho*-substituted aurones (**2k-2m**) in moderate yields (up to 54%) under the optimized reaction conditions (Table 4.3). The molecular structure of bis-spirocyclic compound **3v'** was assigned by using single-crystal X-ray diffraction analysis.[17] Later, we noticed that the reaction at elevated temperature (up to 70 °C) furnished the cyclopentadiene fused spirooxindoles **3t-3w** [benzofuran-3(*2*H)-one ring opened products] in moderate to good yields (up to 72%).

However, the substrate bearing more electron deactivating and less bulky fluoro group at *ortho*-position of aurone **2j** delivered the cyclopentadiene fused spirooxindole product **3s** in 74% yield at room temperature (Table 4.3). The disubstituted aurones also reacted efficiently to give the desired products (**3x-3z)** in moderate yields (up to 64%, Table 4.3**)**. Furthermore, the substates containing furyl and thienyl moieties afforded the corresponding products **3ar** and **3as** in 51% and 50% yields respectively (Table 4.3). However, the aliphatic (alkyl) derivative **2t** did not work under the optimized reaction condition (Table 4.3).

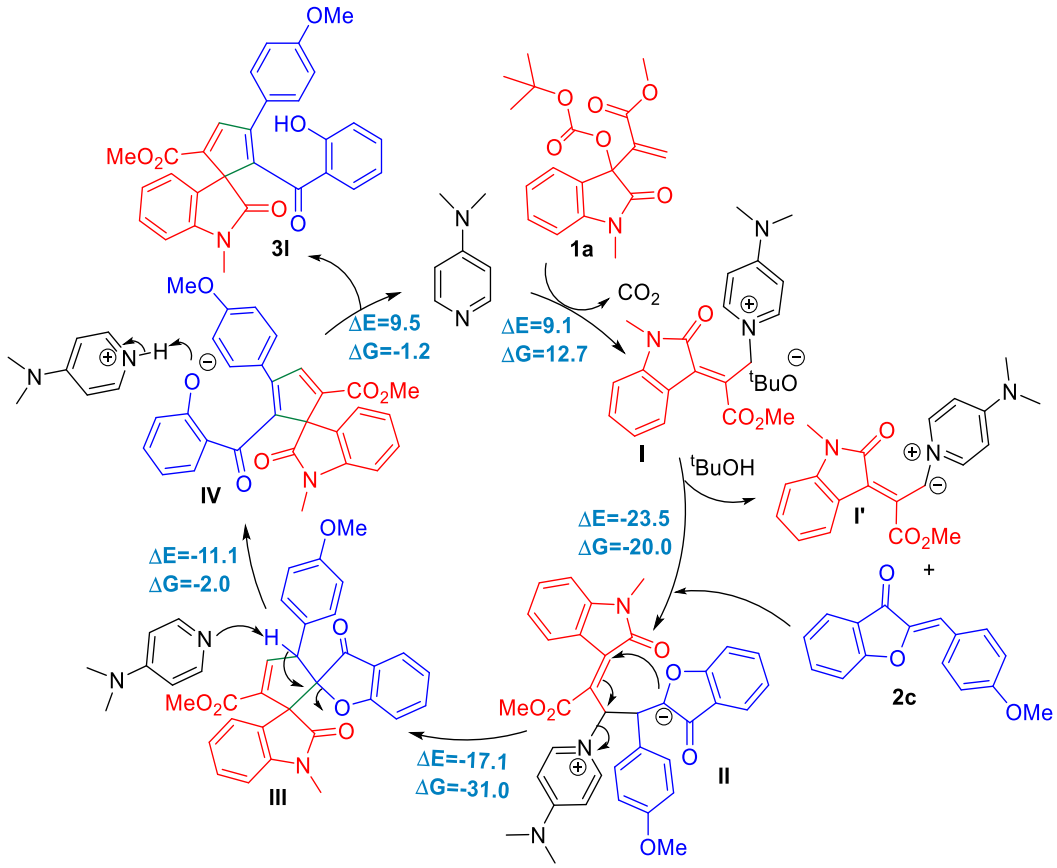
Table 4.3 Substrate scope of Aurones[a-h]



[a]**Optimized reaction condition**: MBH carbonate of isatin **1a** (0.115 mmol), Substituted aurone **2** (0.138 mmol), DMAP (20 mol%) in acetonitrile (2.0 mL) at room temperature; [b]Isolated yield after column chromatography; [c]Spirocyclopentene compounds formed at room temperature; [d]DMAP (20 mol% at 50 °C) or DMAP (100 mol%); [e]DMAP (100 mol% at 70 °C); [f] DMAP (50 mol% at 70 °C); [g]DMAP (30 mol% at 70 °C); [h]DMAP (100 mol%).

Based on our experimental observations, previous literature reports[18] and quantum chemical calculations that we have carried out the plausible catalytic cycle has been depicted in Scheme 4.9. The computational calculations have been performed using density functional

theory (DFT) at the PBE/TZVP level of theory. Based on these findings it is proposed that initially, the nucleophilic DMAP attacks on the MBH carbonate **1a** to form quaternary ammonium salt **I** with the evolution of carbon dioxide and *tert*-butoxide. This process found to be thermodynamically unstable (ΔG = 12.7 kcal/mol). The in situ generated *tert*-butoxide in turn abstracts a proton from quaternary ammonium salt **I** to give an allylic nitrogen ylide **I'**. Subsequently, ylide **I'** reacts with the aurone **2c** to generate an intermediate **II** (reaction free energy ΔG = -20.0 kcal/mol).



Scheme 4.9 Proposed reaction mechanism for the formation of spirooxindole cyclopentadiene

This intermediate **II** cyclizes via a highly favourable (ΔG = -31.0 kcal/mol) intramolecular Michael addition to furnish the corresponding intermediate **III** by regenerating the catalyst DMAP. Further, DMAP abstracts the proton from intermediate **III** leading to the formation of phenoxide intermediate **IV** via ring opening process. Finally, this intermediate **IV** affords the desired compound **3l** via protonation process and by the regeneration of DMAP to complete the catalytic cycle.

Earlier we had observed that unlike *para*-substituted derivatives, *ortho*-substituted aurones (MeO, Br, Cl) required an elevated temperature to form the corresponding cyclopentadiene fused spirooxindoles **3t-3v**. In order to have an insight about this observation, we have also calculated the transition states calculation and the energy barriers for both the cases (*ortho* and *para* substituted aurones) from intermediate **III** to intermediate **IV** (Figure 4.3).

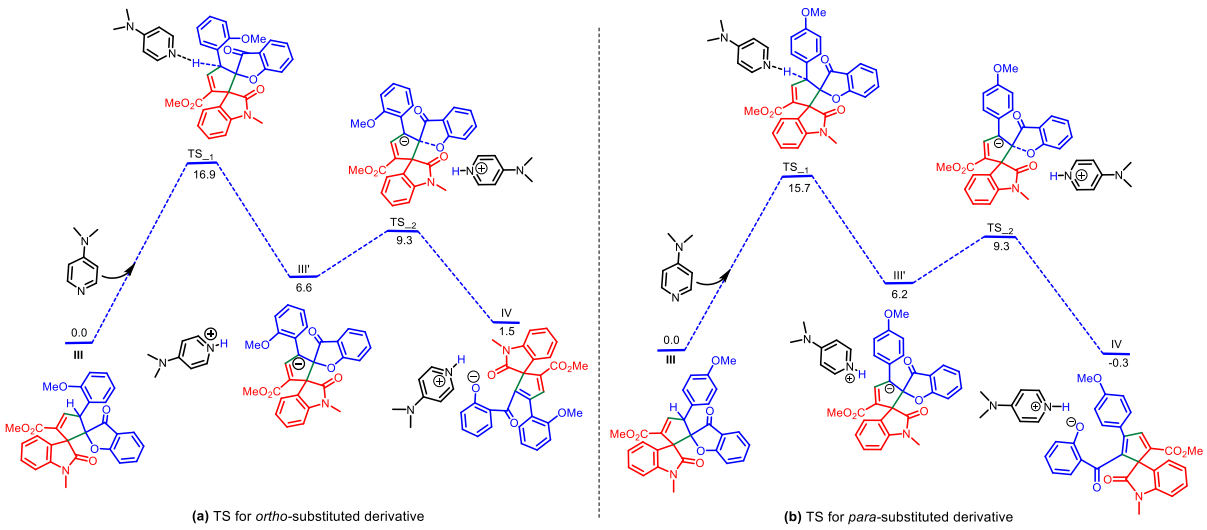


Figure 4.3 Transition state barrier for *ortho* and *para* substituted aurone.

It has been observed that the *ortho*-substituted aurone has 1.2 kcal/mol higher energy barrier than that of the *para*-substituted aurone derivative. Further, the turnover frequencies (TOFs) values have indicated that the transformation with the *para*-substituted aurone is approximately 6.4 times more efficient than for the *ortho*-substituted aurone (Table 4.4).

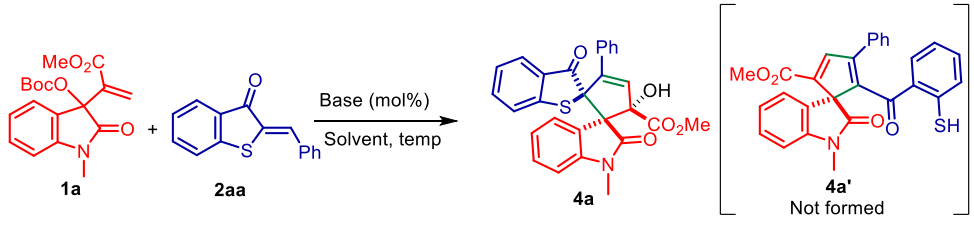
Table 4.4 The values for the turnover frequencies (TOFs) obtained for both *ortho*- and *para*-substituted aurones **2**.

Sr. No	Mechanism	Turnover Frequency (TOF)
1	*ortho* substituted aurone **2k**	3.01 s^{-1}
2	*para* substituted aurone **2c**	1.93* 10^{1} s^{-1}

2-Arylidenebenzo[*b*]thiophen-3(2*H*)-one (Thioaurone) is a sulphur analogue of aurone. Thioaurone and its derivatives have been used in photo-switchable materials,[19] and dyes.[20] Apart from this, thioaurones show cytotoxic activity against HeLa cells line.[21] Moreover, the thioaurones and their derivatives have been used as Michael acceptor in different cycloaddition reactions to construct the complex molecular architecture.[14]

To the best of our knowledge, the use of thioaurone as a Michael acceptor in Morita-Baylis-Hillman type reaction has not been explored yet in organic synthesis. Also, the construction of sulfur analogues of bioactive spirocyclic aurones may be of great interest due to its biological relevance.

Table 4.5. Optimization of the reaction conditions[a-e]



Entry	Base (mol%)	Solvent	Time (h)	*dr*[c]	Yield (%)[b]
1	DMAP (20)	ACN	72	-	NR
2	DMAP (50)	ACN	72	-	NR
3	DMAP (100)	ACN	48	>20:1	30
4	DABCO (100)	ACN	72	>20:1	10
5	DBU (100)	ACN	24	>20:1	56
6	DBU (100)	$CHCl_3$	24	>20:1	40
7	DBU (100)	Toluene	24	>20:1	42
8	DBU (100)	THF	48	>20:1	20
9	DBU (100)	DMF	36	>20:1	50
10[d]	DBU (100)	ACN	24	>20:1	52
11[e]	DBU (100)	ACN	48	>20:1	20
12	DBU (50)	ACN	72	>20:1	30

[a]**Reaction condition**: Unless otherwise stated all the reactions were carried out with MBH carbonate **1a** (0.115 mmol), Thioaurone **2aa** (0.138 mmol), Base (0.115 mmol) in acetonitrile (2.0 mL) at room temperature. [b]Isolated yield after column chromatography. [c]determined by ^{1}H NMR. [d]70 °C. [e]0 °C.

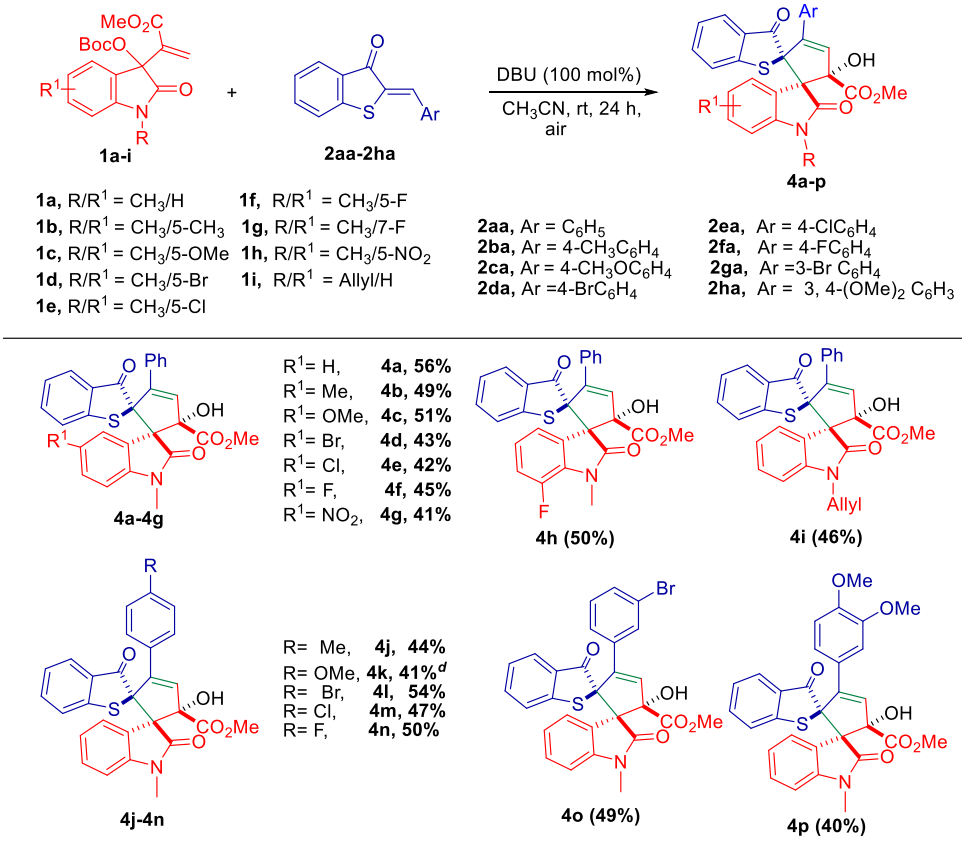
In this regard, we became interested to explore the synthesis of thioaurones (sulphur analogue of aurone) via [3 + 2] annulation reaction. In order to explore the synthesis of spirocyclic benzothiofuranones, we prepared a series of (*Z*)-2-benzylidenebenzo[*b*]thiophen-3(2*H*)-one (**2aa-2ah**) following the reported procedure.[22] Our initial attempts to synthesize the desired spirocyclic benzothiofuranones (**4a'**) were unsuccessful under the optimized reaction condition that was explored for the synthesis of cyclopentadiene fused spirocyclic derivatives **3** (Table 4.5, entry 1). To our surprise, we did not observe any spirooxindole product (**4a'**) formation with the increase in catalyst loading (50 mol% of DMAP) even after the prolonged reaction time (Table 4.5, entry 2). Interestingly, the stoichiometric quantity of 4-dimethylaminopyridine (DMAP 100 mol%) furnished an unanticipated benzo[*b*]thiophen-3(*2*H)-one fused spirooxindole product **4a** in 30% yield with high diastereoselectivity (>20:1 *dr*) and we did not observe any target compound **4a'** formation (Table 4.5, entry 3). The bis-spirocyclic compound **4a** with multiple chiral centres including tertiary hydroxyl group is an unusual and complex molecular scaffold to build from synthetic chemistry point of view. Also, this multi-functional and non-natural bis-spirocyclic hybrid compound containing useful skeleton such as benzothiofuranone, isatin and cyclopentene may be of greater biological significance. This result prompted us to take further interest in optimizing the reaction condition. When DABCO (1, 4-diazabicyclo[2.2.2]octane) was used as a base, we obtained the desired product **4a** in 10% yield (Table 4.5, entry 4). Pleasingly, DBU [1, 8-diazabicyclo (5.4.0)undec-7-ene] as a base in acetonitrile at room temperature delivered the desired spirooxindole product **4a** in 56% yield (Table 4.5, entry 5). Among the screened solvents, acetonitrile was found to be the optimum solvent for the desired transformation (Table 4.5, entries 6-9). The yield of spirooxindole **4a** did not increase even at elevated temperature (Table 4.5, entry 10). At lower temperature (0 °C) the spirooxindole **4a** was formed in poor yield (20%, Table 4.5, entry 11). We noticed that reduction in the loading of 1, 8-diazabicyclo (5.4.0) undec-7-ene (DBU 50 mol%) resulted in decrease in the yield of hydroxylated spirooxindole **4a** (Table 4.5, entry 12).

Based on the optimization studies, MBHCs of isatin **1a** (1 equiv.), thioaurone (1.2 equiv.) and DBU (1.0 equiv.) in CH_3CN (acetonitrile) was found to be the suitable reaction condition to obtain spirooxindole fused benzo[*b*]thiophen-3(*2H*)-one **4a** derivatives.

Having standardised the optimum reaction condition, we then explored the substrate scope for the generality of the protocol. The treatment of various MBH carbonates of isatin (**1a-1i**) with thioaurone (**2aa)** delivered the corresponding hydroxylated spirooxindoles (**4a-4i**)

in moderate yields with high diastereoselectivity via [3 + 2] annulation pathway (up to 56%, *dr* >20:1, Table 4.6).

Table 4.6 Substrate scope of MBH carbonates and thioaurones[a-d]

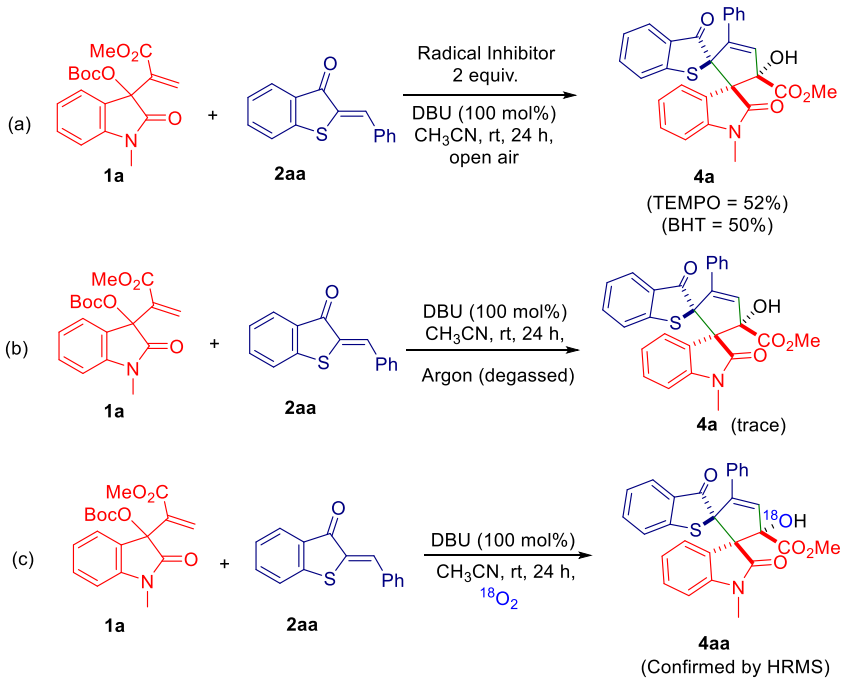


[a]**Optimized Reaction condition**: MBH carbonate **1a** (0.115 mmol), thioaurone **2aa** (0.138 mmol), DBU (0.115 mmol) in ACN (2.0 mL) at room temperature. [b]Isolated yield after column chromatography. [c]diastereomeric ratio >20:1 in all cases and determined by ^{1}H NMR. [d]DBU (2.0 equiv.)

We noticed that, both electron deactivating/withdrawing (Br, Cl, F, NO_2) as well as electron-donating (CH_3, OCH_3) groups on the aryl ring of MBH carbonates did not have any significant effect on the yield of the products and on reaction time. However, the trend of an insignificant variation in the yields of **4a-4h** probably due to the stereo-electronic effect of substituted functional groups. Likewise, *N*-allyl substituted MBH carbonate **1i** reacted smoothly to afford the corresponding spirooxindole derivative **4i** in 46% yield with high stereoselectivity (Table 4.6).

Later, we examined the series of thioaurones (**2ba-2ha**) with MBH carbonate **1a** to explore the generality of protocol under the standard reaction conditions (Table 4.6). To our delight, the [3 + 2] annulation-hydroxylation reactions proceeded smoothly to afford

hydroxylated spirooxindole products **4j-4p** in moderate yields (up to 54%, Table 4.6). It is important to note that both electron-donating/-withdrawing groups at *para*- and *meta*-position of the aryl moiety of thioaurones have been found to be suitable substrates for the facile annulation. While the *ortho*-substituted as well as heteroaryl thioaurones did not react under the optimized reaction condition. We observed that all the spirooxindole (**4a-4p**) products were obtained in high stereoselectivity (>20:1 *dr*). Further, the molecular structure of hydroxylated spirooxindole compound **4a** was established using single-crystal X-ray diffraction analysis.[23] Based on the analogy and other spectroscopic data, the structure of all other products was deduced. Further, we performed some control experiments to understand the plausible reaction pathway of [3 + 2] annulation-hydroxylation reaction (Scheme 4.10).

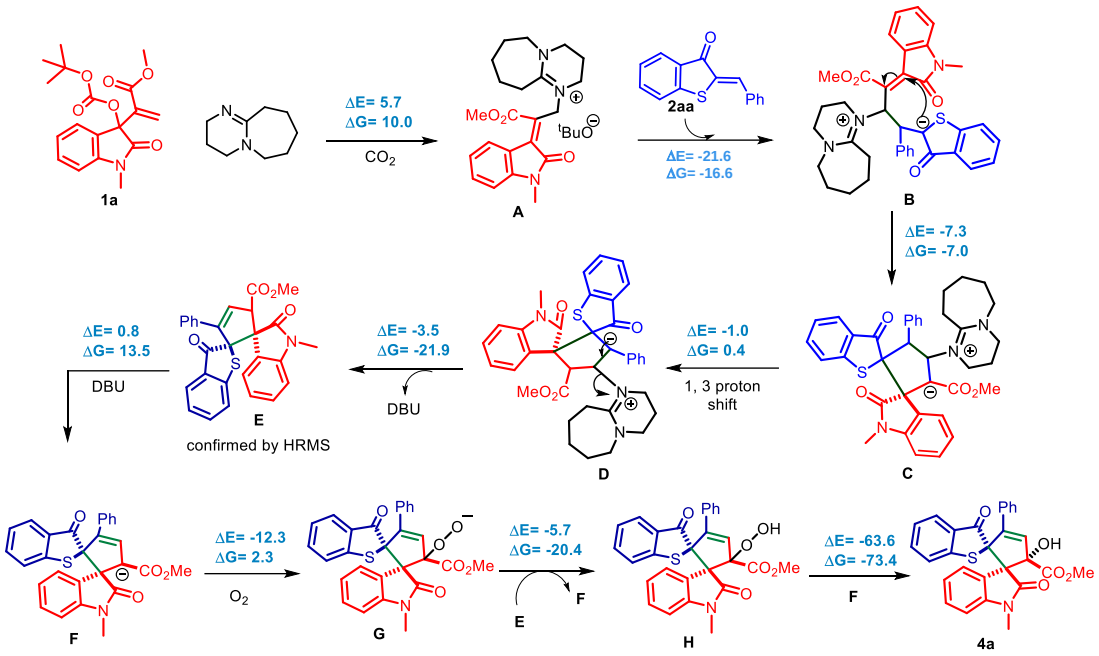


Scheme 4.10 Control experiments

The reaction of **1a** and **2aa** in presence of radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinooxy) or BHT (butylated hydroxytoluene) under standard reaction conditions did not inhibit the reaction and the hydroxylated spirooxindole **4a** was formed in 52% and 50% yield respectively (Scheme 4.10a). These results indicate that the reaction pathway may not be having any free-radical intermediate. Further we observed that a trace amount of hydroxylated spirooxindole compound **4a** was obtained under inert atmosphere, thus indicating the essential role of molecular oxygen for this [3 + 2] annulation-hydroxylation

reaction (Scheme 4.10b). In order to get further insight about the source of oxygen incorporation, we performed $^{18}O_2$ labelling experiment (Scheme 4.10c). We found that the incorporation of labelled oxygen (52% $^{18}O_2$ enrichment, confirmed by HRMS, see experimental section, page 123-124) in the hydroxylated spirooxindole product **4aa**, thus strongly supporting the essential role of oxygen in the desired transformation.

On the basis of our experimental results and the preceding literature reports on [3 + 2] annulation/cycloaddition reactions [17] as well as based on our computational calculations (DFT-PBE/TZVP level of theory) a plausible reaction pathway has been proposed in Scheme 4.11.



Scheme 4.11 Proposed reaction mechanism for [3 + 2] annulation-hydroxylation

Initial nucleophilic attack (S_N2) by the Lewis base DBU on the MBH carbonate **1a** forms the quaternary ammonium salt **A** along with the evolution of CO_2 and *tert*-buotoxide (Brønsted base). As the quaternary ammonium intermediate **A** is thermodynamically unstable (ΔG = 10 kcal/mol), it reacts with the in situ generated *tert*-buotoxide to give the corresponding zwitterionic ylide. Then the α-regioselective attack of the in situ generated ylide intermediate on thioaurone **2aa** affords the intermediate **B** (ΔG = -16.6 kcal/mol). Further, the intermediate **B** undergoes an intramolecular Michael reaction (ΔG = -7.0 kcal/mol) to form the spirocyclic intermediate **C**. Then this spirocyclic intermediate **C** undergoes, 1, 3-proton shift to furnish the highly reactive intermediate **D**.[17e] This intermediate **D** is further converted into the

corresponding spirocyclic intermediate **E** (ΔG = -21.9 kcal/mol; confirmed by HRMS, see experimental section, page 125) by the elimination of DBU. Subsequently, enolate intermediate **F** is formed during the course of reaction by the abstraction of acidic proton by DBU. The anionic intermediate **F** further reacts with molecular oxygen (air) to give the peroxide anionic intermediate **G**, this in turn quickly abstracts the acidic proton (alpha to ester) from an intermediate **E** to form hydroperoxide intermediate **H** along with the generation of intermediate **F**. This reaction step proved to be highly facile as it is evident from the reaction free energy value (ΔG = -20.4 kcal/mol). Finally, the enolate **F** attacks on weak peroxide bond of a highly reactive intermediate **H** to furnish the final product **4a**.[24]

4.5 Conclusions

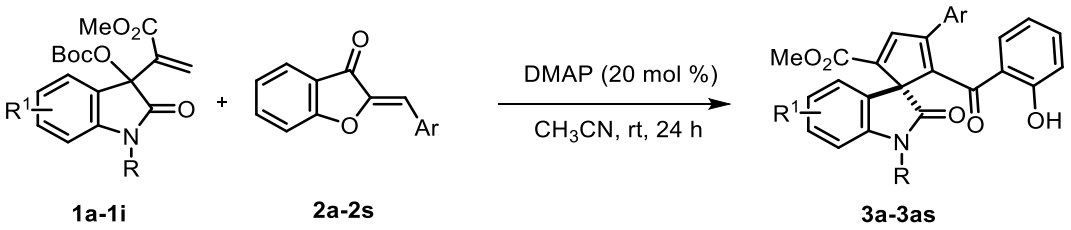
In summary, we have developed a facile, convenient and high yielding protocol to access very useful cyclopentadiene- and cyclopentene-fused spirooxindole derivatives under mild reaction conditions. We have successfully demonstrated the utility of aurones and thioaurones as substrates in the [3 + 2] annulation with MBH carbonates of isatin to construct structurally diverse and pharmacologically relevant spirocarbopentacyclic scaffolds. The structurally similar aurones and thioaurones elicited varied reactivity under different Lewis bases to afford the corresponding cyclopentadiene fused spirooxindoles and hydroxy cyclopentene fused spirooxindoles in moderate to good yields. The experimental findings have been further corroborated by DFT calculations to support the most probable mechanism of cycloaddition reaction.

4.6 Experimental Section

4.6.1 General

Unless otherwise stated, all the reagents were purchased from commercial suppliers (Aldrich, Avar, TCI, Alfa-Aesar, and Spectrochem) and used without purification. All the reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by irradiation with UV light at 254 nm and the solution of Phosphomolybdic Acid (PMA), $KMnO_4$ was used to stain products. The column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate. The NMR spectra were recorded using tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) are given in Hz and integration. All the samples were analyzed by high resolution mass spectrometer (HRMS) using ESI TOF. Melting points were measured using BÜCHI M-560 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Morita-Baylis-Hillman carbonates **1a-1j** were prepared according to the literature procedure.[18f] Substituted aurones **2a-2t** were synthesized according to the literature procedure.[14] Thioaurones **2aa-2ha** were synthesized according to the literature procedure.[22]

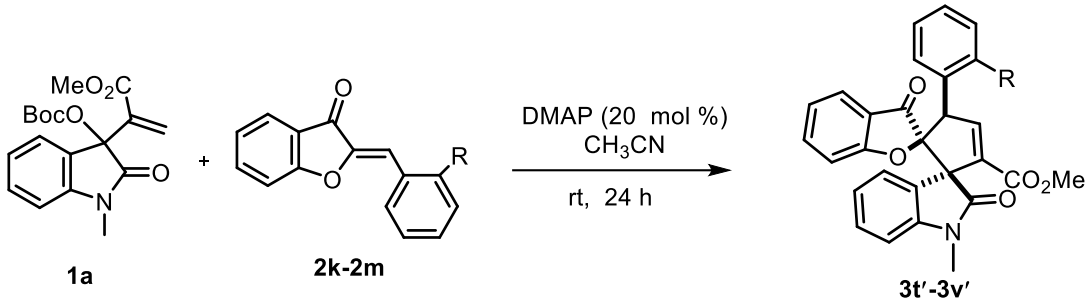
4.6.2 General procedure for the synthesis of spirooxindole cyclopentadiene – GP-1



1a-1i **2a-2s** **3a-3as**

To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), aurone **2a** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.023 mmol, 0.2 equiv.) was added at room temperature. Then the resulting reaction mixture was stirred for 24 h at room temperature After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate).

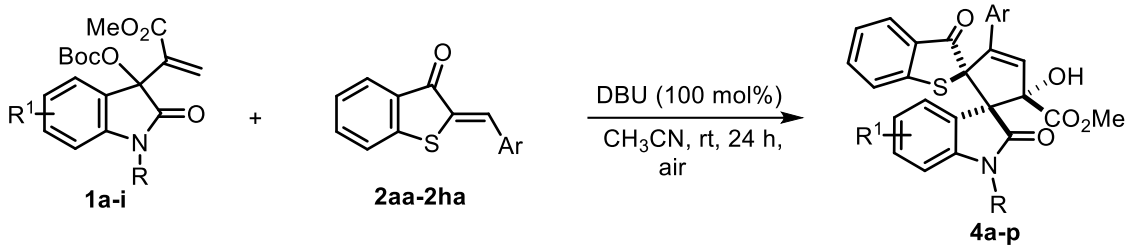
4.6.3 General procedure for the synthesis of Bis-spirocyclic oxindole – GP-2



1a **2k-2m** **3t′-3v′**

To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), substituted aurones (**2k** or **2l** or **2m**) (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.023 mmol, 0.2 equiv.) was added at room temperature. Then the resulting mixture was stirred for 24 h at room temperature. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate).

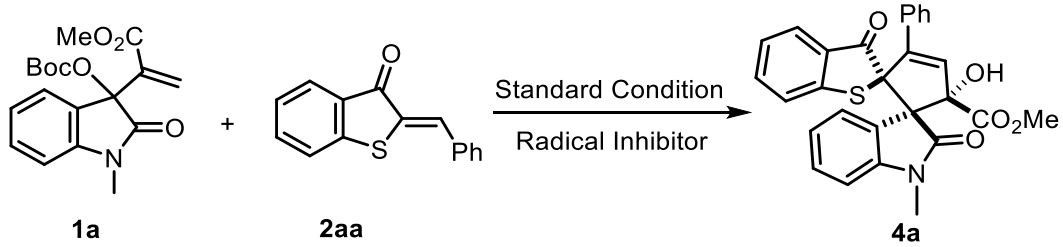
4.6.4 General procedure for the synthesis of dispiro[benzo[*b*]thiophene – GP-3



To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), thioaurone **2aa** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DBU (0.115 mmol, 1.0 equiv.) was added at room temperature. Then the resulting mixture was stirred for 24 h at room temperature. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate).

4.6.5 Mechanistic Studies

A. Control Experiments

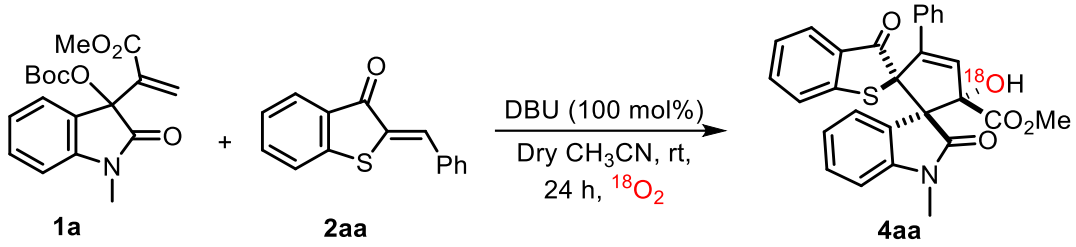


Sr. No.	Radical inhibitor	Yield of **4a** (%)
1	None	56
2	TEMPO	52
3	BHT	50

Reaction conditions-MBH carbonate of isatin **1a** (40 mg, 0.115 mmol), thioaurone **2aa** (33 mg, 0.138 mmol), DBU (17 mg, 0.115 mmol), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 2 equiv.) **or** Butylated hydroxyl toluene (BHT, 2 equiv.), acetonitrile (2.0 mL) were added in a 10 mL round bottom flask and the reaction mixture was stirred under atmosphere of air at

room temperature for 24 h. These control experiments afforded compound **4a** in 50-52% yields respectively after purification over silica gel using column chromatography (See Table above).

B. Procedure for ^{18}O labelling experiment



In an oven dried 20 mL crimp cap vial Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), thioaurone **2aa** (0.138 mmol, 1.2 equiv.) were added at room temperature under argon atmosphere. The vial was purged with argon and sealed with aluminium crimp cap using a crimper. Then 2 mL of dry acetonitrile was added under argon. To this solution DBU (0.115 mmol, 1.0 equiv.) was added under argon and immediately the reaction vial was filled and purged with $^{18}O_2$ gas (98% isotopic purity) and it was kept for stirring for 24 h. The percentage of ^{18}O enrichment product **4aa** was examined by HRMS (ESI TOF, +ve ion mode) as shown Figure 4.4 (page 124). The calculated data showed 52% of ^{18}O enrichment in **4aa**. **HRMS (**ESI TOF) *m/z* calcd. For $C_{28}H_{21}NO_4\ ^{18}OS\ [M + H]^+$ 486.1261, found 486.1260

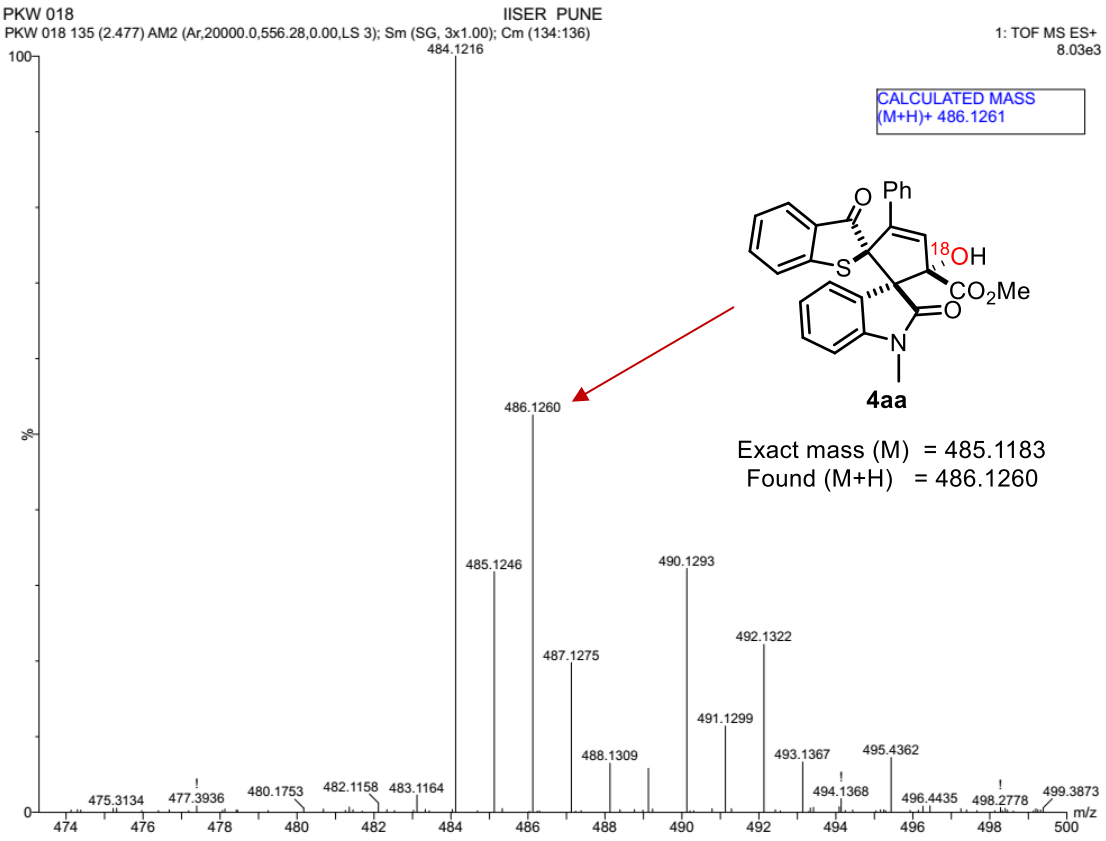


Figure 4. 4 HRMS spectrum of **4aa**- ^{18}O enriched product

C. Detection of the intermediate

In an oven dried 20 mL crimp cap vial, Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), thioaurone **2aa** (0.138 mmol, 1.2 equiv.) were added at room temperature under argon atmosphere. The vial was purged with argon and sealed with aluminium crimp cap using a crimper. Then 2 mL of dry acetonitrile was added under argon. To this solution DBU (0.115 mmol, 1.0 equiv.) was added under argon (to maintain dry and inert atmosphere). After the compete addition of reagents the reaction vial was filled and purged with argon and was kept for stirring for 24 h. After which, the reaction sample was analysed for HRMS. The ESI-MS of crude reaction mixture shown Figure 4.5 (page 125). Intermediate **E** was detected based on HRMS. **HRMS (**ESI TOF) *m/z* calcd. For $C_{28}H_{21}NO_4S$ $[M + H]^+$ 468.1269, found 468.1262

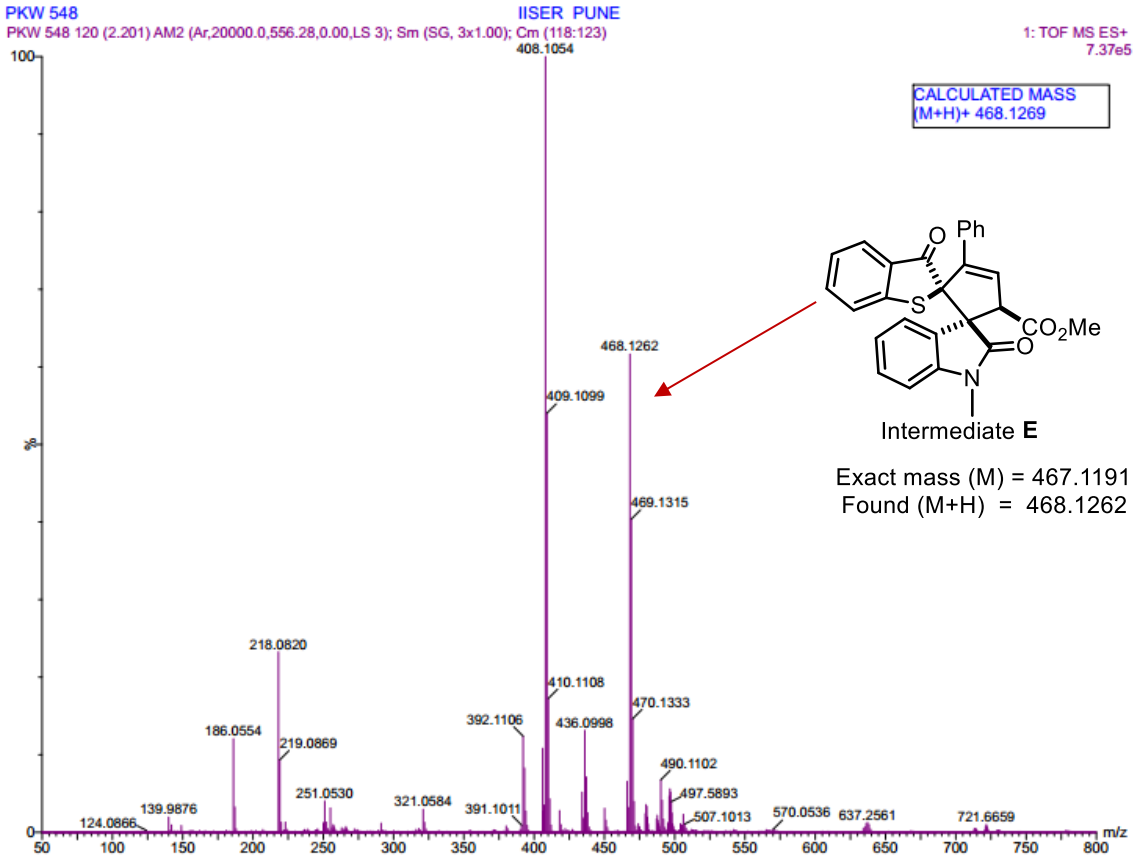
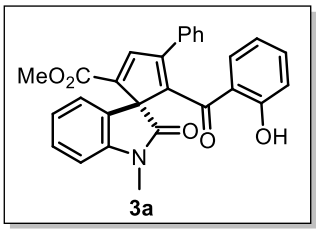


Figure 4.5 HRMS spectrum of intermediate **E**

4.6.6 Experimental Data

Methyl-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-phenyl spiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3a)

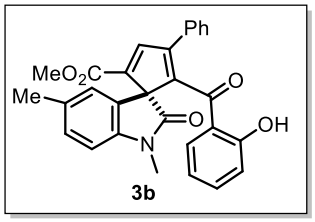
The compound **3a** was prepared following the general procedure **GP-1**



Yellow solid (40 mg, 76%), R_f = 0.15 (petroleum ether/EtOAc 70:30), MP: 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.84 (s, 1H), 7.36 – 7.26 (m, 3H), 7.24 – 7.14 (m, 5H), 6.98 – 6.85 (m, 3H), 6.76 (d, J = 8.6 Hz, 1H), 6.42 – 6.35 (m, 1H), 3.65 (s, 3H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.6, 170.9, 162.4, 161.8, 150.9, 146.2, 145.5, 142.5, 141.8, 136.3, 132.7, 132.3, 129.6, 129.4, 128.6, 128.6, 123.3, 122.5, 122.5, 118.7, 118.6, 117.7, 109.0, 70.3, 52.0, 27.4. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{22}NO_5$ $[M + H]^+$ 452.1498, found 452.1501.

Methyl-2-(2-hydroxybenzoyl)-1', 5'-dimethyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3b)

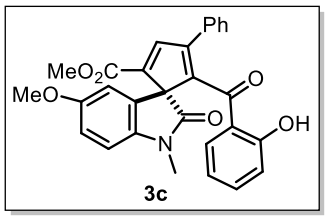
The compound **3b** was prepared following the general procedure **GP-1**



Yellow solid (39 mg, 72%), R_f = 0.24 (petroleum ether/EtOAc 70:30), MP: 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.83 (s, 1H), 7.34 – 7.29 (m, 2H), 7.24 – 7.14 (m, 5H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.83 – 6.71 (m, 3H), 6.39 (t, *J* = 7.6 Hz, 1H), 3.66 (s, 3H), 3.36 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.8, 170.9, 162.5, 162.0, 150.9, 146.2, 143.3, 142.7, 142.1, 136.4, 132.9, 132.5, 132.1, 129.9, 129.7, 128.7, 123.5, 123.4, 118.9, 118.7, 117.8, 108.8, 70.6, 52.1, 27.6, 21.2. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_5$ $[M + H]^+$ 466.1654, found 466.1656.

Methyl-2-(2-hydroxybenzoyl)-5'-methoxy-1'-methyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3c)

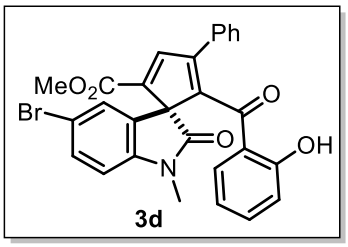
The compound **3c** was prepared following the general procedure **GP-1**.



Yellow solid (38 mg, 69%), R_f = 0.15 (petroleum ether/EtOAc 70:30), MP: 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 7.83 (s, 1H), 7.34 – 7.29 (m, 2H), 7.23 – 7.15 (m, 5H), 6.85 – 6.74 (m, 3H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.42 – 6.35 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.36 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 170.6, 162.5, 162.0, 155.8, 151.0, 146.3, 142.6, 142.0, 139.2, 136.5, 132.8, 132.5, 129.7, 128.8, 124.8, 118.9, 118.7, 117.9, 113.5, 110.3, 109.3, 70.7, 55.7, 52.1, 27.7. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_6$ $[M + H]^+$ 482.16.4, found 482.1604.

Methyl-5'-bromo-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3d)

The compound **3d** was prepared following the general procedure **GP-1**.

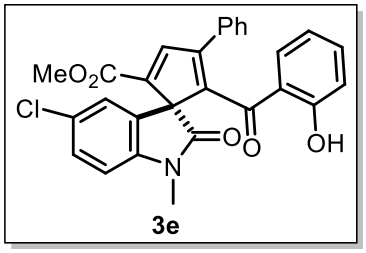


Yellow solid (43 mg, 70%), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 162-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.83 (s, 1H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.31 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.27 – 7.12 (m, 5H), 7.03 (d, *J* = 1.9 Hz, 1H), 6.85 – 6.75 (m, 2H), 6.40 (s, 1H), 3.68 (s, 3H), 3.37 (s,

3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.3, 170.6, 162.5, 161.8, 151.6, 146.6, 144.8, 142.1, 141.6, 136.6, 132.7, 132.4, 132.3, 129.9, 128.8, 128.8, 125.8, 125.8, 118.9, 118.7, 117.9, 115.0, 110.5, 70.0, 52.2, 27.7. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5$ $[M + H]^+$ 530.0603 and 532.0583, found 530.0601 and 532.0588 (isotopic mass).

Methyl-5'-chloro-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2,4-diene-5-carboxylate (3e)

The compound **3e** was prepared following the general procedure **GP-1**.

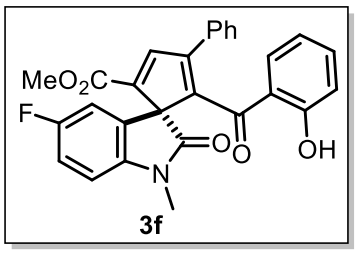


3e

Yellow solid (44 mg, 79%), R_f = 0.18 (petroleum ether/EtOAc 70:30), MP: 163-165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.39 (s, 1H), 7.83 (s, 1H), 7.34 – 7.29 (m, 2H), 7.26 – 7.13 (m, 6H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.43 – 6.36 (m, 1H), 3.68 (s, 3H), 3.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 196.2, 170.5, 162.4, 161.7, 151.5, 146.5, 144.2, 141.9, 141.5, 136.5, 132.5, 132.3, 129.8, 129.3, 128.7, 128.7, 127.7, 125.3, 123.0, 118.7, 118.6, 117.8, 109.8, 69.9, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5$ $[M + H]^+$ 486.1108, found 486.1107.

Methyl-5'-fluoro-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3f)

The compound **3f** was prepared following the general procedure **GP-1**.

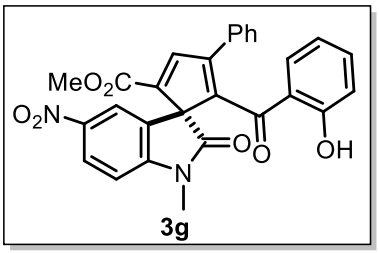


3f

Yellow solid (44 mg, 82%), R_f = 0.18 (petroleum ether/EtOAc 70:30), MP: 161-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.42 (s, 1H), 7.84 (s, 1H), 7.34 – 7.29 (m, 2H), 7.25 – 7.13 (m, 5H), 6.99 (td, *J* = 8.9, 2.6 Hz, 1H), 6.86 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.83 – 6.75 (m, 1H), 6.68 (dd, *J* = 7.6, 2.5 Hz, 1H), 6.39 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.67 (s, 3H), 3.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.3, 170.3, 162.4, 161.7, 158.8(d, $J_{(C-F)}$ = 241.1 Hz), 151.3, 146.5, 141.6, 141.6, 141.5, 136.5, 132.5, 132.3, 129.8, 128.7, 128.7, 125.2, 125.1, 118.7, 118.6, 117.8, 115.6(d, $J_{(C-F)}$ = 23.4 Hz), 110.8(d, $J_{(C-F)}$ = 25.2 Hz), 109.4, 109.3, 70.3, 52.1, 27.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -120.4. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}FNO_5$ $[M + H]^+$ 470.1404, found 470.1406.

Methyl-2-(2-hydroxybenzoyl)-1'-methyl-5'-nitro-2'-oxo-3-phenylspiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3g)

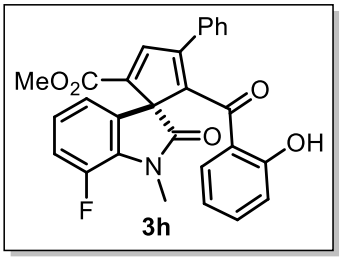
The compound **3g** was prepared following the general procedure **GP-1**



Yellow solid (37 mg, 65%), R_f = 0.17 (petroleum ether/EtOAc 70:30), MP: 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.28 (s, 1H), 8.28 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.87 (s, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.28 – 7.13 (m, 5H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.80 – 6.77 (m, 1H), 6.38 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.69 (d, *J* = 0.6 Hz, 3H), 3.47 (s, 3H). ^{3}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 195.8, 171.1, 162.4, 161.6, 152.4, 151.3, 147.0, 143.2, 141.4, 141.2, 136.8, 132.3, 132.1, 130.1, 128.8, 128.8, 126.7, 124.9, 118.9, 118.4, 118.3, 117.9, 108.4, 69.2, 52.2, 27.9. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}N_2O_7$ $[M + H]^+$ 497.1349, found 497.1350.

Methyl-7'-fluoro-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3h)

The compound **3h** was prepared following the general procedure **GP-1**.

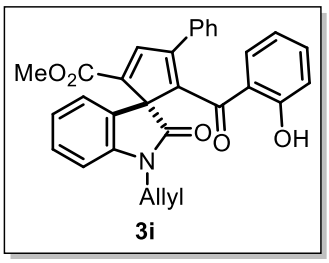


Yellow solid (42 mg, 78%), R_f = 0.36 (petroleum ether/EtOAc 70:30), MP: 170-171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (s, 1H), 7.83 (s, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.12 (m, 5H), 7.00 (dd, *J* = 11.5, 8.4 Hz, 1H), 6.86 – 6.77 (m, 2H), 6.70 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.37 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.68 (s, 3H), 3.60 (d, *J* = 2.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.5, 170.6, 162.5, 161.9, 151.3, 148.07 (d, *J* = 244.2 Hz), 146.5, 142.05(d, $J_{(C-F)}$ = 45 Hz), 136.6, 132.7, 132.5, 132.4, 129.9, 128.8, 128.8, 126.3, 126.3, 123.1, 123.1, 118.8, 118.5, 118.5, 117.9, 117.65 (d, $J_{(C-F)}$ = 19.4 Hz), 70.2, 52.2, 30.06 (d, $J_{(C-F)}$ = 5.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -135.0. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}FNO_5$ $[M + H]^+$ 470.1404, found 470.1406.

Methyl-1'-allyl-2-(2-hydroxybenzoyl)-2'-oxo-3-phenylspiro[cyclopentane-1, 3'-indoline]-2,4-diene-5-carboxylate (3i)

The compound **3i** was prepared following the general procedure **GP-1**

Yellow solid (33 mg, 60%), R_f = 0.33 (petroleum ether/EtOAc 70:30), MP: 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H), 7.86 (s, 1H), 7.36 – 7.30 (m, 2H), 7.25 – 7.15 (m, 6H), 6.94 – 6.85 (m, 3H), 6.77 (dd, *J* = 8.8, 1.1 Hz, 1H), 6.39 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H),

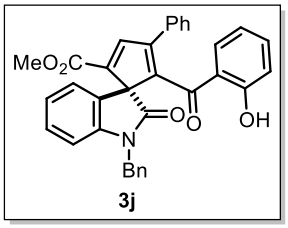


3i

6.03 – 5.88 (m, 1H), 5.51 – 5.42 (m, 1H), 5.28 (dq, *J* = 10.4, 1.5 Hz, 1H), 4.50 (ddt, *J* = 5.3, 3.6, 1.8 Hz, 2H), 3.65 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 170.5, 162.4, 161.8, 150.8, 146.3, 144.7, 142.5, 141.9, 136.4, 132.7, 132.4, 131.2, 129.6, 129.2, 128.6, 128.6, 123.3, 122.6, 122.5, 118.7, 118.6, 117.7, 117.7, 110.0, 70.2, 51.9, 43.5. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{24}NO_5$ $[M + H]^+$ 478.1654, found 478.1656.

Methyl-1'-benzyl-2-(2-hydroxybenzoyl)-2'-oxo-3-phenylspiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3j)

The compound **3j** was prepared following the general procedure **GP-1**

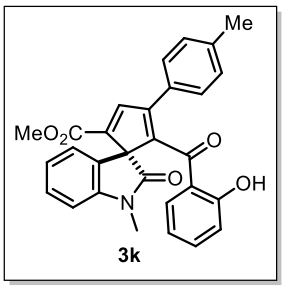


3j

Red solid (24 mg, 40%), R_f = 0.50 (petroleum ether/EtOAc 70:30), MP: 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (s, 1H), 7.90 (s, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.38 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 7.25 – 7.12 (m, 6H), 6.93 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.87 (td, *J* = 7.5, 0.9 Hz, 1H), 6.82 – 6.71 (m, 2H), 6.40 (td, J = 7.7, 1.1 Hz, 1H), 5.11 (d, *J* = 15.8 Hz, 1H), 5.04 (d, *J* = 15.8 Hz, 1H), 3.61 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CDCl3): δ (ppm) 197.0, 171.1, 162.6, 162.0, 150.7, 146.6, 144.8, 142.5, 142.0, 136.6, 135.8, 132.8, 132.6, 129.8, 129.4, 128.8, 128.7, 127.7, 127.6, 123.5, 122.8, 122.7, 118.9, 118.8, 117.9, 110.3, 70.4, 52.1, 45.2. HRMS (ESI TOF) *m/z* calcd. For $C_{34}H_{25}NO_5$ $[M + H]^+$ 528.1811 found 528.1812.

Methyl -2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-(p-tolyl)spiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3k)

The compound **3k** was prepared following the general procedure **GP-1**



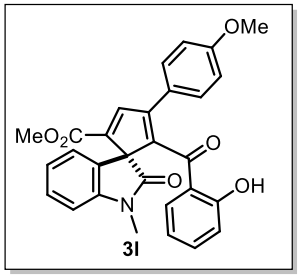
3k

Yellow solid (35 mg, 65%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 7.83 (s, 1H), 7.27 (ddd, *J* = 7.9, 6.4, 2.5 Hz, 1H), 7.24 – 7.12 (m, 4H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.97 – 6.84 (m, 3H), 6.81 – 6.73 (m, 1H), 6.40 (td, *J* = 7.7, 1.1 Hz, 1H), 3.64 (s, 3H), 3.38 (s, 3H), 2.25 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.0, 171.1, 162.5, 162.0, 150.9, 146.5, 145.6, 141.7, 141.7, 140.0, 136.4, 132.5, 129.9, 129.5, 129.4,

128.7, 123.6, 122.7, 122.6, 118.9, 118.8, 117.8, 109.1, 70.4, 52.1, 27.6, 21.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_5$ $[M + H]^+$ 466.1654, found 466.1654.

Methyl-2-(2-hydroxybenzoyl)-3-(4-methoxyphenyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3l)

The compound **3l** was prepared following the general procedure **GP-1**

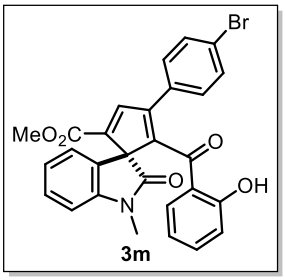


Yellow solid (38 mg, 68%), R_f = 0.12 (petroleum ether/EtOAc 70:30), MP: 150-152 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 7.83 (s, 1H), 7.31 – 7.26 (m, 2H), 7.25 – 7.16 (m, 3H), 6.96 – 6.86 (m, 3H), 6.78 (d, *J* = 8.3 Hz, 1H), 6.75 – 6.69 (m, 2H), 6.45 – 6.39 (m, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.8, 171.2, 162.3, 161.9, 160.6, 150.5, 146.4, 145.5, 141.6, 140.7, 136.2, 132.4, 130.3, 129.3, 125.2, 123.6, 122.5, 122.5, 118.7, 118.7, 117.7, 114.1, 108.9, 70.2, 55.3, 51.9, 27.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_6$ $[M + H]^+$ 482.1604, found 482.1601.

Methyl-3-(4-bromophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3m)

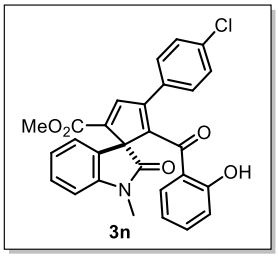
The compound **3m** was prepared following the general procedure **GP-1**



Yellow solid (39 mg, 63%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 7.78 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.0, 4.2 Hz, 1H), 7.25 – 7.14 (m, 4H), 6.95 – 6.88 (m, 3H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.45 (t, *J* = 7.6 Hz, 1H), 3.65 (s, 3H), 3.38 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.5, 170.7, 162.6, 161.9, 149.4, 145.6, 145.6, 143.0, 142.2, 136.8, 132.3, 132.0, 131.7, 130.1, 129.6, 124.1, 123.2, 122.7, 122.7, 119.0, 118.7, 118.0, 109.2, 70.6, 52.2, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5$ $[M + H]^+$ 530.0603 and 532.0583, found 530.0600 and 532.0587 (isotopic mass).

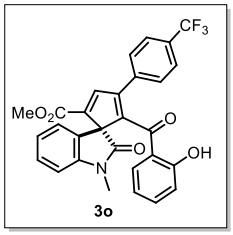
Methyl-3-(4-chlorophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3n)

The compound **3n** was prepared following the general procedure **GP-1**



Yellow solid (39 mg, 70%), R_f = 0.18 (petroleum ether/EtOAc 70:30), MP: 177-179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.41 (s, 1H), 7.79 (s, 1H), 7.31 – 7.22 (m, 4H), 7.22 – 7.15 (m, 3H), 6.95 – 6.86 (m, 3H), 6.82 – 6.76 (m, 1H), 6.49 – 6.39 (m, 1H), 3.65 (s, 3H), 3.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.5, 170.7, 162.6, 161.9, 149.4, 145.7, 145.6, 143.0, 142.2, 136.8, 135.8, 132.3, 131.3, 129.9, 129.6, 129.1, 123.2, 122.7, 122.7, 118.9, 118.7, 118.0, 109.2, 70.6, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5$ $[M + H]^+$ 486.1108, found 486.1112.

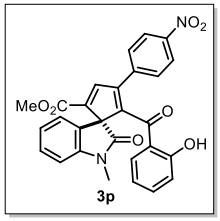
Methyl-2-(2- hydroxybenzoyl) -1' – methyl - 2'-oxo- 3-(4-(trifluoromethyl) phenyl) spiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3o)



The compound **3o** was prepared following the general procedure **GP-1**

Yellow solid (48 mg, 80%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 7.81 (s, 1H), 7.51 – 7.40 (m, 4H), 7.30 (ddd, *J* = 7.9, 5.6, 3.3 Hz, 1H), 7.21 (ddd, *J* = 8.6, 7.3, 1.7 Hz, 1H), 7.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.97 – 6.90 (m, 3H), 6.79 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.41 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.66 (s, 3H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.2, 170.5, 162.5, 161.8, 149.0, 145.6, 145.3, 144.4, 142.4, 136.9, 136.3, 132.2, 131.3 (q, $J_{(C-F)}$ = 33 Hz) , 129.7, 128.9, 125.75 (q, $J_{(C-F)}$ = 3Hz), 123.69 (q, $J_{(C-F)}$ = 271 Hz) 122.9, 122.8, 122.3, 118.9, 118.7, 118.1, 109.3, 70.7, 52.2, 27.6. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -63.0. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{21}F_3NO_5$ $[M + H]^+$ 520.1372, found 520.1367.

Methyl -2-(2-hydroxybenzoyl)-1'-methyl-3-(4-nitrophenyl)-2'-oxospiro[cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3p)



The compound **3p** was prepared following the general procedure **GP-1**

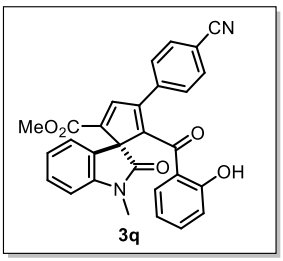
Yellow solid (37 mg, 65%), R_f = 0.12 (petroleum ether/EtOAc 70:30), MP: 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (s, 1H), 8.15 – 8.04 (m, 2H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.31 (dq, *J* = 8.1, 4.0, 3.5 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.02 – 6.89 (m,

3H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.48 – 6.38 (m, 1H), 3.67 (s, 3H), 3.39 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.8, 170.0, 162.5, 161.5, 147.9, 147.8, 145.4, 145.3, 144.6, 142.5, 138.9, 137.1, 131.8, 129.7, 129.4, 123.9, 122.7, 122.5, 118.9, 118.5, 118.2, 109.3, 70.9, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}N_2O_7$ $[M + H]^+$ 497.1349, found 497.1355.

Methyl -3-(4-cyanophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro [cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3q)

The compound **3q** was prepared following the general procedure **GP-1**

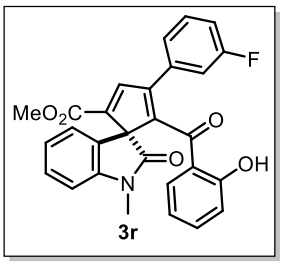
Yellow solid (41 mg, 74%), R_f = 0.10 (petroleum ether/EtOAc 70:30), MP: 226-228 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H), 7.79 (s, 1H), 7.54 – 7.48 (m, 2H), 7.45 – 7.40 (m, 2H), 7.30 (ddd, *J* = 8.0, 5.1, 3.9 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.11 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.96 – 6.90 (m, 3H), 6.83 – 6.78 (m, 1H), 6.46 – 6.39 (m, 1H), 3.66 (s, 3H), 3.38 (s, 3H). ^{13}C $\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.8, 170.1, 162.5, 161.6, 148.4, 145.4, 144.9, 144.7, 142.5, 137.1, 137.0, 132.4, 131.9, 129.7, 129.0, 122.7, 122.7, 122.6, 118.9, 118.5, 118.1, 118.0, 113.1, 109.2, 70.7, 52.1, 27.5. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{21}N_2O_5$ $[M + H]^+$ 477.1450, found 477.1454.

Methyl -3-(3-fluorophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3r)

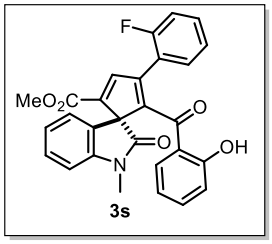
The compound **3r** was prepared following the general procedure **GP-1**



Yellow solid (44 mg, 81%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 222-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 7.79 (s, 1H), 7.32 – 7.27 (m, 1H), 7.26 – 7.12 (m, 3H), 7.10 – 7.02 (m, 2H), 6.97 – 6.89 (m, 4H), 6.81 – 6.76 (m, 1H), 6.44 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.65 (s, 3H), 3.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.3, 170.5, 162.6 (d, $J_{(C-F)}$ = 246 Hz), 162.4, 161.7, 149.2, 149.2, 145.5, 145.5, 143.4, 142.0, 136.6, 134.8, 134.7, 132.1, 130.4, 130.3, 129.5, 124.6, 124.6, 123.0, 122.6, 122.6, 118.7, 118.7, 117.9, 116.54 (d, $J_{(C-F)}$ = 21.1 Hz), 115.19 (d, $J_{(C-F)}$ = 22.6 Hz), 109.1, 70.5, 52.0, 27.5 ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.8. HRMS (ESI TOF) *m/z* calcd. $C_{28}H_{21}FNO_5$ $[M + H]^+$ 470.1404, found 470.1407.

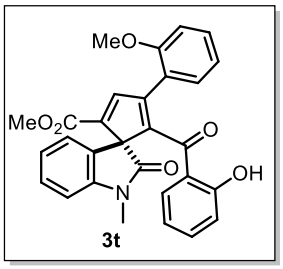
Methyl -3-(2-fluorophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3s)

The compound **3s** was prepared following the general procedure **GP-1**



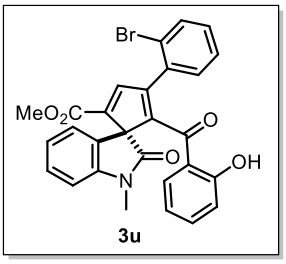
Yellow solid (40 mg, 74%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 166-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.19 (dddd, *J* = 13.8, 8.8, 6.9, 3.5 Hz, 4H), 7.02 – 6.88 (m, 5H), 6.78 – 6.73 (m, 1H), 6.41 (ddd, *J* = 8.3, 7.4, 1.1 Hz, 1H), 3.65 (s, 3H), 3.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):δ (ppm) 195.8, 170.8, 162.2, 161.9, 159.9 (d, $J_{(C-F)}$ = 250.1 Hz), 146.44 (d, $J_{(C-F)}$ = 2.8 Hz), 145.9, 145.7, 145.1, 141.8, 131.9, 131.8, 131.7, 131.0 (d, $J_{(C-F)}$ = 2.8 Hz),, 129.6, 124.5 (d, $J_{(C-F)}$ = 3.6 Hz), 123.3, 122.7 (d, $J_{(C-F)}$ = 5.7 Hz), 121.4, 121.3, 119.0, 118.6, 117.9, 116.1 (d, $J_{(C-F)}$ = 21.6 Hz), 109.2, 69.9, 52.1, 27.6. ^{19}F NMR (377MHz, $CDCl_3$): δ (ppm) -112.0. HRMS (ESI TOF) *m/z* calcd. $C_{28}H_{21}FNO_5$ $[M + H]^+$ 470.1404, found 470.1407.

Methyl-2-(2-hydroxybenzoyl)-3-(2-methoxyphenyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3t)



To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), aurone **2k** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.023 mmol, 0.2 equiv.) was added at room temperature. Then the resulting reaction mixture was stirred for 24 h at 50 °C. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate) to obtain **3t**. Yellow solid (32 mg, 58%), R_f = 0.12 (petroleum ether/EtOAc 70:30), MP: 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 7.79 (s, 1H), 7.29 – 7.26 (m, 1H), 7.25 (dd, *J* = 3.3, 1.5 Hz, 1H), 7.21 – 7.10 (m, 3H), 6.93 (dd, *J* = 7.6, 1.1 Hz, 2H), 6.89 (td, *J* = 7.3, 1.0 Hz, 1H), 6.82 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.35 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.0, 171.5, 162.1, 161.7, 156.6, 148.1, 147.9, 145.7, 143.5, 141.1, 135.8, 131.9, 131.3, 130.3, 129.3, 124.0, 122.6, 122.5, 122.5, 120.8, 119.4, 118.3, 117.4, 110.9, 109.0, 69.6, 55.1, 52.0, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_6$ $[M + H]^+$ 482.1604 found 482.1604.

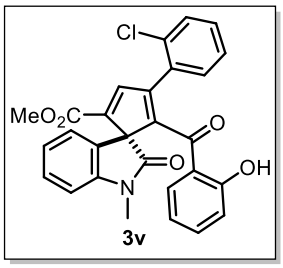
Methyl-3-(2-bromophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3u)



3u

To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), aurone **2l** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.115 mmol, 1.0 equiv.) was added at room temperature. Then the resulting reaction mixture was stirred for 24 h at 70 °C. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate) to obtain **3u**. Yellow solid (37 mg, 61%), R_f = 0.26 (petroleum ether/EtOAc 70:30), MP: 181-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.14 (s, 1H), 7.79 (s, 1H), 7.56 – 7.52 (m, 1H), 7.34 – 7.26 (m, 2H), 7.17 – 7.03 (m, 4H), 7.01 – 6.88 (m, 3H), 6.70 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.46 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.65 (s, 3H), 3.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 195.3, 171.0, 162.0, 161.9, 151.7, 147.0, 145.8, 145.7, 140.8, 136.4, 134.6, 133.1, 132.1, 132.0, 130.9, 129.6, 127.8, 123.3, 122.7, 122.6, 122.1, 119.4, 118.5, 117.7, 109.2, 69.3, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5$ $[M + H]^+$ 530.0603 and 532.0583, found 530.0599 and 532.0583 (isotopic mass).

Methyl-3-(2-chlorophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3v)

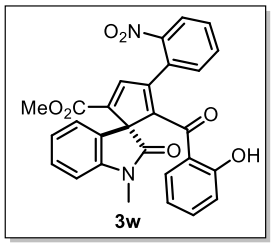


3v

To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), aurone **2m** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.5 equiv.) was added at room temperature. Then the resulting reaction mixture was stirred for 24 h at 70 °C. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate) to afford **3v**. Yellow solid (40 mg, 72%), R_f = 0.26 (petroleum ether/EtOAc 70:30), MP: 183-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.78 (s, 1H), 7.34 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.29 (td, *J* = 7.7, 1.4 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.18 – 7.09 (m, 3H), 7.03 – 6.89 (m, 4H), 6.70 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.44 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.65 (s, 3H), 3.43 (s,

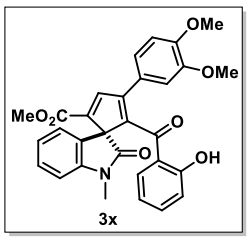
3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.3, 171.0, 162.0, 161.9, 150.3, 146.9, 146.0, 145.7, 141.1, 136.4, 132.6, 132.5, 131.9, 131.7, 130.8, 129.9, 129.6, 127.2, 123.2, 122.7, 122.6, 119.4, 118.5, 117.7, 109.2, 69.4, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5$ $[M + H]^+$ 486.1108, found 486.1104.

Methyl -2-(2-hydroxybenzoyl)-1'-methyl-3-(2-nitrophenyl)-2'-oxospiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate) (3w)



To the stirred solution of Morita-Baylis-Hillman carbonate of isatin **1a** (0.115 mmol, 1.0 equiv.), aurone **2n** (0.138 mmol, 1.2 equiv.) in 2 mL of acetonitrile, DMAP (0.3 equiv.) was added at room temperature. Then the resulting reaction mixture was stirred for 24 h at 70 °C. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified on silica gel (100-200 mesh) column chromatography (petroleum ether/ethyl acetate) to obtain **3w**. Yellow solid (30 mg, 53%), R_f = 0.11 (petroleum ether/EtOAc 70:30), MP: 195-197 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.15 – 8.08 (m, 1H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.30 (td, *J* = 7.8, 1.2 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.09 (m, 2H), 6.98 – 6.91 (m, 2H), 6.69 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.40 (ddd, *J* = 8.2, 7.3, 1.1 Hz, 1H), 3.64 (s, 3H), 3.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 195.0, 171.1, 162.0, 161.8, 149.8, 146.9, 145.6, 145.2, 145.1, 141.3, 136.6, 134.2, 133.1, 131.5, 130.6, 129.7, 129.6, 125.3, 123.0, 122.9, 122.9, 119.8, 118.9, 117.9, 109.3, 69.4, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}N_2O_7$ $[M + H]^+$ 497.1349, found 497.1347.

Methyl-3-(3,4-dimethoxyphenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro [cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3x)

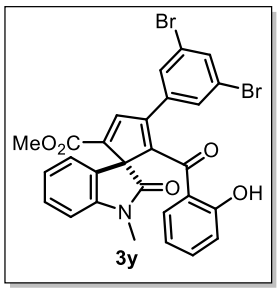


The compound **3x** was prepared following the general procedure **GP-1** Yellow solid (32 mg, 54%), R_f = 0.06 (petroleum ether/EtOAc 70:30), MP: 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.85 (s, 1H), 7.30 – 7.28 (m, 1H), 7.24 – 7.19 (m, 2H), 7.04 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.94 – 6.90 (m, 3H), 6.80 – 6.75 (m, 2H), 6.64 (d, *J* = 2.0 Hz, 1H), 6.45 – 6.41 (m, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.58 (s, 3H), 3.40 (s, 3H).$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 197.1, 171.3, 162.3, 162.0, 150.4, 148.8, 146.3, 145.6, 141.8, 140.8, 136.6, 132.4, 129.5, 125.4, 123.8, 122.7, 121.6, 119.2, 119.0, 117.8, 112.3, 111.0, 109.1, 70.3,

56.0, 55.8, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{26}NO_7$ $[M + H]^+$ 512.1709, found 512.1707.

Methyl-3-(3,5-dibromophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro [cyclopentane-1, 3'-indoline]-2, 4-diene-5-carboxylate (3y)

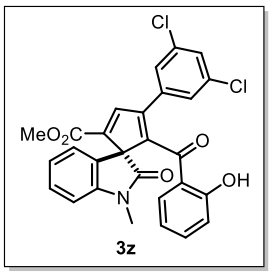
The compound **3y** was prepared following the general procedure **GP-1**



Yellow solid (42 mg, 60%), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 7.74 (s, 1H), 7.51 (t, *J* = 1.7 Hz, 1H), 7.39 (d, *J* = 1.7 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.13 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.00 – 6.88 (m, 3H), 6.84 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.50 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.66 (s, 3H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 195.5, 170.3, 162.4, 161.6, 147.7, 145.5, 144.7, 144.7, 142.5, 136.9, 135.9, 134.8, 131.6, 130.2, 129.6, 123.1, 122.7, 122.6, 118.8, 118.5, 118.1, 109.2, 70.6, 52.1, 27.5. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}Br_2NO_5$ $[M+H]^+$ 607.9708, 609.9688 found 607.9706; 609.9689 and 611.9671 (isotopic mass).

Methyl-3-(3,5-dichlorophenyl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro [cyclopentane-1, 3'-indoline]-2,4-diene-5-carboxylate (3z)

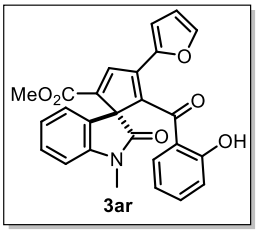
The compound **3z** was prepared following the general procedure **GP-1**



Yellow solid (38 mg, 64%), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 173-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (s, 1H), 7.72 (s, 1H), 7.35 – 7.26 (m, 1H), 7.29 – 7.07 (m, 5H), 7.00 – 6.88 (m, 3H), 6.80 – 6.73 (m, 1H), 6.52 – 6.43 (m, 1H), 3.65 (s, 3H), 3.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 194.9, 170.7, 162.1, 161.8, 148.6, 146.7, 146.1, 145.7, 141.6, 136.6, 134.0, 133.2, 131.6, 131.2, 131.0, 130.9, 130.7, 129.7, 123.0, 122.8, 122.6, 119.3, 118.6, 118.0, 109.3, 69.6, 52.2, 27.7. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}Cl_2NO_5$ $[M + H]^+$ 520.0719, found 520.0720.

Methyl-3-(furan-2-yl)-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxospiro[cyclopentane-1,3'-indoline]-2, 4-diene-5-carboxylate (3ar)

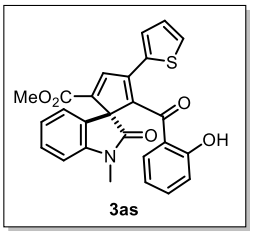
The compound **3ar** was prepared following the general procedure **GP-1**



Yellow solid (26 mg, 51%), R_f = 0.21 (petroleum ether/EtOAc 70:30), MP: 149-151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.49 (s, 1H), 7.84 (s, 1H), 7.45 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.21 (dd, *J* = 1.8, 0.6 Hz, 1H), 6.89 (ddd, *J* = 6.5, 5.7, 2.1 Hz, 4H), 6.69 – 6.62 (m, 1H), 6.52 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.35 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.64 (s, 3H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 171.0, 162.3, 161.9, 147.3, 145.5, 144.8, 143.4, 141.5, 137.8, 137.5, 136.6, 132.4, 129.5, 123.7, 123.0, 122.7, 120.0, 119.0, 118.1, 113.8, 112.2, 109.1, 70.3, 52.1, 27.6. HRMS (ESI TOF) *m/z* calcd. For $C_{23}H_{20}N_3O_5$ $[M + H]^+$ 442.1291, found 442.1299.

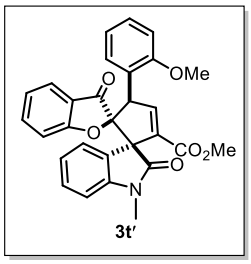
Methyl-2-(2-hydroxybenzoyl)-1'-methyl-2'-oxo-3-(thiophen-2-yl)spiro[cyclopentane-1,3'-indoline]-2,4-diene-5-carboxylate (3as)

The compound **3as** was prepared following the general procedure **GP-1**



Yellow solid (27 mg, 50%), R_f = 0.23 (petroleum ether/EtOAc 70:30), MP: 157-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.48 (s, 1H), 7.82 (s, 1H), 7.46 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.09 (dd, *J* = 3.7, 1.1 Hz, 1H), 6.97 – 6.83 (m, 5H), 6.64 – 6.56 (m, 1H), 3.65 (s, 3H), 3.35 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.8, 170.9, 162.6, 161.9, 145.7, 145.4, 142.0, 141.4, 139.7, 136.9, 134.8, 132.5, 130.1, 129.6, 129.2, 128.0, 123.5, 123.0, 122.7, 119.3, 119.3, 118.1, 109.1, 70.5, 52.1, 27.5. HRMS (ESI TOF) *m/z* calcd. For $C_{26}H_{20}NO_5S$ $[M + H]^+$ 458.1062, found 458.1060.

Methyl-5'-(2-methoxyphenyl)-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzofuran-2,1'-cyclopentane-2', 3''-indolin]-3'-ene-3'-carboxylate (3t')

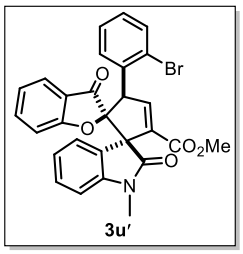


The compound **3t'** was prepared following the general procedure **GP-2**

White solid (23 mg, 42%), R_f = 0.15 (petroleum ether/EtOAc 70:30), MP: 206-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 1.4, 0.6 Hz, 1H), 7.44 (d, *J* = 2.6 Hz, 1H), 7.38 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.30 (dd, *J* = 7.5, 0.8 Hz, 1H), 7.25 – 7.14 (m, 2H), 6.99 (dtd, *J* = 20.6, 7.6, 1.0 Hz, 2H), 6.93 – 6.86 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.67 – 6.58 (m, 2H), 5.02 (d, *J* = 2.5 Hz, 1H), 3.60 (s, 3H), 3.09 (s, 3H), 3.09 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 200.0, 173.7, 171.8, 162.5, 157.1, 147.7, 144.7,

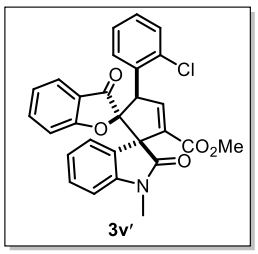
137.7, 136.5, 130.2, 129.2, 129.2, 126.5, 125.6, 124.3, 122.3, 121.9, 120.4, 112.8, 109.2, 107.9, 95.2, 65.3, 54.2, 52.4, 52.0, 26.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_6$ $[M + H]^+$ 482.1604 found 482.1600.

Methyl-5'-(2-bromophenyl)-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzofuran-2,1'-cyclopentane-2',3''-indolin]-3'-ene-3'-carboxylate (3u')



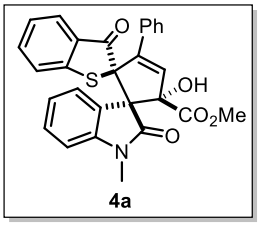
The compound **3u'** was prepared following the general procedure **GP-2** Brown solid (22 mg, 36%), R_f = 0.18 (petroleum ether/EtOAc 70:30), MP: 192-194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.33 – 7.30 (m, 1H), 7.24 – 7.20 (m, 1H), 7.15 (tdd, *J* = 7.7, 2.3, 1.5 Hz, 2H), 6.98 – 6.86 (m, 2H), 6.85 – 6.80 (m, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 2.7 Hz, 1H), 3.60 (s, 3H), 3.11 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 200.2, 174.0, 172.0, 162.4, 147.6, 144.7, 138.1, 136.7, 135.5, 132.4, 132.2, 129.7, 129.3, 127.2, 126.4, 126.1, 125.3, 124.4, 122.5, 122.5, 120.3, 113.0, 107.9, 94.9, 65.4, 56.5, 52.1, 26.9. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5$ $[M + H]^+$ 530.0603 and 532.0583, found 530.0608 and 532.0590 (isotopic mass).

Methyl-5'-(2-chlorophenyl)-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzofuran-2,1'-cyclopentane-2',3''-indolin]-3'-ene-3'-carboxylate (3v')



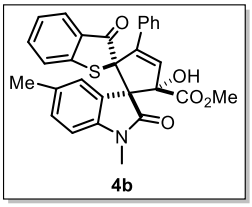
The compound **3v'** was prepared following the general procedure **GP-2** White solid (30 mg, 54%), R_f = 0.12 (petroleum ether/EtOAc 70:30), MP: 273-275 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 1H), 7.43 – 7.34 (m, 3H), 7.33 (d, *J* = 2.7 Hz, 1H), 7.26 – 7.20 (m, 3H), 7.16 (td, *J* = 7.7, 1.2 Hz, 1H), 6.99 – 6.87 (m, 2H), 6.85 – 6.79 (m, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 5.15 (d, *J* = 2.6 Hz, 1H), 3.61 (s, 3H), 3.10 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 200.0, 173.9, 171.9, 162.4, 147.3, 144.7, 138.1, 136.9, 135.1, 133.7, 132.1, 129.4, 129.3, 128.9, 126.7, 126.4, 125.3, 124.4, 122.5, 122.5, 120.1, 112.9, 108.0, 95.0, 65.4, 54.1, 52.1, 26.9. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5$ $[M + H]^+$ 486.1108, found 486.1119.

Methyl-5'-hydroxy-1''-methyl-2'', 3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2, 2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4a)



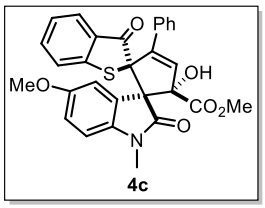
The compound **4a** was prepared following the general procedure **GP-3** Yellow solid (31 mg, 56%), *dr* >20:1. R_f = 0.34 (petroleum ether/EtOAc 60:40), MP: 219-221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.23 – 7.18 (m, 3H), 7.17 – 7.11 (m, 3H), 7.10 – 7.04 (m, 3H), 6.94 (s, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 1H), 3.60 (s, 2H), 3.13 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 175.5, 169.2, 154.3, 148.5, 145.5, 137.3, 135.5, 133.4, 129.5, 129.4, 129.1, 128.5, 128.0, 127.5, 127.0, 125.5, 124.2, 122.8, 122.6, 108.1, 87.4, 77.7, 64.7, 52.8, 26.5. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}NO_5SNa$ $[M + Na]^+$ 506.1038, found 506.1037.

Methyl-5'-hydroxy-1'',5''-dimethyl-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4b)



The compound **4b** was prepared following the general procedure **GP-3** Yellow solid (28mg, 49%), *dr* >20:1, R_f = 0.33 (petroleum ether/EtOAc 60:40), MP: 257-259 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.23 – 7.13 (m, 3H), 7.13 – 7.04 (m, 4H), 7.02 (s, 1H), 6.93 (d, *J* = 4.9 Hz, 2H), 6.59 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 1H), 3.60 (s, 3H), 3.10 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 175.3, 169.2, 154.4, 148.4, 143.1, 137.2, 135.5, 133.4, 131.9, 129.8, 129.5, 129.0, 128.5, 128.3, 127.8, 126.9, 125.4, 124.2, 122.7, 107.8, 87.3, 77.8, 64.8, 52.8, 26.5, 21.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_5S$ $[M + H]^+$ 498.1375, found 498.1377.

Methyl-5'-hydroxy-5''-methoxy-1''-methyl-2'',3-dioxo-3'-phenyl-*3H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4c)

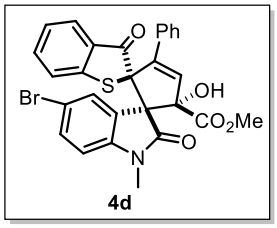


The compound **4c** was prepared following the general procedure **GP-3** Yellow solid (30 mg, 51%), *dr* >20:1, R_f = 0.21 (petroleum ether/EtOAc 60:40), MP: 249-251 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (ddd, *J* = 7.8, 1.3, 0.7 Hz, 1H), 7.46 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.25 – 7.11 (m, 6H), 7.00 (s, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.15 (s, 1H), 3.68 (s, 3H), 3.68 (s, 3H), 3.17 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 175.1, 169.1, 155.5, 154.4, 148.5, 139.0, 137.3, 135.4, 133.4, 129.5, 129.1, 128.5, 127.9, 126.9, 126.9, 126.9, 125.6, 124.3, 123.9, 114.9,

114.3, 108.3, 87.3, 77.7, 64.9, 55.8, 52.8, 26.6. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{23}NO_6SNa$ $[M + Na]^+$ 536.1144, found 536.1143.

Methyl-5''-bromo-5'-hydroxy-1''-methyl-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4d)

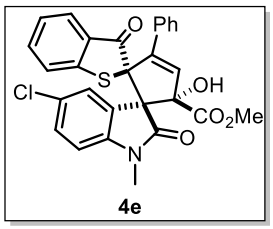
The compound **4d** was prepared following the general procedure **GP-3**



4d

Yellow solid (28 mg, 43%), *dr* >20:1, R_f = 0.33 (petroleum ether/EtOAc 60:40), MP: 230-232 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 1.7 Hz, 1H), 7.34 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.24 – 7.08 (m, 7H), 6.99 (s, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.07 (s, 1H), 3.70 (s, 3H), 3.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.5, 175.1, 169.1, 154.0, 148.4, 144.6, 137.5, 135.2, 133.2, 132.4, 130.6, 129.3, 129.2, 128.5, 128.1, 126.9, 125.8, 124.9, 124.2, 115.2, 109.5, 87.5, 77.6, 64.5, 53.0, 26.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}BrNO_5SNa$ $[M + Na]^+$ 584.0143, found 584.0150.

Methyl-5''-chloro-5'-hydroxy-1''-methyl-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4e)



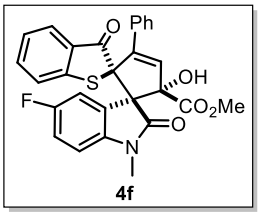
4e

The compound **4e** was prepared following the general procedure **GP-3** Yellow solid (25 mg, 42%), *dr* >20:1, R_f = 0.3 (petroleum ether/EtOAc 60:40), MP: 236-238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.75 (m, 1H), 7.47 – 7.38 (m, 1H), 7.19 (d, *J* = 2.7 Hz, 2H), 7.17 – 7.08 (m, 5H), 7.07 – 7.03 (m, 2H), 6.92 (s, 1H), 6.63 (d, *J* = 8.3 Hz, 1H), 5.04 (s, 1H), 3.63 (s, 3H), 3.11 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.5, 175.2, 169.1, 154.0, 148.5, 144.1, 137.5, 135.2, 133.1, 129.5, 129.3, 129.2, 128.5, 128.1, 127.9, 127.9, 126.9, 126.9, 125.8, 124.5, 124.2, 109.0, 87.5, 77.5, 64.6, 53.0, 26.7. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5S$ $[M + H]^+$ 518.0829, found 518.0823.

Methyl-5''-fluoro-5'-hydroxy-1''-methyl-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4f)

The compound **4f** was prepared following the general procedure **GP-3**

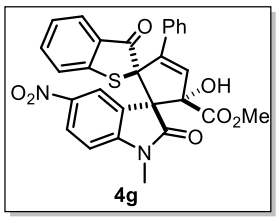
Yellow solid (26 mg, 45%), *dr* >20:1, R_f = 0.3 (petroleum ether/EtOAc 60:40), MP: 184-186 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 1H), 7.42 (td, *J* = 8.0, 1.4 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.17 – 7.07 (m, 4H), 7.05 (dd, *J* = 7.2, 1.6 Hz, 2H), 6.99 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.92 (s, 1H), 6.86 (td, *J* = 8.7, 2.6 Hz, 1H), 6.63 (dd, *J* = 8.5, 4.3 Hz, 1H), 5.06 (s, 1H), 3.62 (s, 3H), 3.12 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.6, 175.3, 169.1, 158.81 (d, $J_{(C-F)}$ = 239.7 Hz), 154.2, 148.6, 141.5, 137.5, 135.2, 133.2, 129.3, 129.2, 128.5, 128.2, 126.9, 125.7, 124.4, 124.3, 124.2, 115.9 (d, $J_{(C-F)}$ = 26 Hz), 115.8(d, $J_{(C-F)}$ = 23 Hz), 108.40 (d, $J_{(C-F)}$ = 8.2 Hz), 87.4, 77.6, 64.7, 52.9, 26.7. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -120.3. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}FNO_5SNa$ $[M + Na]^+$ 524.0944, found 524.0941.

Methyl-5'-hydroxy-1''-methyl-5''-nitro-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4g)

The compound **4g** was prepared following the general procedure **GP-3**

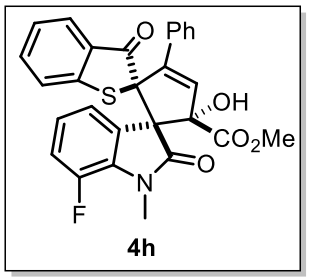


Yellow solid (25 mg, 41%), *dr* >20:1, R_f = 0.23 (petroleum ether/EtOAc 60:40), MP: 227-229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.48 (q, *J* = 6.7, 5.5 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.25 – 7.10 (m, 6H), 7.00 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.18 (s, 1H), 3.72 (s, 3H), 3.27 (s, 3H). ^{13}C {^{1}H} NMR(100 MHz, $CDCl_3$): δ (ppm) 202.1, 175.9, 169.1, 153.5, 151.2, 148.5, 143.2, 141.7, 137.7, 134.8, 132.8, 129.3, 129.0, 128.6, 128.4, 126.8, 126.7, 126.1, 124.2, 123.7, 123.2, 107.7, 87.9, 64.1, 53.1, 26.9. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}N_2O_7S$ $[M + H]^+$ 529.1069, found 529.1076.

Methyl-7''-fluoro-5'-hydroxy-1''-methyl-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2, 2'-cyclopentane-1', 3''-indolin]-3'-ene-5'-carboxylate (4h)

The compound **4h** was prepared following the general procedure **GP-3**

Yellow solid (29 mg, 50%), *dr* >20:1, R_f = 0.5 (petroleum ether/EtOAc 60:40), MP: 188-190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.20 (dt, *J* = 14.8, 7.4 Hz, 4H), 7.10 (dd, *J* = 18.6, 7.5 Hz, 3H), 7.00 (s, 1H), 6.95 (dd, *J* = 11.4, 8.5 Hz, 1H), 6.80 (td, *J* = 8.1, 4.8 Hz, 1H), 5.11 (s, 1H), 3.71 (s, 3H), 3.42 (d, *J* = 2.8 Hz, 3H).

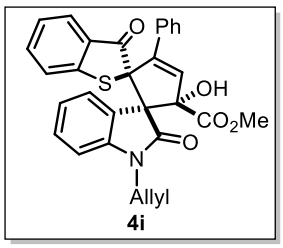


4h

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.6, 175.2, 169.1, 154.2, 148.4, 146.4, 136.3 (d, $J_{(C-F)}$ = 221.2 Hz) , 134.4, 133.2, 132.27 (d, $J_{(C-F)}$ = 8.0 Hz), 129.3, 129.2, 128.5, 128.0, 126.9, 125.6, 124.3, 123.4 (d, $J_{(C-F)}$ = 2.9 Hz), 122.8 (d, $J_{(C-F)}$ = 6.4 Hz) , 117.7 (d, $J_{(C-F)}$ = 19.1 Hz)., 87.5, 77.7, 61.1, 53.0, 29.1. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -136.2. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}FNO_5SNa$ $[M + Na]^+$ 524.0944, found 524.0944.

Methyl-1''-allyl-5'-hydroxy-2'',3-dioxo-3'-phenyl-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4i)

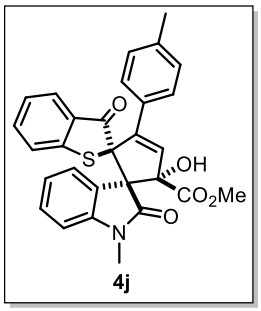
The compound **4i** was prepared following the general procedure **GP-3**



4i

Yellow solid (27 mg, 46%), *dr* >20:1, R_f = 0.46 (petroleum ether/EtOAc 60:40), MP: 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.26 (s, 1H), 7.23 – 7.09 (m, 7H), 7.01 (s, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.85 (ddt, *J* = 15.8, 10.5, 5.4 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 5.19 (s, 1H), 4.39 – 4.25 (m, 2H), 3.67 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 175.1, 169.1, 154.3, 148.5, 144.7, 137.3, 135.5, 133.4, 131.5, 129.5, 129.4, 129.0, 128.5, 128.0, 127.6, 126.9, 125.5, 124.2, 122.8, 122.5, 118.1, 109.0, 87.3, 77.9, 64.7, 52.8, 42.9. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{23}NO_5SNa$ $[M + Na]^+$ 532.1195, found 532.1192.

Methyl-5'-hydroxy-1''-methyl-2'',3-dioxo-3'-(p-tolyl)-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4j)

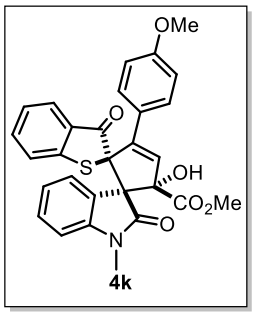


4j

The compound **4j** was prepared following the general procedure **GP-3** Yellow solid (25 mg, 44%), *dr* >20:1, R_f = 0.34 (petroleum ether/EtOAc 60:40), MP: 189-191 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.48 – 7.41 (m, 1H), 7.27 – 7.26 (m, 1H), 7.24 – 7.12 (m, 3H), 7.02 (d, *J* = 0.6 Hz, 4H), 6.97 (d, *J* = 0.7 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 0.7 Hz, 1H), 3.67 (d, *J* = 0.7 Hz, 3H), 3.20 (d, *J* = 0.6 Hz, 3H), 2.28 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 175.5, 169.2, 154.4, 154.4, 148.5, 145.5, 139.1, 137.2, 134.7, 130.5,

129.5, 129.5, 129.2, 128.0, 127.5, 126.8, 126.8, 126.8, 126.8, 126.8, 125.5, 124.2, 122.9, 122.5, 108.1, 87.4, 87.4, 77.7, 64.7, 52.8, 26.5, 21.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_5S$ $[M + H]^+$ 498.1375, found 498.1374.

Methyl-5'-hydroxy-3'-(4-methoxyphenyl)-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1', 3''-indolin]-3'-ene-5'-carboxylate (4k)

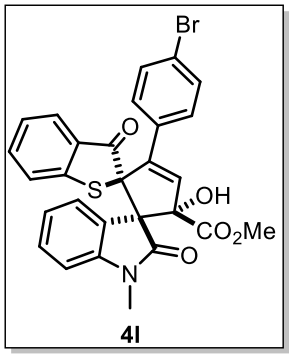


The compound **4k** was prepared following the general procedure **GP-3** Yellow solid (24 mg, 41%), *dr* >20:1, R_f = 0.26 (petroleum ether/EtOAc 60:40), MP: 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.28 (s, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 7.7, 4.5 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.93 (s, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.76 (dd, *J* = 16.5, 8.3 Hz, 3H), 5.12 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.7, 175.4, 169.1, 160.1, 154.2, 147.9, 145.4, 137.1, 133.8, 129.4, 128.1, 127.8, 127.4, 125.7, 125.3, 124.1, 122.8, 122.4, 113.8, 108.0, 87.2, 77.7, 64.6, 55.2, 52.7, 26.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}NO_6S$ $[M + H]^+$ 514.1324, found 514.1324.

Methyl-3'-(4-bromophenyl)-5'-hydroxy-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4l)

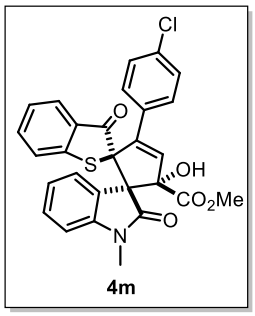
The compound **4l** was prepared following the general procedure **GP-3**

Yellow solid (35 mg, 54%), *dr* >20:1, R_f = 0.34 (petroleum ether/EtOAc 60:40), MP: 205-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 1H), 7.43 – 7.36 (m, 1H), 7.30 – 7.25 (m, 2H), 7.21 (s, 1H), 7.18 – 7.05 (m, 3H), 6.96 – 6.89 (m, 3H), 6.81 (td, *J* = 7.7, 1.0 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 5.09 (s, 1H), 3.60 (s, 3H), 3.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.6, 175.4, 169.0, 154.1, 147.5, 145.4, 137.5, 136.0, 132.3, 131.7, 129.6, 129.3, 128.6, 128.0, 127.5, 125.7, 124.2, 123.3, 122.6, 108.2, 87.3, 77.6, 64.7, 52.9, 26.5. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5S$ $[M + H]^+$ 562.0324 and 564.0303 found 562.0323 and 564.0317 (isotopic mass).



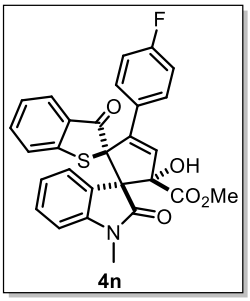
Methyl-3'-(4-chlorophenyl)-5'-hydroxy-1''-methyl-2'', 3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1', 3''-indolin]-3'-ene-5'-carboxylate (4m)

The compound **4m** was prepared following the general procedure **GP-3**



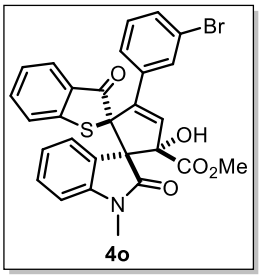
Yellow solid (28 mg, 47%), *dr* >20:1, R_f = 0.37 (petroleum ether/EtOAc 60:40), MP: 175-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.50 – 7.43 (m, 1H), 7.29 – 7.26 (m, 1H), 7.23 – 7.14 (m, 5H), 7.08 – 7.05 (m, 2H), 6.99 (s, 1H), 6.89 (td, *J* = 7.7, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 1H), 3.67 (s, 3H), 3.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.6, 175.4, 169.0, 154.2, 147.4, 145.5, 137.5, 136.0, 135.1, 131.9, 129.6, 129.3, 128.9, 128.7, 128.4, 128.0, 127.5, 125.7, 124.3, 122.6, 108.2, 87.3, 77.6, 64.7, 52.9, 26.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}ClNO_5S$ $[M + H]^+$ 518.0829, found 518.0831.

Methyl-3'-(4-fluorophenyl)-5'-hydroxy-1''-methyl-2'', 3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4n)



The compound **4n** was prepared following the general procedure **GP-3** Yellow solid (29 mg, 50%), *dr* > 20:1, R_f = 0.31 (petroleum ether/EtOAc 60:40), MP: 202-204 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.21 (s, 1H), 7.18 – 7.01 (m, 5H), 6.89 (s, 1H), 6.82 (q, *J* = 7.7, 6.7 Hz, 3H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.08 (s, 1H), 3.60 (s, 3H), 3.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 202.7, 175.4, 169.1, 163.2 (d, $J_{(C-F)}$ = 248.9 Hz), 154.2, 147.5, 145.5, 137.4, 135.5, 129.6, 129.5 (d, $J_{(C-F)}$ = 3 Hz), 129.3, 129.0, 128.9 (d, $J_{(C-F)}$ = 8.3 Hz), 128.0, 127.5, 125.6, 124.2, 122.7, 122.6, 115.5 (d, $J_{(C-F)}$ = 21.7 Hz), 108.2, 87.2, 77.8, 64.7, 52.8, 26.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.22. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{20}FNO_5S$ $[M + H]^+$ 502.1124, found 502.1121.

Methyl-3'-(3-bromophenyl)-5'-hydroxy-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2,2'-cyclopentane-1',3''-indolin]-3'-ene-5'-carboxylate (4o)

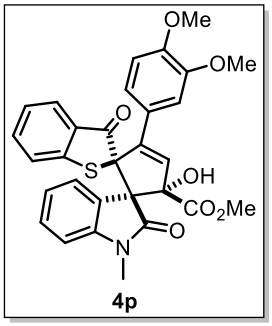


The compound **4o** was prepared following the general procedure **GP-3** Yellow solid (32 mg, 49%), *dr* >20:1, R_f = 0.34 (petroleum ether/EtOAc 60:40), MP: 209-211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.36 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.22 (s, 1H), 7.18 – 7.06 (m, 3H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 1H), 3.61 (s, 3H), 3.13

(s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.5, 175.4, 169.0, 154.2, 147.2, 145.5, 137.5, 136.6, 135.4, 132.0, 130.3, 130.3, 129.9, 129.6, 129.3, 128.1, 127.5, 125.7, 125.4, 124.2, 122.7, 122.6, 122.6, 122.6, 108.2, 100.1, 87.2, 77.6, 64.6, 52.9, 26.6. HRMS (ESI TOF) *m/z* calcd. For $C_{28}H_{21}BrNO_5S$ $[M + H]^+$ 562.0324 and 564.0303 found 562.0337 and 564.0314.

Methyl-3'-(3,4-dimethoxyphenyl)-5'-hydroxy-1''-methyl-2'',3-dioxo-3*H*-dispiro[benzo[*b*]thiophene-2, 2'-cyclopentane-1', 3''-indolin]-3'-ene-5'-carboxylate (4p)

The compound **4p** was prepared following the general procedure **GP-3**



4p

Yellow solid (25 mg, 40 %), *dr* = 84:16 R_f = 0.15 (petroleum ether/EtOAc 60:40), MP: 222-224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.07 (m, 3H), 6.89 (d, *J* = 11.0 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.75 – 6.68 (m, 2H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 1H), 5.10 (s, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 3.41 (s, 3H), 3.14 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 175.5, 169.2, 154.6, 149.7, 148.6, 148.3, 145.5, 137.2, 133.9, 129.6, 129.5, 127.9, 127.6, 126.0, 125.5, 124.2, 122.9, 122.6, 119.6, 111.0, 109.6, 108.2, 87.4, 77.8, 64.6, 56.0, 55.4, 52.8, 26.5. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{26}NO_7S$ $[M + H]^+$ 544.1430, found 544.1427.

4.7 Appendix IV ^{1}H, ^{13}C spectral data of representative compounds

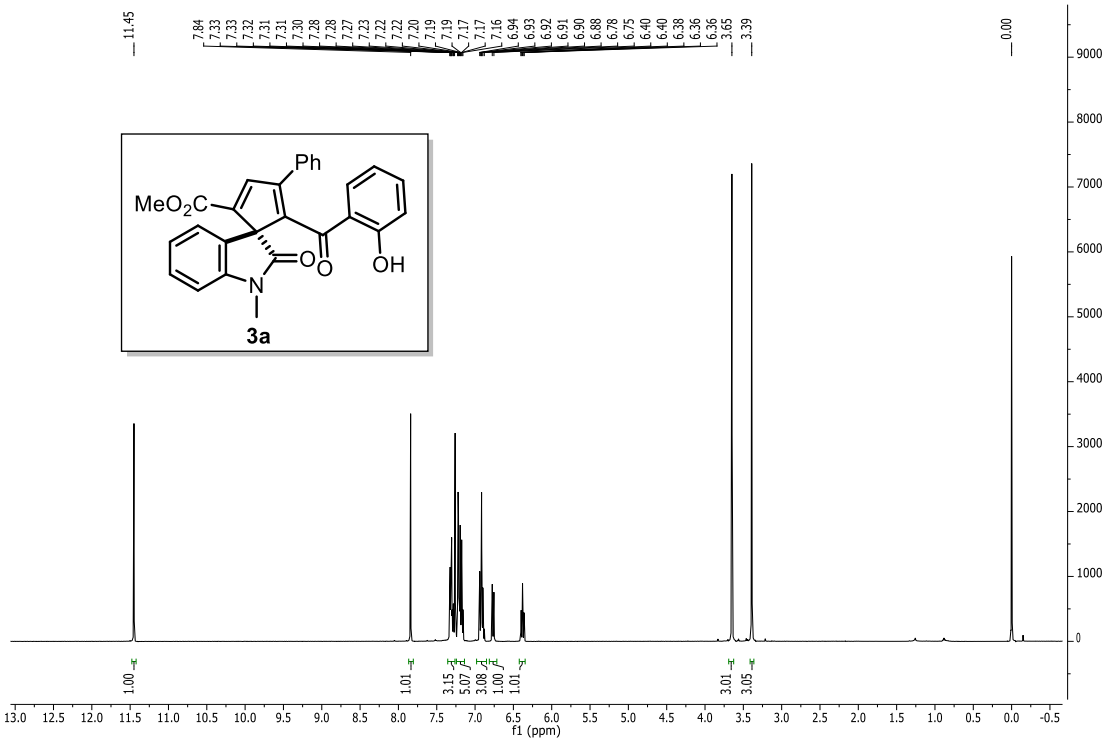


Figure AIV.1 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

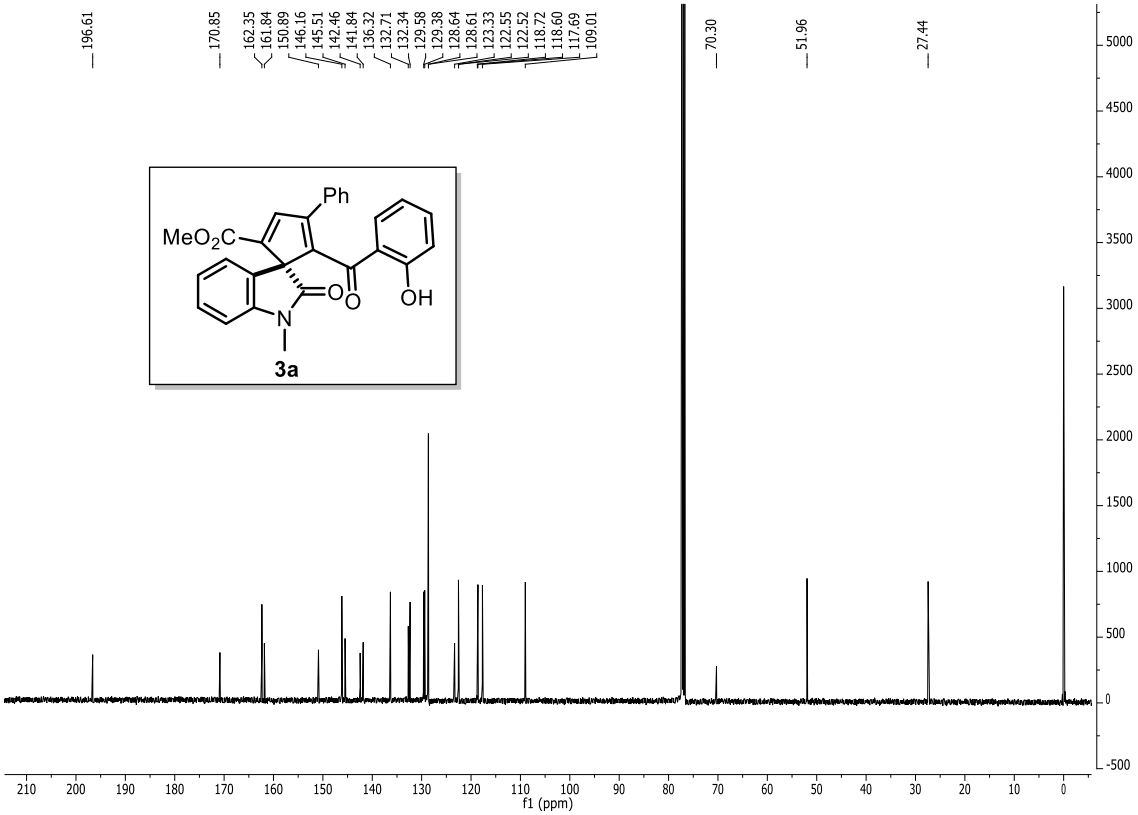


Figure AIV.2 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

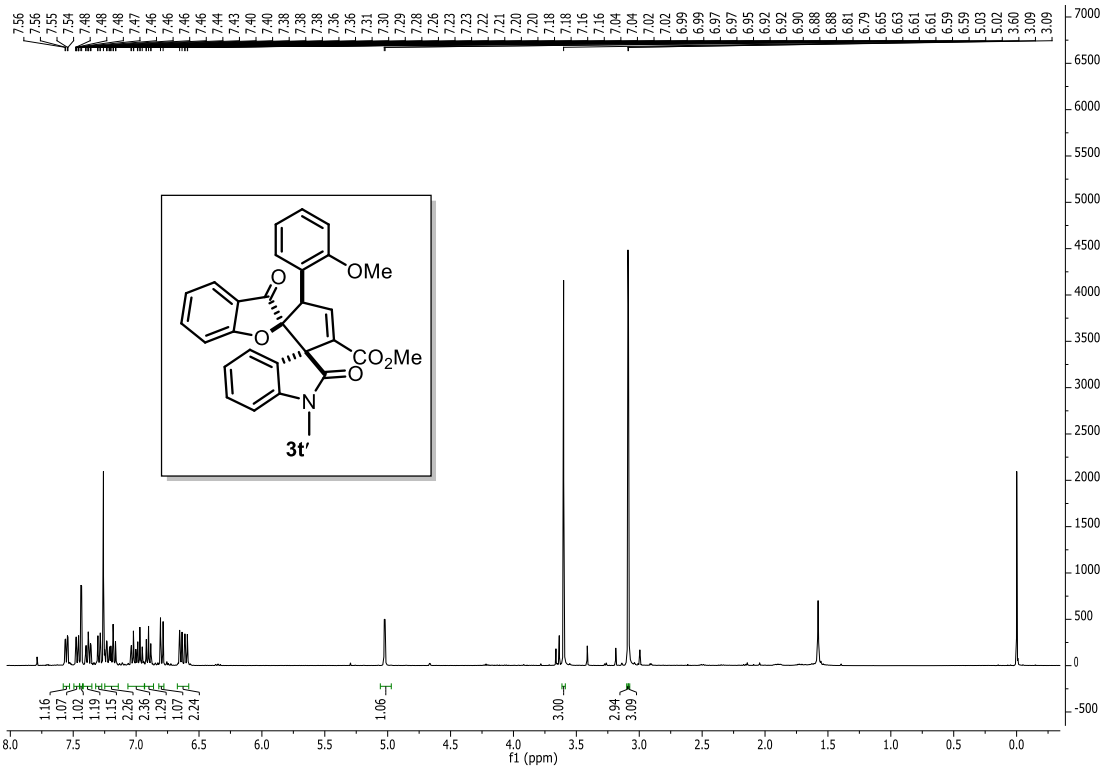


Figure AIV.3 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3t'**

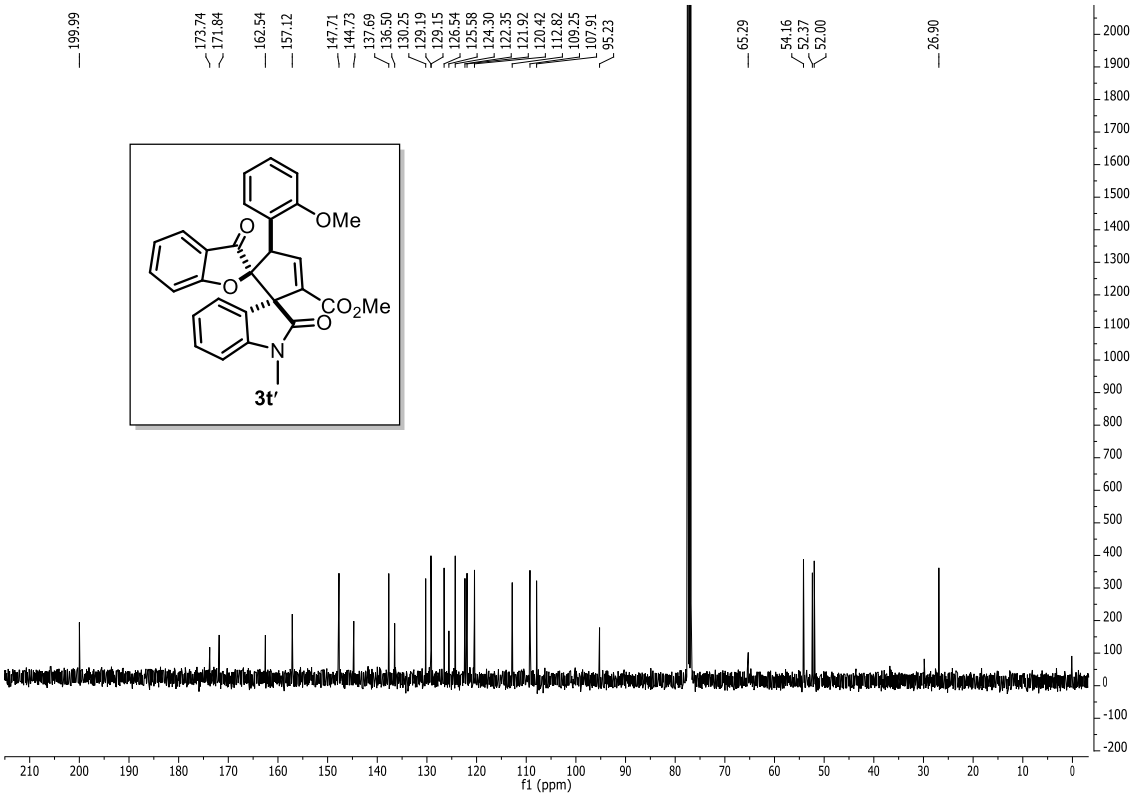


Figure AIV.4 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3t'**

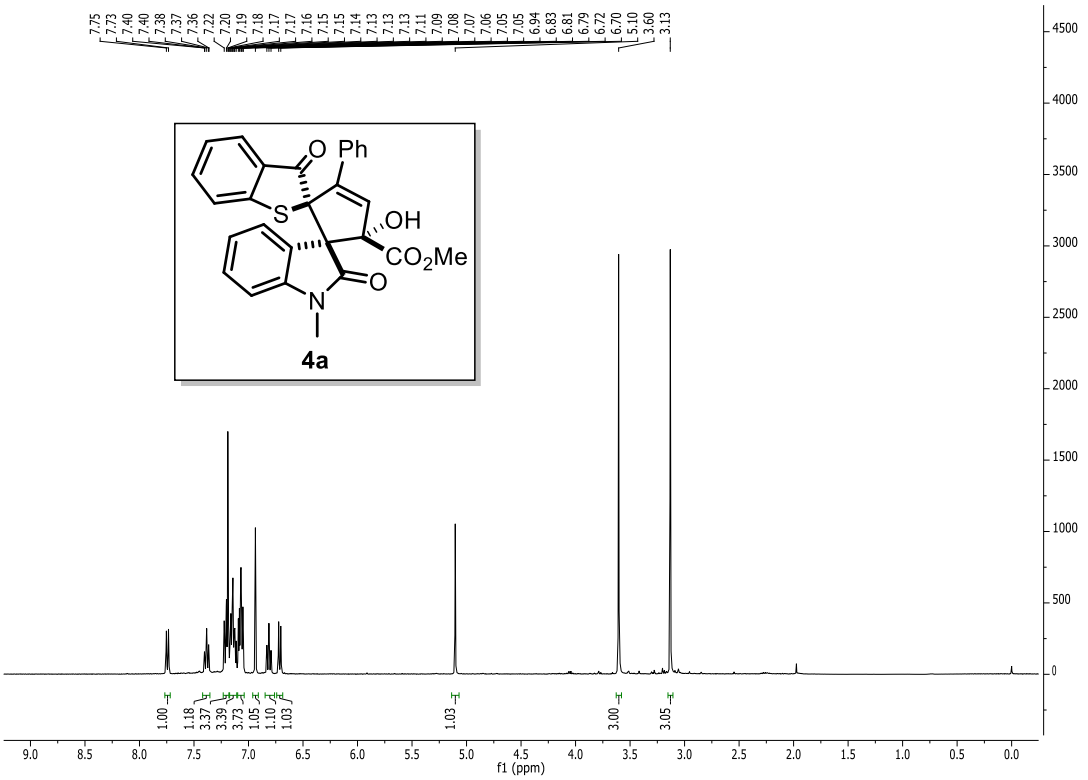


Figure AIV.5 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

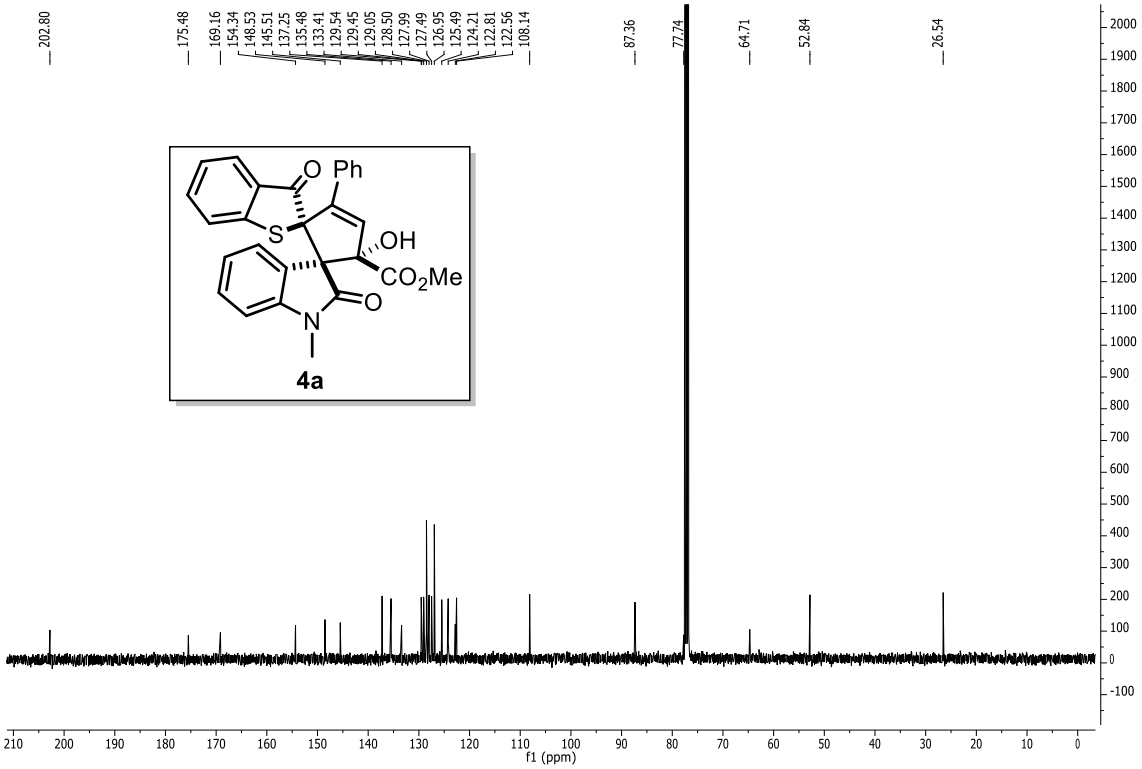


Figure AIV.6 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**

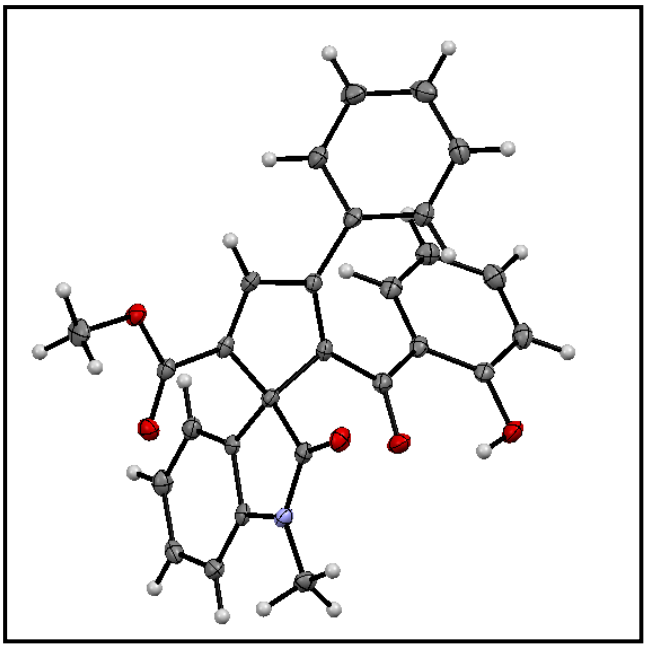


Figure AIV.7 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3a**

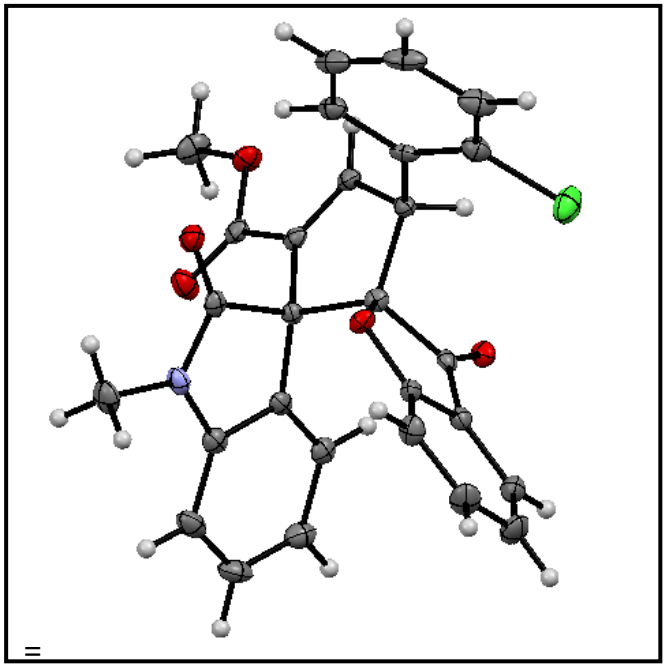


Figure AIV.8 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3v'**

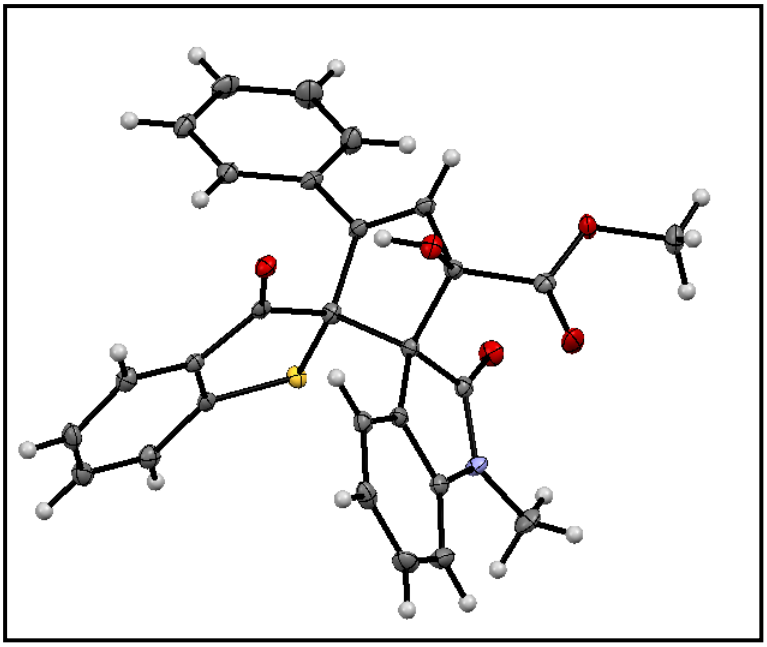


Figure AIV.9 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **4a**

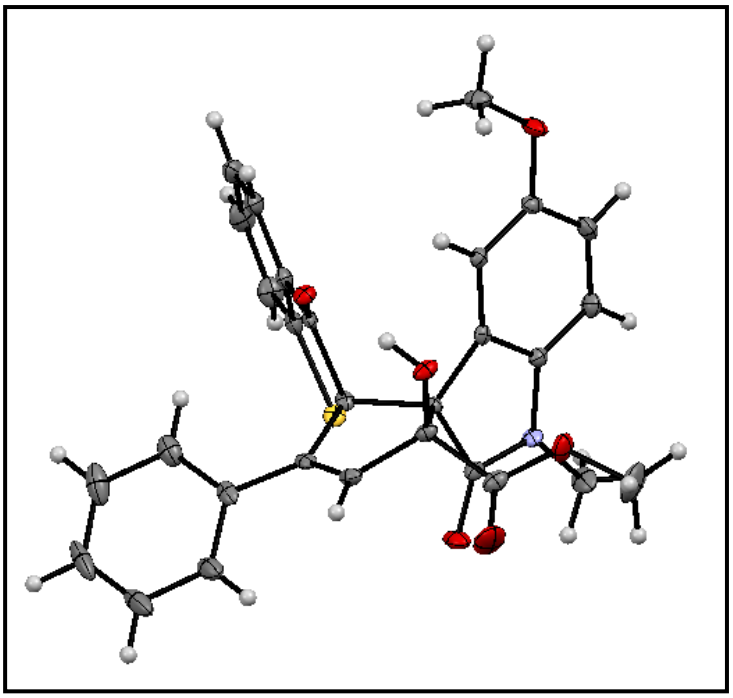


Figure AIV.10 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **4c**

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17. CCDC 2067878 contains the supplementary crystallographic data for compound **3v′**.
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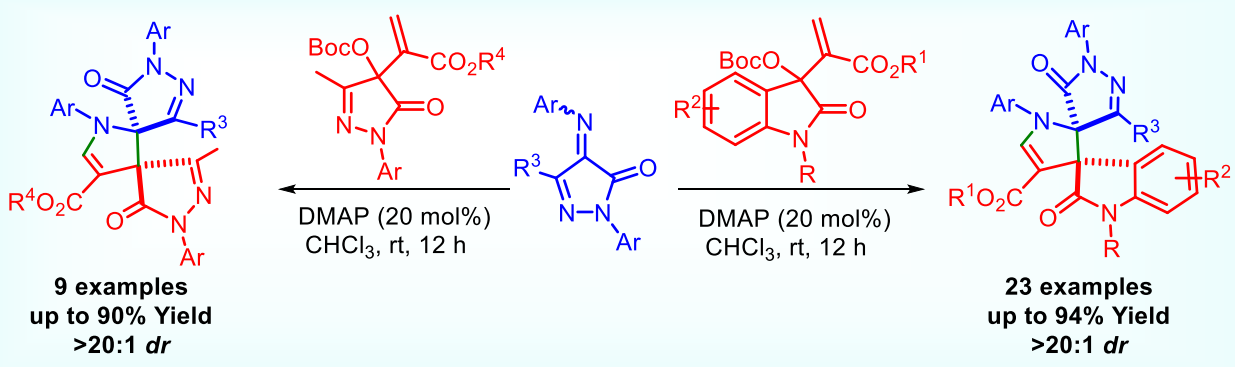
5

Direct Access to Spirooxindole Dihydropyrrole Fused Pyrazolone and Bis-Spiropyrazolone Derivatives

Abstract

A highly regio- and diastereo-selective [3+2] annulation of Morita−Baylis−Hillman carbonates of isatins/pyrazolones with pyrazolinone ketimines has been developed to access spiroheterocycles. The protocol worked effectively to construct spirooxindole dihydropyrrole fused pyrazolone and bis-spiropyrazolone dihydropyrrole derivatives bearing two vicinal quaternary spirocentres in good to excellent yields with very high diastereoselectivities under mild catalytic condition at room temperature. The protocol proved to be efficient with diverse MBH carbonates and ketimine derivatives. The method has successfully demonstrated the utility of commercially viable DMAP as effective catalyst for the desired transformation.



Warghude, P. K.; Bhowmick, A.; Bhat, R. G. Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2022.153791

FIVE

5 Direct Access to Spirooxindole Dihydropyrrole Fused Pyrazolone and Bis-Spiropyrazolone Derivatives

5.1 Introduction

Over the years, tremendous efforts have been made to develop new therapeutic agents in modern drug discovery research. The modification of existing pharmacophores by merging two or more biologically active fragments or potent pharmacophore motifs gives a new scaffold known as a hybrid molecule.[1] The various hybrid molecules are being explored for their pharmacological properties using *in silico* molecular modelling. Some of the newly synthesized hybrid compounds have been successfully used as drugs to treat bacterial resistance infections (resistance to antimicrobial drugs),[2a] multigenic diseases such as cancer,[2b]Alzheimer's,[2c] and Plasmodium elicited infections.[2d] Particularly, spirocyclic compounds have drawn the attention of synthetic as well as medicinal chemists due to their various potent biological properties.[3] Among the various spirocyclic compounds, the multifunctional spirooxindoles, spiropyrazolones and spirooxindole fused pyrazolones have gained significant importance due to their unique structural framework. A large number of natural products and synthetic compounds having this type of spirocyclic scaffold are known to exhibit remarkable biological activities (Figure 5.1).[4-10]

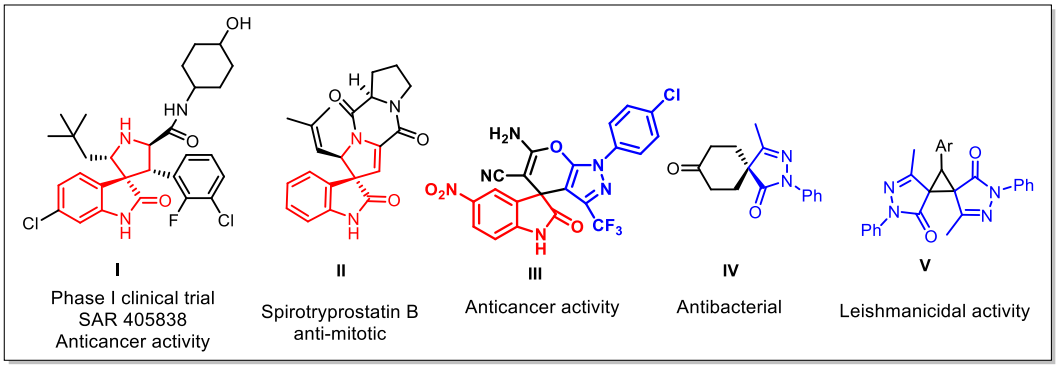


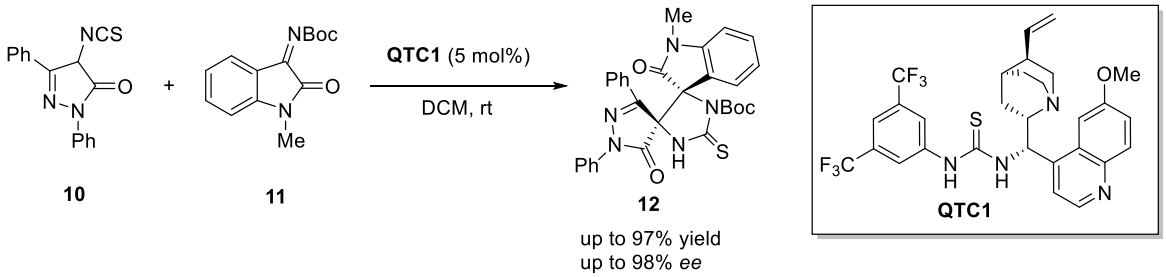
Figure 5.1 Representative examples of bioactive compounds with spirooxindole and spiropyrazolone scaffolds

For example, the spirooxindole compound **I** SAR 405838 showed the potent anticancer activity in phase I clinical trials.[6d] Spirotryprostatin B compound **II** inhibited the G2/M phase (anti-mitotic) of the mammalian cell cycle at micromolar concentrations.[7] The compound **III** containing both oxindole and pyrazolone motifs exhibited the anticancer activity.[8] The spiropyrazolone derivative **IV** elicited antibacterical activity.[9] While, the bis-spiropyrazolone compound **V** showed leishmanicidal activity.[10]

The distinctive structure and pharmacological significance of these spirocyclic frameworks make them very attractive targets for the target-based drug discovery in the fields of medicinal chemistry and also from the synthetic organic chemistry perspective due to their utility. As a result, significant efforts have been focused on the development of effective methods to construct these highly valuable spirocyclic frameworks. However, a very few protocols in the literature have explored the synthesis of a molecule containing oxindole and pyrazolone moieties.

5.2 Selected methods for the synthesis of spirooxindole fused pyrazolone

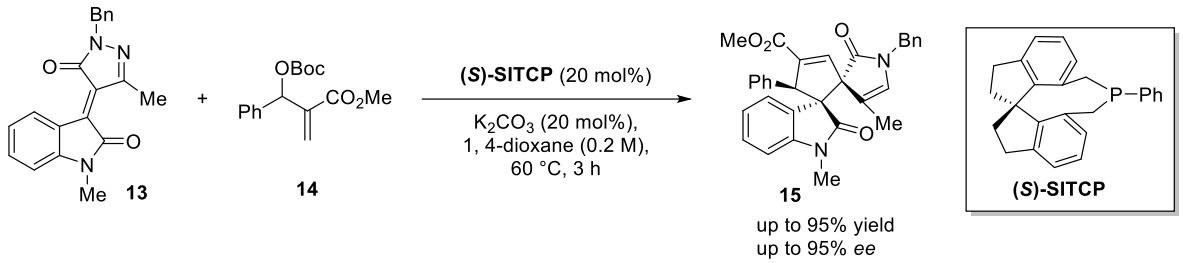
In 2018, the Zhou and Wang group[11] have reported the asymmetric [3 + 2] annulation of 4-isothiocyanato pyrazolones **10** and isatin-derived ketimines **11** in the presence of quinine thiourea catalyst **QTC1** to construct dispiro[pyrazolone/ethylenethiourea/oxindole] **12** products containing two adjacent spiroquaternary chiral centers in very high yields with excellent stereoselectivities (Scheme 5.1).



Scheme 5.1 Asymmetric [3 + 2] annulation of 4-isothiocyanato pyrazolones and isatin-derived ketimines

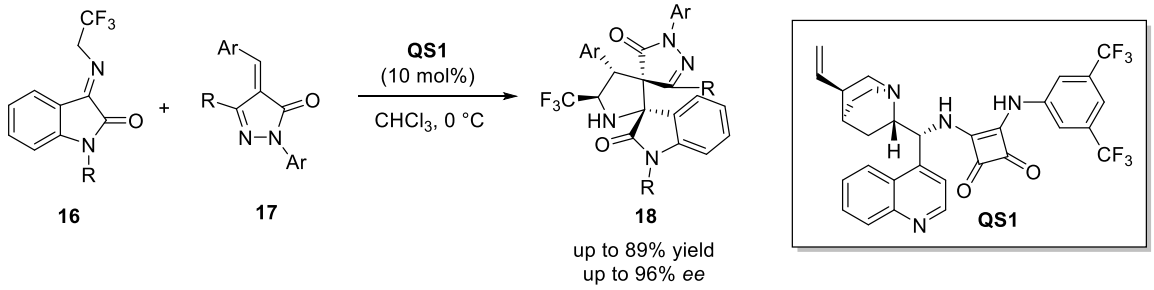
In 2019, Ullah, Lu, and co-workers[12] have described the [3 + 2] annulation between the pyrazoloneyldiene oxindoles **13** and Morita–Baylis–Hillman (MBH) carbonates **14** in the presence of ***(S)*-SITCP** catalyst (20 mol%) in 1,4-dioxane. This asymmetric [3 + 2] annulation

delivered the structurally diverse bispiro[pyrazolone-3,3'-oxindole] **15** derivatives bearing two contiguous quaternary stereogenic centers in excellent yields with stereoselectivities (up to 99% *ee*, Scheme 5.2).



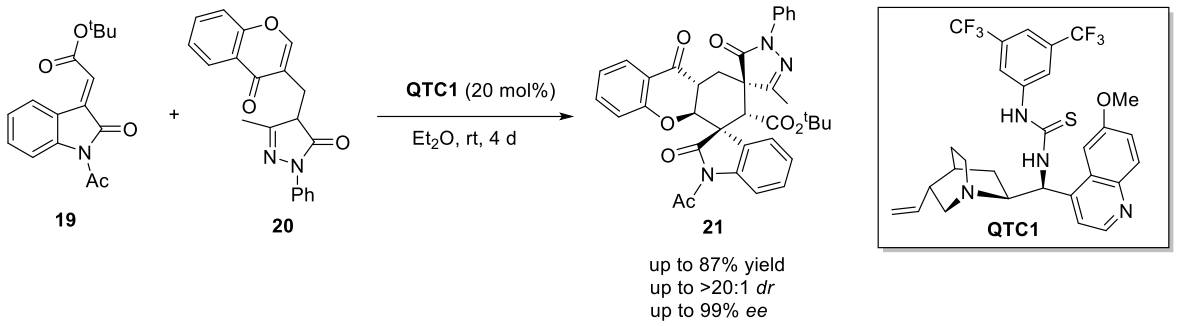
Scheme 5.2 Enantioselective [3 + 2] annulation of oxopyrazolinylideneoxindoles and MBH carbonates

In the year 2019, Yan, Wang, and co-workers have reported an attractive enantioselective method to access spiro-pyrrolidine-linked oxindole and pyrazolone derivatives **18** via an organocatalytic 1, 3-dipolar cycloaddition pathway.[13] The cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines **16** with *α, β*-unsaturated pyrazolones **17** in the presence of cinchonine-derived squaramide catalyst **QS1** (10 mol%) delivered the corresponding spiro-pyrrolidine-linked oxindole and pyrazolone compounds **18** containing four consecutive stereocenters and two adjacent spiroquaternary chiral centers in very high yields (up to 89%) with excellent stereoselectivities (up to 96% *ee*) (Scheme 5.3).



Scheme 5.3 Enantioselective [3 + 2] cycloaddition of *N*-(2,2,2-trifluoroethyl)isatin ketimines and 4-alkylidenepyrazolones

In the same year, Liu et al.[14] have employed the bifunctional quinine derived thiourea catalyst **QTC1** for the domino inter-/intramolecular double Michael cycloaddition reaction to construct chiral spirocyclic scaffolds. This method utilized 3-substituted methyleneoxindole **19** and bifunctional pyrazolone–chromone **20** as starting materials to achieve highly functionalized spiro-pyrazolone-oxindole scaffolds **21** in high yields (up to 87%) with excellent diastereoselectivities (up to >20:1 *dr*) and enantioselectivities (up to >99% *ee*) (Scheme 5.4)



Scheme 5.4 Organocatalytic double Michael cascade reaction

over the years, pyrazolone derived ketimine has also emerged as one of the useful synthons/substrates in asymmetric synthesis to construct functionally diverse pyrazolone fused scaffolds.[15] In 2017, for the first time Enders and co-workers have developed a new class of pyrazolinone ketimines **2** that can serve as an excellent electrophile at C-4 position (Figure 5.2). This pyrazolone scaffold has been utilized in various synthetic transformations to achieve highly functionalized α-amino pyrazolone derivatives. They have explored the synthetic potential of pyrazolone derived ketimines for the synthesis of pyrazolone α-aminonitrile, amino-bipyrazolones and furanonaphtho pyrazolidinone derivatives via Strecker,[16] Mannich,[17] and domino aza-Friedel–Crafts/N,O-acetalization reaction[18] respectively (Figure 5.2). In the year 2018, Yang, Deng and co-workers have reported the asymmetric aza-Friedel-Crafts reaction of 4-hydroxyindoles **27** with pyrazolone derived ketimines **2** to deliver hydroxyindole-pyzalinone **28** derivatives (Figure 5.2 Ref. 19). Recently, Du and co-workers have also explored the enantioselective Mannich reaction between pyrazolone derived ketimines **2** and 3-fluorooxindoles **29** under chiral bifunctional squaramide catalyst to achieve amino-pyrazolone-oxindoles **30** derivatives (Figure 5.2 Ref. 20). Very recently, Gamble, Han and co-workers have disclosed the $Sc(OTf)_3$ catalyzed regiodivergent synthesis of multi-functionalized pyrazolone derivatives **32** from 1,2-dihydroquinolines **31** and pyrazolone derived ketimines **2** (Figure 5.2 Ref. 21). In spite of being an excellent electrophile at C-4 position, surprisingly, the utility of pyrazolone derived ketimines in organic synthesis to construct synthetically useful pyrazolones is limited in the literature. To the best our knowledge, pyrazolone derived ketimines has not been utilized in the annulation reaction till date.

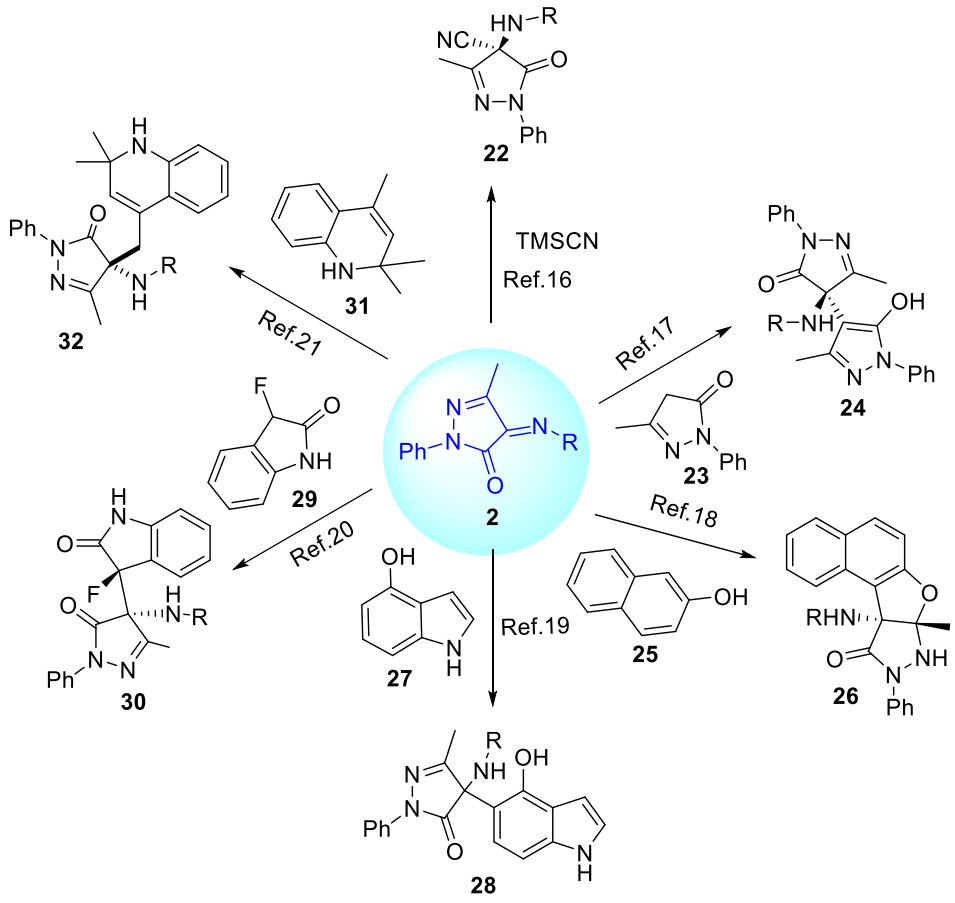
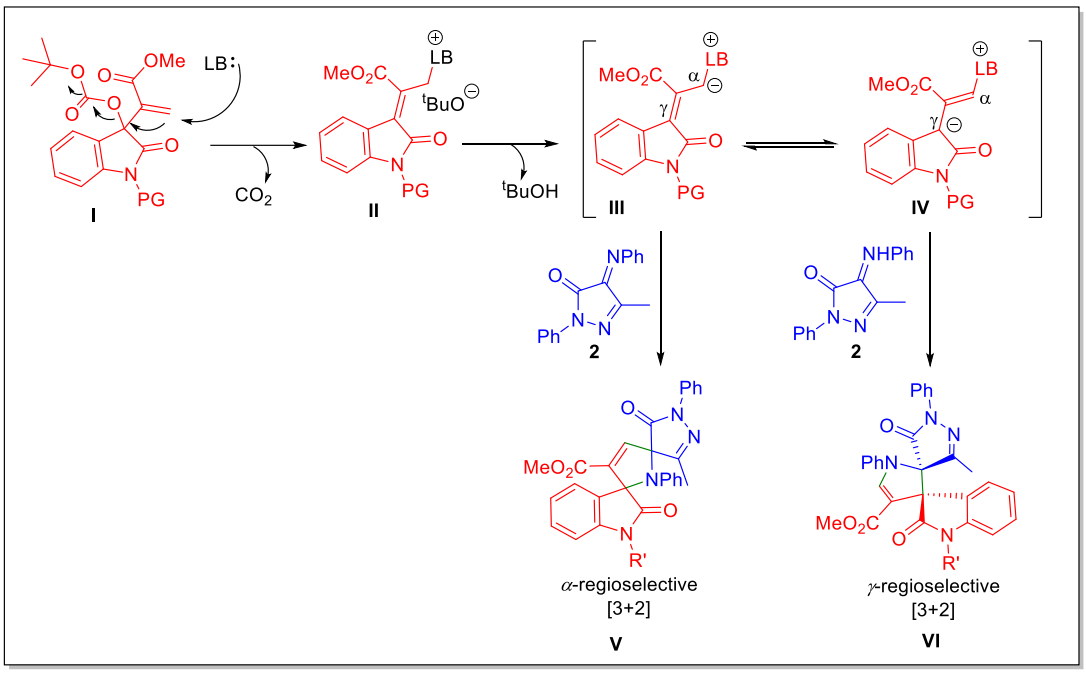


Figure 5.2 Utility of pyrazolone derived ketimine in organic synthesis

Based on our continuous interest in the synthesis of spirocyclic compounds [22] and also as a part of our ongoing research on organocatalytic [3 + 2] annulation reaction, we became interested in spirooxindole fused dihydropyrrole pyrazolone.

5.3 Our hypothesis and synthetic design

We hypothesized that the spirooxindole pyrazolone fused dihydropyrrole compounds could be accessed under organocatalytic conditions starting from MBH carbonate as illustrated in scheme 5.5. Under suitable reaction conditions Lewis base catalyst would attack MBH carbonate **I** via S_N2 pathway to form the intermediate **II** by the explusion of CO2 and *tert*-butoxide anion. Then this intermediate **II** would be deprotonated by the Brønsted base ($^tBuO^-$ generated in situ) to give zwitterionic ylide intermediate **III** or **IV**. These resonating intermediates **III** or **IV** would further react with pyrazolone derived ketimine **2** to give either α- or γ-regioselective **V** or **VI** cycloaddition products respectively (Scheme 5.5).

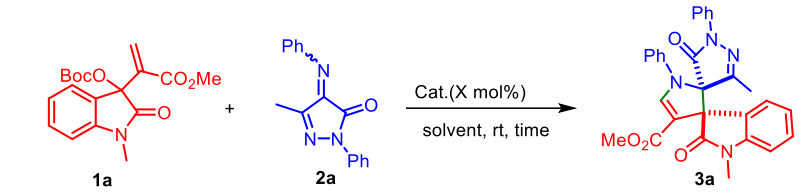


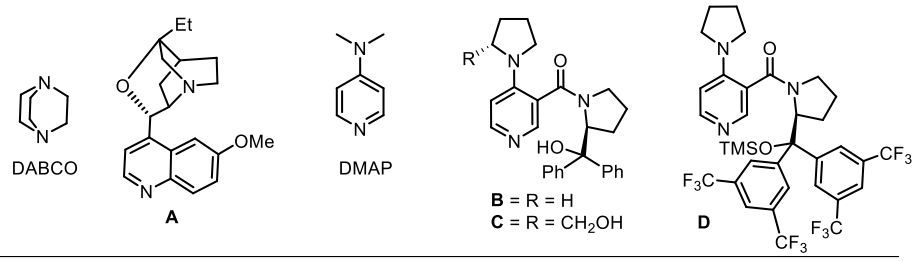
Scheme 5.5 Proposed synthesis of spirooxindole dihydropyrrole pyrazolones

5.4 Results and Discussion

To test the feasibility of our hypothesis, we commenced our study by performing a trial reaction between pyrazolone derived ketimine **2a** and isatin derived MBH carbonate **1a** in presence of 1, 4-diazabicyclo [2.2.2] octane (20 mol%) as a catalyst in dichloromethane (DCM) at room temperature. Pleasingly, the *γ*-regioselective [3 + 2] annulation product **3a** was obtained in moderate yield (60%) with an excellent diastereoselectivity (>20:1 *dr*, Table 5.1, entry 1). In order to enhance the yield of spirooxindole **3a**, we treated MBH carbonate **1a** and pyrazolone derived ketimine **2a** in presence of triphenylphosphine (PPh_3) as nucleophilic catalyst. However, we did not observe any product formation even after prolonged reaction time (Table 5.1, entry 2). When 4-dimethylamonopyridine (DMAP) was used as a catalyst, the reaction was completed in 12 h to furnish compound **3a** in 86% yield with an excellent diastereoselectivity (>20:1 *dr*, Table 5.1, entry 3). Encouraged by this result, we turned our attention to achieve the enantioselective version of this [3 + 2] annulation reaction. In this regard, we screened few chiral tertiary amine catalysts at different reaction conditions, however, unfortunately we did not observe the desired enantioselectivity (Table 5.1, entries 4-7).

Table 5.1 Optimization of the reaction conditions[a-c]





Entry	Catalyst (mol%)	Solvent	Time (h)	*dr*[c]	*ee* (%)[d]	Yield (%)[b]
1	DABCO (20)	CH_2Cl_2	24	>20:1	-	60
2	PPh_3 (20)	CH_2Cl_2	72	-	-	N.R
3	DMAP (20)	CH_2Cl_2	12	>20:1	-	86
4	**A** (20)	CH_2Cl_2	24	-	-	N.R
5	**B** (20)	CH_2Cl_2	24	>20:1	1	72
6	**C** (20)	CH_2Cl_2	24	>20:1	2	75
7	**D** (20)	CH_2Cl_2	24	>20:1	2	85
8	DMAP (20)	$CHCl_3$	12	>20:1	-	92
9	DMAP (20)	THF	12	>20:1	-	84
10	DMAP (20)	CH_3CN	12	>20:1	-	86
11	DMAP (20)	EtOAc	12	>20:1	-	82
12	DMAP (20)	DMF	12	>20:1	-	85
13	DMAP (20)	Toluene	24	>20:1	-	80
14	DMAP (15)	$CHCl_3$	24	>20:1	-	78

[a]**Reaction conditions**: MBH carbonate of isatin **1** (0.115 mmol), Pyrazolone derived ketimine **2a** (0.126 mmol), DMAP (20 mol%) in $CHCl_3$ (2.0 mL) at room temperature; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was determined by ^{1}H NMR.

All of our attempts to obtain the desired enantioselectivity were unsuccessful. Considering the importance of spirooxindole scaffold and looking at the available methods literature, we decided to further explore the diastereoselective version of this [3 + 2] annulation reaction. In this regard, we screened various solvents such as chloroform ($CHCl_3$), tetrahydrofuran (THF), acetonitrile (CH_3CN), ethyl acetate (EtOAc), dimethylformamide (DMF) and toluene to improvise the yield of spirooxindole dihydropyrrole **3a** (Table 5.1, entries 8-13). Among all,

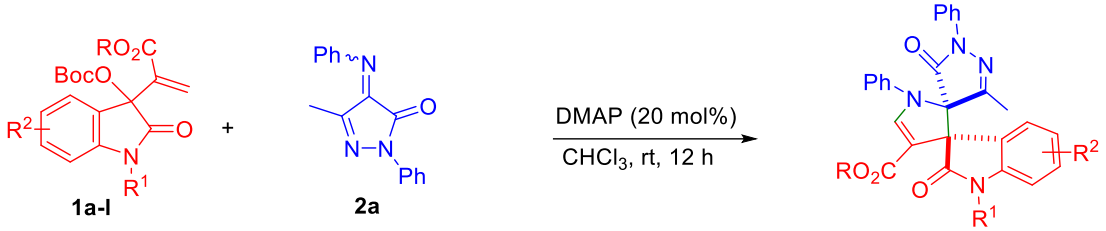
chloroform was found to be advantageous for the desired transformation to afford **3a** in 92% yield with high diastereoselectivity (>20:1 *dr*, Table 5.1, entry 8). The further reduction in DMAP catalyst loading (15 mol%) resulted in decrease in the yield of compound **3a**, however, we observed that the diastereoselectivity remained unchanged (Table 5.1, entry 14). Based on the catalyst and solvent screening, MBH carbonate of isatin **1a** (1.0 equiv.), pyrazolone derived ketimine **2a** (1.1 equiv.) and DMAP (20 mol%) in chloroform for 12 h at room temperature turned out to be the optimum reaction condition to obtain the spiroxindole fused dihydropyrrole derivative **3a**.

With the optimum reaction conditions in hand, initially, we investigated the substrate scope of various isatin derived MBH carbonates **1** and pyrazolone derived ketimine **2** to construct functionally diverse spirooxindole dihydropyrrole fused pyrazolone derivatives **3** via [3 + 2] cycloaddition (Table 5.2). We observed that all the MBH carbonates (**1a-1l**) underwent [3 + 2] annulation smoothly with pyrazolone derived ketimine **2a** to afford the corresponding heterocyclic spirooxindole derivatives (**3a-3l**) bearing two adjacent quaternary spirocenters in very good to excellent yields with excellent diastereoselectivities (up to 94%, >20:1 *dr*, Table 5.2). It is noteworthy that, all the reactions worked efficiently under the optimized reaction conditions, irrespective of the position as well as the nature of the (electron-withdrawing or electron-donating) substituents on the aryl ring of MBH carbonates. Moreover, *N*-allyl and benzyl substituted MBH carbonates (**1j, 1k**) reacted easily with pyrazolone derived ketimine **2a** to furnish the corresponding spirooxindole-dihydropyrrole-pyrazolones **3j** and **3k** in 86% and 84% yield respectively (Table 5.2). Moreover, the ethyl ester substituted MBH carbonate (**1l**) reacted with **2a** to furnish the corresponding dispirocyclic compound **3l** in very good yield with very high diastereoselectivity (89%, >20:1 *dr*).

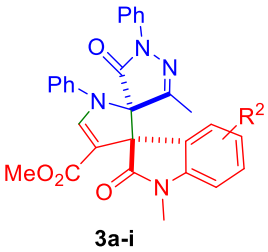
Further, the molecular structure of spirooxindole-dihydropyrrole pyrazolone **3a** was confirmed by using X-ray diffraction analysis.[23] Based on the analogy and other spectroscopic data, the structures of all other products were deduced.

Next, we focused on exploring the substrate scope of various pyrazolone derived ketimines (**2b-2l**) by treating them with MBH carbonate **1a** under the standard optimized reaction conditions (Table 5.3). Gratifyingly, all the substrates underwent facile [3 + 2] annulation to afford the corresponding desired spirooxindole dihydropyrrole products **3m-3w** in moderate to very high yields with excellent diastereoselectivities (62-89%, >20:1 *dr*, Table 5.3). We observed that the pyrazolone derived ketimine substrates (**2b-2e**) with different groups at the R^3 position were compatible under optimized reaction conditions to deliver the corresponding

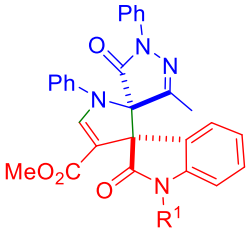
Table 5.2 Substrate scope for isatin derived MBH-carbonates[a-c]



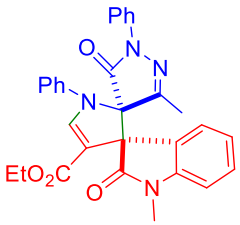
1a, R/R^1/ R^2= Me/Me/H, **1b**, R/R^1/ R^2= Me/Me/5-Me, **1c**, R/R^1/ R^2= Me/Me/5-OMe
1d, R/R^1/ R^2= Me/Me/5-Br, **1e**, R/R^1/ R^2= Me/Me/5-Cl, **1f**, R/R^1/ R^2= Me/Me/5-F
1g, R/R^1/ R^2= Me/Me/5-I, **1h**, R/R^1/ R^2= Me/Me/5-NO_2, **1i**, R/R^1/ R^2= Me/Me/7-F
1j, R/R^1/ R^2= Me/allyl/H, **1k**, R/R^1/ R^2= Me/Bn/H, **1l**, R/R^1/ R^2= Et/Me/H



R^2= H, **3a,** (92%, >20:1 *dr*)
R^2= 5-Me, **3b,** (86%, >20:1 *dr*)
R^2= 5-OMe, **3c,** (92%, >20:1 *dr*)
R^2= 5-Br, **3d,** (89%, 95:5 *dr*)
R^2= 5-Cl, **3e,** (91%, >20:1 *dr*)
R^2= 5-F, **3f,** (94%, >20:1 *dr*)
R^2= 5-I, **3g,** (82%, >20:1 *dr*)
R^2= 5-NO_2, **3h,** (78%, >20:1 *dr*)
R^2= 7-F, **3i,** (83%, >20:1 *dr*)



R^1 = Allyl, **3j** (86%, >20:1 *dr*)
R^1 = Bn, **3k** (84%, >20:1 *dr*)



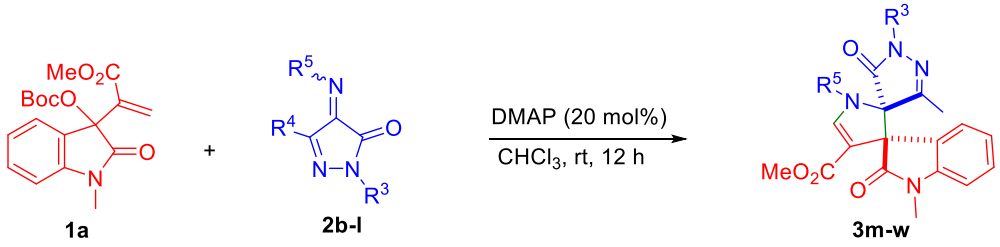
3l (89%, >20:1 *dr*)

[a]**Reaction conditions**: Substituted MBH carbonates of isatin **1** (0.115 mmol), pyrazolone derived ketimine **2a** (0.126 mmol), DMAP (20 mol%) in 2.0 mL of chloroform at room temperature, 12 h; [b]Isolated yield after column chromatography. [c]*dr* was determined by ^{1}H NMR.

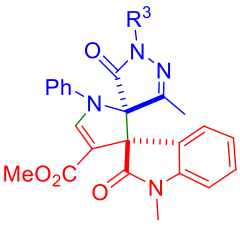
desired products **3m-3p** in high yields with excellent diastereoselectivities (71-83%, >20:1 *dr*, Table 5.3). Moreover, the pyrazolone derived ketiminesubstrates (**2f-2k**) with different aryl groups (R^5 position) reacted smoothly to furnish the corresponding spirooxindole dihydropyrrole pyrazolone derivatives **3q-3v** in moderate to very high yields with excellent diastereoselectivities (62-89%, >20:1 *dr*, Table 5.3). The ketimine substrate 5-isopropyl-2-phenyl-4-(phenylimino)-2, 4-dihydro-3*H*-pyrazol-3-one **2l** tolerated the standard reaction conditions to afford the desired product **3w** in 70% yield with an excellent diastereoselectivity (Table 5.3).

Encouraged by these results, we planned to employ MBH carbonate of pyrazolone to construct new bis-spiropyrazolone scaffold via [3 + 2] annulation reaction. To the best of our knowledge, till date there is no report for the synthesis of bis-spiropyrazolone compounds bearing vicinal quaternary spirocenters. In this regard, we synthesized MBH carbonate of pyrazolone (**4a-4b**) from pyrazolone 4, 5-diones.

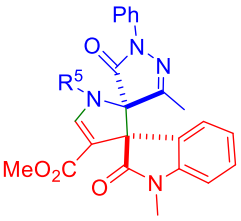
Table 5.3 Substrate scope for pyrazolone ketimines[a-c]



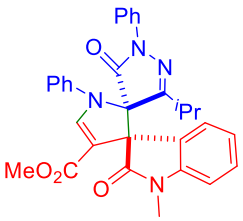
2b, $R^3/R^4/R^5$= 4-MeC_6H_4/Me/Ph, **2c**, $R^3/R^4/R^5$= 4-BrC_6H_4/Me/Ph, **2d**, $R^3/R^4/R^5$= 4-ClC_6H_4/Me/Ph
2e, $R^3/R^4/R^5$= Me/Me/Ph, **2f**, $R^3/R^4/R^5$= Ph/Me/2-ClC_6H_4, **2g**, $R^3/R^4/R^5$= Ph/Me/2-FC_6H_4,
2h,$R^3/R^4/R^5$= Ph/Me/3-BrC_6H_4 **2i**, $R^3/R^4/R^5$= Ph/Me/4-BrC_6H_4, **2j**, $R^3/R^4/R^5$= Ph/Me/4-ClC_6H_4,
2k, $R^3/R^4/R^5$= Ph/Me/4-IC_6H_4, **2l**, $R^3/R^4/R^5$= Ph/^{i}Pr/Ph,



R^3= 4-MeC_6H_4, **3m,** (70%, >20:1 *dr*)
R^3= 4-BrC_6H_4, **3n,** (82%, >20:1 *dr*)
R^3= 4-ClC_6H_4, **3o,** (79%, >20:1 *dr*)
R^3= Me, **3p,** (77%, >20:1 *dr*)



R^5= 2-ClC_6H_4, **3q,** (61%, >20:1 *dr*)
R^5= 2-FC_6H_4, **3r,** (68%, >20:1 *dr*)
R^5= 3-BrC_6H_4, **3s,** (73%, >20:1 *dr*)
R^5= 4-BrC_6H_4, **3t,** (75%, >20:1 *dr*)
R^5= 4-ClC_6H_4, **3u,** (89%, >20:1 *dr*)
R^5= 4-IC_6H_4, **3v,** (70%, >20:1 *dr*)



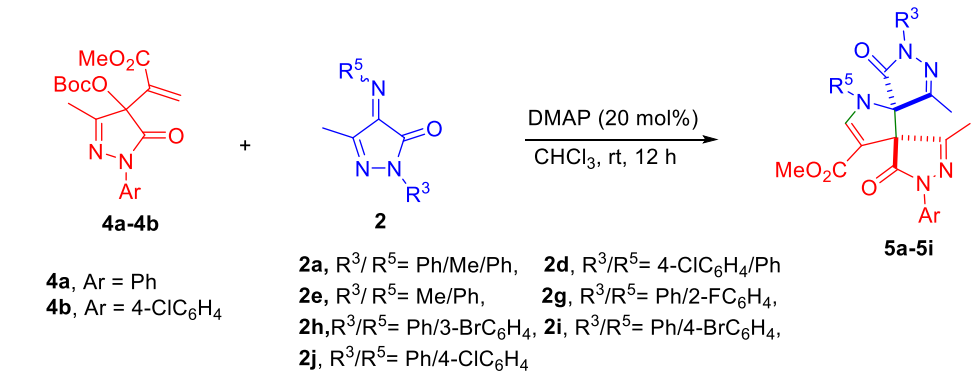
3w, (70%, >20:1 *dr*)

[a]**Reaction conditions**: MBH carbonate of isatin **1** (0.115 mmol), ketimine of pyrazolone **2a** (0.126 mmol), DMAP (20 mol%) in $CHCl_3$ (2.0 mL), 12 h at room temperature; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was calculated by ^{1}H NMR analysis of crude reaction mixture.

Further, we treated the MBH carbonates **4a-4b** with different pyrazolone derived ketimine (**2a, 2d, 2e, 2g-j**) under similar reaction conditions (Table 5.4). Gratifyingly, all the reactions proceeded efficiently to afford the corresponding highly functionalized bis-spiropyrazolone dihydropyrrole **5a-5i** derivatives in moderate to excellent yields with excellent diastereoselectivities (up to 90%, >20:1 *dr*). The molecular structure of bis-spiropyrazolone derivative **5g** was established unambiguously using X-ray diffraction analysis.[24]

Next, we attempted the enantioselective version of this *γ*-regioselective [3 + 2] annulation reaction. In this regard, we treated the MBH carbonate of pyrazolone **4a** with pyrazolone derived ketimine **2a** in presence of 20 mol% of chiral DMAP based catalyst **D** in chloroform at room temperature (Scheme 5.6). Though, the expected γ-regioselective [3 + 2] annulation product was formed in excellent yield, however, unfortunately we observed the poor enantioselectivity (80%, >20:1 *dr*, 20% *ee*, Scheme 5.6).

Table 5.4 Substrate scope for the synthesis of bis-spiropyrazolones[a-c]



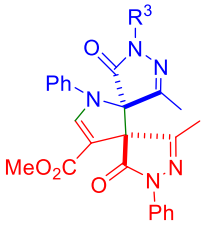
4a-4b

4a, Ar = Ph
4b, Ar = 4-ClC$_6$H$_4$

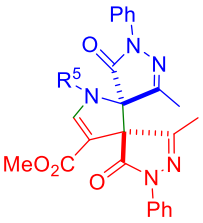
2

2a, R^3/ R^5= Ph/Me/Ph, **2d**, R^3/R^5= 4-ClC$_6$H$_4$/Ph
2e, R^3/ R^5= Me/Ph, **2g**, R^3/R^5= Ph/2-FC$_6$H$_4$,
2h,R^3/R^5= Ph/3-BrC$_6$H$_4$, **2i**, R^3/R^5= Ph/4-BrC$_6$H$_4$,
2j, R^3/R^5= Ph/4-ClC$_6$H$_4$

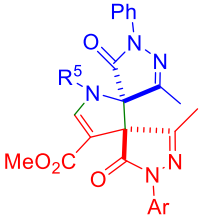
5a-5i



R^3= Ph, **5a,** (88%, >20:1 *dr*)
R^3= 4-ClC$_6$H$_4$, **5b,** (81%, >20:1 *dr*)
R^3= Me, **5c,** (70%, >20:1 *dr*)

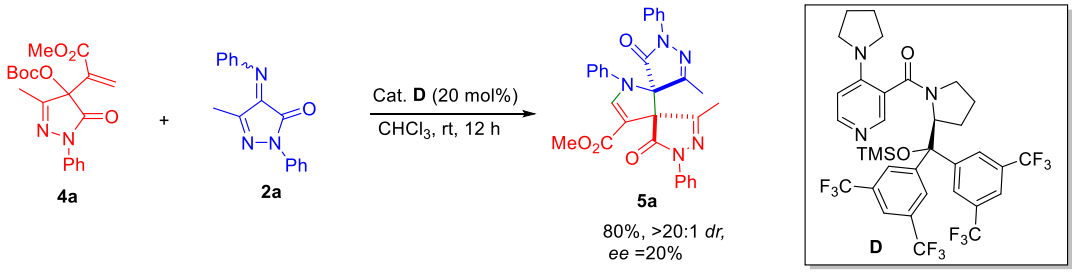


R^5= 2-FC$_6$H$_4$, **5d,** (80%, >20:1 *dr*)
R^5= 3-BrC$_6$H$_4$, **5e,** (90%, >20:1 *dr*)
R^5= 4-BrC$_6$H$_4$, **5f,** (69%, >20:1 *dr*)
R^5= 4-ClC$_6$H$_4$, **5g,** (73%, >20:1 *dr*)



Ar = 4-ClC$_6$H$_4$, R^5= Ph,
5h = (85%, >20:1 *dr*)
Ar = 4-ClC$_6$H$_4$, R^5= 4-ClC$_6$H$_4$
5i = (77%, >20:1 *dr*)

[a]**Reaction conditions**: MBH carbonate of pyrazolone **4** (0.107 mmol), Pyrazolone derived ketimine **2a** (0.117 mmol), DMAP (20 mol%) in $CHCl_3$, at room temperature for 12 h; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was determined by ^{1}H NMR.



4a

2a

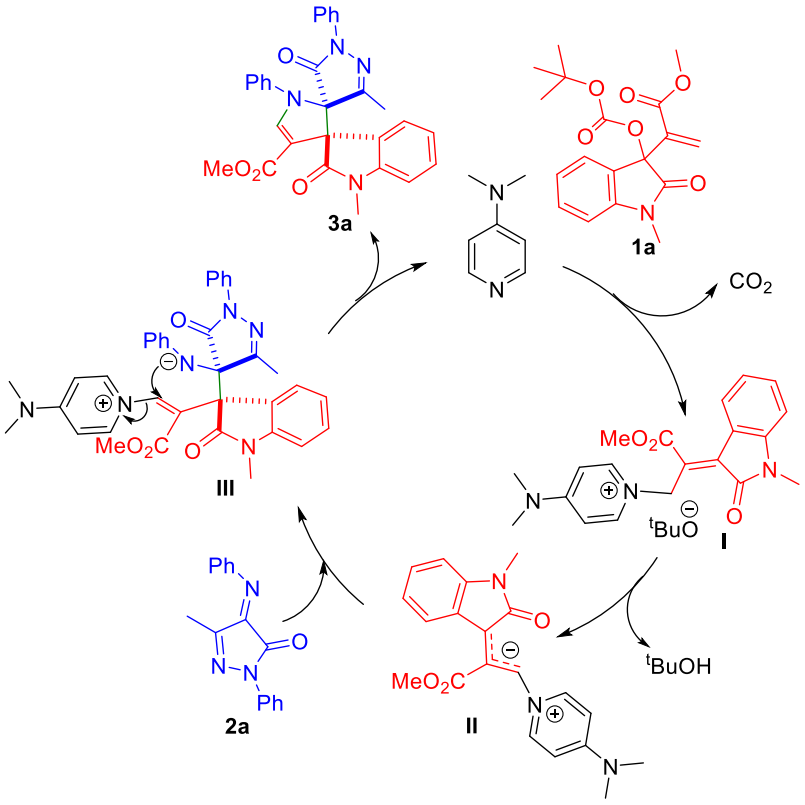
5a

80%, >20:1 *dr*,
ee =20%

Scheme 5. 6 Chiral DMAP catalyzed [3 + 2] annulation

Based on our experimental observations and previous literature reports,[25] the plausible catalytic cycle for [3 + 2] annulation reaction has been outlined in Scheme 5.7. The nucleophilic attack of DMAP on MBH carbonate **1a** forms the corresponding quaternary ammonium salt **I** along with the elimination CO_2 and *tert*-butoxide anion. Next, the in situ generated *tert*-butoxide anion abstracts a proton from the intermediate **I** to generate highly reactive allylic nitrogen ylide **II**. Then, this reactive zwitterionic allylic ylide **II** reacts with the ketimine **2a**

via γ-position to form corresponding intermediate **III**. Subsequently, the intramolecular cyclization of intermediate **III** leads to the formation of compound **3a** by regenerating the catalyst DMAP to complete the catalytic cycle.



Scheme 5.7 Plausible catalytic cycle for the [3 + 2] cycloaddition reaction

5.5 Conclusions

In summary, we have developed a highly efficient strategy for the [3 + 2] annulation of Morita−Baylis−Hillman carbonates of isatins/pyrazolones and pyrazolone derived ketimine to access the spiroheterocycles. The protocol worked effectively to construct spirooxindole dihydropyrrole fused pyrazolone and bis-spiropyrazolone dihydropyrrole derivatives bearing two vicinal quaternary spirocentres in good to excellent yields with very high diastereoselectivities under mild catalytic condition at room temperature. The protocol proved to be efficient with diverse MBH carbonates and ketimine derivatives and utilized the commercially viable DMAP as an effective catalyst for the desired transformation.

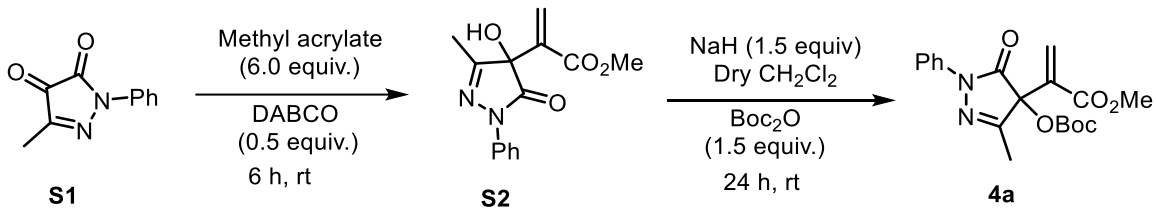
5.6 Experimental Section

5.6.1 General

Unless otherwise stated, all the reagents were purchased from commercial suppliers and used without purification. Isatins and pyrazolones were purchased from Aldrich, TCI chemicals and Alfa Aeser. HPLC grade solvents were purchased from RANKEM. All the reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm). The visualization was accomplished by irradiation with UV light at 254 nm and the solution of phosphomolybdic Acid (PMA) was used to stain products. The column chromatography was performed using silica gel (100-200 mesh) eluting with petroleum ether and ethyl acetate. The NMR spectra were recorded using tetramethylsilane as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for ^{13}C NMR spectroscopy. For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (*J*) are given in Hz and integration Melting points were measured using BUCHI M-560 melting point instrument. All melting points were measured in open glass capillary and values are uncorrected. Catalysts **A, B, C** and **D** were synthesized according to the literature procedures.[26] Morita-Baylis-Hillman carbonates (**1a-1l)** were prepared according to the literature procedure.[27] Pyrazolone derived ketimines **(2a-2l)** were synthesized according to the literature procedure.[16-19]

General Procedures

5.6.2 General Procedure for the synthesis of Morita-Baylis-Hillman (MBH) carbonates of pyrazolone –GP-1



Step 1

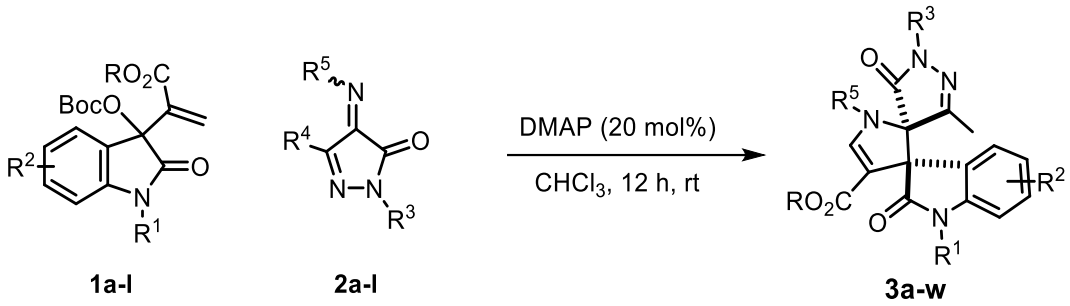
Methyl acrylate (1.44 mL, 15.94 mmol, 6.0 equiv.) was added to the mixture of pyrazolone 4, 5 dione[4] **S1** (500 mg, 2.66 mmol, 1.0 equiv. mg) and DABCO (149 mg, 1.33 mmol, 0.5 equiv.) in a 25 mL round bottom flask at room temperature. The resulting mixture was stirred for 6 h at room temperature. After completion of the reaction (monitored by TLC), excess of methyl acrylate was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (100-200 mesh) using petroleum ether/ethyl acetate (80:20) as an eluent to afford the MBH adduct of pyrazolone **S2** as white solid (625 mg, 86 % yield).

Step 2

To a 50 mL round bottom flask containing **S2** (440 mg, 1.0 equiv.) dissolved in dry DCM (20 mL), sodium hydride-60% dispersed in mineral oil (97 mg, 1.5 equiv.) was slowly added at room temperature and the reaction mixture was stirred for 30 min. Then, to this reaction mixture the solution of Boc_2O (553 mmL, 1.5 equiv.) in 2.0 mL dry DCM was slowly added at room temperature and the reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was further purified by flash chromatography using silica gel (100-200 mesh) eluting with petroleum ether/ethyl acetate (90:10) to afford the MBH carbonate of pyrazolone **4a** as a white solid (480 mg, 80% yield).

The Compounds **4b** was prepared according to the GP-1. The experimental data of **4a** and **4b** are given in section 5.6.5

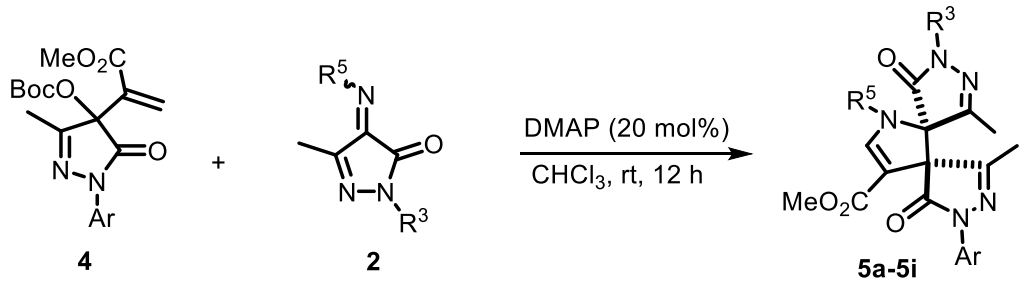
5.6.3 General procedure for the synthesis of spirooxindole-pyrazolone fused dihydropyrrole (3a-3w)- GP-2



1a-l 2a-l 3a-w

To a solution of Morita-Baylis-Hillman carbonate **1a** (40 mg, 0.115 mmol) in 2 mL of chloroform, pyrazolone derived ketimine**2a** (33 mg, 0.126 mmol) and DMAP (2.81 mg, 23 μmol) were added at room temperature. The resulting mixture was stirred for 12 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified by silica gel (100-200 mesh) using column chromatography (petroleum ether/ethyl acetate 70:30) to obtain the desired product **3a** as white solid in 92% yield (52 mg).

5.6.4 General procedure for the synthesis of bis-spiropyrazolone (5a-5i)-GP-3

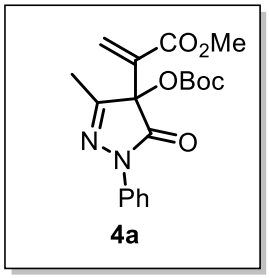


4 2 5a-5i

To a solution of Morita-Baylis-Hillman carbonate **1a** (40 mg, 0.107 mmol) in 2 mL of chloroform, pyrazolone derived ketimine**2a** (31 mg, 0.117 mmol) and DMAP (2.61 mg, 21 μmol) were added at room temperature. The resulting mixture was stirred for 12 h. After completion of the reaction (monitored by TLC), solvent was evaporated under reduced pressure and the residue was purified by silica gel (100-200 mesh) using column chromatography (petroleum ether/ethyl acetate 70:30) to obtain the desired product **5a** as white solid in 88% yield (49 mg).

5.6.5 Experimental Data

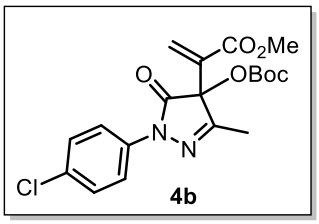
Methyl2-(4-((tert-butoxycarbonyl)oxy)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)acrylate (4a)



4a

The compound **4a** was prepared following the general procedure **GP-1**, White solid (480 mg, 80% yield), R_f = 0.45 (petroleum ether/EtOAc 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.45 – 7.37 (m, 2H), 7.22 – 7.15 (m, 1H), 6.69 (s, 1H), 6.51 (s, 1H), 3.68 (s, 3H), 2.04 (s, 3H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.2, 163.5, 153.8, 149.8, 138.1, 133.2, 131.4, 129.0, 125.3, 119.1, 85.0, 81.8, 77.2, 52.7, 27.7, 13.1. HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{23}N_2O_6$ $[M + H]^+$ 375.1556 found 375.1556.

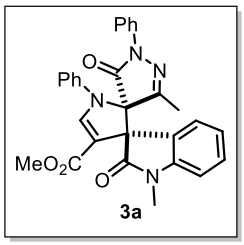
Methyl 2-(4-((tert-butoxycarbonyl)oxy)-1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)acrylate (4b)



4b

The compound **4b** was prepared following the general procedure **GP-1**, White solid (475 mg, 75% yield), R_f = 0.43 (petroleum ether/EtOAc 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.69 (s, 1H), 6.52 (s, 1H), 3.68 (s, 3H), 2.03 (s, 3H), 1.44 (s, 9H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.2, 163.5, 154.0, 149.8, 136.7, 133.0, 131.6, 130.3, 129.0, 120.0, 85.1, 81.6, 77.2, 52.7, 27.7, 13.0. HRMS (ESI TOF) *m/z* calcd. For $C_{19}H_{23}N_2O_6$ $[M + H]^+$ 409.1166 found 409.1176.

Methyl-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3a)

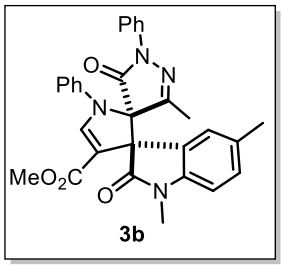


3a

The compound **3a** was prepared following the general procedure **GP-2**, White solid (52 mg, 92% yield, *dr* >20:1), R_f = 0.25 (petroleum ether/EtOAc 70:30), MP: 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.55 – 7.51 (m, 2H), 7.44 – 7.41 (m, 1H), 7.33 – 7.21 (m, 5H), 7.17 – 7.11 (m, 1H), 7.06 (tt, *J* = 7.1, 1.0 Hz, 1H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 3.57 (s, 3H), 3.19 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 167.3, 163.6, 159.4, 147.5, 143.4,

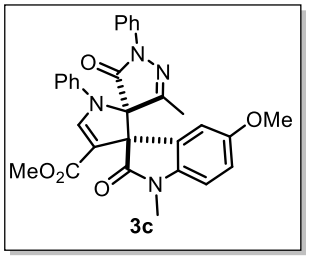
139.5, 137.2, 130.2, 130.0, 128.9, 126.8, 125.7, 124.7, 124.3, 122.6, 119.1, 116.8, 108.8, 108.3, 81.3, 65.3, 51.4, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{25}N_4O_4$ $[M + H]^+$ 493.1876 found 493.1872.

Methyl-1,3'',5-trimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3b)



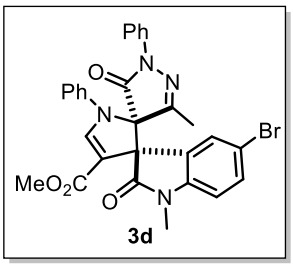
The compound **3b** was prepared following the general procedure **GP-2**, White solid (50 mg, 86% yield, *dr* >20:1), R_f = 0.20 (petroleum ether/EtOAc 70:30), MP: 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.57 – 7.52 (m, 2H), 7.36 – 7.21 (m, 5H), 7.18 – 7.11 (m, 1H), 7.10 – 6.99 (m, 2H), 6.84 – 6.77 (m, 2H), 6.64 (d, *J* = 7.9 Hz, 1H), 3.58 (s, 3H), 3.17 (s, 3H), 2.21-2.20 (d, *J* = 1.5 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 167.4, 163.7, 158.9, 147.7, 141.2, 139.5, 137.2, 132.1, 130.3, 130.2, 128.9, 127.3, 125.6, 124.4, 124.1, 118.9, 118.9, 116.7, 108.5, 108.0, 81.4, 65.3, 51.3, 27.0, 16.8. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{27}N_4O_4$ $[M + H]^+$ 507.2032 found 507.2029.

Methyl-5-methoxy-1, 3''-dimethyl-2, 5''-dioxo-1', 1''-diphenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3c)



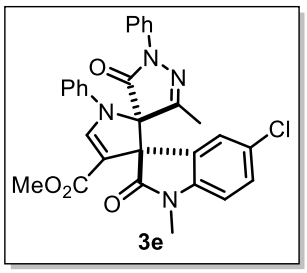
The compound **3c** was prepared following the general procedure **GP-2**, White solid (55 mg, 92% yield, *dr* >20:1), R_f = 0.15 (petroleum ether/EtOAc 70:30), MP: 203-205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.56 (dd, *J* = 8.7, 1.0 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.18 – 7.11 (m, 1H), 7.09 – 7.00 (m, 2H), 6.83 – 6.78 (m, 2H), 6.76 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.17 (s, 3H), 2.21 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.2, 167.3, 163.6, 158.9, 155.8, 147.8, 139.5, 137.2, 137.1, 130.2, 128.9, 125.7, 125.7, 124.2, 119.0, 116.8, 115.0, 113.7, 108.6, 81.4, 65.5, 55.8, 51.3, 27.0, 16.8. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{27}N_4O_5$ $[M + H]^+$ 523.1981 found 523.1977.

Methyl -5-bromo-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3d)



The compound **3d** was prepared following the general procedure **GP-2**, White solid (59 mg, 89% yield, 95:5 *dr*), R_f = 0.25 (petroleum ether/EtOAc 70:30), MP: 227-229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.61 – 7.54 (m, 3H), 7.37 – 7.25 (m, 5H), 7.19 – 7.12 (m, 1H), 7.09 – 7.03 (m, 1H), 6.82 – 6.78 (m, 2H), 6.62 (d, *J* = 8.3 Hz, 1H), 3.59 (s, 3H), 3.16 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 167.0, 163.5, 159.0, 147.8, 142.5, 139.3, 137.1, 132.9, 130.3, 129.8, 129.0, 126.7, 125.8, 124.5, 119.0, 117.0, 115.5, 109.7, 108.3, 81.1, 65.1, 51.5, 27.1, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}BrN_4O_4$ $[M + H]^+$ 571.0981, 573.0960 found 571.0982, 573.0966.

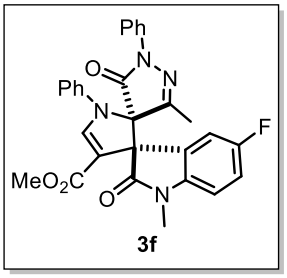
Methyl-5-chloro-1, 3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2', 4''-pyrazole]-4'-carboxylate (3e)



The compound **3e** was prepared following the general procedure **GP-2**, White solid (55 mg, 91% yield, *dr* >20:1), R_f = 0.25 (petroleum ether/EtOAc 70:30), MP: 228-230 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.61 – 7.55 (m, 2H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.37 – 7.26 (m, 4H), 7.23 – 7.13 (m, 2H), 7.11 – 7.04 (m, 1H), 6.83 – 6.79 (m, 2H), 6.68 (d, *J* = 8.3 Hz, 1H), 3.60 (s, 3H), 3.17 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 167.0, 163.4, 159.1, 147.7, 142.0, 139.3, 137.1, 130.3, 130.0, 129.0, 128.2, 127.2, 126.4, 125.8, 124.5, 118.9, 117.0, 109.2, 108.4, 81.0, 65.2, 51.5, 27.1, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}ClN_4O_4$ $[M + H]^+$ 527.1486 found 527.1486.

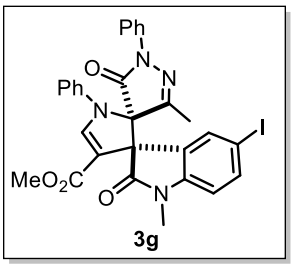
Methyl-5-fluoro-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3f)

The compound **3f** was prepared following the general procedure **GP-2**, White solid (55 mg, 94% yield, *dr* >20:1), R_f = 0.22 (petroleum ether/EtOAc 70:30), MP: 203-205 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.58 (dd, *J* = 8.7, 1.1 Hz, 2H), 7.36 – 7.24 (m, 4H), 7.22 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.95 (td, *J* = 8.8, 2.6 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.68 (dd, *J* = 8.5, 4.1 Hz, 1H), 3.59 (s, 3H), 3.18 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.0, 163.4, 159.2, 159.04 (d, $J_{(C-F)}$= 240 Hz), 147.7, 139.39 (d, $J_{(C-F)}$= 12 Hz), 137.2, 130.3, 129.0, 126.46 (d, $J_{(C-F)}$= 8.4 Hz), 125.8, 124.5, 118.9, 117.0, 116.44 (d, $J_{(C-F)}$= 23.6 Hz), 115.01 (d, $J_{(C-F)}$= 25.8 Hz), 108.7, 108.6, 108.5, 81.1, 65.4, 51.4, 27.1, 16.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -120.2. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}FN_4O_4$ $[M + H]^+$ 511.1782 found 511.1786.

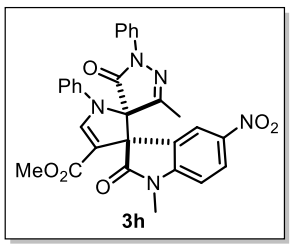
Methyl-5-iodo-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3g)



The compound **3g** was prepared following the general procedure **GP-2**, White solid (58 mg, 82% yield, *dr* >20:1), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 241-243 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.73 – 7.70 (m, 1H), 7.61 – 7.57 (m, 2H), 7.56 – 7.53 (m, 1H), 7.39 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.17 (ddt, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.08 (tt, *J* = 7.1, 1.0 Hz, 1H), 6.84 – 6.75 (m, 2H), 6.53 (d, *J* = 8.2 Hz, 1H), 3.61 (s, 3H), 3.17 (s, 3H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 167.1, 163.5, 158.8, 147.9, 143.2, 139.3, 138.8, 137.0, 135.3, 130.3, 129.1, 126.9, 125.8, 124.5, 119.0, 116.9, 110.2, 108.2, 85.5, 81.1, 64.9, 51.5, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}IN_4O_4$ $[M + H]^+$ 619.0842 found 619.0854.

Methyl-1,3''-dimethyl-5-nitro-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3h)

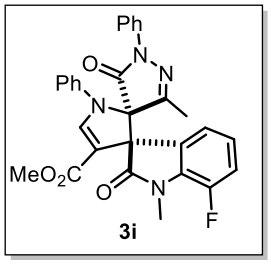
The compound **3h** was prepared following the general procedure **GP-2**, White solid (48 mg, 78% yield, *dr* >20:1), R_f = 0.20 (petroleum ether/EtOAc 70:30), MP: 250-252 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.3 Hz, 1H), 8.25 – 8.21 (m, 1H), 8.13 (s, 1H), 7.62 – 7.54 (m, 2H), 7.31 (ddd, *J* = 8.8, 7.5, 2.1 Hz, 4H), 7.18 – 7.09 (m, 2H), 6.90 – 6.82 (m, 3H), 3.62 (s, 3H), 3.26 (s, 3H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 166.5, 163.3, 159.3, 148.6, 147.7, 143.5, 139.1, 137.1, 130.4, 129.1, 127.0, 125.9,

125.9, 125.0, 122.9, 118.7, 117.4, 108.2, 108.0, 80.8, 64.8, 51.6, 27.4, 17.0. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}N_5O_6$ $[M + H]^+$ 538.1727 found 538.1725.

Methyl(7-fluoro-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3i)

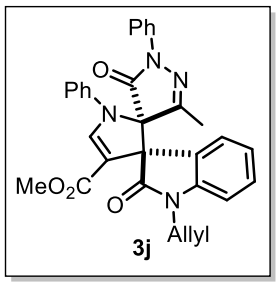


3i

The compound **3i** was prepared following the general procedure **GP-2**, White solid (49 mg, 83% yield, *dr* >20:1), R_f = 0.23 (petroleum ether/EtOAc 70:30), MP: 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.56 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.37 – 7.19 (m, 5H), 7.19 – 7.13 (m, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.01 – 6.88 (m, 2H), 6.84 – 6.78 (m, 2H), 3.60 (s, 3H), 3.40 (d, *J* = 2.7 Hz, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): 173.2, 167.0, 163.5, 159.1, 148.7, 147.53 (d, $J_{(C-F)}$ = 241 Hz), 139.3, 137.2, 130.2, 130.12 (d, $J_{(C-F)}$= 8.7 Hz) , 129.0, 127.49 (d, $J_{(C-F)}$= 2.8 Hz) 125.8, 124.5, 122.96 (d, $J_{(C-F)}$= 6.4 Hz), 122.7 (d, $J_{(C-F)}$= 3.3 Hz), 119.1, 117.9 (d, $J_{(C-F)}$= 19.1 Hz), 117.0, 108.7, 81.2, 65.4, 51.4, 29.5, 16.9. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -136.4. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}FN_4O_4$ $[M + H]^+$ 511.1782 found 511.1778.

Methyl-1-allyl-3''-methyl-2, 5''-dioxo-1',1''-diphenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2', 4''-pyrazole]-4'-carboxylate (3j)

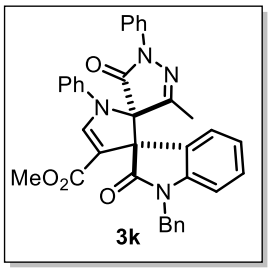
The compound **3j** was prepared following the general procedure **GP-2**, White solid (51 mg, 86% yield, *dr* >20:1), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 203-205 °C.



3j

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.56 – 7.50 (m, 2H), 7.46 – 7.40 (m, 1H), 7.33 – 7.24 (m, 4H), 7.21 (td, *J* = 7.8, 1.3 Hz, 1H), 7.14 (tt, *J* = 7.0, 1.1 Hz, 1H), 7.09 – 7.03 (m, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.72 (d, *J* = 7.7 Hz, 1H), 5.74 (ddt, *J* = 17.2, 10.3, 4.8 Hz, 1H), 5.17 – 5.03 (m, 2H), 4.44 (ddt, *J* = 16.7, 4.9, 1.7 Hz, 1H), 4.18 (ddt, *J* = 16.7, 4.7, 1.7 Hz, 1H), 3.57 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.2, 163.5, 159.7, 147.4, 142.5, 139.5, 137.3, 130.7, 130.2, 130.0, 128.9, 126.9, 125.7, 124.8, 124.2, 122.6, 119.1, 117.4, 116.8, 109.1, 108.9, 81.4, 65.5, 51.4, 42.7, 17.0. HRMS (ESI TOF) *m/z* calcd. For $C_{31}H_{27}N_4O_4$ $[M + H]^+$ 519.2032 found 519.2038.

Methyl-1-benzyl-3''-methyl-2,5''-dioxo-1', 1''-diphenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3k)

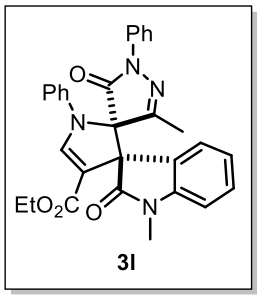


3k

The compound **3k** was prepared following the general procedure **GP-2**, White solid (48 mg, 84% yield, *dr* >20:1), R_f = 0.32 (petroleum ether/EtOAc 70:30), MP: 241-243 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 1H), 7.57 – 7.51 (m, 2H), 7.44 – 7.39 (m, 1H), 7.34 – 7.26 (m, 4H), 7.19 – 7.03 (m, 6H), 7.03 – 6.96 (m, 3H), 6.86 – 6.81 (m, 2H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 3.59 – 3.55 (m, 3H), 2.30 (d, *J* = 0.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 166.9, 163.6, 160.5, 146.9, 142.1, 139.5, 137.4, 135.2, 130.3, 130.0, 129.0, 128.8, 127.5, 127.0, 126.8, 125.6, 125.1, 124.3, 122.6, 119.0, 116.8, 109.4, 109.3, 81.3, 63.6, 51.4, 44.2, 17.2. HRMS (ESI TOF) *m/z* calcd. For $C_{35}H_{29}N_4O_4$ $[M + H]^+$ 569.2186 found 569.2185.

Ethyl-1,3''-dimethyl-2,5''-dioxo-1',1''-diphenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3l)

The compound **3l** was prepared following the general procedure **GP-2**, White solid (52 mg, 89% yield, *dr* >20:1), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 190-192 °C.

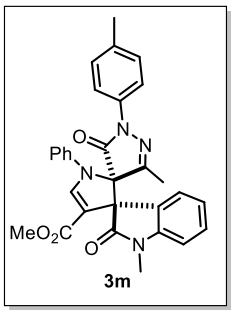


3l

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.57 – 7.51 (m, 2H), 7.45 – 7.41 (m, 1H), 7.34 – 7.20 (m, 5H), 7.17 – 7.11 (m, 1H), 7.08 – 6.96 (m, 2H), 6.84 – 6.78 (m, 2H), 6.74 (d, *J* = 7.8 Hz, 1H), 3.98 (qq, *J* = 6.9, 3.7 Hz, 2H), 3.18 (s, 3H), 2.25 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 167.3, 163.2, 159.5, 147.3, 143.4, 139.5, 137.3, 130.2, 130.0, 128.9, 126.8, 125.6, 125.0, 124.2, 122.6, 119.1, 116.8, 109.3, 108.1, 81.3, 65.4, 60.0, 26.9, 17.0, 14.2. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{27}N_4O_4$ $[M + H]^+$ 507.2032 found 507.2037.

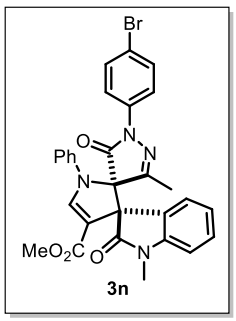
Methyl-1,3''-dimethyl-2, 5''-dioxo-1'-phenyl-1''-(p-tolyl)-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3m)

The compound **3m** was prepared following the general procedure **GP-2**, White solid (41 mg, 70% yield, *dr* >20:1), R_f = 0.23 (petroleum ether/EtOAc 70:30), MP: 210-211 °C.



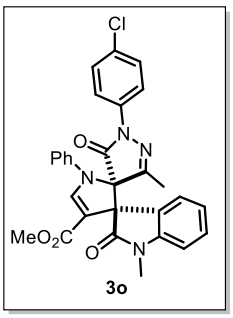
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.45 – 7.37 (m, 3H), 7.26 (s, 3H), 7.13 – 7.08 (m, 2H), 7.05 (tt, *J* = 7.2, 1.0 Hz, 1H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.77 – 6.74 (m, 1H), 3.57 (s, 3H), 3.19 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 167.1, 163.6, 159.1, 147.5, 143.4, 139.5, 135.5, 134.8, 130.2, 130.0, 129.4, 126.8, 124.8, 124.2, 122.6, 119.2, 116.8, 108.8, 108.2, 81.2, 65.2, 51.4, 27.0, 21.1, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{27}N_4O_4$ $[M+H]^+$ 507.2032 found 507.2030.

Methyl-1''-(4-bromophenyl)-1, 3''-dimethyl-2,5''-dioxo-1'-phenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3, 3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3n)



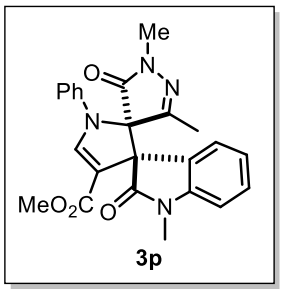
The compound **3n** was prepared following the general procedure **GP-2**, White solid (54 mg, 82% yield, *dr* >20:1), R_f = 0.28 (petroleum ether/EtOAc 70:30), MP: 206-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.54 – 7.48 (m, 2H), 7.43 – 7.35 (m, 3H), 7.34 – 7.21 (m, 3H), 7.19 – 7.12 (m, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71 – 6.65 (m, 2H), 3.57 (s, 3H), 3.19 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.1, 163.3, 158.9, 146.9, 143.5, 138.7, 137.1, 133.2, 130.2, 129.0, 126.7, 125.8, 124.5, 122.7, 119.1, 118.4, 117.0, 109.6, 108.3, 81.2, 65.3, 51.4, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}BrN_4O_4$ $[M+H]^+$ 571.0981, 573.0960 found 571.0978, 573.0962.

Methyl-1''-(4-chlorophenyl)-1,3''-dimethyl-2,5''-dioxo-1'-phenyl-1'',5''-dihydro-1'H-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3o)



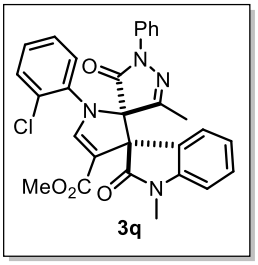
The compound **3o** was prepared following the general procedure **GP-2,** White solid (48 mg, 79% yield, *dr* >20:1), R_f = 0.26 (petroleum ether/EtOAc 70:30), MP: 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.55 – 7.48 (m, 2H), 7.43 – 7.38 (m, 1H), 7.26 (s, 5H), 7.10 – 7.03 (m, 1H), 6.99 (td, *J* = 7.6, 1.0 Hz, 1H), 6.83 – 6.73 (m, 3H), 3.57 (s, 3H), 3.19 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$,): δ (ppm) 173.4, 167.2, 163.5, 159.8, 147.4, 143.4, 139.4, 135.8, 130.8, 130.2, 130.1, 129.0, 126.7, 124.6, 124.4, 122.6, 120.0, 116.8, 108.8, 108.3, 81.3, 65.4, 51.4, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}ClN_4O_4$ $[M + H]^+$ 527.1486 found 527.1492.

Methyl -1,1'',3''-trimethyl-2,5''-dioxo-1'-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3p)



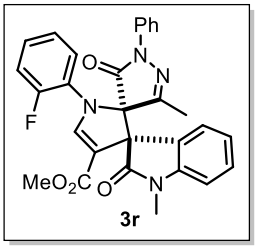
The compound **3p** was prepared following the general procedure **GP-2**, White solid (38 mg, 77% yield, *dr* >20:1), R_f = 0.35 (petroleum ether/EtOAc 70:30), MP: 248-250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.38 (d, *J* = 7.1 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.05 (dt, *J* = 15.3, 7.5 Hz, 2H), 6.78 (dd, *J* = 19.5, 7.8 Hz, 3H), 3.56 (s, 3H), 3.21 (s, 3H), 3.03 (s, 3H), 2.13 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.5, 169.3, 163.6, 158.4, 147.4, 143.4, 139.6, 130.1, 129.9, 126.6, 124.9, 124.2, 122.5, 116.8, 109.0, 108.2, 80.2, 64.7, 51.3, 31.7, 26.9, 16.7. HRMS (ESI TOF) *m/z* calcd. For $C_{24}H_{23}N_4O_4$ $[M+H]^+$ 431.1719 found 431.1719.

Methyl-1'-(2-chlorophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3q)



The compound **3q** was prepared following the general procedure **GP-2**, White solid (37 mg, 61% yield, *dr* >20:1), R_f = 0.26 (petroleum ether/EtOAc 70:30), MP: 221-223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.94 (m, 1H), 7.66 – 7.60 (m, 1H), 7.56 – 7.52 (m, 2H), 7.49 – 7.43 (m, 1H), 7.32 – 7.22 (m, 3H), 7.17 – 7.10 (m, 3H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.96 – 6.88 (m, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 3.58 (s, 3H), 3.19 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 167.4, 163.6, 158.9, 150.4, 143.4, 137.2, 137.1, 131.7, 130.0, 128.9, 128.8, 128.4, 127.4, 126.8, 125.6, 124.5, 122.9, 122.7, 119.1, 108.6, 108.3, 82.2, 65.0, 51.4, 26.9, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}ClN_4O_4$ $[M+H]^+$ 527.1486 found 527.1492.

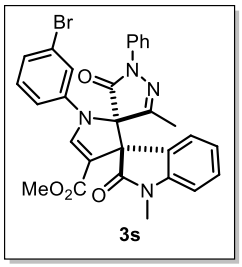
Methyl-1'-(2-fluorophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3r)



The compound **3r** was prepared following the general procedure **GP-2**, White solid (40 mg, 68% yield, *dr* >20:1), R_f = 0.24 (petroleum ether/EtOAc 70:30), MP: 196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 3.1 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.49 – 7.46 (m, 1H), 7.31 – 7.22 (m, 4H), 7.17 – 7.05 (m, 3H), 7.01 (tdd, *J* = 7.4, 3.1, 1.1 Hz, 2H), 6.82 (td, *J* = 8.1, 1.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 3.58 (s, 3H), 3.18 (s, 3H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 167.2, 163.5, 159.3, 155.03 (d, $J_{(C-F)}$= 247.5 Hz), 149.30 (d, $J_{(C-F)}$= 7 Hz) , 143.2, 137.3, 130.0, 128.9, 127.77 (d, $J_{(C-F)}$= 10.3 Hz),

126.8, 126.38 (d, $J_{(C-F)}$= 7.8 Hz), 125.6, 125.44 (d, $J_{(C-F)}$= 3.7 Hz), 124.6, 122.6, 121.2, 119.2, 117.35 (d, $J_{(C-F)}$= 20.5 Hz), 109.4, 108.3, 81.8, 65.1, 51.4, 26.9, 16.8. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -123.1. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}FN_4O_4$ $[M + H]^+$ 511.1782 found 511.1789.

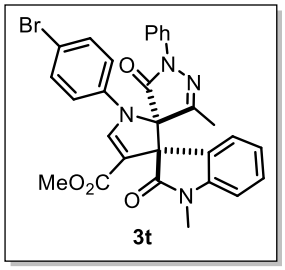
Methyl-1'-(3-bromophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3s)



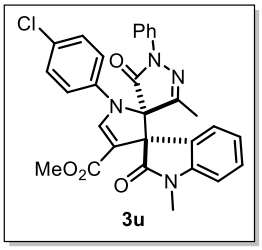
The compound **3s** was prepared following the general procedure **GP-2**, White solid (48 mg, 73% yield, *dr* >20:1), R_f = 0.28 (petroleum ether/EtOAc 70:30), MP: 193-195 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.50 (dt, *J* = 8.8, 1.7 Hz, 2H), 7.44 – 7.39 (m, 1H), 7.34 – 7.23 (m, 3H), 7.20 – 7.13 (m, 2H), 7.13 – 7.07 (m, 2H), 7.00 (td, *J* = 7.6, 0.9 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.57 (ddd, *J* = 8.2, 2.4, 0.7 Hz, 1H), 3.59 (s, 3H), 3.20 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.1, 163.3, 158.8, 146.6, 143.5, 140.8, 137.0, 131.4, 130.2, 129.0, 127.1, 126.8, 125.9, 124.4, 124.0, 122.7, 120.1, 119.4, 114.7, 110.0, 108.4, 81.0, 65.2, 51.5, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}BrN_4O_4$ $[M + H]^+$ 571.0981, 573.0960 found 571.0986, 573.0969 (isotopic mass).

Methyl-1'-(4-bromophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3t)

The compound **3t** was prepared following the general procedure **GP-2**, White solid (49.5 mg, 75% yield, *dr* >20:1), R_f = 0.28 (petroleum ether/EtOAc 70:30), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.55 – 7.48 (m, 2H), 7.44 – 7.36 (m, 3H), 7.26 (s, 3H), 7.18 – 7.11 (m, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.71 – 6.65 (m, 2H), 3.57 (s, 3H), 3.19 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.1, 163.3, 158.9, 147.0, 143.5, 138.6, 137.0, 133.1, 130.2, 128.9, 126.7, 125.8, 124.5, 122.7, 119.0, 118.4, 117.0, 109.6, 108.3, 81.2, 65.3, 51.4, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}BrN_4O_4$ $[M + H]^+$ 571.0981, 573.0960 found 571.0988, 573.0969 (isotopic mass)..(we need to highlight as isotopic mass values)

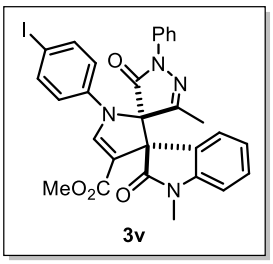


Methyl-1'-(4-chlorophenyl)-1, 3''-dimethyl-2, 5''-dioxo-1''-phenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3u)



The compound **3u** was prepared following the general procedure **GP-2**, White solid (54 mg, 89% yield, *dr* >20:1), R_f = 0.30 (petroleum ether/EtOAc 70:30), MP: 206-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.55 (dt, *J* = 8.9, 1.7 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.37 – 7.26 (m, 5H), 7.22 – 7.14 (m, 1H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.82 – 6.76 (m, 3H), 3.61 (s, 3H), 3.23 (s, 3H), 2.27 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 167.1, 163.4, 158.9, 147.1, 143.5, 138.2, 137.1, 130.3, 130.2, 129.6, 129.0, 126.7, 125.8, 124.5, 122.7, 119.1, 118.2, 109.5, 108.3, 81.3, 65.3, 51.4, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}ClN_4O_4$ $[M + H]^+$ 527.1486 found 527.1489.

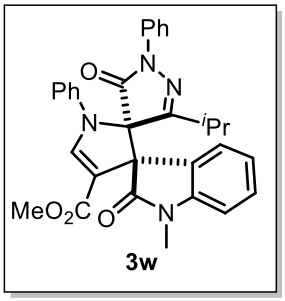
Methyl-1'-(4-iodophenyl)-1,3''-dimethyl-2,5''-dioxo-1''-phenyl-1'',5''-dihydro-1'*H*-dispiro[indoline-3,3'-pyrrole-2',4''-pyrazole]-4'-carboxylate (3v)



The compound **3v** was prepared following the general procedure **GP-2**, White solid (50 mg, 70% yield, *dr* >20:1), R_f = 0.29 (petroleum ether/EtOAc 70:30), MP: 222-224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.59 – 7.53 (m, 2H), 7.51 (dt, *J* = 8.9, 1.8 Hz, 2H), 7.40 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.33 – 7.22 (m, 3H), 7.15 (tt, *J* = 7.0, 1.1 Hz, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.58 – 6.54 (m, 2H), 3.57 (s, 3H), 3.19 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 167.1, 163.3, 159.0, 146.7, 143.5, 139.3, 139.0, 137.1, 130.2, 129.0, 126.7, 125.8, 124.5, 122.7, 119.1, 118.5, 109.7, 108.3, 87.2, 81.1, 65.3, 51.5, 27.0, 16.9. HRMS (ESI TOF) *m/z* calcd. For $C_{29}H_{24}IN_4O_4$ $[M + H]^+$ 619.0842 found 619.0842.

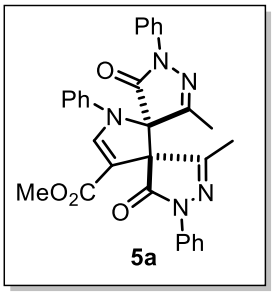
Methyl-3''-isopropyl-1-methyl-2, 5''-dioxo-1',1''-diphenyl-1'', 5''-dihydro-1'*H*-dispiro[indoline-3, 3'-pyrrole-2', 4''-pyrazole]-4'-carboxylate (3w)

The compound **3w** was prepared following the general procedure **GP-2**, White solid (42 mg, 70% yield, *dr* >20:1), R_f = 0.27 (petroleum ether/EtOAc 70:30), MP: 237-239 °C.



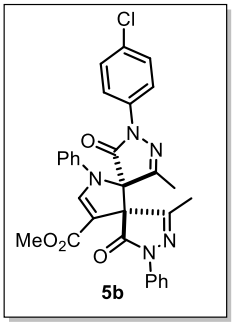
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.64 – 7.56 (m, 2H), 7.46 – 7.40 (m, 1H), 7.36 – 7.30 (m, 2H), 7.27 – 7.20 (m, 3H), 7.19 – 7.12 (m, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.95 (td, *J* = 7.6, 1.0 Hz, 1H), 6.78 – 6.70 (m, 3H), 3.57 (s, 3H), 3.27 – 3.20 (m, 1H), 3.19 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 167.2, 165.9, 163.6, 148.2, 143.7, 140.0, 137.4, 130.0, 129.9, 128.9, 126.7, 125.7, 124.6, 124.0, 122.6, 119.1, 116.9, 108.6, 108.2, 81.4, 65.2, 51.3, 30.2, 27.0, 22.7, 20.6. HRMS (ESI TOF) *m/z* calcd. For $C_{31}H_{29}IN_4O_4$ $[M + H]^+$ 521.2189 found 521.2191.

Methyl-1, 10-dimethyl-4, 7-dioxo-3, 8, 11-triphenyl-2, 3, 8, 9, 11-pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5a)



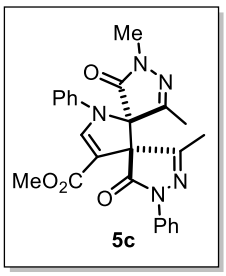
The compound **5a** was prepared following the general procedure **GP-3**, White solid (49 mg, 88% yield, *dr* >20:1), R_f = 0.45 (petroleum ether/EtOAc 80:20), MP: 173-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.79 – 7.73 (m, 4H), 7.39 – 7.28 (m, 6H), 7.23 – 7.10 (m, 3H), 6.95 – 6.87 (m, 2H), 3.68 (s, 3H), 2.38 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 166.6, 163.0, 159.1, 158.2, 147.8, 139.0, 137.7, 137.2, 130.5, 129.1, 128.9, 126.2, 125.7, 125.5, 119.7, 119.4, 117.8, 105.6, 81.9, 68.8, 51.9, 17.2, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{26}N_5O_4$ $[M + H]^+$ 520.1985 found 520.1986.

Methyl-8-(4-chlorophenyl)-1, 10-dimethyl-4, 7-dioxo-3, 11-diphenyl-2, 3, 8, 9, 11-pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5b)



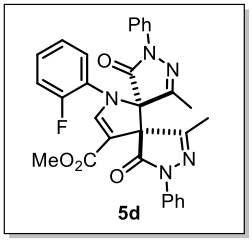
The compound **5b** was prepared following the general procedure **GP-3**, White solid (48 mg, 81% yield, *dr* >20:1), R_f = 0.40 (petroleum ether/EtOAc 80:20), MP: 226-228 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.78 – 7.71 (m, 4H), 7.33 (dtd, *J* = 12.8, 6.6, 5.8, 1.9 Hz, 6H), 7.21 – 7.12 (m, 2H), 6.89 (dd, *J* = 7.7, 1.1 Hz, 2H), 3.68 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.8, 166.6, 163.0, 159.5, 158.1, 147.7, 138.9, 137.7, 135.8, 131.4, 130.5, 129.2, 129.0, 125.7, 125.6, 120.4, 119.7, 117.9, 105.7, 82.0, 68.9, 52.0, 17.3, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}ClN_5O_4$ $[M + H]^+$ 554.1595 found 554.1590.

Methyl-1, 8, 10-trimethyl-4, 7-dioxo-3, 11-diphenyl-2, 3, 8, 9, 11 pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5c)



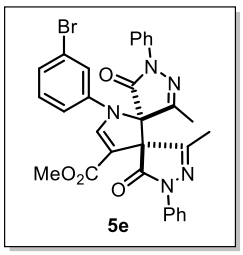
The compound **5c** was prepared following the general procedure **GP-3**, White solid (34 mg, 70% yield, *dr* >20:1), R_f = 0.38 (petroleum ether/EtOAc 80:20), MP: 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.86 – 7.81 (m, 2H), 7.42 – 7.29 (m, 4H), 7.22 – 7.12 (m, 2H), 6.89 – 6.83 (m, 2H), 3.66 (s, 3H), 3.23 (s, 3H), 2.33 (s, 3H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 168.7, 163.1, 158.4, 158.4, 147.8, 139.1, 137.9, 130.4, 128.9, 125.5, 125.5, 119.5, 117.9, 105.7, 80.7, 68.5, 51.9, 32.3, 17.1, 16.0. HRMS (ESI TOF) *m/z* calcd. For $C_{25}H_{24}N_5O_4$ $[M+H]^+$ 458.1828 found 458.1830.

Methyl-11-(2-fluorophenyl)-1,10-dimethyl-4,7-dioxo-3,8-diphenyl-2,3,8,9,11-pentaazadispiro[4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5d)



The compound **5d** was prepared following the general procedure **GP-3**, White solid (46 mg, 80% yield, *dr* >20:1), R_f = 0.40 (petroleum ether/EtOAc 80:20), MP: 152-154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J_{(C-F)}$ = 3.9 Hz, 1H), 7.80 – 7.75 (m, 2H), 7.74 – 7.69 (m, 2H), 7.38 – 7.31 (m, 4H), 7.22 – 7.12 (m, 4H), 7.07 – 7.00 (m, 1H), 6.94 (td, *J* = 8.1, 1.4 Hz, 1H), 3.69 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 166.3, 162.9, 159.3, 158.0, 155.2 (d, $J_{(C-F)}$ = 248 Hz), 149.77 (d, $J_{(C-F)}$ = 7.1 Hz), 137.7, 137.1, 129.0, 128.9, 127.45 (d, $J_{(C-F)}$ = 7.9 Hz) ,126.93 (d, $J_{(C-F)}$ = 10.2 Hz), 126.1, 125.70 (d, $J_{(C-F)}$ = 3.8 Hz) 125.6, 121.6, 119.7, 119.4, 117.55 (d, $J_{(C-F)}$ = 20.6 Hz), 105.6, 82.6, 68.3, 51.9, 16.94 (d, $J_{(C-F)}$ = 1.9 Hz), 16.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -123.5. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}FN_5O_4$ $[M + H]^+$ 538.1991 found 538.1893.

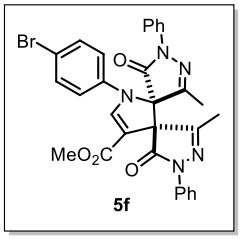
Methyl-11-(3-bromophenyl)-1,10-dimethyl-4,7-dioxo-3,8-diphenyl-2,3,8,9,11-pentaazadispiro[4.0.4^6.3^5]trideca-1, 9, 12-triene-13-carboxylate (5e)



The compound **5e** was prepared following the general procedure **GP-3**, White solid (58 mg, 90% yield, *dr* >20:1), R_f = 0.37 (petroleum ether/EtOAc 80:20), MP: 175-176°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.75 (ddt, *J* = 12.0, 8.9, 1.7 Hz, 4H), 7.41 – 7.31 (m, 4H), 7.28 – 7.11 (m, 5H), 6.71 (ddd, *J* = 8.2, 2.4, 0.7 Hz, 1H), 3.70 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.6, 166.3, 162.8,

158.7, 157.8, 146.8, 140.1, 137.6, 137.0, 131.7, 129.1, 128.9, 128.3, 126.4, 125.7, 124.2, 120.8, 119.7, 115.5, 106.9, 81.6, 68.7, 52.1, 17.2, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}BrN_5O_4$ $[M + H]^+$ 598.1090 and 600.1069 found 598.1094 and 600.1079 (isotopic mass).

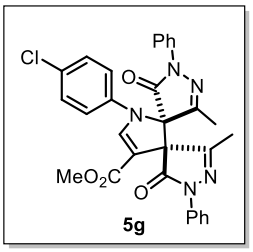
Methyl -11-(4-bromophenyl)-1, 10-dimethyl-4, 7-dioxo-3, 8-diphenyl-2, 3, 8, 9, 11-pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5f)



The compound **5f** was prepared following the general procedure **GP-3**, White solid (44 mg, 69% yield, *dr* >20:1), R_f = 0.34 (petroleum ether/EtOAc 80:20), MP: 187-189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.75 (ddd, *J* = 5.4, 4.4, 2.3 Hz, 4H), 7.45 – 7.31 (m, 6H), 7.24 – 7.14 (m, 2H), 6.81 – 6.75 (m, 2H), 3.69 (s, 3H), 2.36 (s, 3H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.7, 166.4, 162.8, 158.7, 157.9, 147.2, 138.1, 137.6, 137.1, 133.5, 129.2, 128.9, 126.3, 125.7, 119.7, 119.4, 119.3, 118.5, 106.5, 81.8, 68.8, 52.1, 17.2, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}BrN_5O_4$ $[M+H]^+$ 598.1090 and 600.1069 found 598.1072 and 600.1066 (isotopic mass).

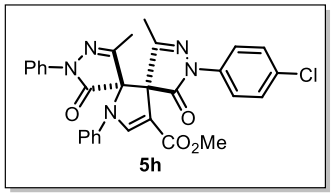
Methyl-11-(4-chlorophenyl)-1, 10-dimethyl-4, 7-dioxo-3, 8-diphenyl-2, 3, 8, 9, 11-pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5g)

The compound **5g** was prepared following the general procedure **GP-3,** White solid (43 mg, 73% yield, *dr* >20:1), R_f = 0.39 (petroleum ether/EtOAc 80:20), MP: 185-187°C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.78 – 7.70 (m, 4H), 7.39 – 7.30 (m, 4H), 7.29 – 7.26 (m, 2H), 7.24 – 7.12 (m, 2H), 6.86 – 6.82 (m, 2H), 3.68 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.7, 166.4, 162.9, 158.8, 157.9, 147.3, 137.7, 137.6, 137.1, 131.0, 130.5, 129.2, 128.9, 126.3, 125.7, 119.7, 119.4, 119.2, 106.4, 82.0, 68.8, 52.1, 17.2, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}ClN_5O_4$ $[M + H]^+$ 554.1595 found 554.1603.

Methyl-3-(4-chlorophenyl)-1,10-dimethyl-4,7-dioxo-8,11-diphenyl-2,3,8,9,11-pentaazadispiro[4.0.4^6.3^5]trideca-1, 9, 12-triene-13-carboxylate (5h)

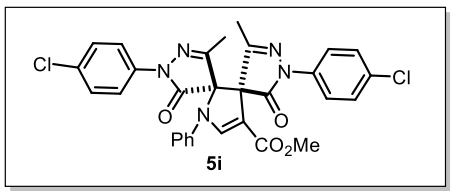


5h

The compound **5h** was prepared following the general procedure **GP-3**, White solid (50.5 mg, 85% yield, *dr* >20:1), R_f = 0.46 (petroleum ether/EtOAc 80:20), MP: 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.79 – 7.72 (m, 4H), 7.39 – 7.27 (m, 6H), 7.23 – 7.12 (m, 2H), 6.94 – 6.89 (m, 2H), 3.68 (s, 3H), 2.37 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.8, 166.6, 163.0, 159.0, 158.5, 147.7, 138.9, 137.2, 136.3, 130.7, 130.5, 129.1, 129.0, 126.3, 125.6, 120.6, 119.4, 117.9, 105.5, 81.9, 68.9, 52.0, 17.2, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{25}ClN_5O_4$ $[M + H]^+$ 554.1595 found 554.1593.

Methyl -3, 8-bis (4-chlorophenyl)-1, 10-dimethyl-4, 7-dioxo-11-phenyl-2, 3, 8, 9, 11-pentaazadispiro [4.0.4^6.3^5] trideca-1, 9, 12-triene-13-carboxylate (5i)

The compound **5i** was prepared following the general procedure **GP-3**, White solid (48.5 mg, 77% yield, *dr* >20:1), R_f = 0.39 (petroleum ether/EtOAc 80:20), MP: 215-217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.78 – 7.71 (m, 4H), 7.31 (tt, *J* = 7.1, 1.8 Hz, 6H), 7.21 – 7.12 (m, 1H), 6.92 – 6.86 (m, 2H), 3.68 (s, 3H), 2.37 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 168.7, 166.5, 162.9, 159.4, 158.4, 147.7, 138.9, 136.3, 135.7, 131.5, 130.8, 130.5, 129.2, 129.0, 125.7, 120.6, 120.4, 117.9, 105.6, 81.9, 68.9, 52.0, 17.3, 16.1. HRMS (ESI TOF) *m/z* calcd. For $C_{30}H_{24}Cl_2N_5O_4$ $[M + H]^+$ 588.1205 found 588.1208.



5i

5.7 Appendix V ^{1}H, ^{13}C and HPLC spectral data of representative compounds

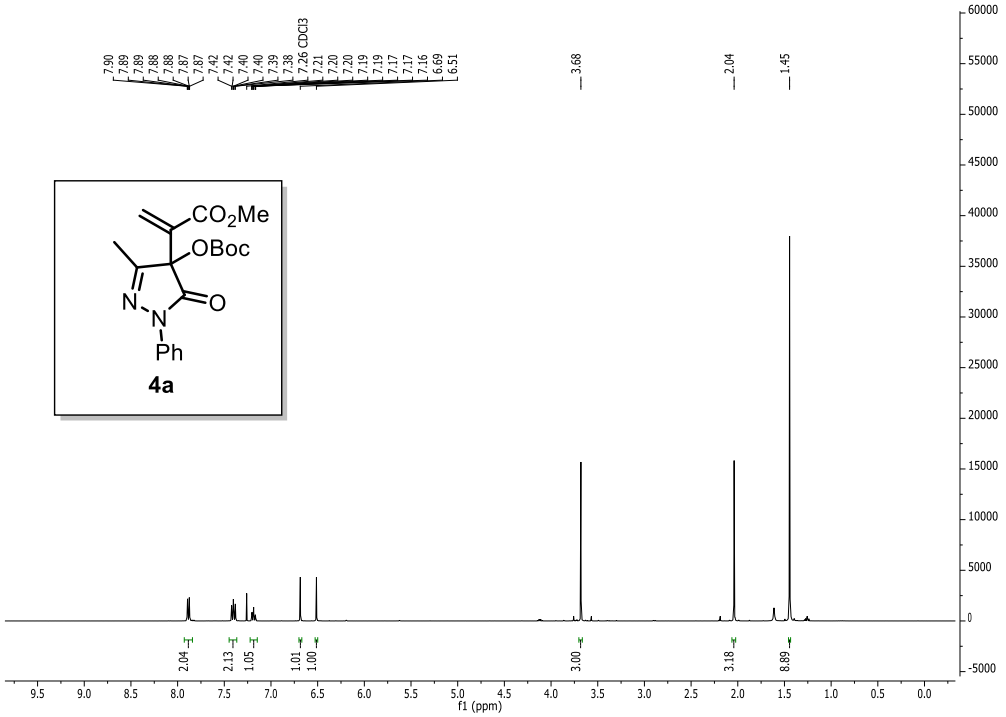


Figure AV.1 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

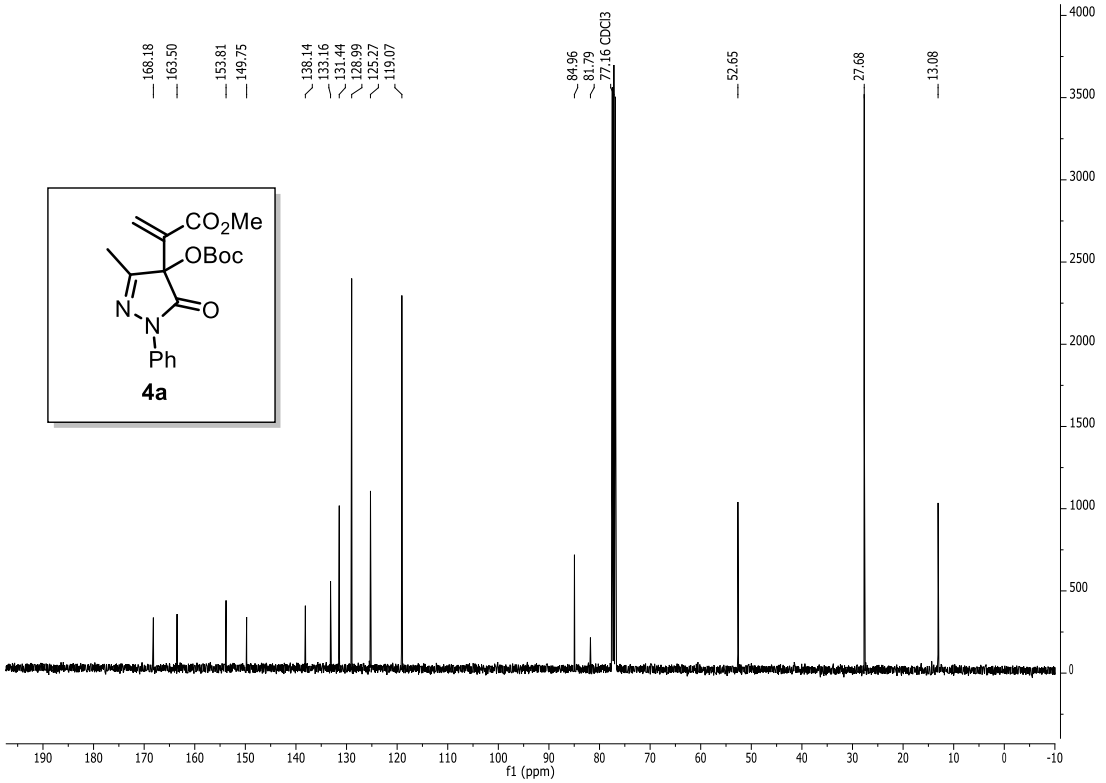


Figure AV.2 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**

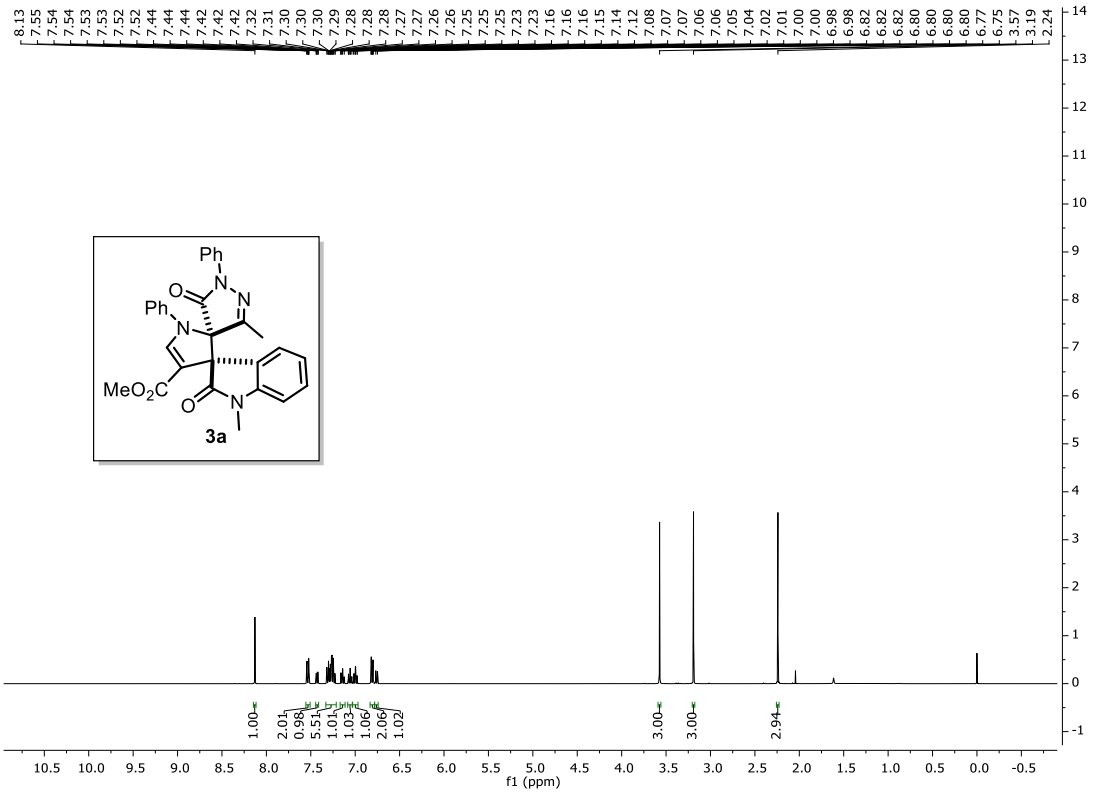


Figure AV.3 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

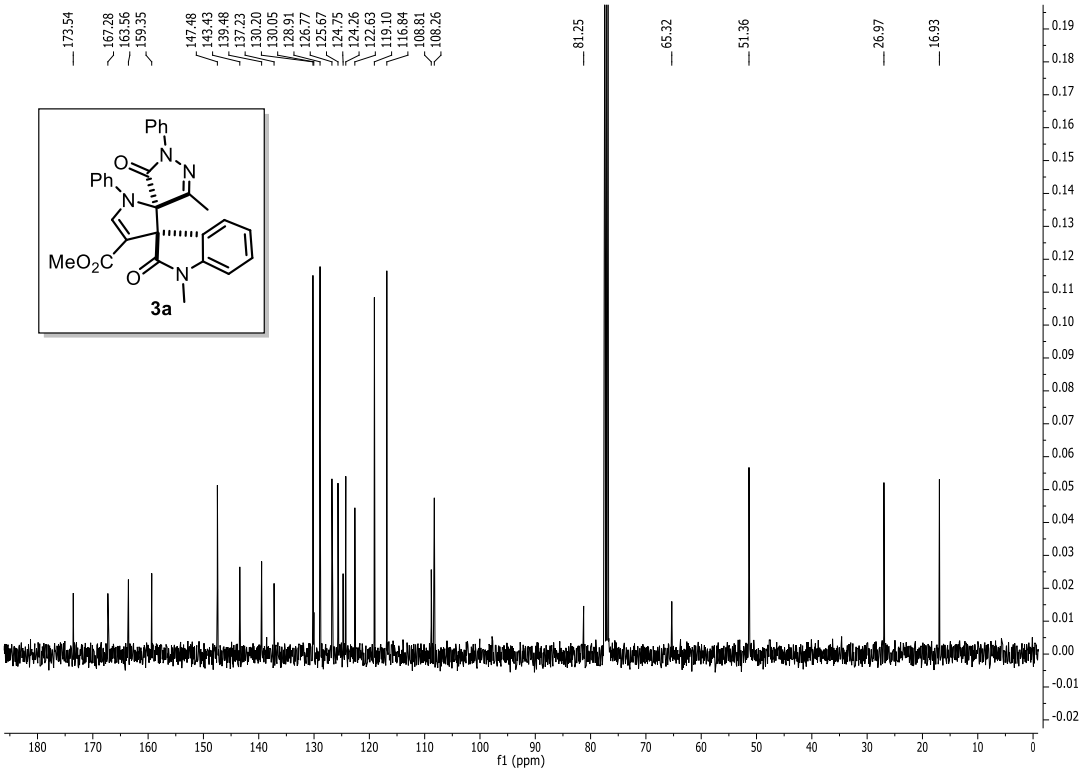
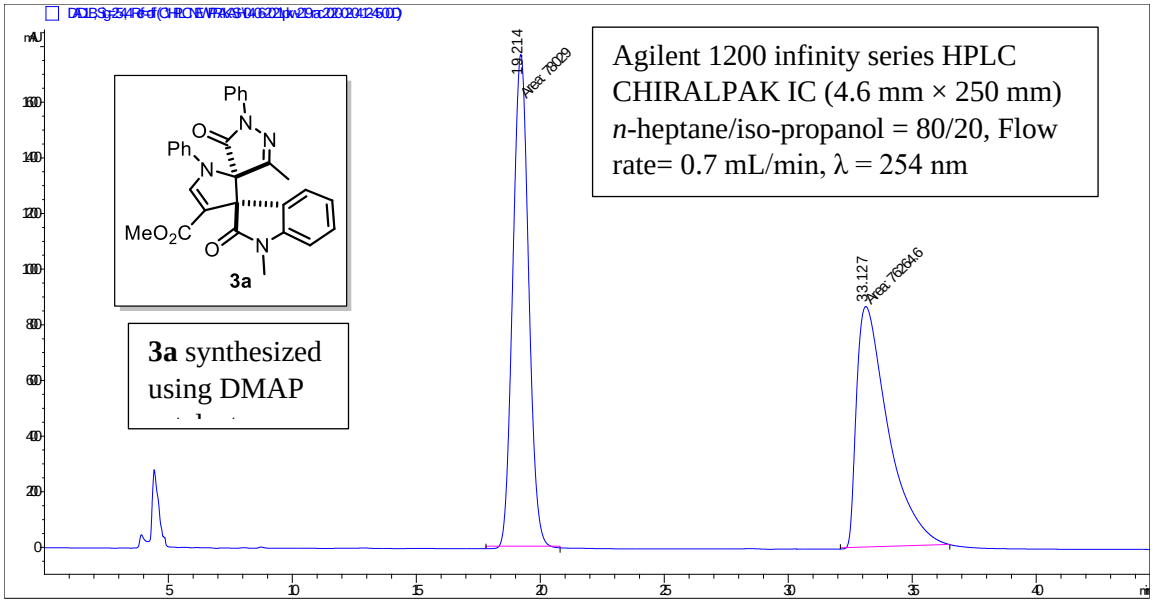


Figure AV.4 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**



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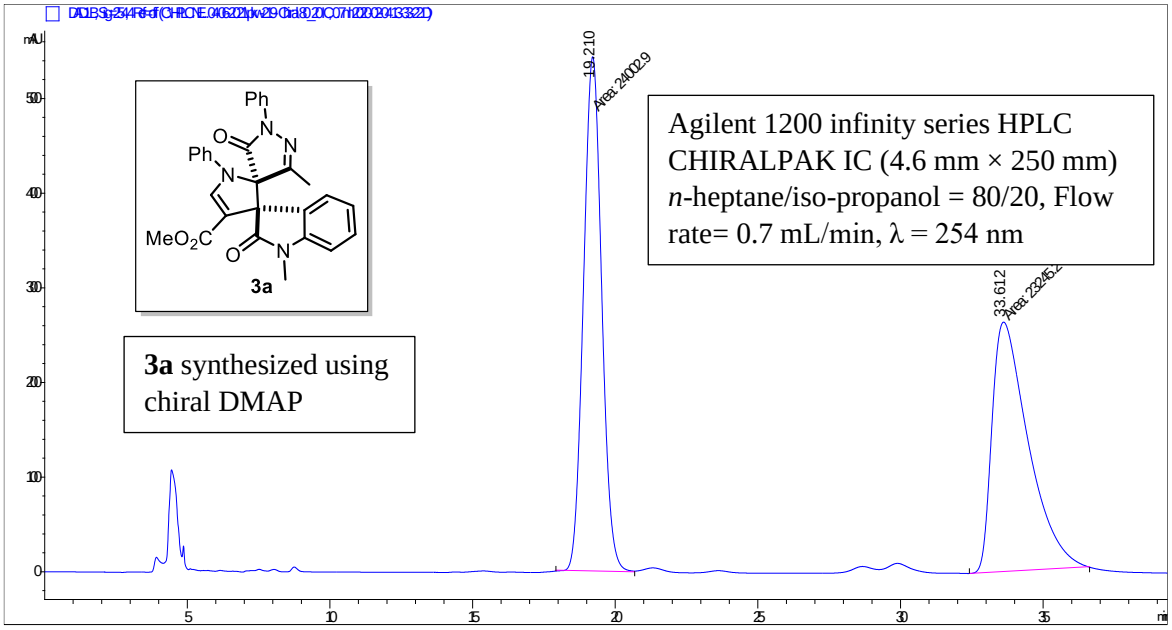
1	19.214	78029	1767.4	0.7358	50.572	0.97
2	33.127	76264.6	864.4	1.4704	49.428	0.397



#	Time	Area	Height	Width	Area%	Symmetry
1	19.21	24002.9	543.4	0.7362	50.802	0.974
2	33.612	23245.2	263.6	1.4695	49.198	0.455

Figure AV.5 HPLC profile of compound **3a**

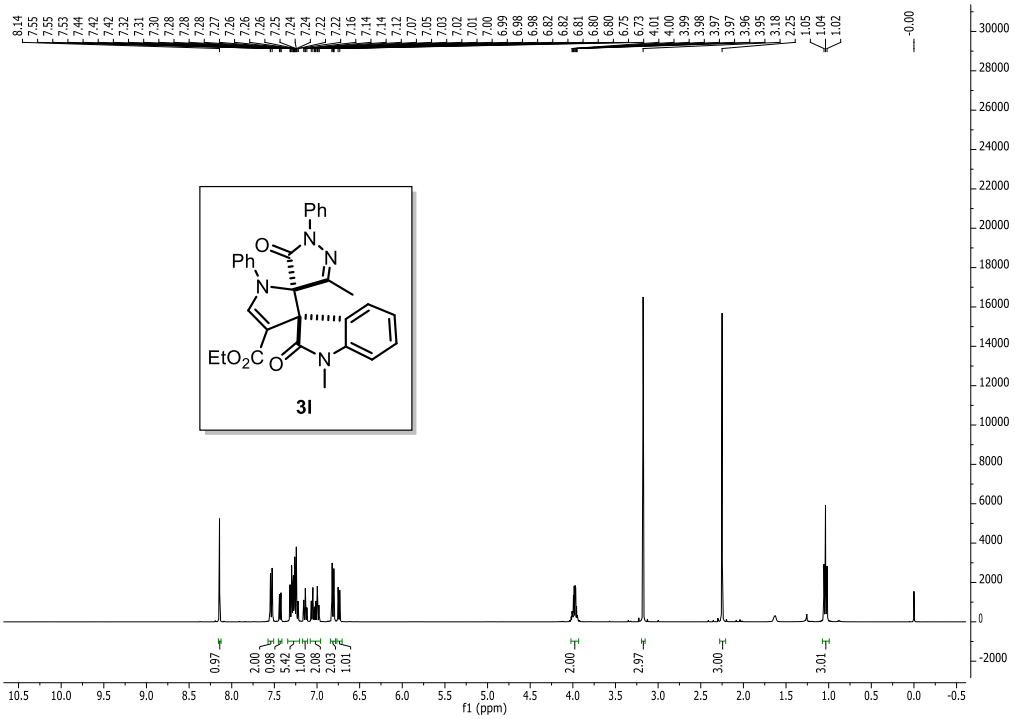


Figure AV.6 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3l**

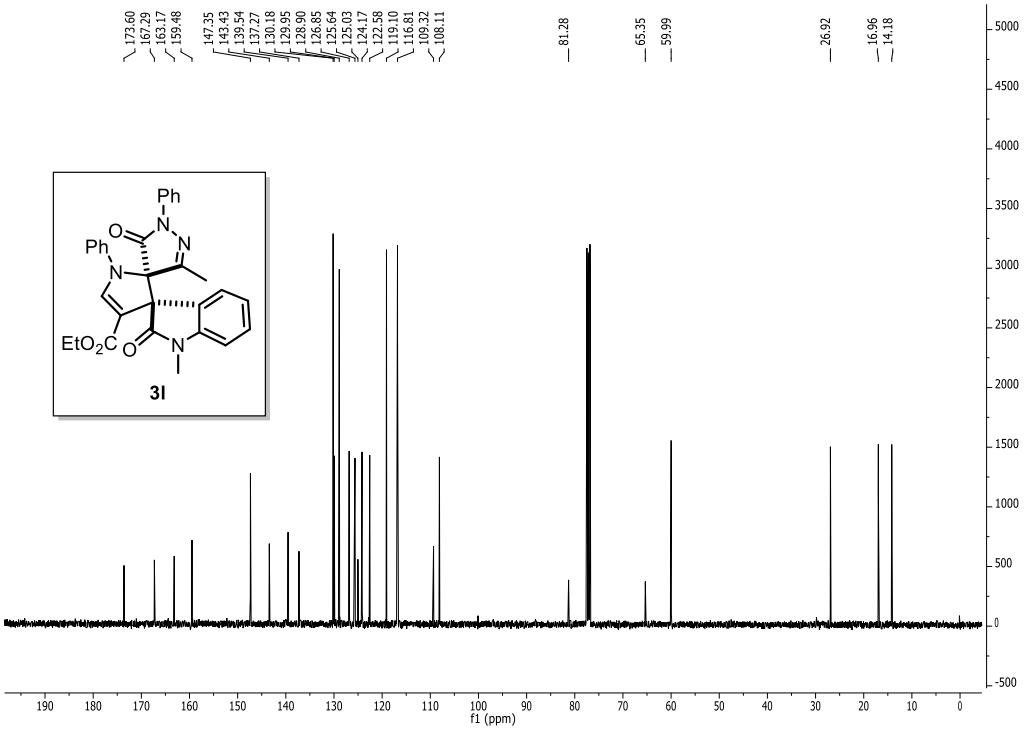


Figure AV.7 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3l**

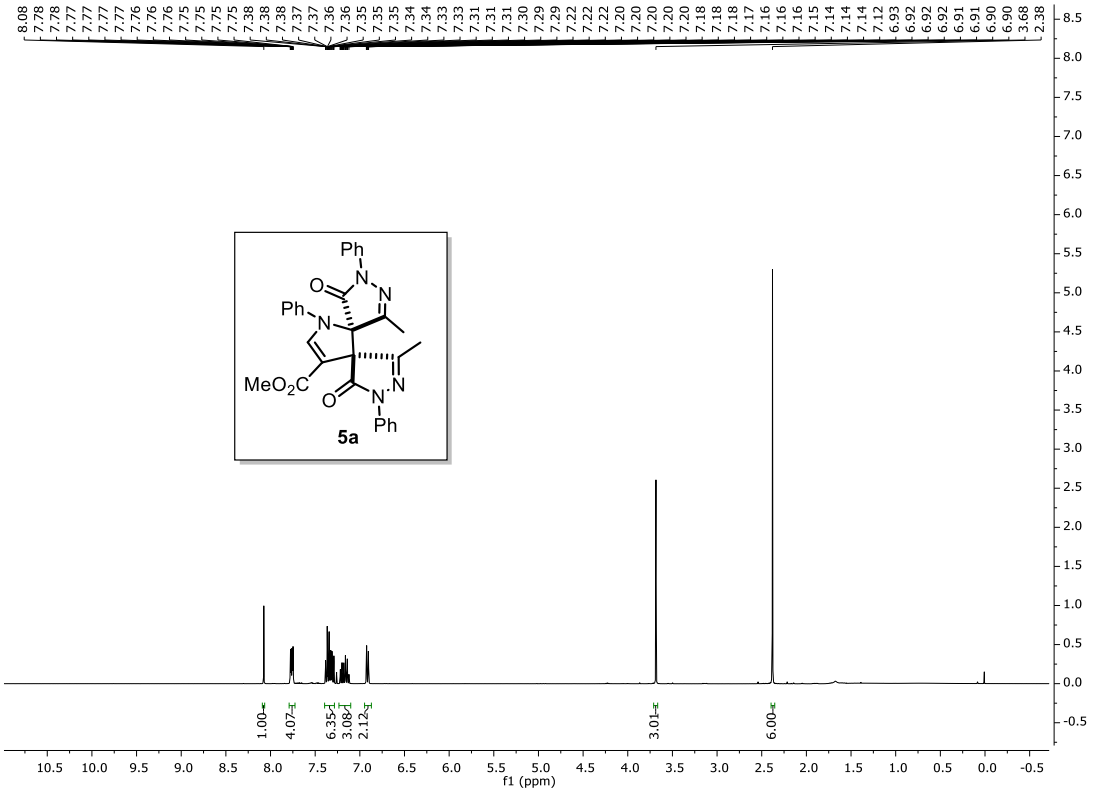


Figure AV.8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a**

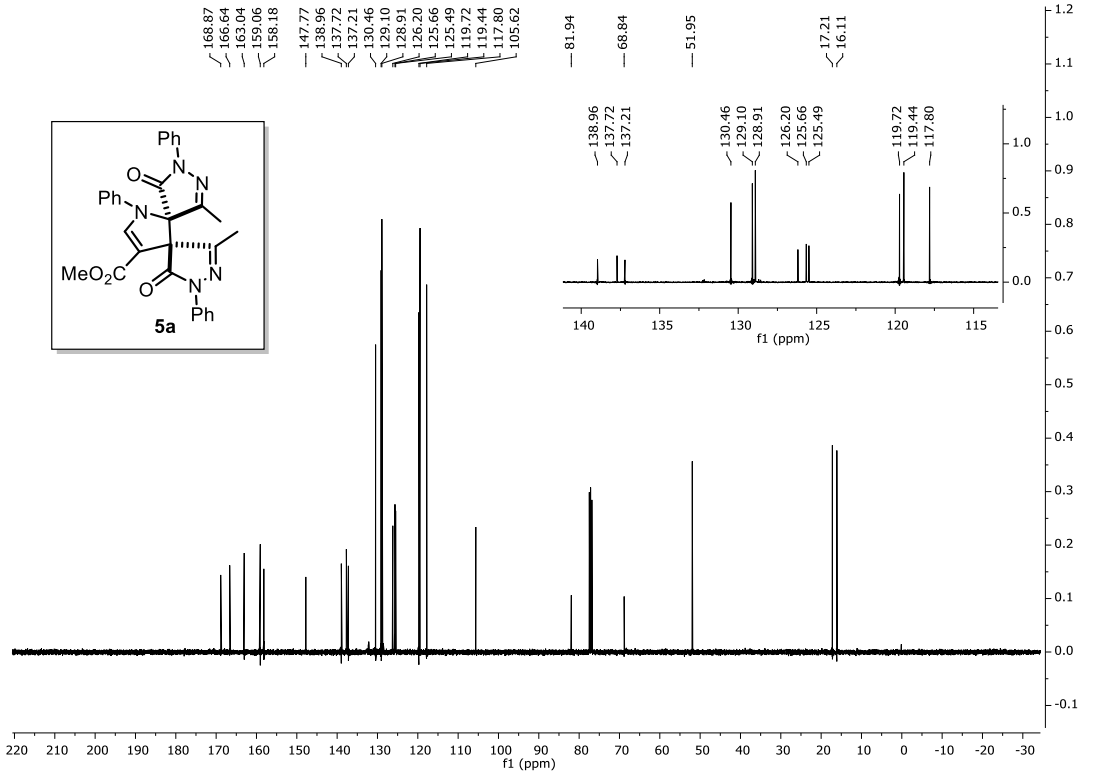
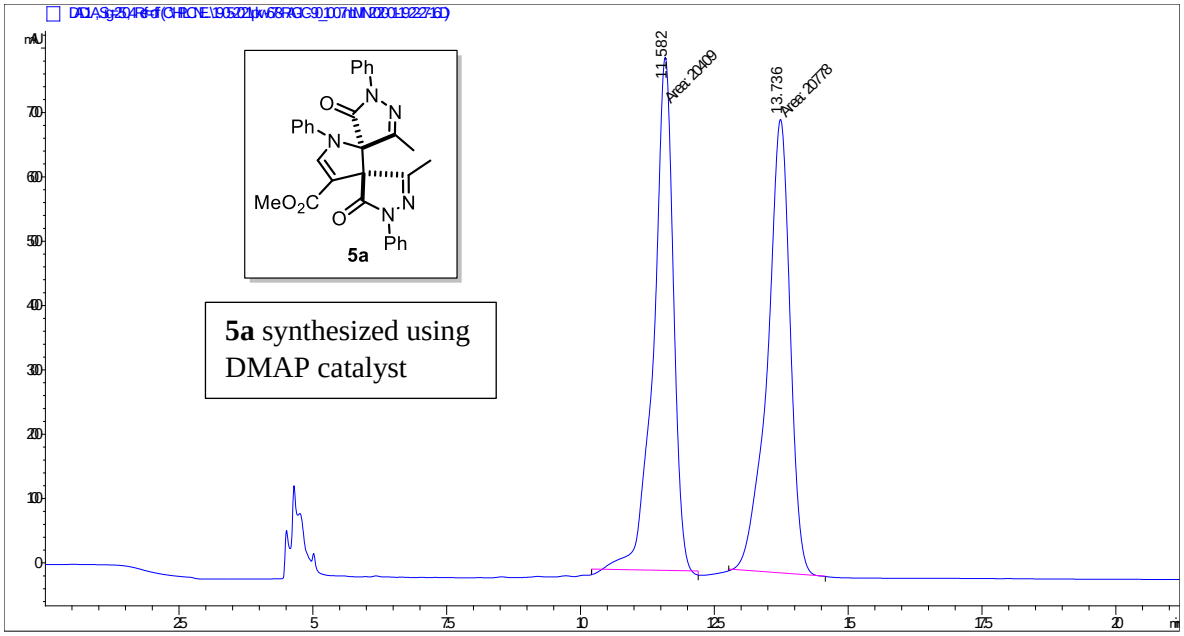
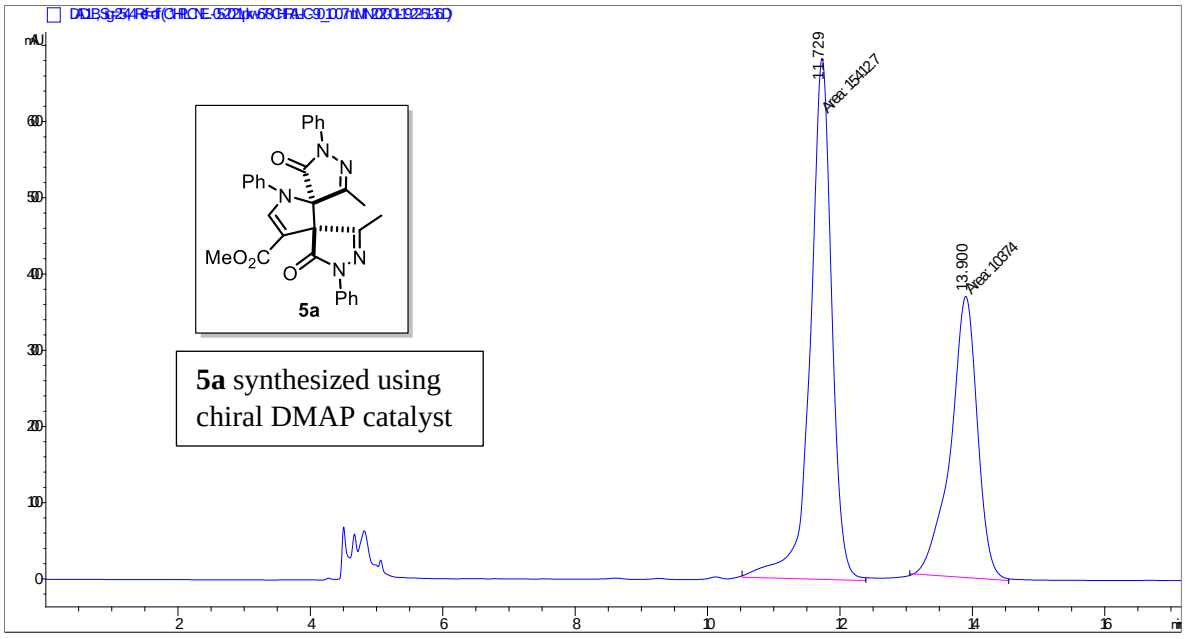


Figure AV.9 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5a**



#	Time	Area	Height	Width	Area%	Symmetry
1	11.582	20409	797.5	0.4265	49.552	1.361
2	13.736	20778	704.9	0.4913	50.448	1.313



#	Time	Area	Height	Width	Area%	Symmetry
1	11.729	15412.7	683.9	0.3756	59.770	1.176
2	13.9	10374	369	0.4686	40.230	1.257

Figure AV.10 HPLC profile of compound **5a**

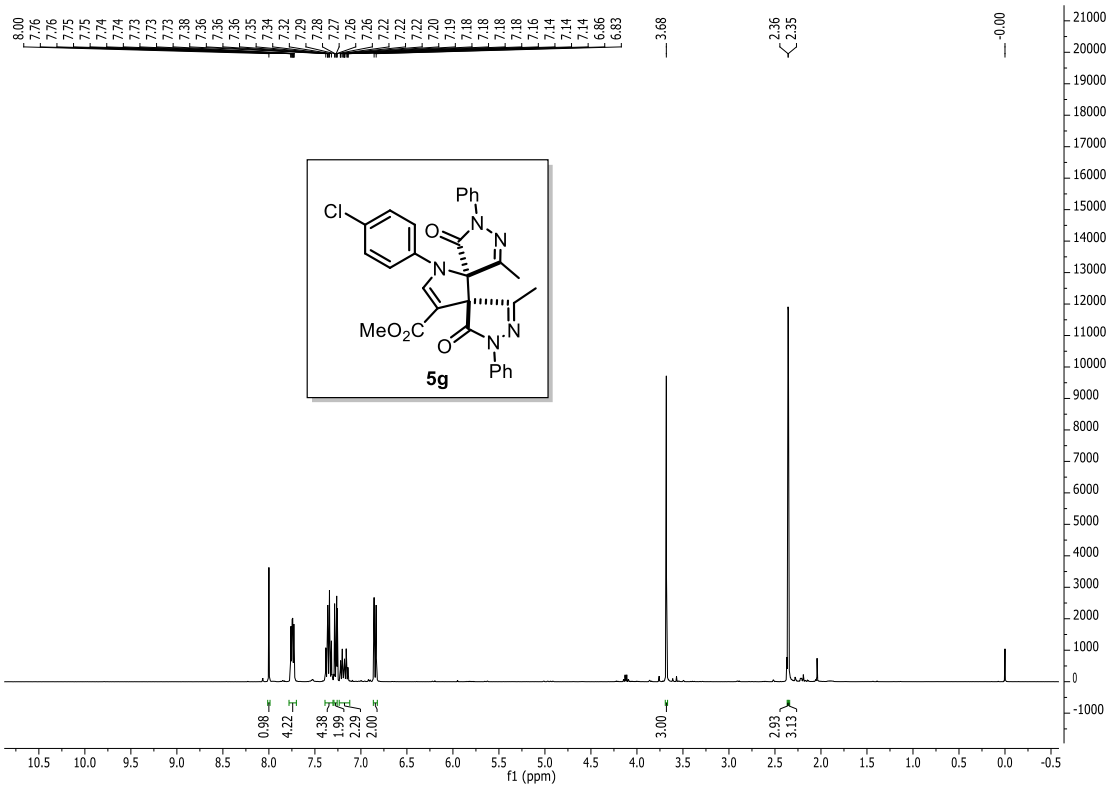


Figure AV.11 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5g**

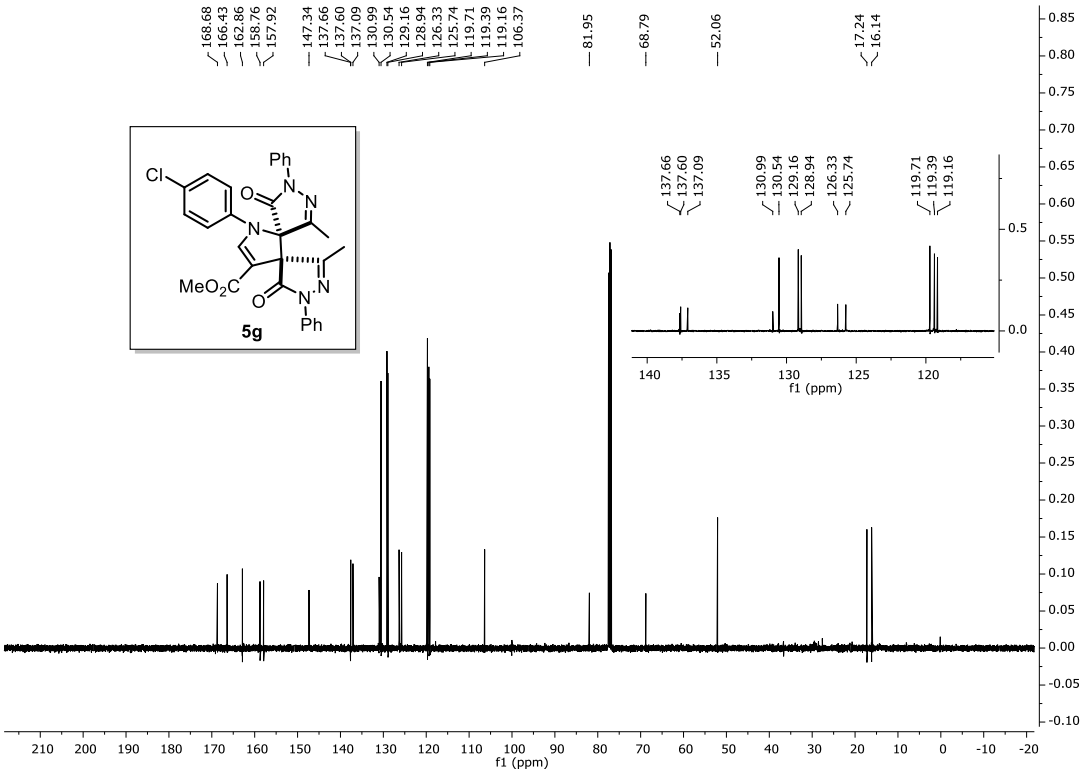


Figure AV.12 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **5g**

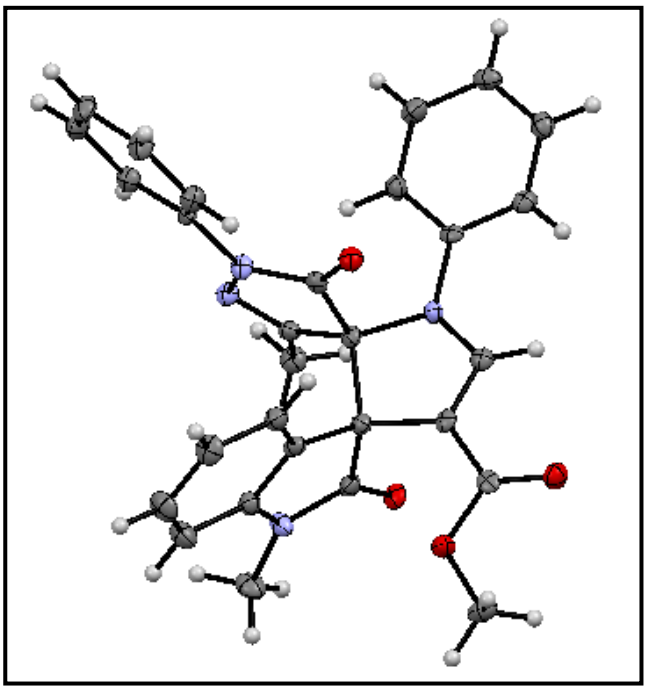


Figure AV.13 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **3a**

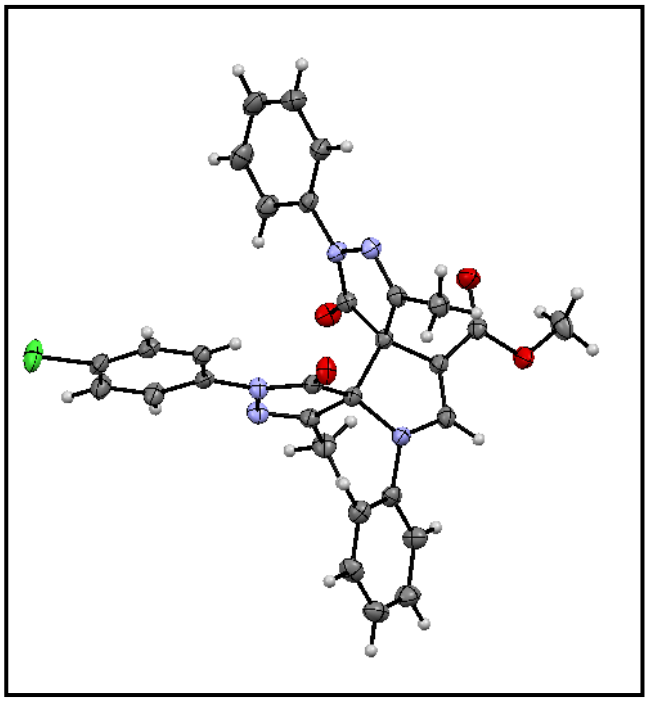


Figure AV.14 ORTEP plot (thermal ellipsoids set at 50% probability) of the structures obtained from single crystal X-ray diffraction analyses of **5g**

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Summary

The carbon−carbon bond forming reactions have always remained as one of the most indispensable reactions in organic synthesis. Among various carbon−carbon bond forming reactions, the Morita−Baylis−Hillman (MBH) reaction is one of the very useful and potential transformations with enormous synthetic utility. The dense functionalities and versatile reactivity of Morita-Baylis-Hillman (MBH) adducts make them powerful precursors for building various carbocyclic, heterocyclic and other important compounds of biological significance. In recent the years, isatin-derived Morita-Baylis-Hillman (MBH) carbonates have emerged as versatile synthons for constructing multi-functional spirooxindole scaffolds under organocatalytic conditions. In this thesis novel uses of MBH carbonates of isatin have been explored for the efficient organocatalytic transformations to synthesize useful scaffolds such as spiroheterocycles.

Various interesting and useful spiroheterocycles such as bis-spirooxindoles, cyclopropyl spirooxindoles, spirooxindole dihydofuran fused pyrazolones, spirocyclopentadienes, cyclopenetene spirooxindoles and spirooxindole dihydopyrrole fused pyrazolones have been synthesized by utilizing Morita-Baylis-Hillman carbonates of isatin under tertiary amine catalysis. We have developed highly efficient organocatalytic [3+2] and [2+1] annulations between isatin-derived Morita−Baylis−Hillman carbonate and 3-methyleneoxindoles to access bis-spirooxindoles appended with cyclopentene and cyclopropane derivatives. Later, we explored the utility of cinchona derived chiral tertiary amine catalyst in the cycloaddition between isatin-derived Morita−Baylis−Hillman adducts and pyrazolone 4, 5-diones to construct enantiopure spirooxindole dihydrofuran fused pyrazolones scaffold. We have successfully employed aurones and thioaurones as a suitable C2 synthon in [3+2] annulation with MBH carbonates of isatin to construct structurally diverse and multi-functionalized sprio fused carbopentacyclic scaffold under suitable Lewis base catalysis. Further, we have also synthesized the spirooxindole dihydropyrrole fused pyrazolone derivatives utilizing Morita−Baylis−Hillman carbonates of isatins and pyrazolone derived ketimines under DMAP catalysis.

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Chapter 2

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Cycloaddition of isatin-derived MBH carbonates and 3-methyleneoxindoles to construct diastereoselective cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles: Catalyst controlled [3 + 2] and [2 + 1] annulations

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ABSTRACT

A highly diastereoselective organocatalytic synthesis of cyclopentenyl bis-spirooxindoles and cyclopropyl spirooxindoles has been achieved *via* [3 + 2] and [2 + 1] annulations. The tertiary amine catalysts have been effectively employed to tune the cycloaddition of isatin-derived MBH carbonates and 3-methyleneoxindoles for the outcome of two different spirooxindole frameworks with vicinal quaternary spiro centers and three contiguous stereocenters. The reactions worked under mild and practical conditions to afford the spirooxindoles in good to excellent yields with very high diastereoselectvity.

Introduction

The spirooxindole scaffolds are abundant in numerous natural products and pharmacologically active compounds [1]. In particular, bis-spirocyclic oxindole structural motifs with two vicinal quaternary spirocenters show prominent bioactivity such as anti-tumor, anti-cancer and acetylcholinesterase (AChE) inhibitory activities (Fig. 1) [2]. As a result, considerable efforts have been devoted for developing creative methodologies to construct bis-spirocyclic system [3].

However, most of the strategies were concentrated on the synthesis of three- [4], five- [5], and six-membered spirooxindole skeletons with single spirostereocenters [6]. Nevertheless, catalytic protocols to access bis-spirooxindole backbone in regioselective fashion with quaternary chiral centers are limited in the literature [4–7]. Therefore, the development of highly efficient and more accessible protocol for the synthesis of structurally diverse bis-spirooxindoles is highly desirable.

Due to their dense functionalities and versatile reactivity, Morita-Baylis-Hillman (MBH) adducts have been widely used as powerful precursors for the building of various carbocyclic, heterocyclic and biologically important compounds in the past decade [8]. In this arena, isatin-derived MBH carbonate, being a valuable three-carbon synthon, has been employed in the construction of enantiomerically pure multifunctional spirocyclicoxindole compounds [9,10]. These valuable compounds have been synthesized by using various electrophilic substrates containing C=N, C=C, and C=S double bonds under nucleophilic tertiary-amine or tertiary-phosphine organocatalysis. The reaction pathway is believed to undergo *via* the formation of either zwitterionic allylic N or P ylides [8–11]. Similarly, 3-methylene oxindole derivatives have been explored as Michael acceptors and dienophiles in various organocatalytic Michael and Diels-Alder reactions respectively to construct the spirooxindoles [12,13]. We believed that isatin-derived MBH carbonate and 3-methyleneoxindole can be effectively employed for the [3 + 2] and [2 + 1] annulations to synthesize various bis-spirooxindole derivatives appended with cyclopentenyl and cyclopropyl skeletons.

In this regard, we hypothesized the synthesis of bis-spirooxindole as illustrated in Scheme 1. A Lewis base catalyst (phosphine or amine) may initiate S_N^2 reaction to form intermediate **II** starting from MBH carbonate **I**, which would be subsequently deprotonated by in situ generated Brønsted base (*tert*-butoxide) to form a zwitterionic intermediate **III**, which further reacts with 3-methyleneoxindole **IV** to afford bis-spirooxindole **V**.

To validate the feasibility of our hypothesis, initially we performed a model reaction between MBH carbonate **1a** derived from

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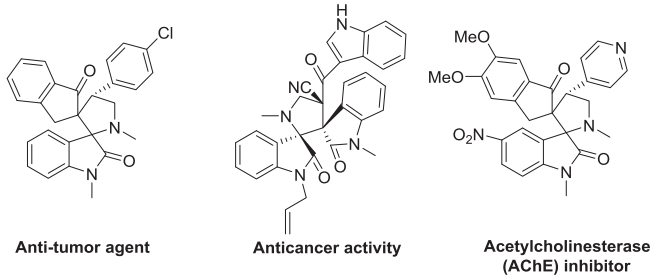


Fig. 1. Representative biologically active compounds containing bis-spirooxindole framework.

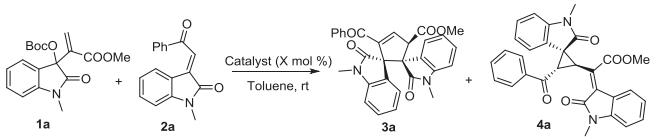
isatin and 3-methyleneoxindole **2a** using 20 mol % of PPh_3 as a catalyst in toluene at room temperature. To our delight, the reaction proceeded smoothly and delivered the α-regioselective [3 + 2] annulation product **3a** in good yield with very high diastereoselectivity (Table 1, entry 1).

Encouraged by this immediate success we screened various phosphine catalysts including chiral phosphine catalysts. However, surprisingly the reactions did not work under any of these phosphine catalysts (Table 1, entries 2–3). Later, we turned our attention towards the tertiary amine catalysts. Interestingly, when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used as catalyst an unexpected [2 + 1] cyclopropanation product **4a** was obtained in good yield with an excellent diastereoselectivity (Table 1, entry 4). It was observed that neither DIPEA nor Et_3N catalyzed the reaction even after prolonged reaction time (Table 1, entries 5–6). Gratifyingly, DMAP as a catalyst successfully afforded the corresponding desired [3 + 2] annulation product **3a** in excellent yield with very high diastereoselectivity (Table 1, entry 7). Encouraged by this we turned our attention towards the chiral amine catalysts to achieve enantioselective [3 + 2] annulation. However, unfortunately, all our attempts towards the enantioselective synthesis of bis-spirooxindoles did not succeed in spite of screening different chiral cinchona based catalysts (Entry 8–12, see ESI for details). Hence, we planned to explore the diastereoselective synthesis of bis-spirooxindoles systematically. Further reduction in the catalyst loading of 4-dimethylamino pyridine (DMAP) (15–5 mol %) afforded the corresponding desired product **3a** in relatively lower yields however, with very high diastereoselectivity (Table 1, entries 13–15). In order to optimize the reaction condition further, we screened various solvents (See ESI, Appendix-I). Halogenated solvents such as dichloromethane and chloroform afforded the desired compound **3a** in excellent yield with very high diastereoselectivity in 7–8 h (See ESI, Appendix-I). Both protic and aprotic polar solvents such as EtOH, ^{t}BuOH and CH_3CN, THF, DMF, DMSO respectively afforded **3a** in relatively lower yields with longer reaction times (24–30 h) (See ESI, Appendix-I). Toluene proved to be the optimum solvent for the desired transformation.

After the exhaustive screening, MBH carbonate **1a** (1 equiv.), 3-methyleneoxindole (1.1 equiv.) and DMAP (20 mol %) in toluene proved to be the optimum reaction condition for the [3 + 2] annulation.

In order to explore the substrate scope we synthesized different MBH carbonates **1a-1d** and 3-methyleneoxindoles **2a-2j** derived

Table 1
Screening of catalysts for annulation reaction.[a]

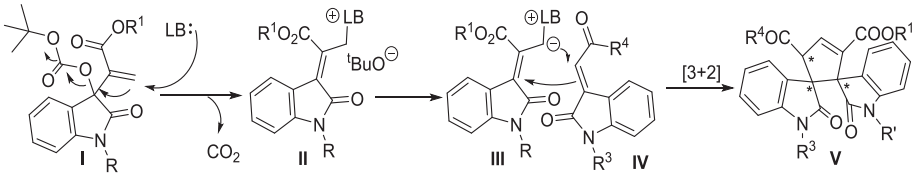


Entry	Catalyst	Time [h]	Product & Yield [%][b]	*d.r.* [%][c]
1	PPh_3	24	**3a**, 85	>20:1
2	*R*-BINAP	120	NR	–
3	*S*-BINAP	120	NR	–
4	DABCO	12	**4a**, 85	>20:1
5	DIPEA	120	NR	–
6	Et_3N	120	NR	–
7	DMAP	4	**3a,** 97	>20:1
8	C1	120	NR	–
9	*C2*	120	NR	–
10	C3	120	NR	–
11	C4	120	NR	–
12	C5	120	NR	–
13[d]	DMAP	12	**3a**, 92	>20:1
14[e]	DMAP	24	**3a**, 87	>20:1
15[f]	DMAP	40	**3a**, 82	>20:1

[a] Unless otherwise specified, the reactions were carried out using MBH carbonate **1a** (0.28 mmol) and (*E*)-1-methyl-3-(2-oxo-2-phenylethylidene) indolin-2-one **2a** (0.31 mmol) with 20 mol % catalyst in 2 mL toluene at room temperature.
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR spectroscopy.
[d] 15 mol % DMAP.
[e] 10 mol % DMAP.
[f] 5 mol % DMAP. NR = no reaction; C1 = Quinine, *C2* = Quinidine, C3 = 1-(3,5-bis (trifluoromethyl)phenyl)-3-((*S*)-(6-methoxyquinolin-4-yl)((1*S*, 2*R*, 4*S*, 5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea, C4 = $(DHQ)_2PHAL$, C5 = (−)-Sparteine.

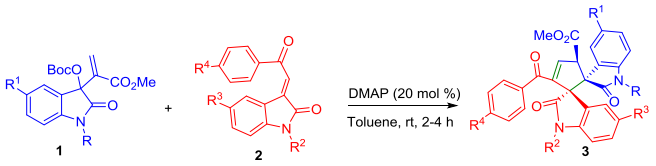
from isatin. Under the optimized reaction conditions MBH carbonates **1a-1d** reacted with different 3-methyleneoxindoles **2a-2j** to afford the corresponding bis-spirooxindole derivatives **3a-3t** in good to excellent yields with very high diastereoselectivity (Table 2). All the substrates underwent [3 + 2] annulation smoothly and afforded the desired compounds with adjacent quaternary spirocenters under the reaction conditions. We did not observe any side products emanating from [2 + 1] cycloaddition during the course of the reaction. We observed that both electron donating as well as weakly electron deactivating substituents on either MBH carbonates **1** or 3-methyleneoxindoles **2** did not affect the yield and diastereoselectivity. Further, the molecular structure of compound **3f** was established unambiguously using single crystal X-ray diffraction analysis (see ESI) [14].

Earlier, while optimizing the reaction conditions for the synthesis of bis-spirooxindole *via* [3 + 2] annulations, serendipitously we had obtained an unexpected [2 + 1] annulated cyclopropanation product **4a** (Table 1, entry 4). Excited by this observation we turned our attention towards the synthesis of spirooxindole appended cyclopropane derivatives. Surprisingly, there are only seldom reports on the synthesis of such scaffolds in the literature [15]. Molecular architecture containing strained three membered cyclopropyl ring would be of a great importance as the ring strain makes



Scheme 1. . Proposed synthesis of bis-spirocyclic oxindole.

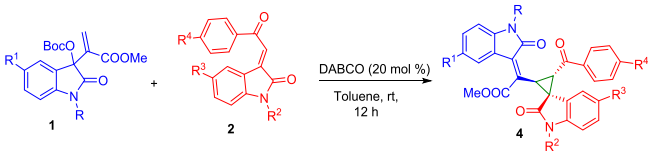
Table 2
Substrate scope of [3 + 2] annulation.[a]



Entry	1/R/R^1	2/R^2/R^3/R^4	3	Yield [%][b]	*d.r.* [%][c]
1	**1a**/Me/H	**2a**/Me/H/H	**3a**	97	>20:1
2	**1a**/Me/H	**2b**/allyl/H/Cl	**3b**	96	>20:1
3	**1a**/Me/H	**2c**/Bn/H/Me	**3c**	97	>20:1
4	**1a**/Me/H	**2d**/Me/H/Cl	**3d**	95	>20:1
5	**1a**/Me/H	**2e**/Bn/H/Cl	**3e**	96	>20:1
6	**1a**/Me/H	**2f**/allyl/H/Me	**3f**	98	>20:1
7	**1a**/Me/H	**2g**/allyl/H/H	**3g**	94	>20:1
8	**1b**/allyl/H	**2f**/allyl/H/Me	**3h**	95	>20:1
9	**1b**/allyl/H	**2b**/allyl/H/Cl	**3i**	93	>20:1
10	**1b**/allyl/H	**2c**/Bn/H/Me	**3j**	81	>20:1
11	**1b**/allyl/H	**2e**/Bn/H/Cl	**3k**	88	>20:1
12	**1a**/Me/H	**2h**/Me/Br/H	**3l**	90	>20:1
13	**1a**/Me/H	**2i**/Me/Cl/H	**3m**	92	>20:1
14	**1c**/Me/Br	**2a**/Me/H/H	**3n**	91	>20:1
15	**1c**/Me/Br	**2d**/Me/H/Cl	**3o**	88	>20:1
16	**1c**/Me/Br	**2f**/allyl/H/Me	**3p**	95	>20:1
17	**1c**/Me/Br	**2g**/allyl/H/H	**3q**	90	>20:1
18	**1d**/Bn/H	**2g**/allyl/H/H	**3r**	87	>20:1
19	**1d**/Bn/H	**2a**/Me/H/H	**3s**	86	>20:1
20	**1c**/Me/Br	**2j**/Me/Br/Cl	**3t**	81	>20:1

[a] Unless otherwise specified, all the reactions were carried out using MBH carbonate **1** (0.28 mmol) and 3-methyleneoxindole **2** (0.31 mmol) with DMAP (20 mol %) as a catalyst in 2 mL toluene at room temperature.
[b] Isolated yields after column chromatography.
[c] Determined by ^{1}H NMR spectroscopy.

Table 3
Substrate scope of [2 + 1] annulation.[a]



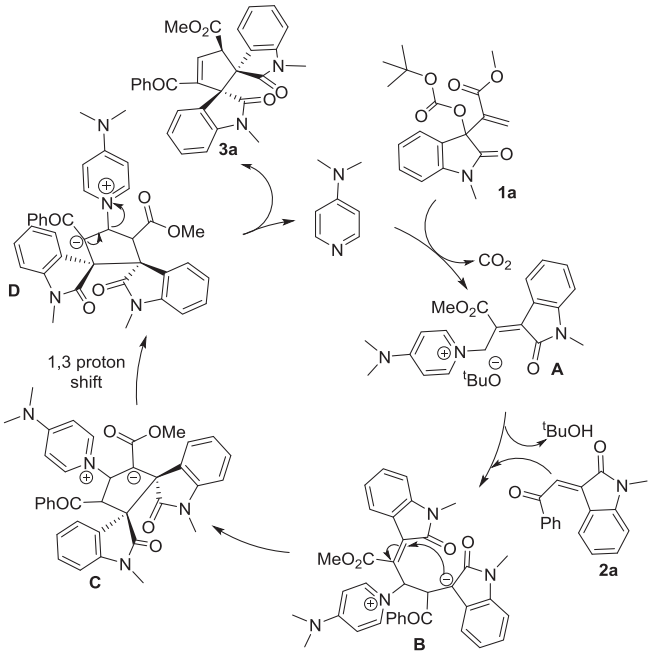
Entry	1/R/R^1	2/R^2/R^3/R^4	4	Yield [%][b]	*d.r.* [%][c]
1	**1a**/Me/H	**2a**/Me/H/H	**4a**	85	>20:1
2	**1a**/Me/H	**2d**/Me/H/Cl	**4b**	82	>20:1
3	**1a**/Me/H	**2h**/Me/Br/H	**4c**	79	>20:1
4	**1a**/Me/H	**2i**/Me/Cl/H	**4d**	83	>20:1
5	**1c**/Me/Br	**2a**/Me/H/H	**4e**	75	>20:1
6	**1c**/Me/Br	**2h**/Me/Br/H	**4f**	72	>20:1
7	**1b**/allyl/H	**2a**/Me/H/H	**4g**	83	>20:1
8	**1b**/allyl/H	**2d**/Me/H/Cl	**4h**	80	>20:1
9	**1c**/Me/Br	**2i**/Me/Cl/H	**4i**	70	>20:1
10	**1d**/Bn/H	**2a**/Me/H/H	**4j**	70	>20:1
11	**1b**/allyl/H	**2h**/Me/Br/H	**4k**	72	>20:1
12	**1c**/Me/Br	**2k**/Me/Cl/Me	**4l**	75	>20:1

[a] Unless otherwise specified, reactions were carried out using MBH carbonate **1** (0.28 mmol) and **2** (0.31 mmol) with DABCO (20 mol %) as a catalyst in 2 mL toluene at room temperature.
[b] Isolated yields after column chromatography.
[c] Determined by ^{1}H NMR spectroscopy.

them remarkably reactive for the various reactions to access synthetically useful compounds [16]. In this regard, we planned to explore the catalytic reactivity of 1,4-diazabicyclo[2.2.2]octane (DABCO) for the [2 + 1] annulation. In order to demonstrate the generality of [2 + 1] annulation, we treated different MBH carbonates **1a-1d** derived from isatin with few 3-methyleneoxindoles (**2a, 2d, 2h, 2i, 2k)** in presence of DABCO (20 mol %) in toluene to afford the corresponding cyclopropyl spirooxindoles **(4a-4l)** in very good yields with excellent diastereoselectivity (Table 3).

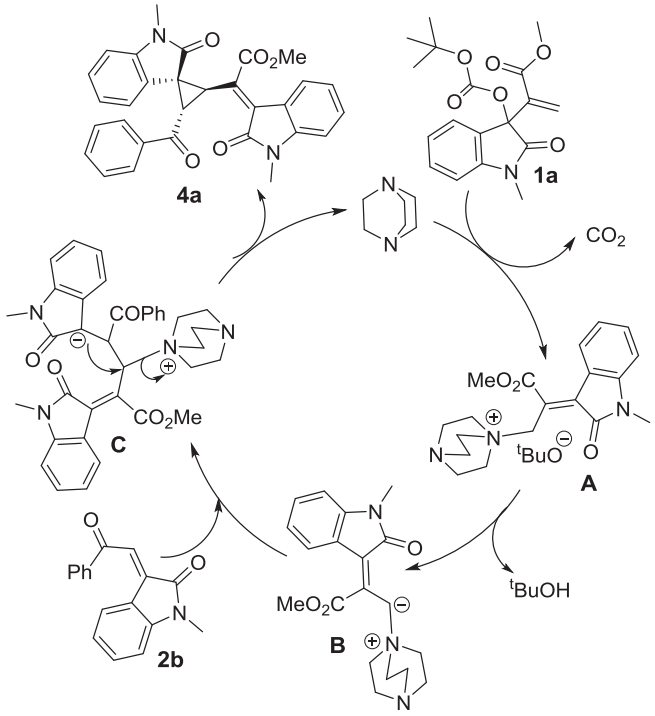
The molecular structure of compound **4d** was established unambiguously using single crystal X-ray diffraction analysis (see ESI) [14]. On the basis of previous literature on Lewis base catalyzed [3 + 2] and [2 + 1] annulation reactions of MBH carbonate, plausible mechanisms have been proposed (Scheme 2 and 3) [9–11,14a]. DMAP initiates the reaction by the nucleophilic attack on MBH carbonate **1a** to form the corresponding ammonium salt **A**. Further, the counter anion *tert*-butoxide abstracts an acidic proton to generate an allylic nitrogen-ylide. Subsequently, this reacts with **2a** to generate an intermediate **B**, followed by an intramolecular Michael addition to afford the corresponding intermediate **C**. Finally, 1,3-proton shift furnishes the annulated intermediate **D** which subsequently leads to the product **3a** by regenerating the catalyst (Scheme 2).

Likewise, the catalyst DABCO reacts with MBH carbonate **1a** to generate an ammonium intermediate **A**. The in situ generated counter anion ($^-$O^{t}Bu) deprotonates the intermediate **A** to form a reactive nitrogen ylide **B**. This in turn reacts with 3-methyleneoxindole **2b** to give a zwitterionic intermediate **C** that subsequently undergoes [2 + 1] annulation to afford cyclopropyl spirooxindole **4a** by regenerating the catalyst (Scheme 3).



Scheme 2. Plausible reaction mechanism for [3 + 2] annulation.

In conclusion, we have developed a highly efficient organocatalytic [3 + 2] and [2 + 1] annulations between isatin-derived Morita–Baylis–Hillman carbonate and 3-methyleneoxindoles. The protocol gave a direct access to bis-spirooxindoles appended with cyclopentene and cyclopropane derivatives in good to excellent yields with very high diastereoselectivity. We have demonstrated the catalyst controlled outcome of cycloaddition reactions to afford useful precursors of biologically active compounds. The method proved to be straightforward for the direct construction of diastereoselective spirocyclic oxindole derivatives.



Scheme 3. Plausible reaction mechanism for [2 + 1] annulation.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.10.004.

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Access to highly enantioselective and diastereoselective spirooxindole dihydrofuran fused pyrazolones†

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A tertiary amine catalyzed highly diastereoselective and enantioselective [3 + 2] annulation between Morita–Baylis–Hillman (MBH) carbonates derived from isatin and pyrazolone 4,5-diones has been developed. A series of structurally diverse and multifunctional spirooxindole dihydrofuran fused pyrazolone derivatives with two adjacent quaternary spirocenters has been achieved in excellent yields with good to excellent enantioselectivity. Further synthetic utility of this protocol has been successfully demonstrated by employing the bromo derivative of spirooxindole dihydrofuran fused pyrazolone to Suzuki coupling.

Introduction

Among the various spirocyclic compounds,[1] heterocyclic spirooxindole is an important structural scaffold, widely present in numerous natural products and clinical pharmaceuticals. Compounds containing this scaffold exhibit a wide range of biological activities.[2] Particularly, spirooxindole containing two vicinal quaternary spirocenters is known to exhibit notable biological activities.[3] Therefore, considerable efforts have been focused on the development of highly efficient and practical methods for the synthesis of various carbocyclic and heterocyclic spirooxindole architectures with structural diversity and complexity.[4] Among the various heterocyclic spirooxindoles, spirooxindolyl five-membered oxaheterocycles have drawn attention in asymmetric synthesis due to their presence in a variety of natural and synthetic bioactive compounds (Fig. 1a).[5] There are a few elegant methods available in the literature for the preparation of the spirooxindole-dihydrofuran framework.[6] Some of the methods include transition-metal mediated cyclization,[6a–c] ceric ammonium nitrate catalyzed [3 + 2] oxidative cycloaddition,[6d] intramolecular Friedel–Crafts reaction,[6e] dimethyl sulfide catalyzed Baylis–Hillman annulation,[6f] reductive [1 + 4] annulation,[6g] iodide-mediated reaction,[6h] and tandem Michael-cyclization.[6i] However, the number of protocols to access spirooxindole-dihydrofuran in a catalytic and enantioselective fashion is very limited in the literature.[7] Hence, the development of more effective and catalytic protocols for the enantioselective synthesis of spirooxindole and its derivatives is in high demand and challenging.

On the other hand, pyrazolones and their derivatives represent a unique class of five membered aza-heterocycles. They have attracted the attention of synthetic chemists in recent years due to their potential utility as pharmacologically active agents, photographic couplers, chelating agents and synthetic scaffolds in medicinal chemistry.[8] In particular, spiropyrazolone scaffolds bearing contiguous stereocenters fused with different carbocyclic and heterocyclic units such as cyclohexane, cyclopentane and oxindole exhibit significant biological activity.[9] Compound **I** containing a spirocyclic pyrazolone skeleton is known to act as an antibacterial agent,[9a] whereas the spiropyrazolone derivative **II** and **III** are known inhibitors of type-4-phospodiesterase.[9b,c] In addition, compound **IV** con-

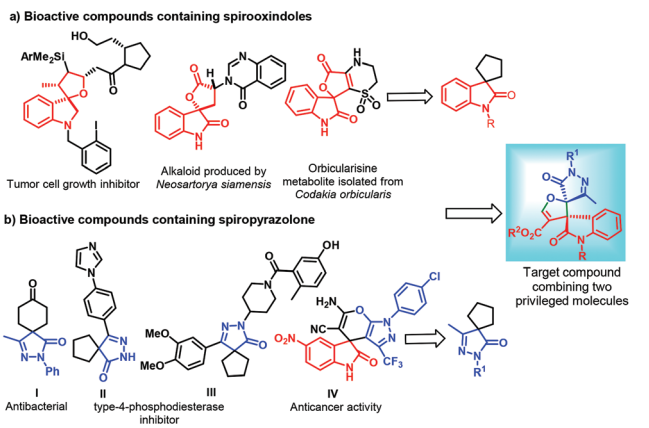

Fig. 1 Natural products containing the spiro-scaffold and precursors to access spirooxindole dihydrofuran pyrazolones.

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†Electronic supplementary information (ESI) available. CCDC 1967741. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob00007h

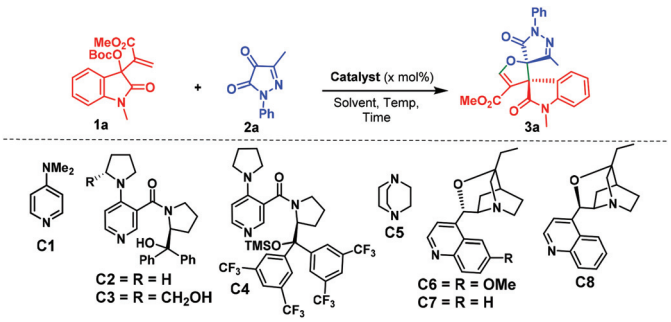
taining both oxindole and pyrazolone scaffolds shows anticancer activity (Fig. 1b).[9d]

As a consequence, great efforts have been devoted to the diastereoselective and enantioselective construction of the spiropyrazolone framework in the last decade.[10] However, the number of reports on the catalytic enantioselective synthesis of bis-spirocyclic compounds containing pyrazolone and oxindole scaffolds are very limited in the literature.[11] Thus, the development of a highly efficient strategy for the construction of structurally diverse spirooxindole fused pyrazolone scaffolds in an enantiomerically pure form is highly desirable (Fig. 1).

Recently, the [3 + 2] cycloaddition reaction of Morita–Baylis–Hillman carbonate (MBH) has emerged as an easy and powerful strategy for building multi-functionalized spirocarbo-/spirohetero-cyclic compounds.[12] In this realm, isatin derived MBH adducts have been successfully employed as three carbon synthons in different annulation reactions for the construction of five membered fused carbo/hetero cyclic spirooxindole molecules.[13] Similarly, pyrazolone 4,5-dione derivatives have been employed for various organocatalytic transformations in recent years.[14]

However, interestingly the cycloaddition of pyrazolone 4,5-dione at the electrophilic C-4 position has not been reported to date. In this context, we envisioned that enantiomerically enriched spirooxindole dihydrofuran fused pyrazolone compounds can be achieved by the organocatalytic asymmetric [3 + 2] cycloaddition reaction. Herein, we wish to report a chiral Lewis base catalyzed [3 + 2] cycloaddition reaction of isatin derived MBH carbonates with pyrazolone 4,5-diones for the construction of biologically relevant novel spirooxindole dihydrofuran pyrazolone derivatives containing two vicinal quaternary spirocenters.

Table 1 Optimization of the reaction conditions[a,b,c,d,e,f]



Entry	Cat.	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	C1	CH_2Cl_2	rt	2	95	>20 : 1	—
2	C2	CH_2Cl_2	rt	12	95	>20 : 1	36
3	C3	CH_2Cl_2	rt	12	88	>20 : 1	42
4	C4	CH_2Cl_2	rt	12	75	>20 : 1	40
5	C3	CH_2Cl_2	−20	16	86	>20 : 1	40
6	C5	CH_2Cl_2	rt	12	62	>20 : 1	—
7	C6	CH_2Cl_2	rt	30	58	>20 : 1	70
8	C7	CH_2Cl_2	rt	30	50	>20 : 1	30
9	C8	CH_2Cl_2	rt	30	48	>20 : 1	20
10	C6	CH_2Cl_2	0	30	60	>20 : 1	79
11	C6	CH_2Cl_2	−20	36	66	>20 : 1	89
12	C6	CH_2Cl_2	−40	72	60	>20 : 1	95
13	C6	Toluene	−20	30	58	>20 : 1	86
14	C6	$CHCl_3$	−20	36	52	>20 : 1	75
15	C6	CH_3CN	−20	24	60	>20 : 1	78
16	C6	THF	−20	20	75	>20 : 1	93
17[e]	C6	THF	−20	50	58	>20 : 1	90
18[f]	C6	THF	−20	72	50	>20 : 1	84

[a] Reaction conditions: Unless otherwise noted, the reactions were carried out with **1a** (0.15 mmol, 50 mg), **2a** (0.15 mmol, 22 mg), Cat. (20 mol%) in 1.0 mL of solvent at a specified temperature for the specified time. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess of the major diastereoisomer was determined by HPLC using the chiral stationary phase. [e] 15 mol% **C6**. [f] 10 mol% **C6**.

Results and discussion

In order to validate the hypothesis, initially we performed a model reaction between isatin derived MBH carbonate **1a** and pyrazolone 4,5-dione **2a** in the presence of the catalyst 4-dimethyl amino pyridine **C1** (20 mol%) (DMAP) in dichloromethane (DCM) at room temperature. To our delight, the reaction was completed within 2 h to furnish the corresponding [3 + 2] cycloaddition product **3a** in excellent yield with excellent diastereoselectivity (Table 1, entry 1). Inspired by this initial result we turned our attention to achieve an enantioselective version of this protocol. In this regard, we synthesized and screened different chiral DMAP based organocatalysts for the desired transformation. We observed that the reactions performed in the presence of catalysts **C2**, **C3** and **C4** at room temperature proceeded smoothly to afford the corresponding [3 + 2] annulation product **3a** in good to excellent yield with very high diastereoselectivity; however, the enantiomeric excess was found to be poor (Table 1, entries 2–4). Further lowering of the reaction temperature (−20 °C) did not have any significant change in the enantioselectivity (Table 1, entry 5). We surmised that the lack of enantioselectivity was probably due to the insufficient spatial interaction between the chiral DMAP derived organocatalyst with either the MBH carbonate or with pyrazolone 4,5-dione. In order to validate this and to establish better stereointeraction, we planned to explore quinine based organocatalysts. Initially, we examined the racemic reaction using 20 mol% of 1,4-diazabicyclo[2.2.2] octane (DABCO) **C5** as a catalyst in DCM at room temperature.

Gratifyingly, the expected [3 + 2] cycloaddition product **3a** was formed in moderate yield with very high diastereoselectivity (Table 1, entry 6). Encouraged by this initial result, we screened different quinine based catalysts β-isoquinidine **C6**, β-isocinchonine **C7** and α-isocinchonidine **C8** to optimize the reaction. The [3 + 2] annulation reaction in the presence of catalyst **C6** proceeded smoothly to afford the desired product **3a** in moderate yield with good enantiomeric excess (Table 1, entry 7), while we observed that the catalysts **C7** and **C8** proved to be not advantageous for the desired transformation (Table 1, entries 8 and 9). In order to investigate the catalytic efficiency, we further screened some more catalysts containing free hydroxyl group and a bi-functional thiourea catalyst (see

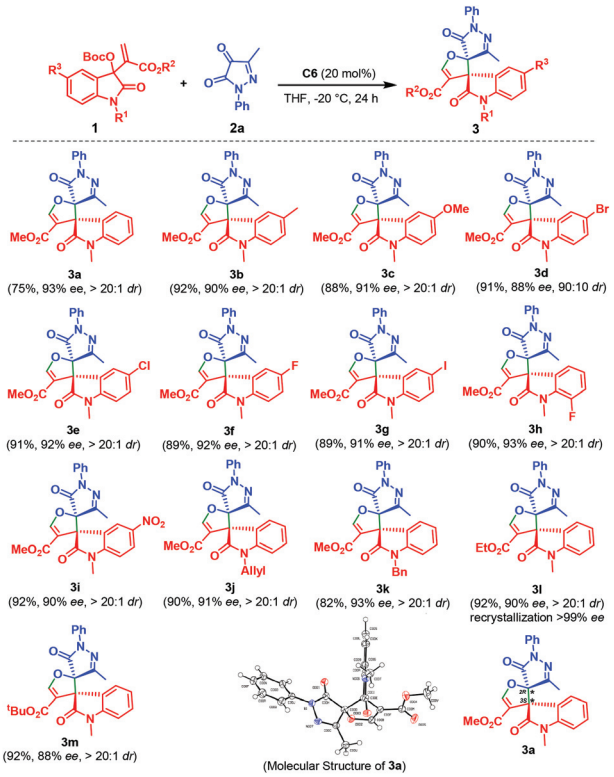
Appendix-I, page S3, ESI†). However, the reactions did not proceed in the presence of any of these catalysts.

Though the catalyst **C6** was found to be satisfactory, further optimization was needed to enhance the enantioselectivity. After various attempts, we planned to lower the reaction temperature as we had obtained good enantioselectivity at room temperature with catalyst **C6**. The reaction at 0 °C resulted in a marginal increase in the yield and enantioselectivity of **3a** (Table 1, entry 10). It is very important to note that further lowering the reaction temperature to −20 °C afforded the corresponding [3 + 2] annulation product **3a** in good yield (66% yield) with very high diastereoselectivity (>20 : 1 dr) and enantioselectivity (>89% ee) (Table 1, entry 11). However, we observed that further reduction in the reaction temperature (−40 °C) proved to be not beneficial as the reaction proceeded sluggishly (Table 1, entry 12). Subsequently, we examined the effects of various solvents such as toluene, $CHCl_3$, acetonitrile and THF to achieve better selectivity and yield (Table 1, entries 13–16). Based on our observation THF was found to be the optimal solvent for the desired transformation to afford the compound **3a** in very good yield with high enantioselectivity (Table 1, entry 16). Later, in order to evaluate the efficiency of the catalyst over the desired transformation, we further lowered the catalyst (**C6**) loading (15 to 10 mol%). This resulted in a significant reduction of the yield **3a** with a marginal reduction in enantioselectivity (Table 1, entries 17 and 18). Based on exhaustive screening, isatin derived MBH carbonate **1a** (1 equiv.), pyrazolone 4,5-dione (1 equiv.) and β-isoquinidine **C6** (20 mol%) in THF at −20 °C proved to be the optimal reaction conditions for the desired [3 + 2] cyclization.

Having obtained the optimum reaction conditions, we then explored the substrate scope for the synthesis of novel spirooxindole dihydrofuran pyrazolone derivatives *via* asymmetric [3 + 2] cycloaddition. To begin with we synthesized various isatin based MBH carbonates (**1a–1m**) and substituted pyrazolone 4,5-diones (**2a–2f**).[14]

Having synthesized different substrates we investigated the substrate scope of various MBH carbonates (**1a–1m**) with pyrazolone 4,5-dione **2a** under the optimized reaction conditions. We observed that all the MBH carbonates (**1a–1m**) reacted smoothly with **2a** to afford the corresponding spirooxindole dihydrofuran pyrazolones (**3a–3m**) in excellent yields (up to 96%) with excellent diastereoselectivity and very high enantioselectivity (>20 : 1 dr, up to 92% ee; see Scheme 1).

We observed that, the electron-donating (CH_3, OCH_3) as well as electron-withdrawing (Br, Cl, F, I, NO_2) substituents at different positions on the aryl ring of MBH carbonates were compatible under the optimum reaction conditions. Also, *N*-protected allyl and benzyl groups on MBH carbonates reacted smoothly to furnish the spirooxindole dihydofuran pyrazolones in excellent yields with high enantioselectivity and diastereoselectivity (Scheme 1). Moreover, different ester-substituted Morita–Baylis–Hillman carbonates underwent the [3 + 2] annulation reaction easily to give the corresponding products (**3l**, **3m**) in excellent yields with high stereoselectivity



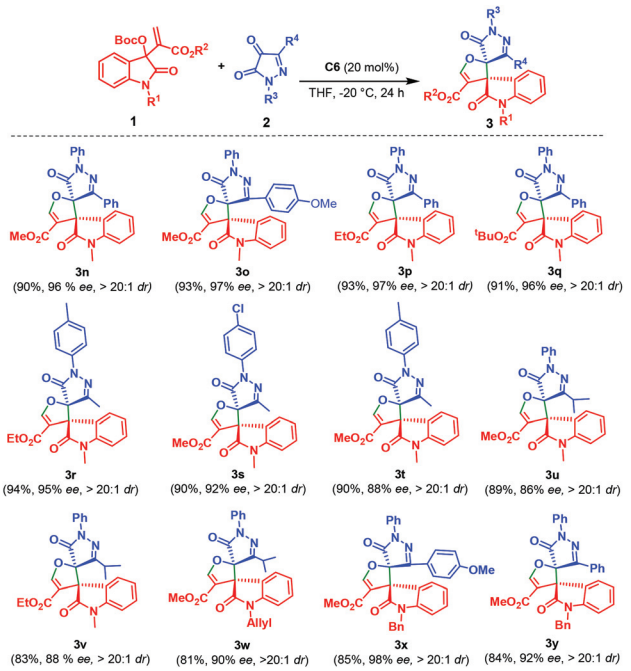
Scheme 1 Substrate scope for isatin derived MBH-carbonates.[a–d] Reaction conditions: [a]Unless otherwise mentioned, all the reactions were carried out with **1** (1 equiv.), **2** (1 equiv.), Cat. **C6** (20 mol%) in 1.0 mL of solvent at a specified temperature for the specified time. [b]Isolated yield after column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR. [d]Enantiomeric excess was determined by HPLC using the chiral stationary phase.

(Scheme 1). Very importantly, we observed that recrystallization further enhances the optical purity of the product as the recrystallization of compound **3l** enhanced the enantioselectivity from 90% ee to >99% ee (Scheme 1).

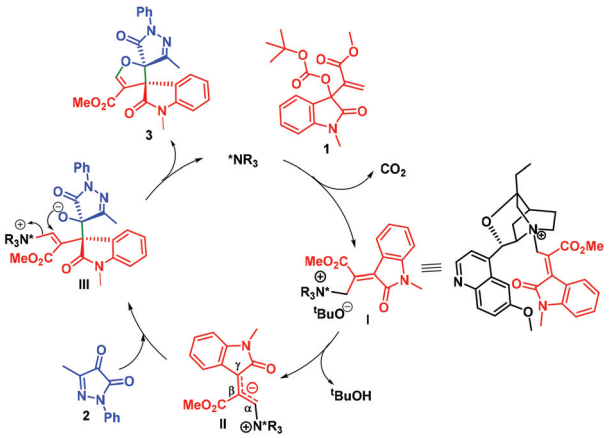
Later, we investigated the substrate scope of various pyrazolone 4,5-diones (**2b–2f**) with a few MBH carbonates (**1a**, **1j**, **1k**, **1l**, **1m**) under the standard optimum reaction conditions (Scheme 2).

Gratifyingly, the reactions proceeded smoothly to afford the corresponding [3 + 2] annulation products **3n–3y** in very good to excellent yields (88–94%) with very high diastereoselectivity (>20 : 1 dr) and good to excellent enantioselectivity (88–98% ee, Scheme 2).

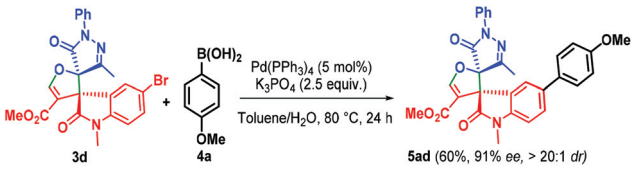
It is very important to note that the reactions of C-3 aryl substituted pyrazolone 4,5-diones (**2b** and **2c**) proceeded smoothly to afford the corresponding desired spirooxindole dihydrofuran pyrazolones (**3n**, **3o**, **3p** and **3q**) in excellent yields (up to 93%) with very high diastereoselectivity (>20 : 1 dr) and enantioselectivity (up to 97% ee), while the reaction of 3-isopropyl-1-phenyl-1*H*-pyrazole-4,5-dione **2f** with MBH carbonates (**1a**, **1j**, **1l**) afforded the corresponding products (**3u**, **3v**, **3w**) in very good yields (up to 90%) with very good stereoselectivity (>20 : 1 dr, up to 88% ee). It is significant to note



Scheme 2 Substrate scope for pyrazolone 4,5-diones.[a–d] Reaction conditions: [a]Unless otherwise mentioned, all the reactions were carried out with **1** (1 equiv.), **2** (1 equiv.), Cat. **C6** (20 mol%) in 1.0 mL of solvent at a specified temperature for the specified time. [b]Isolated yield after column chromatography. [c]Diastereomeric ratio was determined by ^{1}H NMR. [d]Enantiomeric excess was determined by HPLC using the chiral stationary phase.



Scheme 3 Proposed catalytic cycle for the asymmetric [3 + 2] cycloaddition reaction.



Scheme 4 Application-Suzuki coupling reaction.

that the aryl moiety substituted at the C-3 position of pyrazolone 4,5-diones afforded the desired products in higher stereoselectivity in comparison with the aliphatic group substituted at the C-3 position. Our repeated attempts to synthesize *N*-alkyl pyrazolone 4,5-dione derivatives were unsuccessful. The molecular structure of compound **3a** was established unambiguously using single-crystal X-ray diffraction analysis and it was established as 2*R*,3*S* (Scheme 1).[15]

Based on previous literature reports[12,13] and our experimental observation the plausible catalytic cycle for the asymmetric cycloaddition reaction is depicted in Scheme 3.

Initially, the catalytic cycle is initiated by the nucleophilic attack of the chiral tertiary amine catalyst on **1** to form the corresponding quaternary ammonium salt **I** by liberating carbon dioxide and *tert*-butoxide. This intermediate **I** further reacts with the *in situ* generated *tert*-butoxide to form a reactive allylic nitrogen ylide **II** intermediate. Then the C-4 position of pyrazolone 4,5-dione **2** is attacked by the intermediate **II** (*via* γ-position) to give the corresponding intermediate **III**. Subsequently the intermediate **III** undergoes intramolecular cyclization to form compound **3** and regenerates the catalyst to complete the catalytic cycle.

In order to demonstrate the synthetic potential of this protocol, Suzuki coupling was performed on compound **3d** (Scheme 4). The reaction of methoxyphenyl boronic acid **4a** with **3d** in the presence of $Pd(PPh_3)_4$ and K_3PO_4 at 80 °C furnished the corresponding product **5ad** in high enantioselectivity and diastereoselectivity (91% ee, >20 : 1).

Conclusions

In summary, we have developed a highly diastereoselective and enantioselective [3 + 2]-annulation between isatin-derived Morita–Baylis–Hillman adducts and pyrazolone 4,5-diones to access enantiopure spirooxindole dihydrofuran fused pyrazolones. In the presence of a tertiary amine catalyst, a wide range of highly functionalized spirooxindole dihydrofuran fused pyrazolones containing two vicinal spiro-quaternary chiral centers were successfully obtained with excellent stereoselectivity.

Conflicts of interest

There are no conflicts to declare.

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An easy and practical approach to access multifunctional cylcopentadiene- and cyclopentene-spirooxindoles *via* [3 + 2] annulation†

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A highly regioselective [3 + 2] annulation of Morita–Baylis–Hillman (MBH) carbonates of isatin with aurone/thioaurone is developed. Spiroheterocycles such as spirooxindole cyclopentadiene and spirooxindole fused hydroxy cyclopentene derivatives are constructed in one pot by exploring the reactivity of Lewis bases. Combined experimental and density functional theory (DFT) calculations offered an insight into the reaction mechanism.

Introduction

The construction of multifunctional spirocyclic frameworks is of great interest in the field of asymmetric synthesis.[1] More importantly, spirooxindole scaffolds have received great attention, due to their presence in numerous natural products and pharmaceutical compounds.[2,3] Their unique three-dimensional structure and potential pharmacological significance has paved the way for the development of effective methods for the synthesis of molecules containing spiro-carbocyclic and spiro-heterocyclic oxindole scaffolds.[4] Among the carbocyclic oxindoles, the spirocyclopentane oxindole skeleton exists in a variety of naturally occurring bioactive compounds such as notoamide A, (−)-paraherquamide A and cyclopiamine B (Fig. 1).[5] Due to their biological significance, enormous efforts have been focused on the racemic and enantioselective synthesis of the spirocyclic architecture.[4] Though there are many elegant reports on the synthesis of spirocarbocylic scaffolds, the synthesis of densely functionalized spirocyclopentadiene oxindole derivatives is rare in the literature.[6] In 2011, Chen and co-workers reported the asymmetric synthesis of spirocyclic 2-oxindoles incorporating a cyclopentadiene motif using Morita–Baylis–Hillman carbonates of isatins with propargyl sulfones under β-ICD catalysis.[6a] Later, the same group developed the chiral tertiary-amine catalyzed enantioselective [3 + 2] annulation of Morita–Baylis–Hillman carbonates of isatins with nitroolefins to construct spirooxindole cyclopentadiene.[6b] In a recent article, Cui and Chen reported the enantioselective synthesis of spiro-cyclopentene/cyclopentadiene-oxindoles through an asymmetric [3 + 2] cycloaddition of isatin-derived MBH carbonates and β,γ-unsaturated α-keto esters.[6c]

Recently, isatin based Morita–Baylis–Hillman (MBH) carbonates have emerged as versatile and useful building blocks for the synthesis of highly functionalized spirocyclic oxindole architectures.[7] The basic approach in this process involved the nucleophilic attack of a Lewis base (tertiary amine or phosphine) on MBH carbonates of isatin to generate a highly reactive 1,3-dipole namely a zwitterionic allylic ylide *in situ*. This allylic ylide further undergoes diverse annulation reactions

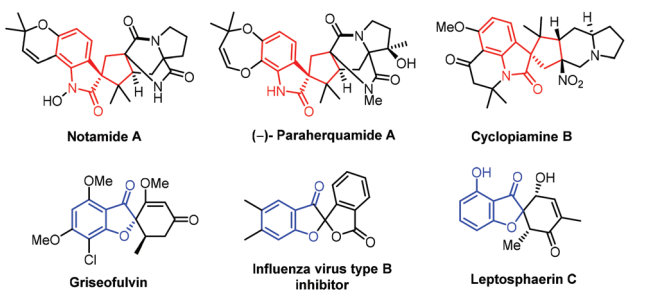

Fig. 1 Natural products containing spirooxindole and spirocyclic benzofuranones.

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with different electrophilic substrates to give structurally unique spirooxindole derivatives.[8]

Spirocyclic benzofuranones are privileged structural motifs found in natural and synthetic molecules that have remarkable biological properties (Fig. 1).[9] Griseofulvin is an orally active antifungal medication used to treat different types of dermatophytoses.[9a] The spiro[benzofuran-2,1′-isobenzofuran]-3,3-dione is active against type B influenza virus.[9b] In addition, the spirocyclohexane benzofuran-3-one core belongs to the polyketide leptosphaerin C class, exhibiting antifungal activity.[9c] Surprisingly, in spite of high biological significance, the number of reports on the synthesis of spirocyclic benzofuranones are limited in the literature.[10]

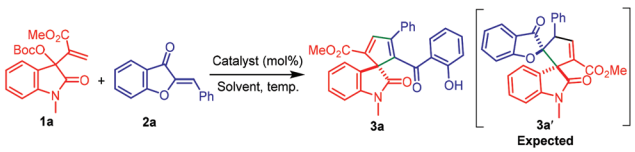
Therefore, the development of an effective and practical method is in high demand. The key precursor for the preparation of spirocyclic benzofuranones is 2-benzylidenebenzofuran-3(2*H*)-one (aurone) that is also present in a number of natural and synthetic products.[11] The class of aurones are easy to prepare and their derivatives have been employed in various cycloaddition reactions to construct complex spiroheterocycles.[12] In 2014, Zhao and co-workers disclosed the NHC catalyzed asymmetric [3 + 2] annulation of aurone and α,β-unsaturated aldehydes to access spiroheterocycles.[12a] Likewise, other research groups have explored similar approaches of [3 + 2] and [3 + 4] cycloaddition reactions of aurones utilizing asymmetric NHC catalysis.[12b,c] Later, Li and Cheng reported the enantioselective [4 + 2] cycloaddition of allenoates with 2-olefinic benzofuran-3-ones in the presence of a chiral Lewis base catalyst.[12d] Recently, Lan, Ullah and Lu developed the regiodivergent [3 + 2] annulation of aurones and allenoates under chiral dipeptide phosphine catalysis.[12e] Despite these recent advances in annulation reactions, the cycloaddition of aurones with MBH carbonates of isatin has rarely been explored.[12f] Similarly, thioaurone, the sulphur analogue of aurone, is also utilized as an excellent electrophilic substrate for various cycloaddition reactions.[13]

In this context, we envisioned that aurones and thioaurones could be employed as suitable C2 synthons in [3 + 2] annulation with MBH carbonates of isatin to construct structurally diverse and multi-functionalized spiro fused carbopentacyclic scaffolds using a suitable Lewis base organocatalyst. Herein, we report the one pot synthesis of spirooxindole cyclopentadiene and spirooxindole fused hydroxy cyclopentene derivatives in a practical manner.

Results and discussion

In order to validate the hypothesis, we commenced with the reaction of MBH carbonate **1a** and aurone **2a** as model substrates in the presence of DMAP (20 mol%) in dichloromethane at room temperature. Interestingly, the reaction afforded the unexpected spiro cyclopentadiene oxindole **3a** in 65% yield and the anticipated compound **3a′** was not obtained (Table 1, entry 1). A literature survey revealed that the synthesis of the spirocyclopentadiene scaffold has been rarely attempted.[6] In this regard, we planned further optimization of reaction conditions. Several attempts of enantioselective synthesis of spiro cyclopentadiene oxindole **3a** using **1a** and **2a** in the presence of a chiral DMAP derived catalyst did not work under various reaction conditions (see the ESI, Appendix I, page S5†). Later, we switched our attention to screen chiral quinine based organocatalysts. Unfortunately, even these catalysts did not afford the desired product (see the ESI, Appendix I, page S5†). After exhaustive screening with various chiral catalysts and reaction conditions we focussed our attention further on optimizing the reaction conditions for the racemic synthesis of spirooxindole cyclopentadiene **3a**. The reaction of **1a** and **2a** in the presence of PPh_3 as a catalyst did not afford the desired product **3a** even after prolonged reaction time (Table 1, entry 2). Later, we turned our attention towards tertiary amine catalysts for the desired transformation. The independent reactions of **1a** and **2a** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the spirooxindole cyclopentadiene **3a** in 40% and 55% yields, respectively (Table 1, entries 3 and 4). Based on the initial results, DMAP proved to be a suitable catalyst for the desired transformation. In order to optimize the reaction conditions further, we screened different solvents such as chloroform, toluene, ethyl acetate, THF and acetonitrile in the presence of 20 mol% of DMAP (Table 1, entries 5–9). Among all, acetonitrile proved to be the optimum solvent by providing the desired product **3a** in 76% yield (Table 1, entry 9). Further reduction in catalyst loading (15 mol% DMAP) drastically lowered the yield of spirooxindole **3a** (40%, Table 1, entry 10). We observed that lowering the reaction temperature to 0 °C significantly lowered the yield of **3a** (30%, Table 1, entry 11). Based on the screening, MBH carbonate **1a** (1 equiv.), aurone (1.2 equiv.) and DMAP (20 mol%) in acetonitrile proved to be

Table 1 Optimization of the reaction conditions[a,b,c]



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1	DMAP (20)	CH_2Cl_2	24	65
2	PPh_3 (20)	CH_2Cl_2	48	NR
3	DABCO (20)	CH_2Cl_2	24	40
4	DBU (20)	CH_2Cl_2	24	55
5	DMAP (20)	$CHCl_3$	24	68
6	DMAP (20)	Toluene	24	70
7	DMAP (20)	Ethyl acetate	24	72
8	DMAP (20)	THF	24	68
9	DMAP (20)	CH_3CN	24	76
10	DMAP (15)	CH_3CN	24	40
11[c]	DMAP (20)	CH_3CN	24	30

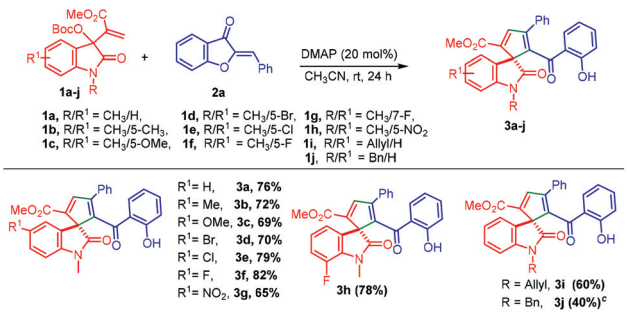
[a] Reaction conditions: the reactions were carried out with **1a** (0.115 mmol, 40 mg), **2a** (0.138 mmol, 31 mg), and Cat. (20 mol%) in 2.0 mL of solvent at room temperature for the specified time. [b] Isolated yield after purification by column chromatography. [c] Reaction at 0 °C.

the optimum reaction conditions for [3 + 2] annulation followed by ring opening to access the desired product **3a**.

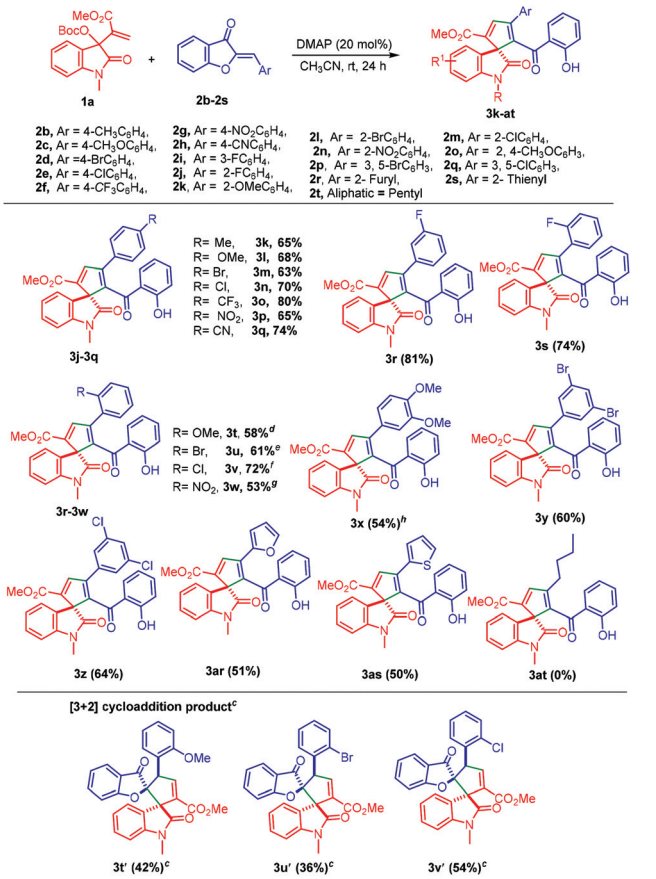
After establishing the optimum reaction conditions, we explored the substrate scope for the synthesis of new spirooxindole cyclopentadiene derivatives *via* [3 + 2] cycloaddition. To begin with, we synthesized various isatin based MBH carbonates[8g] (**1a–1j**) and substituted aurones[10g] (**2a–2t**). Having obtained different substrates, we further investigated the substrate scope of various MBH carbonates (**1a–1j**) with aurone **2a** under the optimized reaction conditions. We observed that all the MBH carbonates (**1a–1j**) reacted smoothly with aurone **2a** to furnish the corresponding spirooxindole cyclopentadienes (**3a–3j**) in very good yields (up to 82%, see Scheme 1). We observed that all the reactions proceeded smoothly irrespective of the electron-donating (CH_3 and OCH_3) and electron-deactivating/withdrawing (Br, Cl, F, and NO_2) nature of substituents at different positions on the aryl ring of MBH carbonates. Likewise, *N*-allyl and *N*-benzyl protected MBH carbonates (**1i** and **1j**) reacted smoothly to furnish the spirooxindole cyclopentadienes **3i** and **3j** in 60% and 40% yield, respectively (Scheme 1). Furthermore, the molecular structure of compound **3a** was established unambiguously using single-crystal X-ray diffraction analysis.[18]

After the initial success, we further investigated the substrate scope of various aurones (**2b–2s**) with MBH carbonate **1a** under the standard reaction conditions (Scheme 2). Gratifyingly, all the reactions proceeded smoothly to afford the corresponding [3 + 2] annulation products **3j–3at** in moderate to good yields (50–81%, Scheme 2). It is important to note that both electron donating (CH_3 and OCH_3) and electron deactivating/withdrawing (F, Cl, Br, CF_3, CN, and NO_2) groups at the *meta* and *para*-positions of aurones were found to be suitable substrates for the desired transformation to afford **3k–3r** in moderate to good yields (63–81%, Scheme 2). To our surprise, *ortho*-substituted aurones (**2k–2m**) furnished the bis-spirocyclic compounds **3t'–3v'** (with the benzofuran-3(2*H*)-one ring intact) in moderate yields (up to 54%) under optimized reaction conditions (Scheme 2). Also, the molecular structure of compound **3v'** was established unambiguously using single-crystal X-ray diffraction analysis.[19] Later, we observed that reaction at elevated temperature (up to 70 °C) delivered the spirocyclopentadienes **3t–3w** (benzofuran-3(2*H*)-one ring opened products) in moderate to good yields (up to 72%). However, the substrate containing a relatively less bulky and more electron deactivating fluoro group (**2i**) at the *ortho* position of aurone furnished the spirooxindole cyclopentadiene product **3s** (benzofuran-3(2*H*)-one ring opened product) in good yield at room temperature (74%, Scheme 2), while the disubstituted aurones reacted smoothly to afford the products (**3x–3z**) in moderate yields (up to 64%, Scheme 2). Moreover, the substrates containing heteroaryl moieties such as furyl and thienyl moieties gave the corresponding products **3ar** and **3as** in satisfactory yields (51% and 50%, Scheme 2). However, the alkyl substituted derivative **2t** did not work under the optimized reaction conditions (Scheme 2).

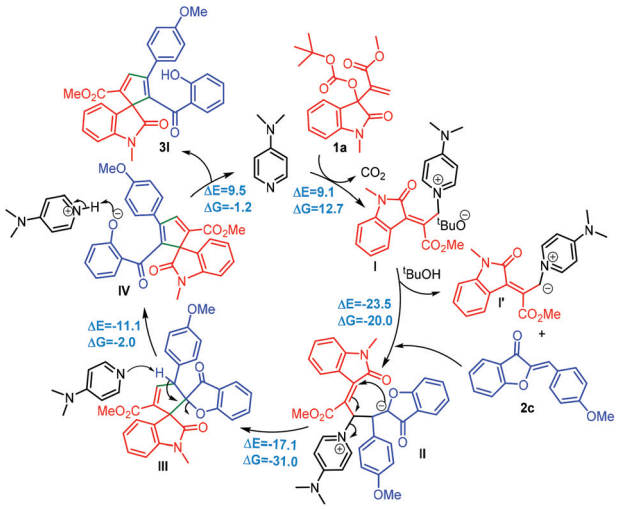
Based on the experimental results, previous literature reports[7,8] and quantum chemical calculations that we have carried out, the plausible catalytic cycle is depicted in



Scheme 1 Substrate scope for isatin derived MBH-carbonates. Reaction conditions: the reactions were carried out with MBH carbonate of isatin **1** (0.115 mmol), aurone **2a** (0.138 mmol), and DMAP (20 mol%) in 2.0 mL of MeCN at room temperature; Isolated yield after column chromatography. 50 mol% DMAP.



Scheme 2 Substrate scope of aurones. Reaction conditions: the reactions were carried out with MBH carbonate of isatin **1a** (0.115 mmol), aurone **2** (0.138 mmol), and DMAP (20 mol%) in 2.0 mL of MeCN at room temperature; isolated yield after column chromatography; spirocyclopentene compounds (benzofuran-3(2*H*)-one ring intact) formed at room temperature; 20 mol% DMAP at 50 °C or 100 mol% DMAP; 100 mol% DMAP at 70 °C; 50 mol% DMAP at 70 °C; 30 mol% DMAP at 70 °C. DMAP: 100 mol%.



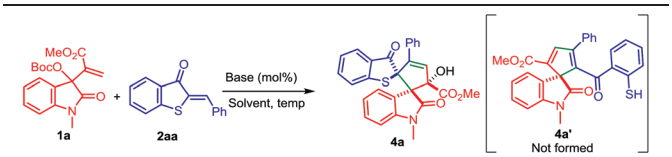
Scheme 3 Proposed reaction mechanism for the formation of spirooxindole cyclopentadiene.

Scheme 3. Computational calculations have been performed using density functional theory (DFT) at the PBE/TZVP level of theory. Based on these findings it is proposed that initially, the nucleophilic DMAP attacks on the MBH carbonate **1a** to form the quaternary ammonium salt **I** with the evolution of carbon dioxide and *tert*-butoxide. This process is found to be thermodynamically unstable (ΔG = 12.7 kcal mol^{-1}). The *in situ* generated *tert*-butoxide in turn abstracts a proton from the quaternary ammonium salt **I** to give an allylic nitrogen ylide **I′**. Subsequently, ylide **I′** reacts with the aurone **2c** to generate an intermediate **II** (reaction free energy ΔG = −20.0 kcal mol^{-1}). This intermediate cyclizes *via* a highly favourable (ΔG = −31.0 kcal mol^{-1}) intramolecular Michael addition to afford the corresponding intermediate **III** by eliminating DMAP. Furthermore, DMAP abstracts the proton from intermediate **III** leading to the formation of the phenoxide intermediate **IV** *via* ring opening. Finally, this intermediate furnishes the desired compound **3l** *via* protonation and regeneration of DMAP to complete the catalytic cycle.

Earlier we had observed that unlike *para*-substituted derivatives, *ortho*-substituted aurones (MeO, Br, and Cl) required an elevated temperature to form the corresponding spirooxindole cyclopentadienes **3t–3v**. In order to understand this observation, we also calculated the transition states and thus the barriers, for both the cases from intermediate **III** to intermediate **IV** (see the ESI, Fig. 4a and 4b, page S13, 14†). It was observed that the *ortho*-substituted aurone has a 1.2 kcal mol^{-1} higher energy barrier than the *para* derivative. Furthermore, the turnover frequency (TOF) values indicate that the mechanism with the *para*-substituted aurone is approximately 6.4 times more efficient than that with the *ortho*-substituted aurone (see the ESI, Appendix II, page S11†).

Thioaurone, 2-arylidenebenzo[*b*]thiophen-3(2*H*)-one, is a sulphur analogue of aurone and its derivatives have been used in photoswitchable materials[14] and dyes,[15] and also thioaurones show cytotoxic activity against the HeLa cell line.[16] In addition, thioaurones have been effectively used as Michael acceptors in different cycloaddition reactions.[13] Interestingly, the application of thioaurone in Morita–Baylis–Hillman chemistry has not been explored yet. Also, the synthesis of sulfur analogues of bioactive spirocyclic aurones may be of great interest due to their biological relevance. In this regard, we became interested in exploring the synthesis of thioaurones (sulfur analogues of aurones) *via* [3 + 2] annulation reaction. In order to explore the synthesis of spirocyclic benzothiofuranones, we prepared a series of (*Z*)-2-benzylidenebenzo[*b*]thiophen-3(2*H*)-ones (**2aa–2ah**) following a reported procedure.[20] Initial attempts to synthesize the desired spirocyclic benzothiofuranones (**4a′**) were unsuccessful under the optimized reaction conditions explored for the synthesis of spirocyclic cyclopentadiene derivatives **3** (Table 2, entry 1). To our dismay, we did not observe any desired product (**4a′**) formation with the increase in DMAP loading (50 mol%) even after prolonged reaction time (Table 2, entry 2). Interestingly, the stoichiometric amount of DMAP (100 mol%) furnished an unanticipated spirooxindole fused benzo[*b*]thiophen-3(2*H*)-one **4a** in 30% yield with high diastereoselectivity (>20 : 1) and we did not observe the target compound **4a′** (Table 2, entry 3). The bis-spiro compound **4a** with three contiguous chiral centres with a tertiary hydroxyl group is an unusual and complex scaffold to build from the synthesis point of view. Also, this non-natural and multifunctional bis-spirocyclic hybrid compound containing a useful skeleton such as cyclopentene, isatin and benzothiofuranone may be of greater biological significance. This result prompted us to take further interest in optimizing the reaction conditions. The reaction in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) gave the desired product **4a** in 10% yield (Table 2, entry 4).

Table 2 Optimization of the reaction conditions[a,b,c,d,e]

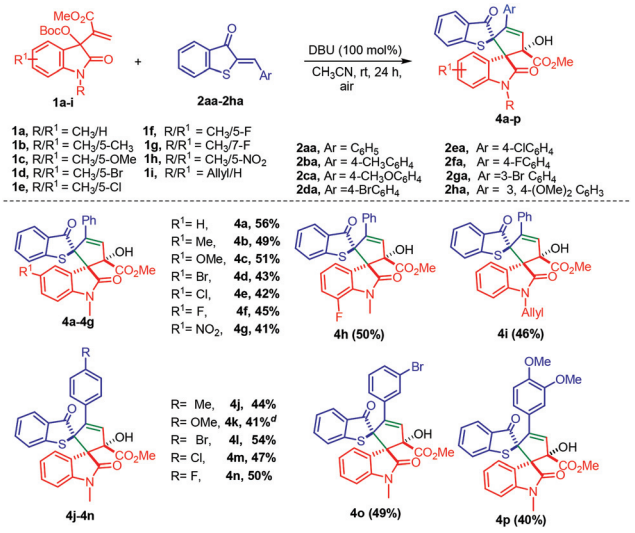


Entry	Base (mol%)	Solvent	Time (h)	dr[c]	Yield[b] (%)
1	DMAP (20)	CH_3CN	72	—	NR
2	DMAP (50)	CH_3CN	72	—	NR
3	DMAP (100)	CH_3CN	48	>20 : 1	30
4	DABCO (100)	CH_3CN	72	>20 : 1	10
5	DBU (100)	CH_3CN	24	>20 : 1	56
6	DBU (100)	$CHCl_3$	24	>20 : 1	40
7	DBU (100)	Toluene	24	>20 : 1	42
8	DBU (100)	THF	48	>20 : 1	20
9	DBU (100)	DMF	36	>20 : 1	50
10[d]	DBU (100)	CH_3CN	24	>20 : 1	52
11[e]	DBU (100)	CH_3CN	48	>20 : 1	20
12	DBU (50)	CH_3CN	72	>20 : 1	30

[a] Reaction conditions: the reactions were carried out with MBH carbonate **1a** (0.115 mmol), thioaurone **2aa** (0.138 mmol), and a base (0.115 mmol) in 2.0 mL of MeCN at room temperature. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR. [d] At 70 °C. [e] At 0 °C.

Gratifyingly, 1,8-diazabicyclo (5.4.0)undec-7-ene (DBU) in acetonitrile at room temperature afforded the desired spirooxindole **4a** in 56% yield (Table 2, entry 5). Among all the solvents screened acetonitrile proved to be the optimum solvent for the desired transformation (Table 2, entries 6–9). Further increase in the reaction temperature did not improve the yield of spirooxindole **4a** (Table 2, entry 10), while the lowering of the reaction temperature (0 °C) significantly reduced the yield of **4a** (20%, Table 2, entry 11). We observed that reduction in the loading of DBU (50 mol%) resulted in a lower yield of spirooxindole **4a** (Table 1, entry 12). Based on the screening, MBH carbonate **1a** (1 equiv.), thioaurone (1.2 equiv.) and DBU (100 mol%) in acetonitrile proved to be the optimum reaction conditions for [3 + 2] annulation to access spirooxindole fused benzo[*b*]thiophen-3(2*H*)-one **4a**.

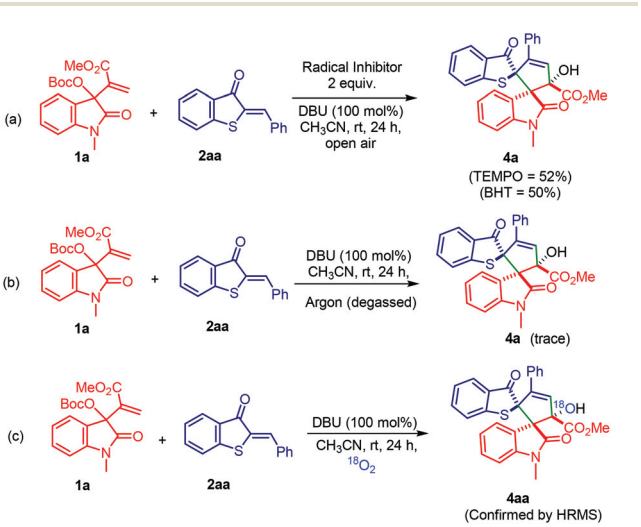
Having standardised the optimum reaction conditions, we explored the substrate scope for the generality of the protocol. The reaction of various MBH carbonates of isatin (**1a–1i**) with different thioaurones (**2aa–2ha**) afforded the corresponding [3 + 2] annulation-hydroxylation products (**4a–4i**) in moderate yields with high diastereoselectivity (up to 56%, >20 : 1, Scheme 4). We observed that, both electron-donating (CH_3, OCH_3) and electron deactivating/withdrawing (Br, Cl, F, and NO_2) substituents at different positions on the aryl ring of MBH carbonates did not have a significant effect on the yield and reaction time. However, the trend of an insignificant variation in the yields of **4a–4h** was probably due to the stereoelectronic effect of substituted functional groups. Likewise, *N*-allyl protected MBH carbonate **1i** reacted smoothly to furnish the corresponding spirooxindole fused benzo[*b*]thiophen-3(2*H*)-one **4i** in 46% yield (Scheme 4).



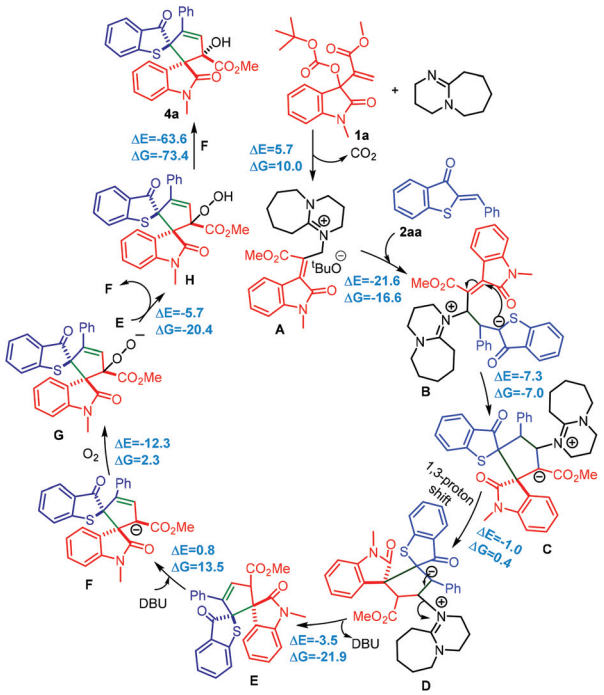
Scheme 4 Substrate scope of MBH carbonates and thioaurones. Reaction conditions: the reactions were carried out with MBH carbonate **1a** (0.115 mmol), thioaurone **2aa** (0.138 mmol), and DBU (0.115 mmol) in 2.0 mL of MeCN at room temperature. Isolated yield after column chromatography. Diastereomeric ratio >20 : 1 in all cases and determined by ^{1}H NMR. DBU: 2.0 equiv.

Later, we investigated the substrate scope of various thioaurones (**2ba–2ha**) with MBH carbonate **1a** under the standard reaction conditions (Scheme 4). Gratifyingly, all the reactions proceeded smoothly to afford the corresponding [3 + 2] annulation-hydroxylation products **4j–4p** in moderate yields (up to 54%, Scheme 4). Even the reaction of a thioaurone derivative with a 3,4-disubstituted aryl group with **1a** proceeded smoothly to furnish the desired product **4p** (Scheme 4). It is important to note that substrates containing electron-donating/-withdrawing groups at the *para* and *meta*-positions of the aryl moiety of thioaurones reacted smoothly, while the *ortho*-substituted and heteroaryl thioaurones did not react under the optimized reaction conditions. We observed that all the spirooxindole fused benzo[*b*]thiophen-3(2*H*)-ones (**4a–4p**) were obtained with high diastereoselectivity (>20 : 1 dr). Furthermore, the molecular structure of compound **4a** was established unambiguously using single-crystal X-ray diffraction analysis.[21] Based on analogy and other spectroscopic data, the structures of all other products were deduced.

Furthermore, we carried out control experiments to understand the plausible mechanistic pathway of [3 + 2] annulation-hydroxylation reaction (Scheme 5). The addition of the radical scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or butylated hydroxytoluene (BHT) under standard conditions did not inhibit the reaction and **4a** was obtained in 52% and 50% yield, respectively. These experimental results ruled out the involvement of a free-radical intermediate in this transformation. When we performed the reaction under an inert atmosphere, a trace amount of **4a** was obtained, thus supporting the essential requirement of molecular oxygen for this transformation. In order to gain further insight into the source of oxygen incorporation, we performed the labelling experiment using $^{18}O_2$. We observed the incorporation of labelled oxygen in the desired product **4aa**, thus supporting the essential role



Scheme 5 Control experiments.



Scheme 6 Proposed reaction mechanism for [3 + 2] annulation-hydroxylation.

of oxygen in the desired transformation (confirmed by HRMS, see the ESI, page S7†).

In accordance with previous reports[8] and based on our experimental results, and quantum chemical calculations (DFT-PBE/TZVP level of theory) a plausible mechanism is described in Scheme 6. The reaction is initiated by the nucleophilic attack of DBU on MBH carbonate **1a** to generate quaternary ammonium salt **A** with the liberation of CO_2 and *tert*-butoxide. As the intermediate **A** is relatively thermodynamically unstable (ΔG = 10 kcal mol^{-1}) it reacts with the *in situ* generated *tert*-butoxide to form an ylide. Then thioaurone **2aa** quickly reacts with the *in situ* generated ylide *via* favourable α-regioselective attack[22] to give intermediate **B** with a reaction free energy ΔG = −16.6 kcal mol^{-1}. Furthermore, the intermediate **B** undergoes intramolecular cyclization (ΔG = −7.0 kcal mol^{-1}) to form the spirocyclic intermediate **C**. Then this spirocyclic intermediate **C** undergoes a 1,3 proton shift to give the highly reactive intermediate **D**.[8c] This undergoes facile conversion to afford the corresponding spirocyclic intermediate **E** (ΔG = −21.9 kcal mol^{-1}; confirmed by HRMS, ESI, page S8†) by the elimination of DBU. Subsequently, the enolate intermediate **F** is formed during the course of reaction by the abstraction of an acidic proton by DBU.

The anionic intermediate **F** further reacts with oxygen (air) to give the peroxide anionic intermediate **G**, which in turn quickly abstracts the acidic proton (alpha to ester) from intermediate **E** to form the hydroperoxide intermediate **H** along with the generation of intermediate **F**. This reaction step proved to be highly facile as is evident from the reaction free energy value (ΔG = −20.4 kcal mol^{-1}). Finally, the enolate **F** attacks on the weak peroxide bond of a highly reactive intermediate **H** to furnish the final product **4a**.[17]

Conclusions

In summary, we have developed a protocol for the synthesis of cyclopentadiene- and cyclopentene-spirooxindole derivatives in a practical manner. We have successfully employed aurones and thioaurones as suitable C2 synthons in [3 + 2] annulation with MBH carbonates of isatin to construct structurally diverse and multi-functionalized spiro fused carbopentacyclic scaffolds using a suitable Lewis base. The structurally similar aurone and thioaurone showed different reactivities under different bases to afford spirooxindole fused cyclopentadiene and spirooxindole fused hydroxy cyclopentene derivatives, respectively. The experimental findings were further corroborated by DFT calculations to support the probable mechanism of the annulation reaction.

Conflicts of interest

There are no conflicts to declare.

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18 CCDC 2067873† contains the supplementary crystallographic data for compound **3a**.

19 CCDC 2067878† contains the supplementary crystallographic data for compound **3v′**.

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21 CCDC 2067874† contains the supplementary crystallographic data for compound **4a** and CCDC 2067877† contains the supplementary crystallographic data for compound **4c**.

22 We believe that the α-regioselective attack may be preferable over γ-regioselective attack to avoid the steric crowding thus leading to higher diastereoselectivity.

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Direct access to spirooxindole dihydropyrrole fused pyrazolones and bis-spiropyrazolone derivatives

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ABSTRACT

A highly regio- and diastereo-selective [3 + 2] annulation of Morita–Baylis–Hillman carbonates of isatins/pyrazolones with pyrazolone derived ketimines has been developed to access spiroheterocycles. The protocol worked effectively to construct spirooxindole dihydropyrrole fused pyrazolone and bis-spiropyrazolone dihydropyrrole derivatives bearing two vicinal quaternary spirocentres in good to excellent yields with very high diastereoselectivities under mild catalytic condition at room temperature. The protocol proved to be efficient with diverse MBH carbonates and ketimine derivatives. The method has successfully demonstrated the utility of DMAP as the commercially viable catalyst for this transformation.

Introduction

Over the years, tremendous efforts have been made to develop new therapeutic agents in modern drug discovery research. The modification of existing pharmacophores by merging two or more biologically active fragments gives an access to new scaffold known as a hybrid molecule [1]. The various hybrid molecules are being explored for their pharmacological properties using *in silico* molecular modelling. Some of the hybridization strategies have contributed to the development of hybrid molecules as new antimicrobials with an ability to overcome resistance [2a], multi-targeted agents for cancer [2b], Alzheimer's [2c] and Plasmodium elicited infections [2d]. The spiroheterocycles have drawn the attention of synthetic organic as well as medicinal chemists due to their biological significane [3]. Among the various spirocyclic compounds, the multi-functional spirooxindoles, spiropyrazolones and spirooxindole fused pyrazolones have gained the greater importance owing to their unique structural framework. A large number of natural products and synthetic products containing the spirocyclic scaffold are known to exhibit remarkable biological activities (Fig. 1) [4–6].

Over the last few years, enormous efforts have been made on the design and synthesis of these structurally diverse and valuable spirocyclic scaffolds in diastereoselective as well as enantioselective manner [7,8]. In 2013, Wang and co-workers have reported the very first organocatalytic Michael–cyclization cascade reaction between 3 and isothiocyanato oxindoles and unsaturated pyrazolones to construct spirooxindole fused pyrazolone compounds via enantioselective [3 + 2] cyclization using chiral tertiary amine derived thiourea catalyst (Scheme 1a) [9]. Subsequent year, Yuan and co-workers have reported a similar protocol to access spirooxindole fused pyrazolones under quinine catalysis [10]. Later, in 2015, Du and co-workers have disclosed the diastereoselective Michael/alkylation cascade reaction of 3-chlorooxindoles and arylidenepyrazolones to achieve the spiropyrazolone-cyclopropane-oxindole derivatives [11]. In 2018, Bao et al. have developed the organocatalytic asymmetric [3 + 2] cyclization for the synthesis of spirooxindole fused pyrazolones using isatin-derived ketimines and 4-isothiocyanato pyrazolones [12]. In 2019, Liu et al. have reported the organocatalytic double Michael tandem strategy for the synthesis of bis-spirocarbocyclic pyrazolones utilizing 3-substituted methyleneoxindole/methylene benzofuranone and bifunctional pyrazolone–chromones (Scheme 1b) [13]. Recently, Du (Scheme 1c) [14] Wang/Yan [15] and Zhong [16] research groups have employed the [3 + 2] annulation strategy to construct the spirooxindole fused spiropyrazonole derivatives. Very recently, our research group [17] has also developed the method for the synthesis of spirooxindole fused spiropyrazolone scaffolds under organocatalytic conditions.

Despite these recent advances in the synthesis of spirooxindole fused pyrazolone derivatives, interestingly, very few methods have been disclosed for the construction of scaffold embedded with three different moieties such as oxindole, dihydropyrrole and pyra-

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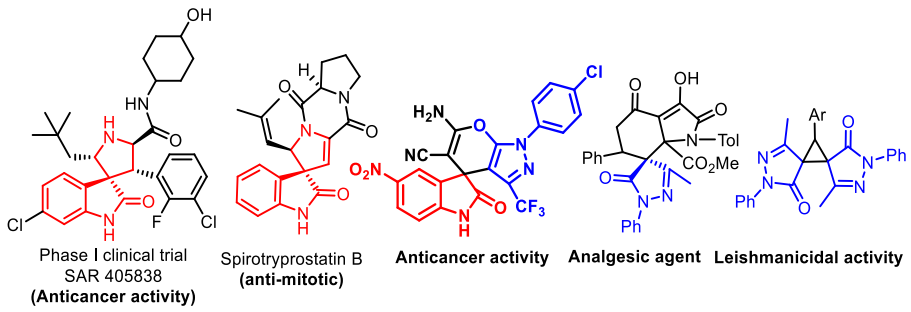
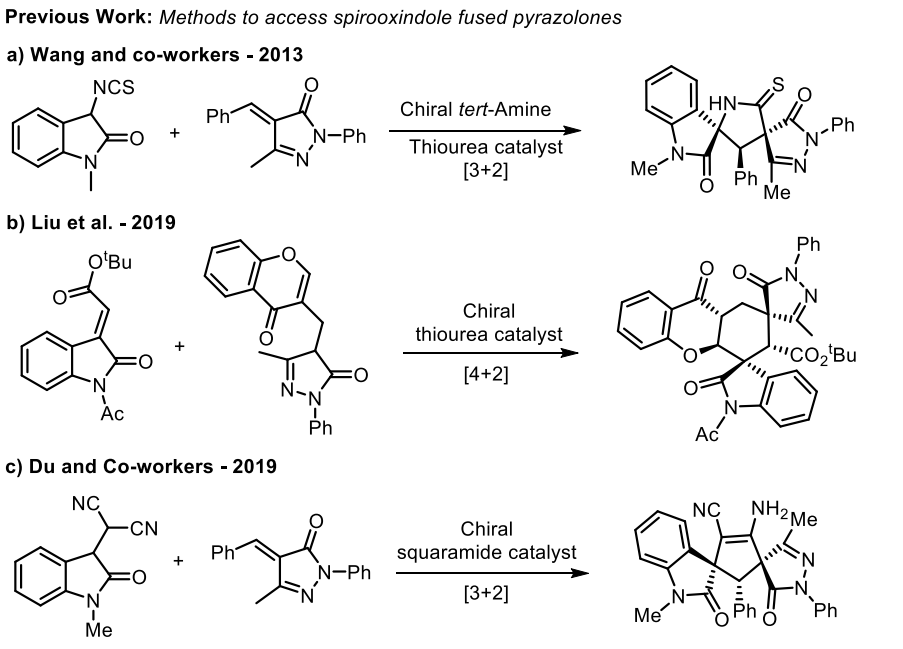


Figure 1. Representative examples of bioactive compounds with spirooxindole and spiropyrazolone scaffolds.



Scheme 1. Selected methods for the synthesis of spirooxindole fused pyrazolones.

zolone in a diastereoselective manner. The development of practical, catalytic and one-pot strategy to construct highly functionalized spirocyclic oxindoles and pyrazolones is highly challenging as well as desirable.

In recent years, pyrazolone derived ketimine has also emerged as a useful synthon/substrate in asymmetric synthesis to construct functionally diverse pyrazolone scaffolds [18]. In 2017, for the first time Enders and co-workers have designed and developed a new class of pyrazolinone ketimines that can serve as excellent electrophiles at C-4 position [19–21]. This pyrazolone scaffold has been utilized in the various synthetic transformations to achieve highly functionalized α-amino pyrazolone derivatives. The synthetic potential of pyrazolone derived ketimines has been also explored for the synthesis of pyrazolone α-aminonitrile, amino-bipyrazolone and furanonaphtho pyrazolidinone derivatives via Strecker [19], Mannich [20], and domino aza-Friedel-Crafts/*N*,*O*-acetalization reaction [21] respectively. Yang/Deng and co-workers have reported the asymmetric aza-Friedel-Crafts reaction of 4-hydroxyindoles with pyrazolinone ketimines to synthesize hydroxyindole fused pyrazolinone derivatives [22]. Recently, Du and co-workers have explored the enantioselective Mannich reaction between pyrazolinone ketimines and 3-fluorooxindoles under chiral bifunctional squaramide catalyst to achieve amino-pyrazolone-oxindoles derivatives [23]. Very recently, Gamble/Han and co-workers have described the $Sc(OTf)_3$ catalyzed regiodivergent synthesis of multi-functionalized pyrazolone derivatives from 1,2-dihydroquinolines and pyrazolinone ketimines [24]. In spite of being an excellent electrophile at C-4 position, surprisingly, the utility of

pyrazolone derived ketimine to construct synthetically useful spiropyrazolones is limited in the literature. To the best our knowledge, pyrazolone derived ketimine has not been utilized in the annulation till date.

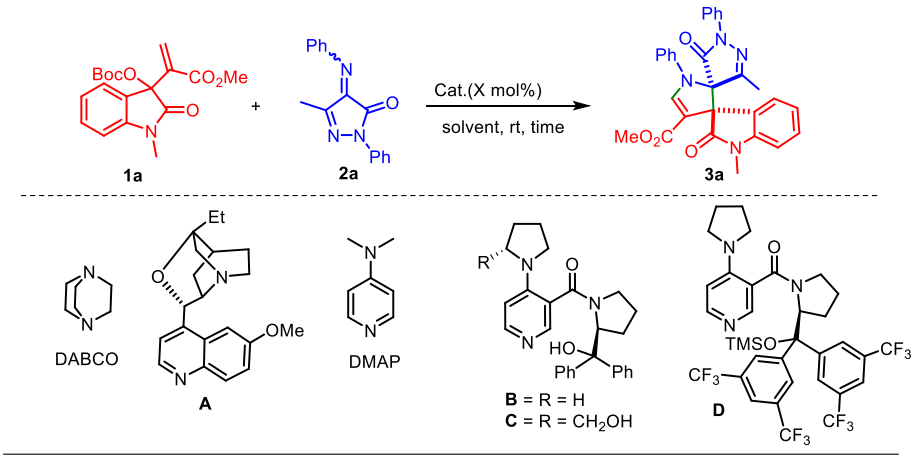
Based on our continuous interest in the synthesis of spirocyclic compounds [25] and also as a part of our ongoing research on organocatalytic [3 + 2] annulation, we became interested in spirooxindole fused dihydropyrrole pyrazolones. We hypothesized that this scaffold could be accessed via the cycloaddition reaction of isatin based Morita-Baylis-Hillman carbonate and pyrazolone derived ketimine under suitable Lewis base catalyst. Herein, we report DMAP catalyzed highly diastereoselective [3 + 2] annulation of MBH carbonates and pyrazolone derived ketimines to construct diverse spirooxindole fused pyrazolone/bis-spiropyrazolone dihydropyrroles bearing vicinal quaternary spirocenters.

In order to validate the hypothesis, initially we performed a model reaction between isatin derived MBH carbonate **1a** and pyrazolone derived ketimine **2a** in presence of 20 mol% of 1, 4-diazabicyclo[2.2.2]octane (DABCO) in dichloromethane (DCM) at room temperature. To our delight, the reaction proceeded smoothly to deliver the γ–regioselective [3 + 2] annulation product **3a** in moderate yield with an excellent diastereoselectivity (60%, >20:1 *dr*, Table 1, entry 1).

In order to enhance the yield of **3a**, we treated **1a** and **2a** in presence of triphenylphosphine (PPh_3) as a nucleophilic catalyst. However, we did not observe any product formation even after the prolonged reaction time (Table 1, entry 2). While the reaction **1a** and **2a** in presence of 4-dimethylamonopyridine (DMAP) completed in 12 h to furnish the desired compound **3a** in 86% yield with an excellent diastereoselectivity (Table 1, entry 3). Encouraged by this result, we turned our attention to explore the enantioselective [3 + 2] annulation reaction. In this regard, we screened few different chiral tertiary amine catalysts (Table 1, entries 4–7, for more details see ESI-Appendix I, Page 7). Unfortunately, we did not observe the desired enantioselectivity and all our attempts at different reaction conditions were unsuccessful. Considering the importance of spirooxindole scaffold, we decided to explore the diastereoselective version of this [3 + 2] annulation reaction. Further, in order to optimize the reaction condition, we screened different solvents such as chloroform ($CHCl_3$), tetrahydrofuran (THF), acetonitrile (CH_3CN), ethyl acetate (EtOAc), dimethylformamide (DMF) and toluene (Table 1, entries 8–13). Among all, chloroform was found to be advantageous for the desired transformation to afford **3a** in excellent yield with high diastereoselectivity (92%, >20:1 *dr*, Table 1, entry 8). Lowering of the catalyst loading (15 mol% DMAP) further furnished the compound **3a** in relatively lower yield, however, the diastereoselectivity remain unchanged (Table 1, entry 14). Based on the screening, MBH carbonate of isatin **1a** (1 equiv.), pyrazolone derived ketimine **2a** (1.1 equiv.) and DMAP (20 mol%) in chloroform was found to be the optimum reaction conditions for the desired [3 + 2] cycloaddition reaction to access spirooxindole fused dihydropyrrole derivatives.

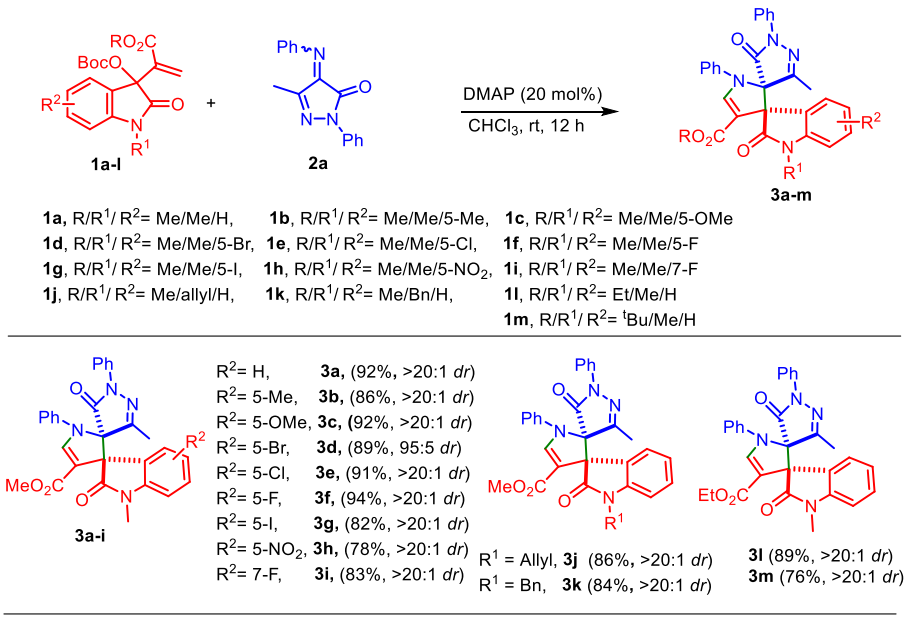
Having obtained the optimum reaction conditions, initially, we explored the substrate scope of various isatin derived MBH carbonates and pyrazolone derived ketimines to construct functionally diverse spirooxindole dihydropyrrole fused pyrazolone derivatives

Table 1
Optimization of the Reaction Conditions.[a-d]

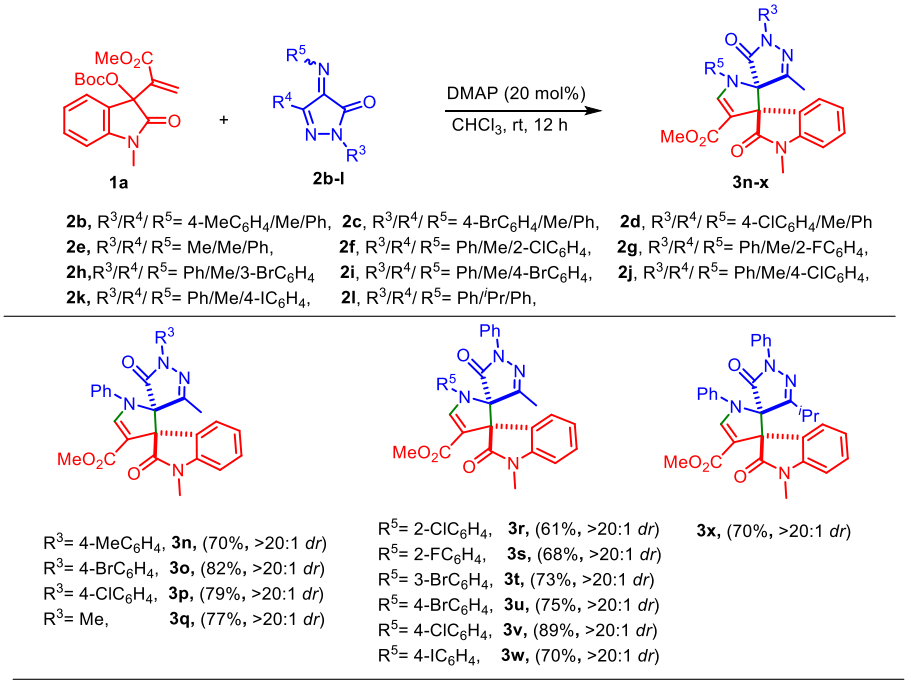


Entry	Catalyst (mol%)	Solvent	Time (h)	*dr*[c]	*ee* (%)[d]	Yield (%)[b]
1	DABCO (20)	CH_2Cl_2	24	>20:1	–	60
2	PPh_3 (20)	CH_2Cl_2	72	–	–	N.R
3	DMAP (20)	CH_2Cl_2	12	>20:1	–	86
4	A (20)	CH_2Cl_2	24	–	–	N.R
5	B (20)	CH_2Cl_2	24	>20:1	1	72
6	C (20)	CH_2Cl_2	24	>20:1	2	75
7	D (20)	CH_2Cl_2	24	>20:1	2	85
8	DMAP (20)	$CHCl_3$	12	>20:1	–	92
9	DMAP (20)	THF	12	>20:1	–	84
10	DMAP (20)	CH_3CN	12	>20:1	–	86
11	DMAP (20)	EtOAc	12	>20:1	–	82
12	DMAP (20)	DMF	12	>20:1	–	85
13	DMAP (20)	Toluene	24	>20:1	–	80
14	DMAP (15)	$CHCl_3$	24	>20:1	–	78

[a]**Reaction conditions**: All the reactions were carried out with MBH carbonate of isatin **1a** (0.115 mmol), Pyrazolone derived ketimine **2a** (0.126 mmol), cat. (20 mol%) in 2.0 mL of solvent at room temperature; [b]Isolated yield after column chromatography; [c]determined by ^{1}H NMR of crude reaction mixture; [d]Enantiomeric excess was determined by HPLC using the chiral stationary phase.



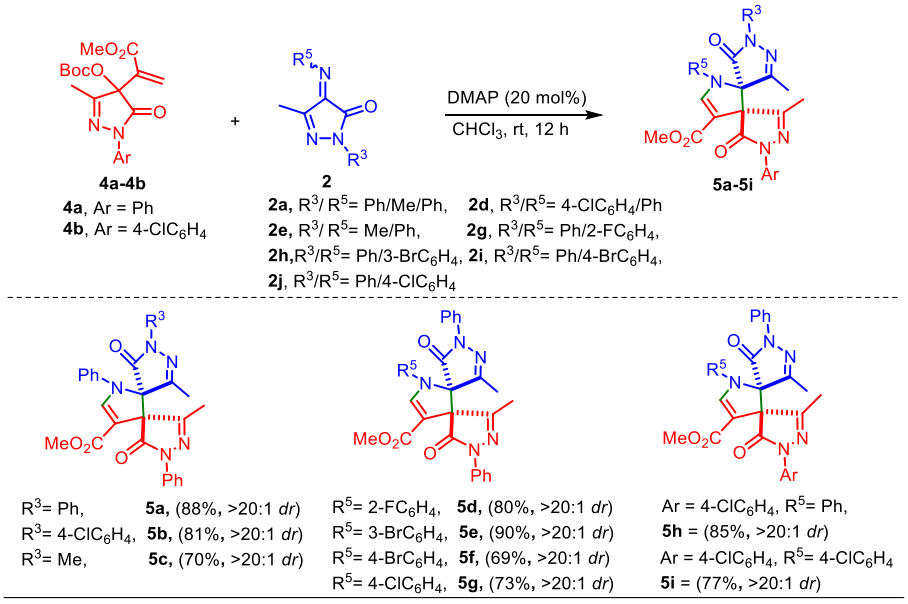
Scheme 2. Substrate scope for isatin derived MBH-carbonates[a-c]. **Reaction conditions**: [a]The reactions were carried out with MBH carbonate of isatin **1** (0.115 mmol), Pyrazolone derived ketimine **2a** (0.126 mmol), DMAP (20 mol%) in 2.0 mL of $CHCl_3$ at room temperature; [b]Isolated yield after column chromatography. [c]determined by ^1H NMR of crude reaction mixture.



Scheme 3. Substrate scope for pyrazolone derived ketimines[a-c]. **Reaction conditions**: [a]The reactions were carried out with MBH carbonate of isatin **1a** (0.115 mmol), Pyrazolone derived ketimine **2** (0.126 mmol), DMAP (20 mol%) in 2.0 mL of $CHCl_3$ at room temperature; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was determined by ^1H NMR of crude reaction mixture.

via [3 + 2] cycloaddition (Scheme 2). We observed that all the MBH carbonates **1a-1m** reacted smoothly with pyrazolone derived ketimine **2a** to furnish the corresponding heterocyclic spirooxindole **3a-3m** derivatives bearing two adjacent quaternary spirocenters in very good to excellent yields with excellent diastereoselectivities (up to 94%, >20:1 *dr*, Scheme 2).

It is important to note that under optimum reaction conditions all the substrates reacted smoothly regardless of the electron-donating (CH_3, OCH_3) and electron-deactivating/withdrawing (Br, Cl, F, I, NO_2) nature of the substituents at different positions on the aryl ring of MBH carbonates. In addition, *N*-allyl as well as *N*-benzyl protected MBH carbonates **1j, 1k** reacted easily with pyrazolone derived ketimine **2a** to afford the corresponding spirooxindole-dihydropyrrole-pyrazolones **3j** and **3k** in 86% and 84% yield respectively (Scheme 2). Moreover, the ethyl and tert-butyl ester substituted MBH carbonates **1l** and **1m** reacted with **2a** to furnish



Scheme 4. Substrate scope for the synthesis of bis-spiropyrazolones[a-c]. **Reaction conditions**: [a]The reactions were carried out with MBH carbonate of pyrazolone **4** (0.107 mmol), Pyrazolone derived ketimine **2** (0.117 mmol), DMAP (20 mol%) in 2.0 mL of $CHCl_3$ at room temperature; [b]Isolated yield after column chromatography. [c]diastereomeric ratio was determined by ^{1}H NMR of crude reaction mixture.

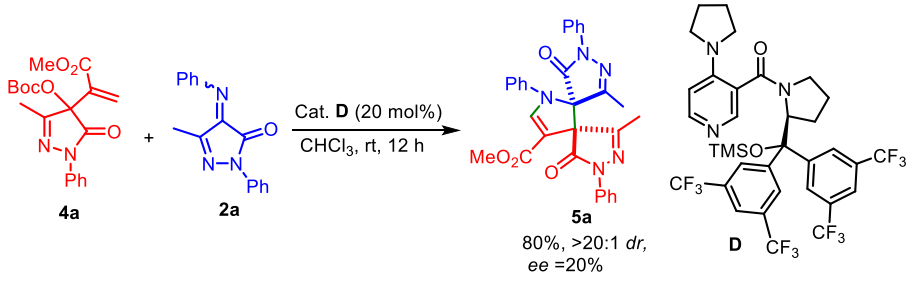
the corresponding dispirocyclic compound **3l** and **3m** in very good yields with very high diastereoselectivity (up to 89%, >20:1 *dr*). Further, the molecular structure of compound **3a** was established unambiguously using single-crystal X-ray diffraction analysis [26]. Based on the analogy and other spectroscopic data, the structures of all other products were deduced.

Later, in order to have the generality of the protocol and wider substrate scope, we treated different pyrazolone derived ketimines **2b-2l** with the MBH carbonate **1a** under the standard optimized reaction conditions (Scheme 3). Gratifyingly, all the substrates reacted smoothly to afford the corresponding [3 + 2] annulation products **3n-3x** in moderate to very high yields with excellent diastereoselectivities (61–89%, >20:1 *dr*, Scheme 3).

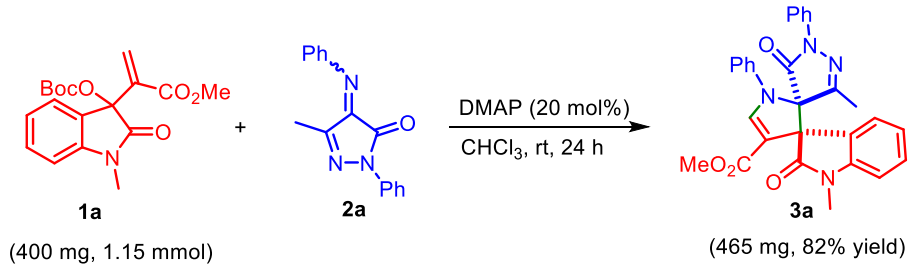
We observed that the pyrazolone derived ketimines **2b-2e** with different groups (at R^3 position) were compatible under optimized reaction conditions to deliver the corresponding desired products **3n-3q** in high yields with excellent diastereoselectivities (70–82%, >20:1 *dr*, Scheme 3). In addition, the pyrazolone derived ketimines **2f-2 k** with different aryl groups (R^5 position) reacted efficiently to furnish the corresponding spirooxindole dihydropyrrole pyrazolone **3r-3w** derivatives in moderate to very high yields with excellent diastereoselectivities (61–89%, >20:1 *dr*, Scheme 3). The ketimine substrate 5-isopropyl-2-phenyl-4-(phenylimino)-2, 4-dihydro-3*H*-pyrazol-3-one **2l** tolerated the optimum reaction conditions to afford the corresponding desired product **3x** in 70% yield with an excellent diastereoselectivity.

Encouraged by these results, we planned to employ MBH carbonate of pyrazolone to construct new bis-spiropyrazolone scaffold via [3 + 2] annulation reaction. To the best of our knowledge, there is no report for the synthesis of bis-spiropyrazolone compounds bearing vicinal quaternary spirocenters till date. In this regard, we synthesized different MBH carbonate of pyrazolones **4a-4b** from pyrazolone 4, 5-diones. The treatment of MBH carbonates **4a-4b** with different pyrazolone derived ketimines **2a, 2d, 2e, 2g-j** under the optimum reaction conditions afforded the corresponding products **5a-5i** (Scheme 4). Gratifyingly, all the reactions proceeded efficiently to afford the corresponding highly functionalized bis-spiropyrazolone dihydropyrrole **5a-5i** derivatives in moderate to excellent yields with excellent diastereoselectivities (up to 90%, >20:1 *dr*). The molecular structure of compound **5g** was established unambiguously using single-crystal X-ray diffraction analysis [27]. Based on analogy and other spectroscopic data, the structure of all other products were deduced.

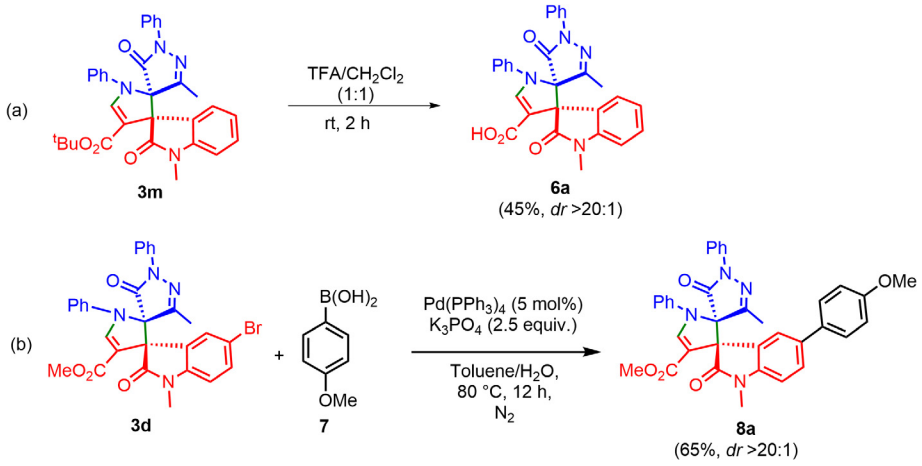
Next, we attempted the enantioselective version of this γ-regioselective [3 + 2] annulation reaction. In this regard, we treated the MBH carbonate of pyrazolone **4a** with pyrazolone derived ketimine **2a** in presence of 20 mol% of chiral DMAP based catalyst **D** in



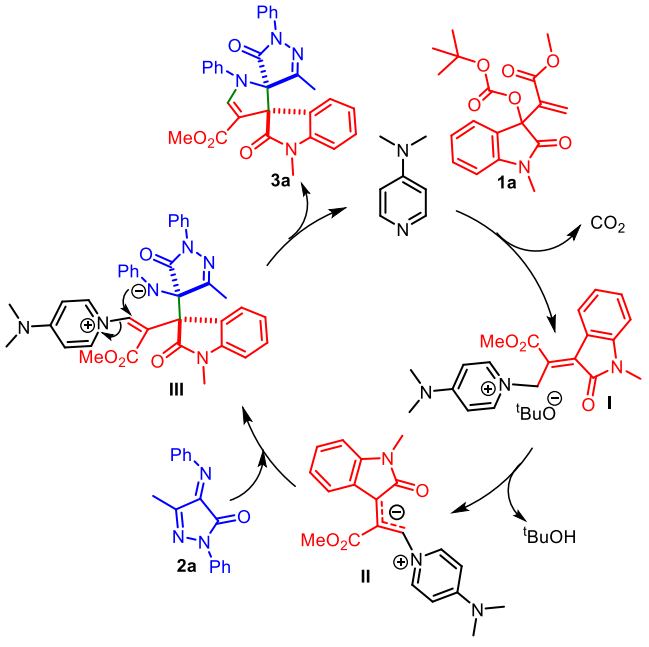
Scheme 5. Chiral DMAP catalyzed [3 + 2] annulation.



Scheme 6. Scale up synthesis.



Scheme 7. Synthetic transformations.



Scheme 8. Plausible catalytic cycle for the [3 + 2] cycloaddition reaction.

chloroform at room temperature. Though, the expected γ-regioselective [3 + 2] annulation product was formed in excellent yield, unfortunately we observed the poor enantioselectivity (80%, >20:1 *dr*, 20% *ee*, Scheme 5, for more details see ESI, Appendix II, page 8).

To make the protocol more practical and also for the wider applicability we demonstrated the mmol-synthesis of spirooxindole fused pyrazolone **3a** (82%) starting from the MBH carbonate **1a** and pyrazolone derived ketimine **2a** under optimum reaction conditions (Scheme 6).

In order to demonstrate the synthetic potential of this protocol, few synthetic transformations were carried starting from spirooxindole fused pyrazolones **3m** and **3d**. The treatment of the compound **3m** with TFA/DCM (1:1 v/v) gave the corresponding carboxylic acid derivative **6a** in 45% yield (Scheme 7a). Later, we have demonstrated the Suzuki coupling on the compound **3d** (Scheme 7b). The reaction of methoxyphenyl boronic acid **7** with compound **3d** in the presence of $Pd(PPh_3)_4$ and K_3PO_4 in toluene/water at 80 °C furnished the corresponding product **8a** in 65% yield.

Based on our experimental results and previous literature reports [28], the plausible catalytic cycle for [3 + 2] annulation reaction is outlined in Scheme 8. The nucleophilic attack of DMAP on MBH carbonate **1a** generates the corresponding quaternary ammonium salt **I** with the evolution of carbon dioxide and tert-butoxide. Next, the in situ generated Brønsted base (tert-butoxide) reacts with intermediate **I** to form highly reactive allylic nitrogen ylide **II**. Then, the zwitterionic allylic ylide **II** reacts with the pyrazolone derived ketimine **2a** via γ-position to form corresponding intermediate **III**. Subsequently, the intramolecular cyclization of intermediate **III** leads to the formation of spirooxindole fused pyrazolone **3a** by regenerating the catalyst DMAP to complete the catalytic cycle.

In summary, we have developed a highly efficient [3 + 2] annulation of Morita–Baylis–Hillman carbonates of isatins/pyrazolones and pyrazolone derived ketimines. The protocol worked effectively to construct spirooxindole dihydropyrrole fused pyrazolones and bis-spiropyrazolone dihydropyrrole derivatives bearing two vicinal

quaternary spirocentres in good to excellent yields with very high diastereoselectivities under mild catalytic condition at room temperature. The protocol proved to be efficient with diverse MBH carbonates and pyrazolone derived ketimine derivatives. We have successfully demonstrated the utility of easily accessible DMAP as an effective catalyst for this synthetic transformation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.153791.

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