Organocatalytic Asymmetric Reactions with Hydroxy Containing Carbon Nucleophiles

A Dissertation

Submitted in Partial Fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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June 2020

Dedicated to

My Family

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STATEMENT

I do hereby declare that the matter embodied in this thesis entitled *"**Organocatalytic Asymmetric Reactions with Hydroxy Containing Carbon Nucleophiles**"* is the result of investigations carried out by me under the supervision of Prof. Subhas Chandra Pan in the Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that Megha Balha (Roll No - 156122029) has been working under my supervision since July 2015 as a regular registered Ph.D. student. Her thesis entitled "***Organocatalytic Asymmetric Reactions with Hydroxy Containing Carbon Nucleophiles***" contains the results obtained from the research work carried out by her in the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding her thesis to submit for the Ph.D. (Science) degree from this institute as she has fulfilled all the requirements according to the rules of this institute and this work has not been submitted elsewhere for a degree.

Guwahati — Prof. Subhas Chandra Pan

June 2020 — Supervisor

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Megha Balha

Table of Contents

Abbreviation

Ac	Acetyl
AcOH	Acetic acid
anh.	Anhydrous
aq.	Aqueous
Å	Angstrom
Ar	Aryl
Bn	Benzyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
br.	Broad
Boc	tert-Butyloxycarbonyl
Bu	Butyl
CCDC	Cambridge crystallographic data centre
CAN	Chloroform
$CHCl_3$	Ceric ammonium nitrate
COSY	Correlation spectroscopy
Cy	Cyclohexyl
^oC	Degree Celsius
CH_2Cl_2	Dichloromethane
d	Doublet or day
dd	Doublet of doublet
δ	Chemical shift or delta
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
δ	Delta
EtOAc	Ethyl acetate
ent	Enantiomer
ee	Enantiomeric excess
er	Enantiomeric ratio
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group
FT-IR	Fourier-transform infrared spectroscopy
g	Grams
γ	Gamma
h	Hours
H-bonding	Hydrogen-bonding

HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Iso
J	Coupling constant
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m	*Meta*
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Miligram
mL	Mililitre
mmol	Milimole
m.p.	Melting point
MS	Molecular sieves
MTBE	Methy tertiary butyl ether
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
o	*Ortho*
ω	Omega
ORTEP	Oak ridge thermal ellipsoid plot program
p	*Para*
PG	Protecting group
Ph	Phenyl
Pr	Propyl
ppm	Parts per million
p-TSA	*p*-Toluenesulfonic acid
PCC	Pyridinium chlorochromate
q	Quartet
rac	Racemic
rt	Room temperature
s	Singlet
SOMO	Singly occupied molecular orbital
THF	Tetrahydrofuran
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TES	*tert*-Butyldiethylsilyl
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
$PhCH_3$	Toluene
Ts	*p*-Tolylsulfonyl
uv	Ultraviolet
XRD	X-ray diffraction

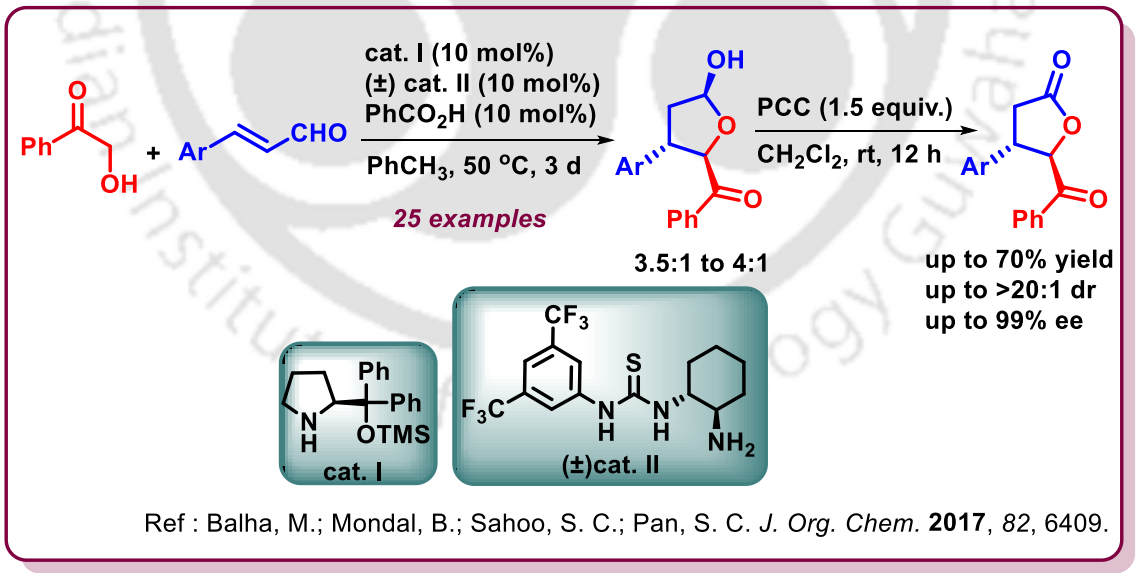
Abstract

The present thesis, entitled as ***"Organocatalytic Asymmetric Reactions with Hydroxy Containing Carbon Nucleophiles"*** is divided into five chapters, based on the obtained results of experimental works performed during the complete course of the Ph.D. research period.

Chapter I: Overview

Chapter 1 contains a general overview of asymmetric organocatalysis with special emphasis on the generic modes of catalyst activation, induction, and reactivity. A brief description of the reactivity of α-hydroxy carbonyl compounds is also discussed here.

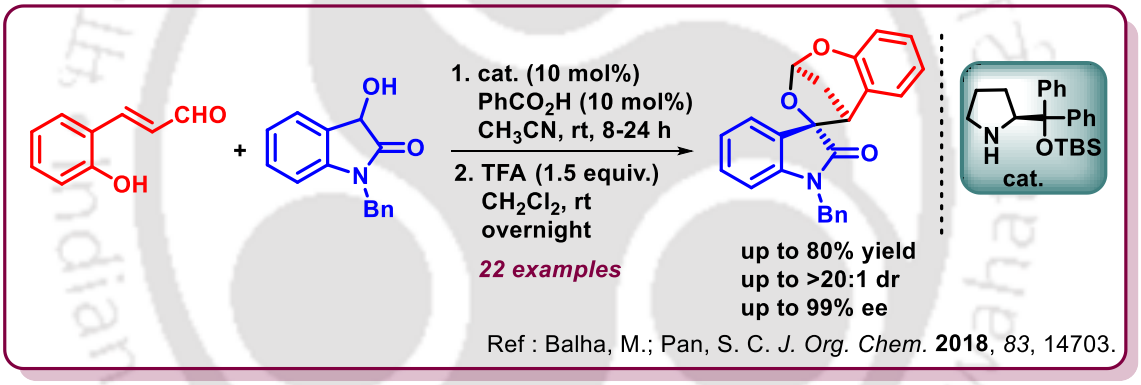
Chapter-II: Organocatalytic Asymmetric Michael-Hemiacetalization Reaction between 2-Hydroxyacetophenones and Enals: A Route to Chiral β,γ-Disubstituted γ-Butyrolactones



The nonracemic γ-butyrolactone motif is found to be present in a variety of biologically significant natural products, including antibiotic and antitumor agents. Further, it serves as an important building block in synthetic organic chemistry. However, the synthesis of

chiral β,γ-disubstituted γ-butyrolactone derivatives have been less reported. In this chapter, we have reported a highly asymmetric synthesis of β,γ-disubstituted γ-butyrolactones from a Michael-hemiacetalization reaction between 2-hydroxyacetophenones and α,β-unsaturated aldehydes followed by pyridinium chlorochromate (PCC) oxidation. The combination of a primary amine and a secondary amine catalyst was found to be the best choice for this methodology. The desired products were obtained in high yields with excellent enantio- and diastereoselectivities. The utility of our method was then demonstrated by subjecting the hemiacetal to several useful organic transformations.

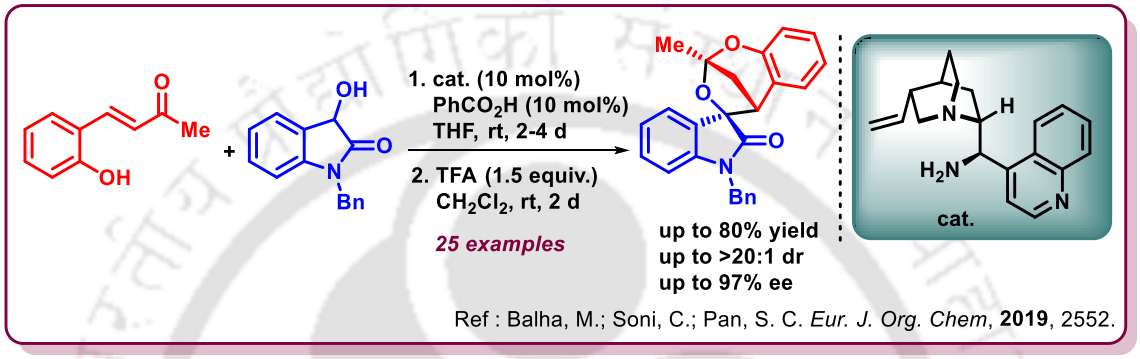
Chapter-III: Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton



Chiral *O,O*-acetals are important structural motifs present in a range of natural products and pharmaceuticals and display a wide range of bioactivities. In recent years, considerable efforts have been devoted for the asymmetric synthesis of these compounds. However, catalytic asymmetric synthesis of spirooxindoles having bridged acetal structure is still not known despite the high medical importance of bridged acetals and spirooxindoles individually. In this chapter, we have discussed the first highly diastereo- and enantioselective synthesis of bridged *O,O*-acetals embedded with spirooxindoles. Dioxindoles and 2-hydroxy cinnamaldehydes were employed as the reaction partners in this method. The desired products were obtained via diaryl prolinol TBS ether catalyzed Michael reaction followed by acetal formation with TFA. The

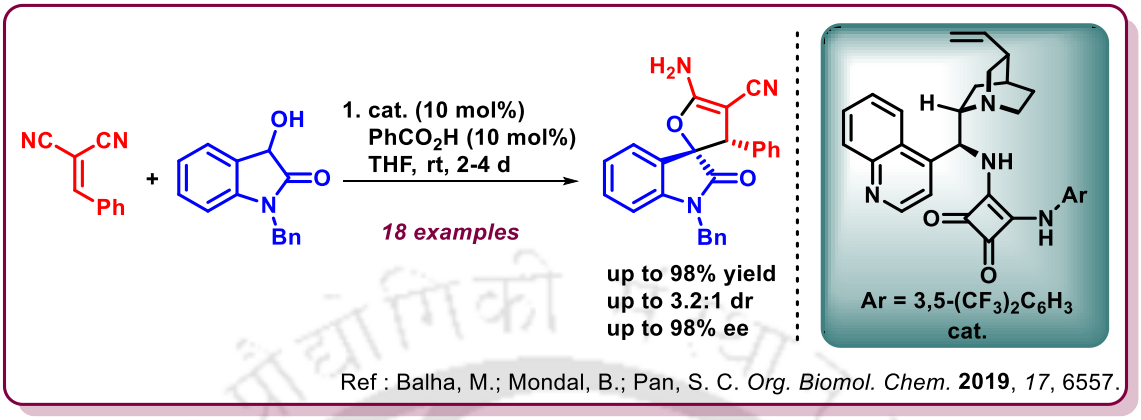
desired spirooxindole products were obtained in good to high yields with excellent enantio- and diastereoselectivities in operationally simple reaction conditions. Also, few products have been further functionalized via Suzuki coupling reaction.

Chapter-IV: Organocatalytic Asymmetric Synthesis of Bridged *O,O*-Ketals with Spirooxindole Motif



Chiral *O,O*-acetals and ketals are prevalent in many natural products and pharmaceuticals and a wide range of bioactivities are associated with them. Thus, a large number of synthetic research groups are engaged in the asymmetric synthesis of these compounds. Realizing the potential of chiral *O,O*-acetals, and ketals for medicinal chemistry, in this chapter, we embarked on the first organocatalytic enantioselective synthesis of bridged *O,O*-ketals embedded with spirooxindoles. Dioxindoles and *ortho*-hydroxy-benzylidene acetones were engaged as the reaction partners in this method. The methodology proceeds through primary amine catalyzed conjugate addition, followed by diastereoselective ketalization with TFA. The spirooxindole products were isolated in good to high yields with high diastereo- and enantioselectivities under mild and operationally simple reaction conditions. To exhibit the synthetic utility of our method, few derivatives were also prepared. Given the high pharmaceutical significance of spirooxindoles and bridged ketals, our products might be useful for drug discovery.

Chapter-V: Organocatalytic Asymmetric Synthesis of Dihydrofuran-Spirooxindoles from Benzylidene Malononitriles and Dioxindoles



Spirooxindoles are privileged structural motifs frequently found in a range of natural products and pharmaceutical molecules. Thus, significant interest has been observed over the years from a large number of chemists for the development of efficient and practical synthetic methods for this class of structural frameworks. In this chapter, we described the first organocatalytic enantioselective synthesis of dihydrofuran-spirooxindoles, having a linkage at the 2-position of the dihydrofuran motif. Dioxindoles and benzylidene malononitriles were employed in this method. The desired spirooxindole products were obtained *via* a Michael reaction followed by a Pinner reaction and isomerization, and good to high yields with moderate diastereo- and good to high enantioselectivities were observed. To demonstrate the synthetic potential of our method, a Suzuki coupling reaction was carried out on several spirooxindole products. Given the high medicinal importance of spirooxindoles and dihydrofurans, our products are expected to be useful in drug discovery.

Chapter I

Introduction

I. Asymmetric Synthesis

The term "asymmetric" means a lack of equality or lack of equivalence between parts or aspects of something that could be anything like nature, molecules, or the human body. In 1801, the phenomenon of chirality was first noticed by the French mineralogist René Just Haüy in quartz crystals. In 1847, Louis Pasteur discovered molecular chirality by examining paratartrate crystals.[1] He found that crystals of tartaric acid exist in two forms. These two forms were later identified as mirror images. Such compounds are called enantiomers.[2-3] Molecular chirality is the backbone of stereochemistry, and his studies revealed that asymmetry was one of the fundamental characteristics of living matter. Despite their identical chemical and physical properties in an achiral environment, enantiomers interact differently in the chiral environment. Physical properties include melting point, boiling point, color, hardness, density, etc. Enantiomers differ in their action towards plane-polarized light. One rotates the plane-polarized light to the right (+) is dextrorotatory *d*-(+) and the other rotates towards the left is levorotatory *l*-(–). The extent of rotation in two cases is the same except the direction of rotation, which is opposite to each other. For example, orange and lemon smell differently, being the left- and right-handed version of the same molecule, i.e., they are the enantiomeric form of limonene (Figure 1).[4] Since our nasal receptors are made up of chiral molecules, that's why we can distinguish between these two enantiomers. Enantiomers are chiral molecules that are non-superimposable mirror images of each other.

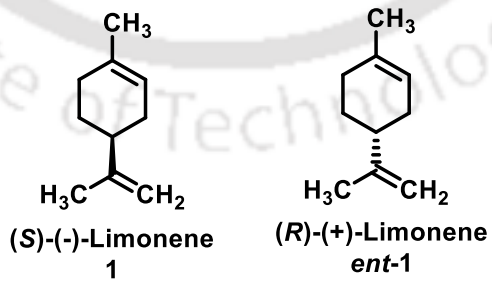


Figure 1: The enantiomers of limonene

On the other hand, the L-form of the tryptophan **2** is bitter, whereas D-form *ent*-**2** tastes sweet. (Figure 2).[5]

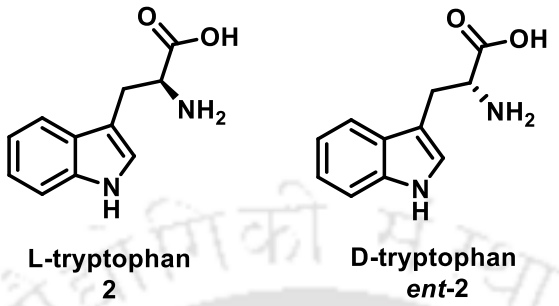


Figure 2: The enantiomers of tryptophan

Living organisms are the primary source of optically active substances, which produce mainly one of the isomers. One of the most essential and universal rules of biological activity is the chiral determination of the substance, the ability to distinguish the structure of a molecule from its mirror image.[6] In biological systems, enzymes are the essential catalysts, which are optically active; thus, stereochemical specificity is a rule rather than an exception in these systems. Numerous drugs differ in the biological activity of their enantiomers.[7] For example, the drug thalidomide was sold in the 1960s to pregnant women. (*R*)-Thalidomide **3** helped against nausea, while the other one, i.e. (*S*)-thalidomide *ent*-**3** is responsible for the teratogenic side effects (Figure 3).[8]

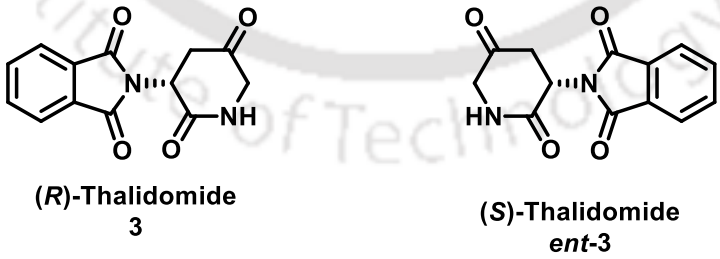


Figure 3: The enantiomers of thalidomide

Similarly, dopamine is an effective drug for Parkinson's disease, and only (*S*)-Dopa **4** is effective in restoring nerve function while (*R*)-Dopa *ent*-**4** is toxic (Figure 4).[9]

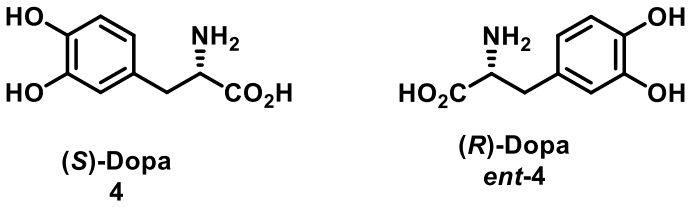


Figure 4: The enantiomers of dopamine

Since the two enantiomers of a chiral molecule often have very different effects on cells, it is highly required to prepare drug molecules in enantiomerically pure forms. These are the key processes in modern chemistry and are particularly important in the field of pharmaceuticals. This is where asymmetric synthesis comes into the picture. Synthesis, which favors the formation of one stereoisomer (enantiomer or diastereomer) over another, is known as asymmetric synthesis. Asymmetric synthesis can be classified into four major categories: (1) substrate-controlled methods; (2) auxiliary-controlled methods; (3) reagent-controlled methods; and (4) catalyst-controlled methods.

Substrate-controlled asymmetric synthesis: Diastereoselective reactions where the formation of a new chiral center is controlled by another chiral center already present in the substrate.

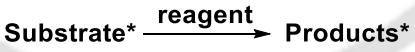


Figure 5: Substrate-controlled asymmetric synthesis

Auxiliary-controlled asymmetric synthesis: Synthesis in which a chiral auxiliary, which is a chiral molecular unit, is temporarily attached to an achiral substrate to guide the selective formation of one of two stereo-isomers. Chiral auxiliaries are optically active compounds and introduce chirality in otherwise achiral starting materials. A chiral auxiliary physically blocks one of two possible trajectories of attack on an achiral

substrate, leaving only the desired trajectory open for the reaction. The stereochemistry of the new chiral center can be rationalized based on steric considerations.

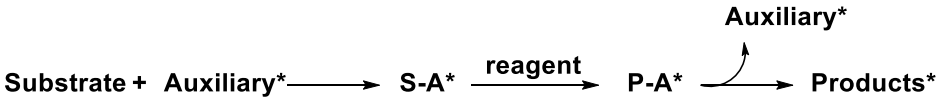


Figure 6: Auxiliary-controlled asymmetric synthesis

Reagent-controlled asymmetric synthesis: In this method, the formation of a new chiral center is induced by a chiral reagent.

Figure 7: Reagent-controlled asymmetric synthesis

Chiral pool synthesis and the use of chiral auxiliaries were among the most attractive strategies during the early decades of asymmetric synthesis.[10] However, considering the step- and atom-economical aspects of synthesis, catalytic methods emerge as a more powerful tool during the past few decades.

Catalyst-controlled asymmetric synthesis: Chiral catalysts control the formation of a new chiral center. In this method, catalysts are required in a catalytic amount, which makes this method quite economical and sustainable.

Figure 8: Catalyst-controlled asymmetric synthesis

Based on the nature of the catalyst used in the synthesis, catalyst-controlled methods can be further sub-classified as:

(a) Biocatalysis

(b) Metal catalysis and,

(c) Organocatalysis

Biocatalysis[11] is the use of natural substances that include enzymes from biological sources or whole cells to catalyze chemical reactions. In most cases, a group of proteins called enzymes will be carrying out the catalysis, but a combination of enzymes as well as cells can be used. The advantage of using bio-catalysts is its specificity and ability to function in mild conditions. Bio-catalysis has proven to be an extremely efficient approach for inducing high levels of stereo-, chemo-, and regio-selectivities.[12] However, many disadvantages are also there like narrow substrate scope, insufficient stability at extreme conditions (e.g., high temperature and extreme pH), and, most importantly, the unavailability of the enzyme for synthesizing the opposite enantiomer.

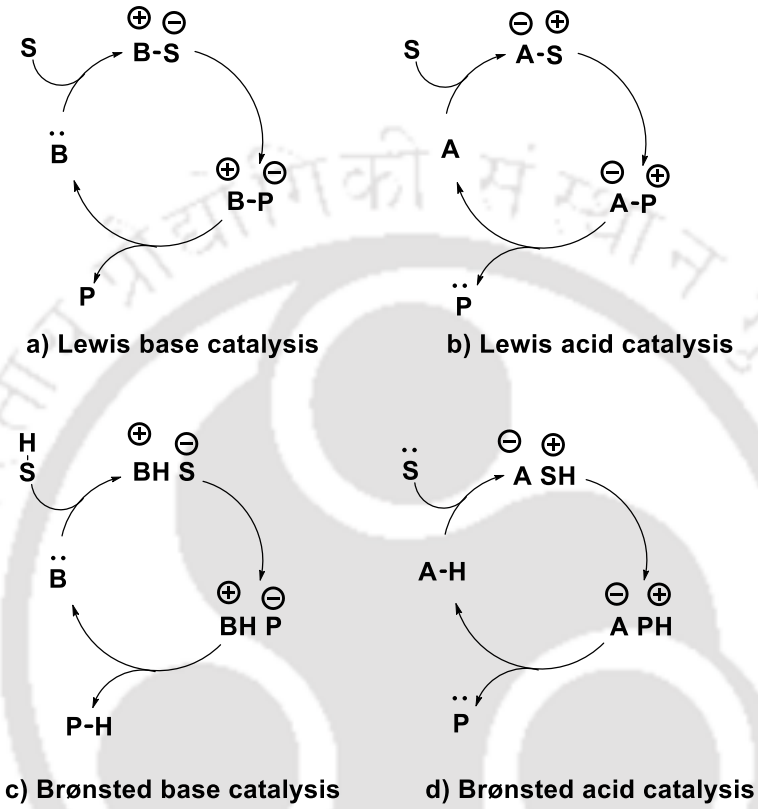
As metal catalysts possess properties such as variable oxidation state (oxidation number), complex ion formation, and catalytic activity, they hold a vast significance in modern organic chemistry.[13] Several organic transformations such as asymmetric hydrogenation, epoxidation, and dihydroxylation of olefins, cross-coupling reactions, olefin metathesis, etc. have been performed using transition metal catalysts, which had been challenging to achieve by classical synthetic pathway.[14] Despite several advantages, metal catalysis has its limitations such as toxicity, and demanding removal of trace metal impurities.[15]

In addition to biocatalysts and metal complexes, a third approach has been introduced called organocatalysis. Organocatalysis, or the use of small organic molecules to catalyze organic transformations, is a relatively new and popular field within the domain of chiral molecule (or enantioselective) synthesis.[16] Organocatalysis has become a field of great importance to chemical synthesis and has been adopted as a significant research area on a global scale.

II. Asymmetric organocatalysis

In organocatalysis, the reaction is catalyzed by a small molecule called "organocatalyst," which is purely organic and metal-free. In the past decade, the concept of organocatalysis has emerged significantly because of their wide range of practical advantages.[17] Organocatalysts have several advantages over traditional catalysts like they are usually robust, bench-stable, inexpensive, non-toxic, and in some instances, commercially

available. Most of the organocatalysts can be broadly classified into four categories according to their mode of action: (i) Lewis base, (ii) Lewis acid, (iii) Brønsted base, and (iv) Brønsted acid. The corresponding catalytic cycles are shown in Scheme 1.[18]



Scheme 1: Organocatalytic cycles

In a Lewis base catalysis, the majority of organocatalysts are N-, C-, O-, P-, and S based Lewis bases that accelerated the reaction by the nucleophilic addition of the catalyst (**B:**) to the substrate (**S**) and the resulting intermediate undergoes subsequent reaction followed by the release of the product (**P**) and catalyst regeneration for further turnover (Scheme 1a). Common examples of Lewis base catalysis include Enamine/iminium catalysis, Morita–Baylis–Hillman reaction, phosphine-catalyzed reactions of allenoates or alkynoates, DMAP-catalyzed acylation, NHC-catalysis, etc.[19]

In Lewis acid catalysis, the catalyst (**A**) activates nucleophilic substrates (**S:**) to form an activated complex (Scheme 1b). After the reaction, the product (**P:**) and the catalyst is

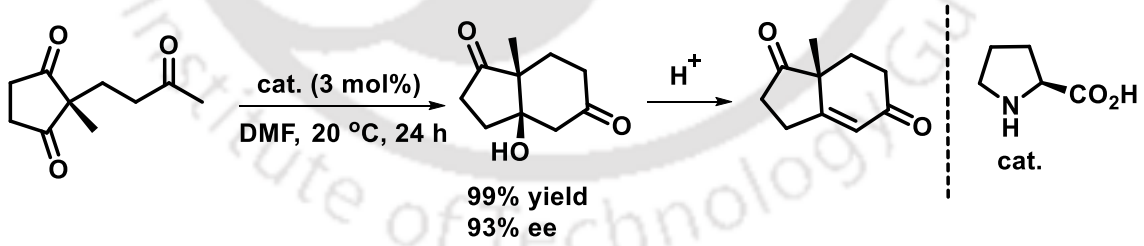
released. Typical examples of Lewis acid catalysis include ketone-catalyzed epoxidation and Baeyer-Villiger oxidation are the representative examples.[20]

Brønsted base catalytic cycles are initiated *via* partial or complete deprotonation of the substrate (**S-H**) by the catalyst (**B:**) followed by the chemical transformation to give the product (**P-H**) and regeneration of the catalyst (Scheme 1c). Representative examples of Brønsted base catalysis are tertiary amine and guanidine catalyzed Strecker, Michael and Henry reactions.[21]

Brønsted acid catalytic cycles are initiated *via* partial or complete protonation of the substrate (**S:**) by the catalyst (**A-H**), and the resulting ion-pair reacts to give the product (**P:**) followed by the catalyst regeneration (Scheme 1d). Examples of Brønsted acid catalysts include TADDOL, phosphoric and carboxylic acids, thiourea derivatives etc.[22]

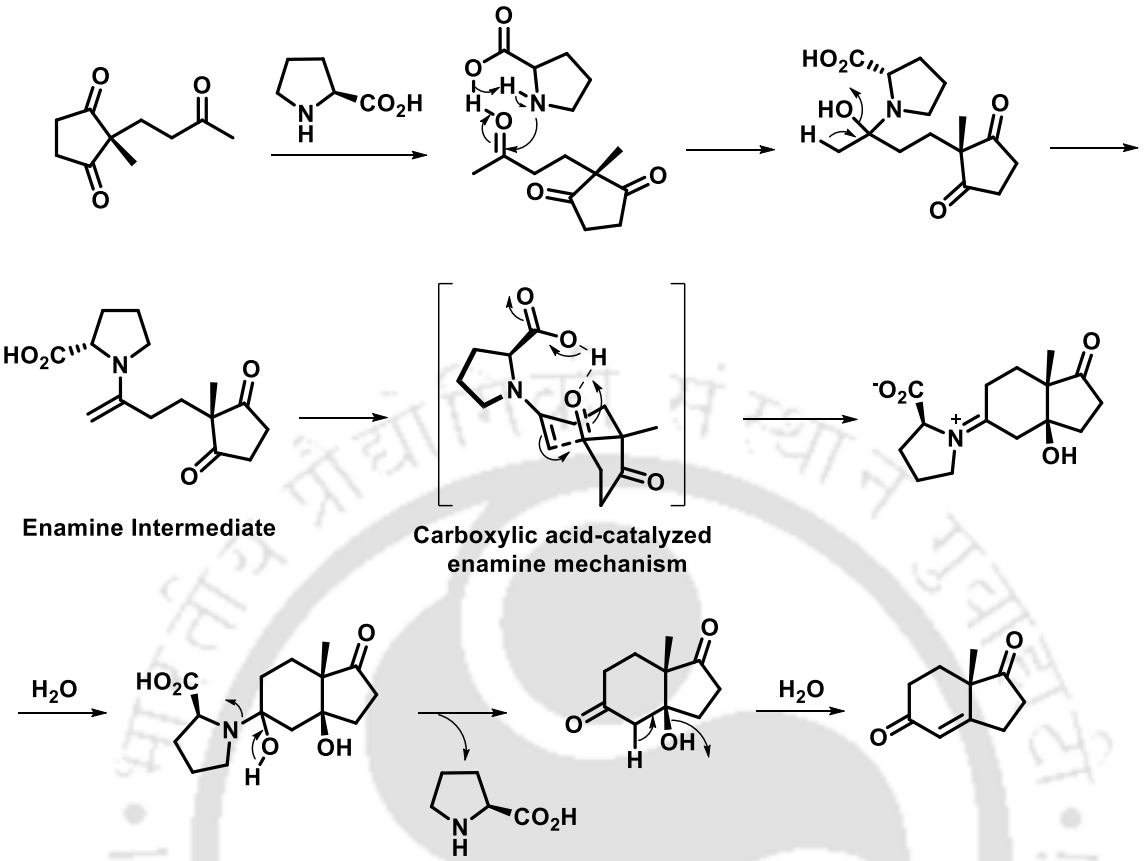
III. Enamine catalysis

In 1971, two research groups, one led by Zoltan Hajos and David Parrish[23] and another led by Rudolf Weichert, Gerhard Sauer and Ulrich Eder[24] reported an independent report on enantioselective intramolecular aldol reaction catalyzed by proline for the synthesis of the Wieland–Miescher ketone (Scheme 2). This is the first example of asymmetric enamine catalysis.



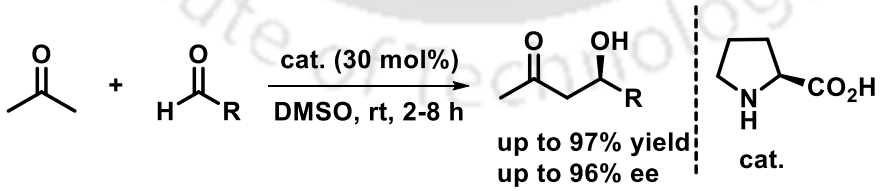
Scheme 2 The Hajos-Parrish-Eder-Sauer-Wiechert reaction

The mechanism involved in the nucleophilic addition of the neutral enamine to carbonyl group is illustrated below (Scheme 3).[25]



Scheme 3. Proposed Mechanism

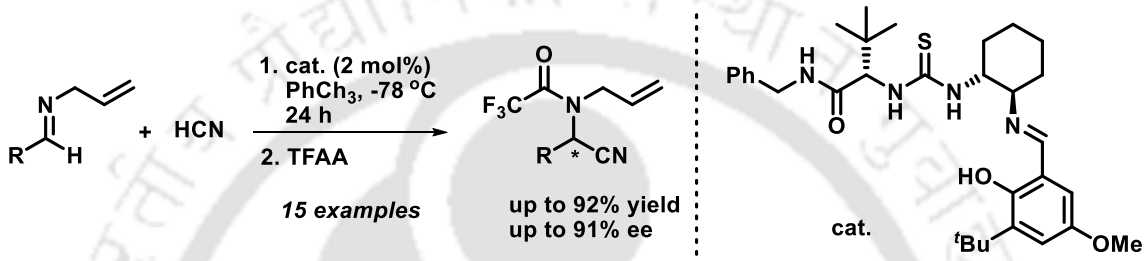
In 2000, Barbas, Lerner, and List used enamine catalysis to functionalize carbonyl-containing compounds at the *α*-carbon (Scheme 4).[26] It is due to this work that enamine catalysis has become more prominent and since then, various research groups have got engaged to identify new types of chiral enamine catalysts.



Scheme 4. Proline catalyzed intermolecular aldol reaction with acetone

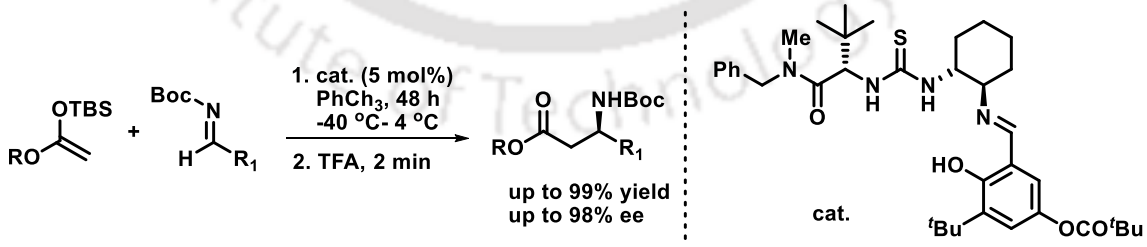
IV. Hydrogen-bonding catalysis

In the early 1980s, many research groups discovered that in several catalytic asymmetric processes, hydrogen-bonding interactions could be responsible for the activation of a substrate and helps in the organization of the transition state.[27-29] In 1998 and 1999, an asymmetric variant of the Strecker reaction was independently reported by two groups: the group of Jacobsen[30] and the group of Corey[31] that used well-defined hydrogen-bonding organocatalyst which activates imine electrophiles (Scheme 5).



Scheme 5. Asymmetric Strecker reaction

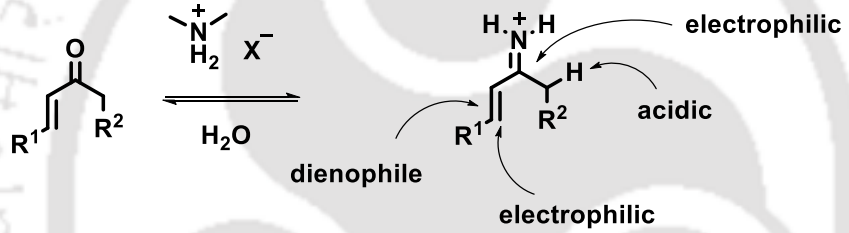
In 2002, after four years, Jacobsen *et al.* showed that urea derivatives are highly effective catalysts for the asymmetric addition of silyl ketene acetal derivatives to aldimines (Scheme 6).[32] This led to a new era in which thiourea catalysts has gain importance and become the foundation of a large area of research, and more than 30 new asymmetric reactions have been developed based on this principle.[33]



Scheme 6. Asymmetric catalytic Mannich reaction

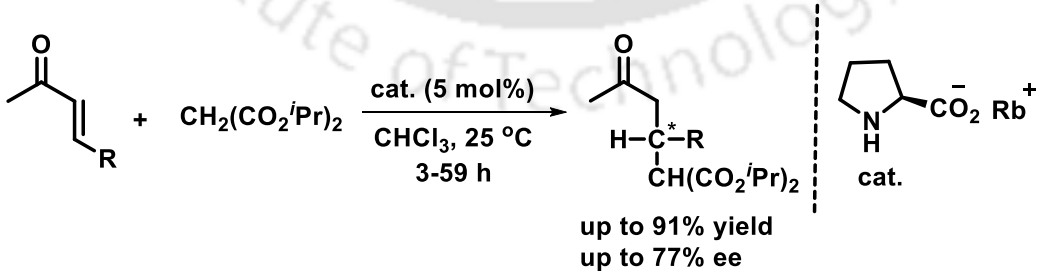
V. Iminium catalysis

The first organocatalytic activation mode, which was established as a general strategy for asymmetric organic synthesis, was Iminium catalysis. The catalysis depends on the capability of chiral amines to serve as enantioselective catalysts in several organic transformations that traditionally used Lewis acid catalysts. In mechanistic studies, it was assumed that iminium ion formed from an unsaturated carbonyl compound, which lowers the LUMO energy of the system and is thus beneficial for the reactivity of the compound. Condensation of the amine with an enal or an enone led to the reversible formation of an iminium ion (Scheme 7).[34] The iminium catalysis, along with its family of imidazolidinone catalysts, is widely used in more than 50 highly enantioselective protocols,[35] most of which were developed by MacMillan and Jørgensen group.



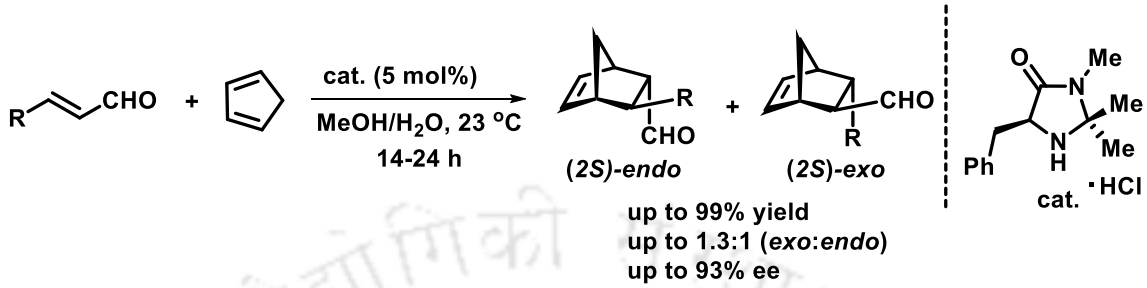
Scheme 7. Iminium catalysis

In 1993, Yamaguchi *et al.* reported the first catalytic enantioselective Michael addition reaction of simple malonate to prochiral *α,β*-unsaturated ketones and aldehydes using a rubidium salt of L-proline (Scheme 8).[36] The products were obtained in good yields with moderate enantioselectivities.



Scheme 8. Asymmetric catalytic conjugate addition reaction

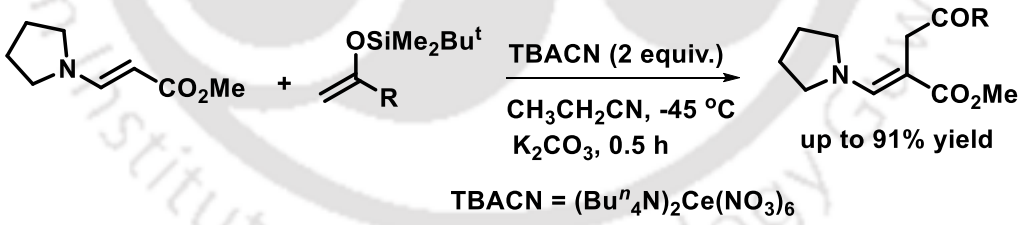
In 2000, MacMillan *et al.* reported the first highly enantioselective Diels-Alder reaction between *α,β*-unsaturated aldehydes and various dienes catalyzed *via* chiral secondary amine•HCl salts (Scheme 9).[37]



Scheme 9. Asymmetric Diels-Alder reaction

VI. SOMO catalysis

In 2006, SOMO catalysis was introduced by the MacMillan group, which suggested that one-electron oxidation of an electron-rich enamine selectively generates a reactive radical cation with three π-electrons. The formal *α*-alkylation products were formed due to the electrophilicity of the singly occupied molecular orbital (SOMO) of this enamine intermediate which allows it to react readily with a variety of weakly nucleophilic carbon-based 'SOMOphiles' at the *α*-carbon of the parent enamine (Scheme 10).[38]



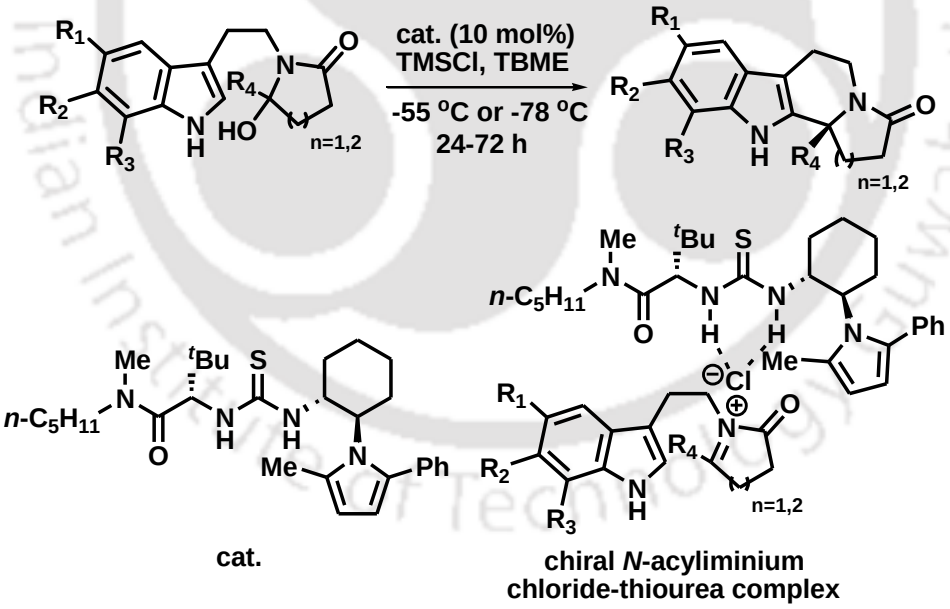
Scheme 10. Reaction of olefins with radical cations generated from enamines

A huge success was achieved with the application of the SOMO catalysis principle in a catalytic system that employs chiral secondary amines along with a suitable one-electron oxidant. This has widened new prospects for catalyzing the asymmetric *α*-functionalization of carbonyl-containing compounds. Despite being the latest discovered activation mode, SOMO catalysis has produced a series of enantioselective transformations that complement those formed by enamine catalysis.[39-41]

VII. Counterion catalysis

Recently, Jacobsen developed counterion catalysis. It is a conceptually novel form of organocatalytic activation that directs highly enantioselective additions into transiently generated *N*-acyl-iminium ions and oxocarbenium ions.[42] Chiral thiourea catalysts are known to form stable complexes with halide ions. In this system, the first chiral thiourea catalyst forms a chiral *N*-acyliminium chloride-thiourea complex by binding electrostatically to, and ionize, the weak carbon–chlorine bonds of chloroamides and chloroacetals. Then this anionic catalyst–chloride complex functions as a chiral counterion, which restricts the attack of the nucleophiles to one face of one enantiomer of the short-lived *α*-hetero atom-stabilized cationic species. The stereochemical information is passed from the catalyst to the substrate through the forces which act through space rather than through bonds with high fidelity.

In 2007, Jacobsen *et al.* reported chiral thiourea catalyzed enantioselective Pictet-Spengler-type cyclizations of hydroxylactams (Scheme 11).[42a]



Scheme 11. Enantioselective Pictet-Spengler-type cyclization

In asymmetric catalysis, there are a lot of tenacious problems, which might get solved with this mode of activation despite being in its initial phase.

VIII. Hydroxy Containing Carbon Nucleophiles

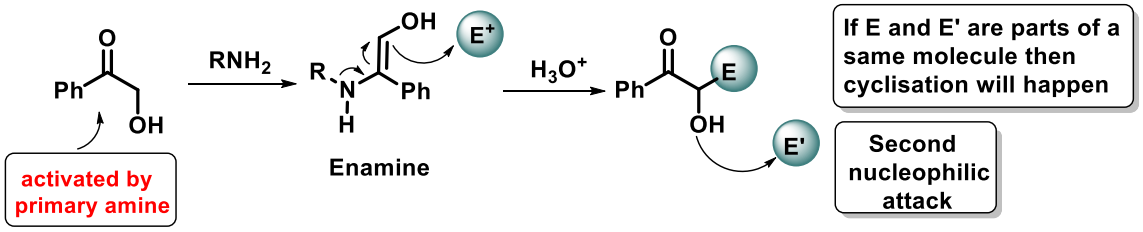
Nucleophiles are an electron-pair donor, i.e., Lewis Bases. Lone pair present on the atoms of Group V, VI, or VII, makes them act as an electron-pair donor, whereas, Group IV elements do not contain any lone pair; thus, they are neutral.

Organic chemists are interested in the formation of carbon-carbon bonds through organic transformations, which involve the coupling of a nucleophilic carbon with an electrophilic carbon. Thus, nucleophiles play a vital role in organic transformations.

The work embodied in this thesis deals with the nucleophilic addition of hydroxy-containing carbon nucleophiles to Michael acceptors, followed by cyclization reactions.

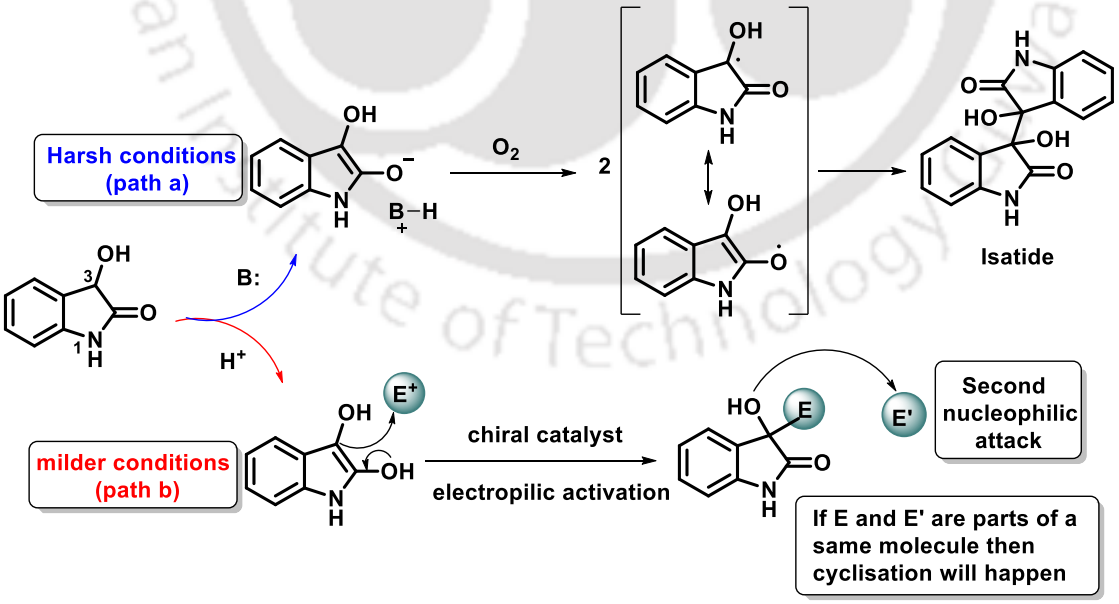
Hydroxy carbonyl compounds: Conjunctive bivalent 1,2- and 1,3-reagents[43] have played a pivotal role in asymmetric organocatalysis due to their potential to form multiple C−C and C−X bonds.[44] α-Hydroxy ketones are an important class of compounds with diverse biological and medicinal applications.[45] They are widely used in organic chemistry. This class of compounds has inherently high nucleophilicity, which shows they are outstanding nucleophiles. There are various types of hydroxy-containing carbon nucleophiles, whereas, in this thesis, we have focused on 2-hydroxyacetophenones and 3-hydroxy oxindoles.

In 2000, List *et al.* reported proline catalyzed aldol reaction between hydroxyacetone and various aldehyde for the asymmetric synthesis of *anti*-1,2-diols with excellent enantioselectivities.[46] Aromatic hydroxy ketones (i.e., 2-hydroxyacetophenones) have also been used in asymmetric metal-catalyzed aldol and Michael reactions by Trost and Shibasaki.[47] However, it was found quite challenging to employ 2-hydroxyacetophenones in organocatalysis by secondary amine catalysts. The bivalent character of 2-hydroxyacetophenone was exploited by the Chang group.[48] Given the bivalent nature of 2-hydroxyacetophenone, we envisioned whether it can be activated by primary amine catalysis and applied in the organocatalytic Michael-hemiacetalization reaction. The primary amine catalyst activates the 2-hydroxyacetophenone, which results in the formation of enamine, followed by a nucleophilic attack to Michael acceptor (Scheme 12).



Scheme 12. Reactivity of 2-hydroxyacetophenone

Next, we will examine the reactivity of 3-hydroxy oxindole. The organic catalysts, i.e., less basic catalysts, can activate the 3-hydroxy oxindole by abstracting the hydrogen atom at the C3 position, which results in the conjugate addition to a Michael acceptor. Under harsh conditions, 3-hydroxy oxindole undergoes an oxidative dimerization pathway, which has already been reported.[49] Dioxindole, in the presence of a strong base upon exposure to the aerobic atmosphere, led to the formation of its dimeric form isatide.[50] Isatin radical is formed by the oxidation of the enolate intermediate, which led to this oxidative dimerization (Scheme 13). The dioxindole radicals are merostabilized carbon free radicals. In 1980, Koch *et al.* explained the stability of dioxindole radicals by dipolar resonance structure since the radical centre lies between the electron-donating hydroxyl substituent and the electron-withdrawing carbamido substituent. This phenomenon is known as Captodative effect.[51]



Scheme 13. Reactivity of 3-hydroxy oxindole

IX. Conclusion and focal theme of the present work

In this thesis, we have focused mainly on the employment of different types of organocatalysts in various organocascade reactions.

Chapter-I describes a general overview of organocatalysis with special emphasis on the reactivity of *α*-hydroxy carbonyl compounds.

Chapter-II shows a vital route for the synthesis of chiral *β*,*γ*-disubstituted *γ*-butyrolactones. Chiral butyrolactones were obtained via Michael-hemiacetalization reaction between 2-hydroxyacetophenones and *α*,*β*-unsaturated aldehydes. This chapter deals with synergistic catalysis in which we have employed the combination of a primary amine and a secondary amine catalyst.

Chapter-III reveals the first highly diastereo- and enantioselective synthesis of bridged *O*,*O*-acetals embedded with spirooxindoles using dioxindoles and 2-hydroxy cinnamaldehydes as reaction partners. The desired products were obtained *via* diaryl prolinol TBS ether catalyzed Michael reaction followed by acetal formation with TFA.

Chapter-IV discloses the first organocatalytic enantioselective synthesis of bridged *O*,*O*-ketals embedded with spirooxindoles. The desired products were obtained *via epi*-cinchonine primary amine catalyzed Michael reaction, followed by ketal formation with TFA.

Chapter-V demonstrates the enantioselective synthesis of dihydrofuran-spirooxindoles having a linkage at the 2-position of the dihydrofuran motif. Dioxindoles and benzylidene malononitriles were employed in this method. The desired spirooxindole products were obtained *via* cinchonidine squaramide catalyzed Michael reaction, followed by a Pinner reaction and isomerization.

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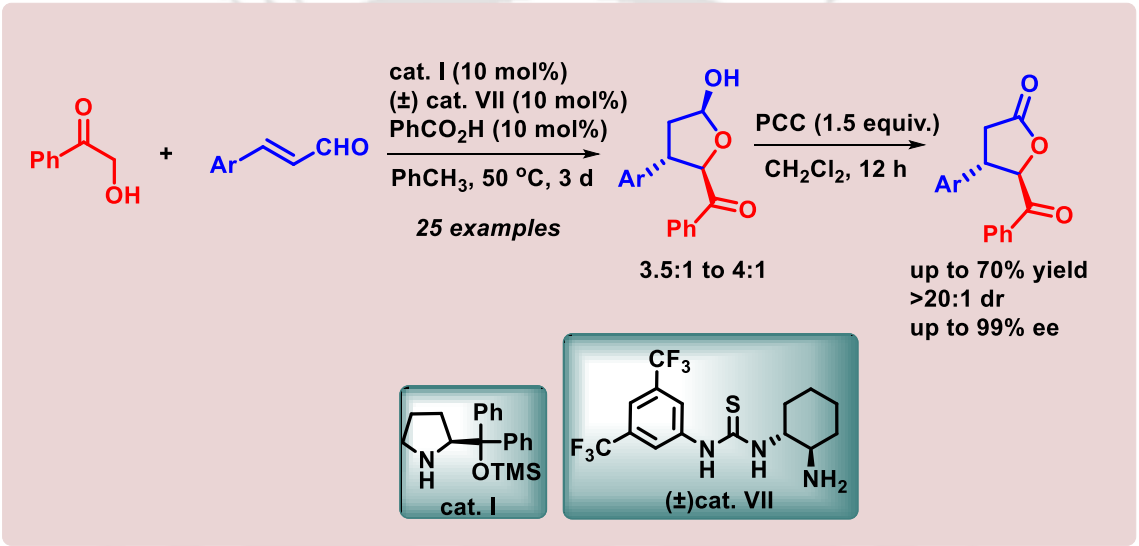
Chapter 2

Organocatalytic Asymmetric Michael-Hemiacetalization Reaction between 2-Hydroxyacetophenones and Enals: A Route to Chiral β,γ-Disubstituted γ-Butyrolactones



J. Org. Chem. **2017**, *82*, 6409-6416.

2.1 Introduction

Numerous biologically significant natural products contain non-racemic γ-butyrolactone motif[1] which serve as an important building block in synthetic organic chemistry.[2] Due to their diverse medicinal properties such as antifungal, antibacterial, antileukemia, glaucoma, heterocyclic oxygen compounds bearing a γ-butyrolactone ring system have attracted considerable attention during the last two decades.[3-5] Some natural products with γ-butyrolactone ring system are depicted in Figure 1.[6]

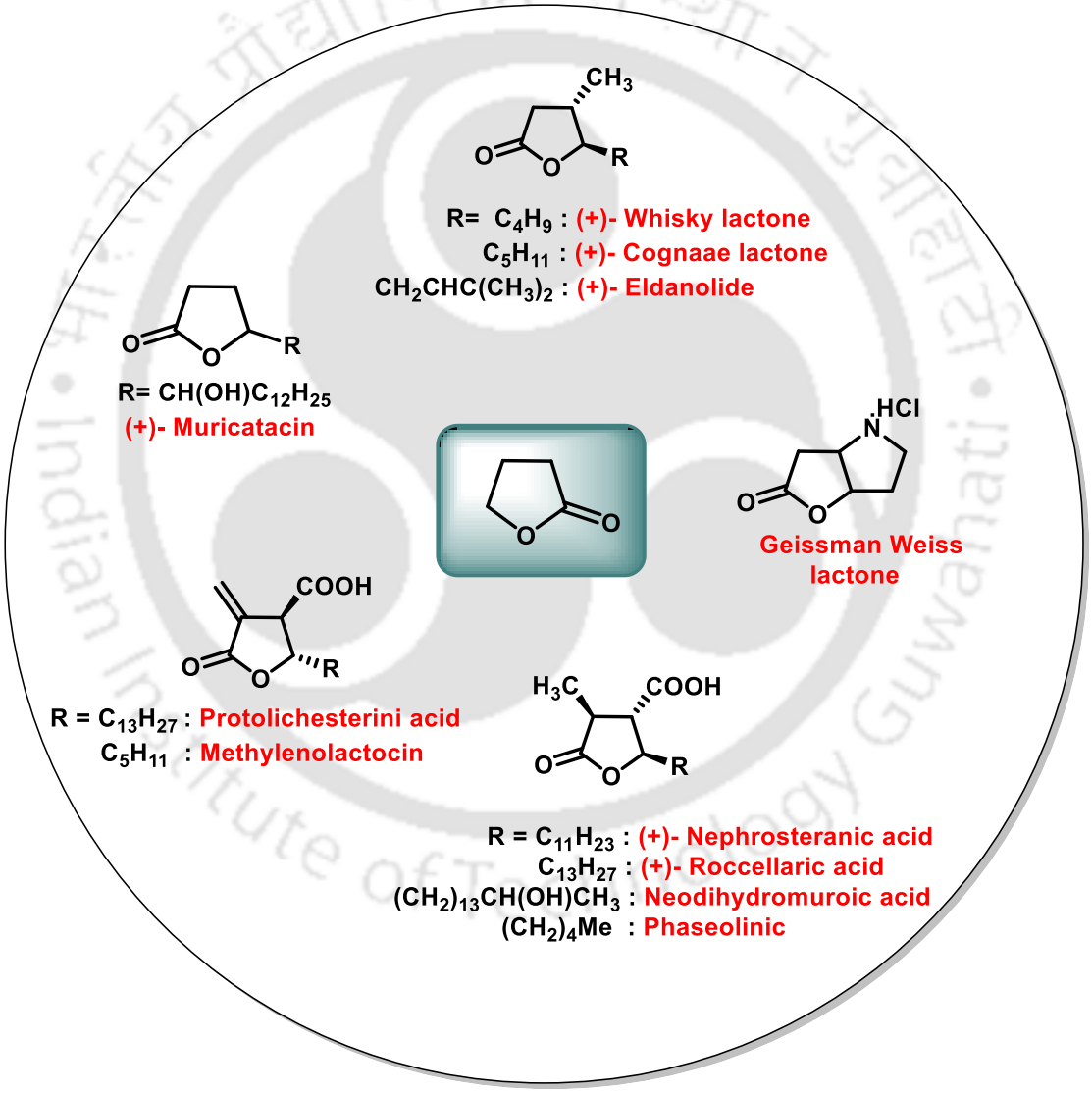
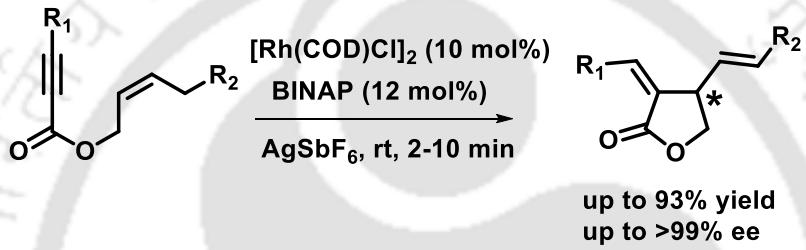


Figure 1. Representative natural products containing γ-butyrolactone scaffold

2.2 Selected previously reported strategies for the asymmetric synthesis of functionalized γ-butyrolactones:

2.2.1 Highly enantioselective synthesis of functionalized α-methylene-γ-butyrolactones

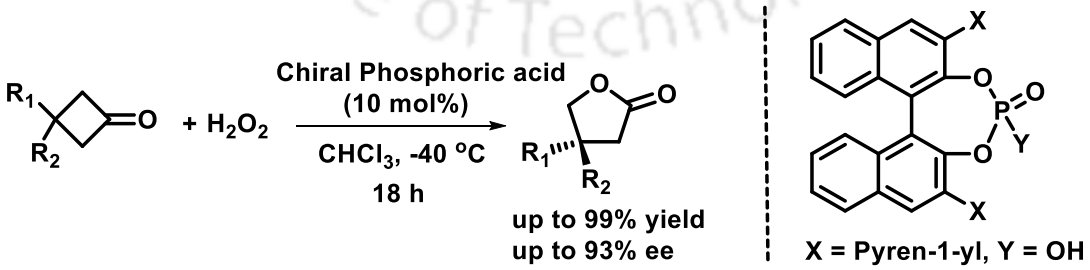
A highly enantioselective Rh-catalyzed intramolecular Alder ene reaction for the synthesis of functionalized α-methylene-γ-lactones was reported by Zhang and co-workers in 2002. Under the optimized reaction conditions, various functionalized α-methylene-γ-butyrolactones were formed in high yields with greater than 99% enantiomeric excesses (Scheme 1).[7]



Scheme 1. Asymmetric Rh-catalyzed intramolecular Alder ene reaction by Zhang *et al.*

2.2.2 Chiral phosphoric acid-catalyzed enantioselective Baeyer-Villiger oxidation for the synthesis of γ-butyrolactone

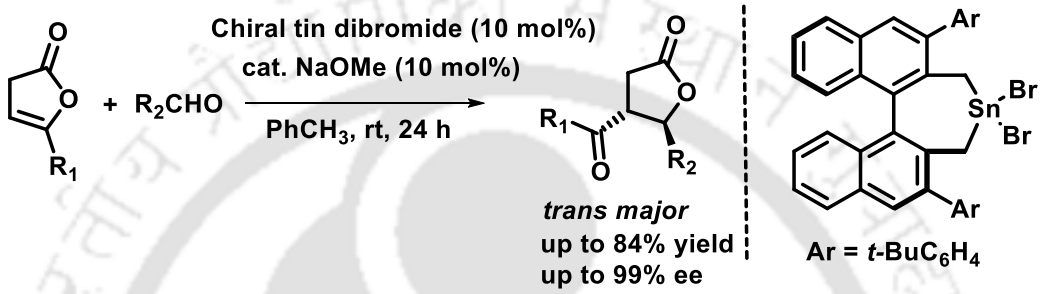
In 2008, Ding *et al.* reported an enantioselective Baeyer-Villiger oxidation of 3-substituted cyclobutanones catalyzed by a chiral Brønsted acid and 30% aqueous H_2O_2 was used as the oxidant. This protocol allowed an efficient synthesis of corresponding γ-lactones in excellent yields and up to 93% enantiomeric excess (Scheme 2).[8]



Scheme 2. Phosphoric acid-catalyzed asymmetric Baeyer-Villiger oxidation of 3-substituted cyclobutanone with H_2O_2 by Ding *et al.*

2.2.3 Catalytic enantioselective synthesis of chiral γ-butyrolactone

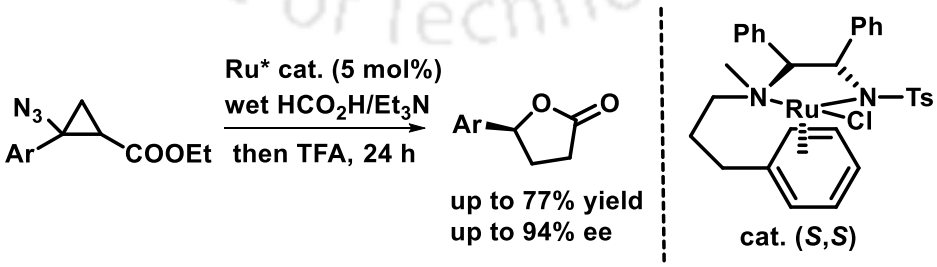
In 2011, Yanagisawa *et al.* reported the catalytic asymmetric synthesis of optically active γ-butyrolactones from β,γ-didehydro-γ-butyrolactones through a tandem enantioselective aldol reaction/cyclization (Scheme 3).[9] This strategy allowed the synthesis of various nonracemic β,γ-disubstituted-γ-butyrolactones with enantioselectivities of up to 99% ee by the use of *in situ* generated chiral tin bromide methoxide as a chiral catalyst.



Scheme 3. Chiral tin-catalyzed asymmetric synthesis of chiral γ-butyrolactones by Yanagisawa *et al.*

2.2.4 Synthesis of enantioenriched γ-substituted lactones *via* asymmetric transfer hydrogenation

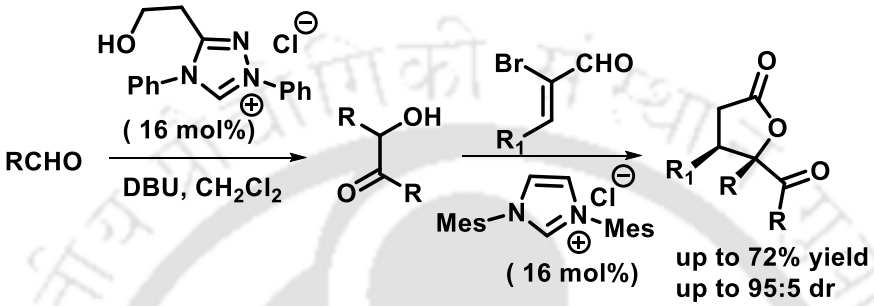
In 2014, Gu group reported an efficient conversion of a range of racemic β-azidocyclopropane carboxylates to enantioenriched γ-substituted lactones through an asymmetric transfer hydrogenation process (Scheme 4).[10] γ-Lactones were obtained in good to excellent enantioselectivities *via* a four-step sequence of azide reduction/cyclopropane ring rearrangement/asymmetric transfer hydrogenation of γ-oxo ester/γ-lactonization.



Scheme 4. Chiral γ-lactone from a racemic β-azidocyclopropane carboxylate by Gu *et al.*

2.2.5 NHC catalyzed synthesis of γ-lactone

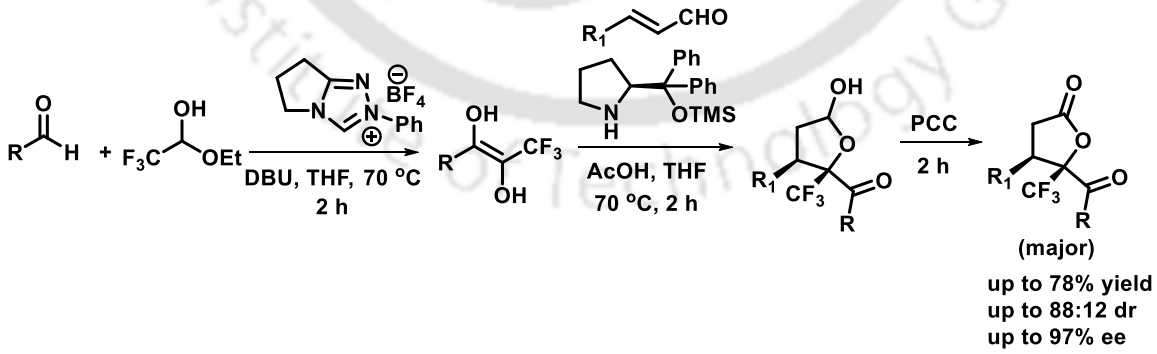
In 2015, Huang *et al.* reported NHC-catalyzed [3+2] annulation of α,β-unsaturated acylazoliums with 1,2-bisnucleophiles (Scheme 5).[11] This protocol allowed an efficient synthesis of a functionalized γ-lactone scaffolds bearing a quaternary carbon center. The desired products were obtained in moderate to good yields with high diastereoselectivities.



Scheme 5. NHC-catalyzed [3+2] annulation of α,β-unsaturated acylazoliums by Huang *et al.*

2.2.6 Asymmetric synthesis of CF_3-substituted γ-butyrolactone derivatives

Han group developed a sequential NHC-amine catalytic cascade reaction for efficient synthesis of CF_3-substituted γ-butyrolactones in 2016 (Scheme 6).[12] The desired products were obtained in high yields as well as with good stereoselectivities. The reaction proceeded through a highly chemoselective cross-benzoin reaction followed by a highly regioselective Michael-acetalization reaction.

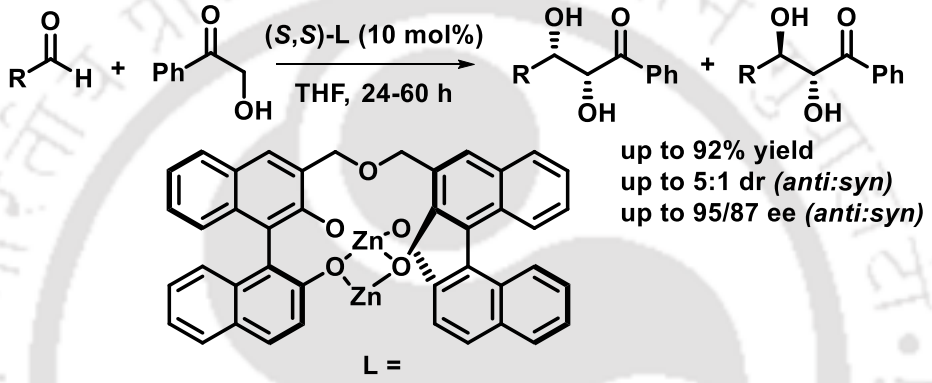


Scheme 6. Catalytic asymmetric synthesis of trifluoromethylated γ-butyrolactones by Han *et al.*

2.3 Selected previously reported strategies for the employment of hydroxyacetophenones in asymmetric reactions:

2.3.1 Catalytic asymmetric aldol reaction

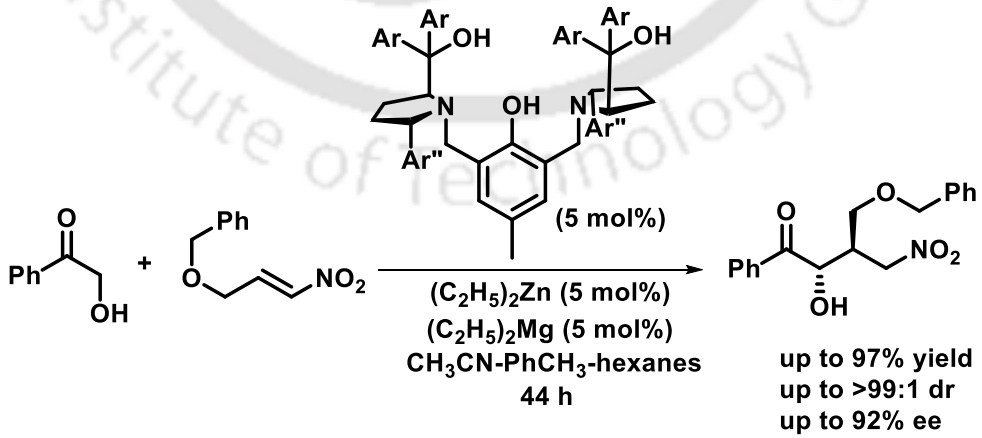
In 2001, Shibasaki and co-workers developed a direct catalytic asymmetric aldol reaction of primary aldehydes with hydroxyacetophenones which lead to the formation of *anti*-*α*,*β*-dihydroxy ketones using heterobimetallic catalysis (Scheme 7).[13] It is also reported that *syn*- or *anti*- *α*,*β*-dihydroxy ketones were synthesized in a highly enantioselective manner.



Scheme 7. Direct catalytic asymmetric aldol reaction by Shibasaki *et al.*

2.3.2 Asymmetric Michael reaction of hydroxyacetophenones

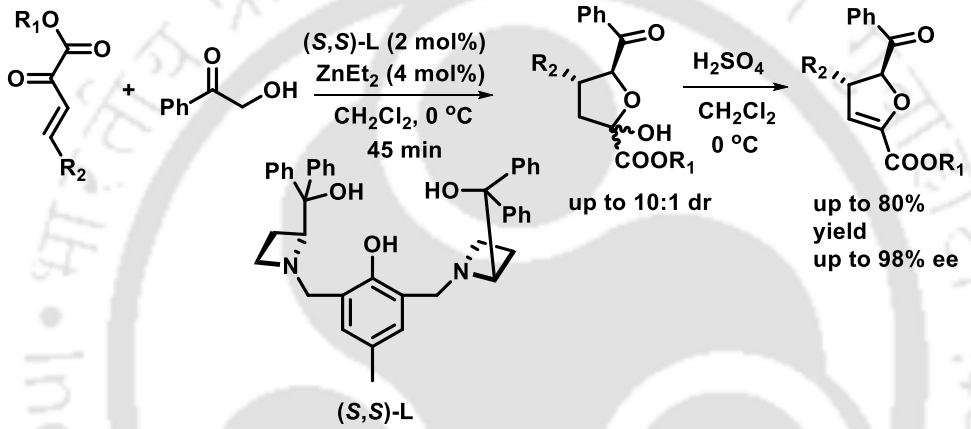
In 2006, Trost *et al.* reported the use of hydroxyacetophenones as donors in asymmetric Michael reactions with nitroalkene acceptors (Scheme 8).[14]



Scheme 8. Conjugate additions of *α*-hydroxyketones to *β*-substituted nitroalkenes by Trost *et al.*

2.3.3 Asymmetric domino Michael/hemiketalization reaction of *α*-hydroxyacetophenone

In 2015, Chang and co-workers reported highly enantioselective Michael/hemiketalization reaction of *α*-hydroxyacetophenone with *β*,*γ*-unsaturated-*α*-ketoesters for the synthesis of 2,2,4,5-tetrasubstituted chiral tetrahydrofurans (Scheme 9).[15] It is also reported that even with low catalyst loading under the same reaction conditions, multi-substituted chiral tetrahydrofurans were obtained with moderate to good yields and up to 98% ee.

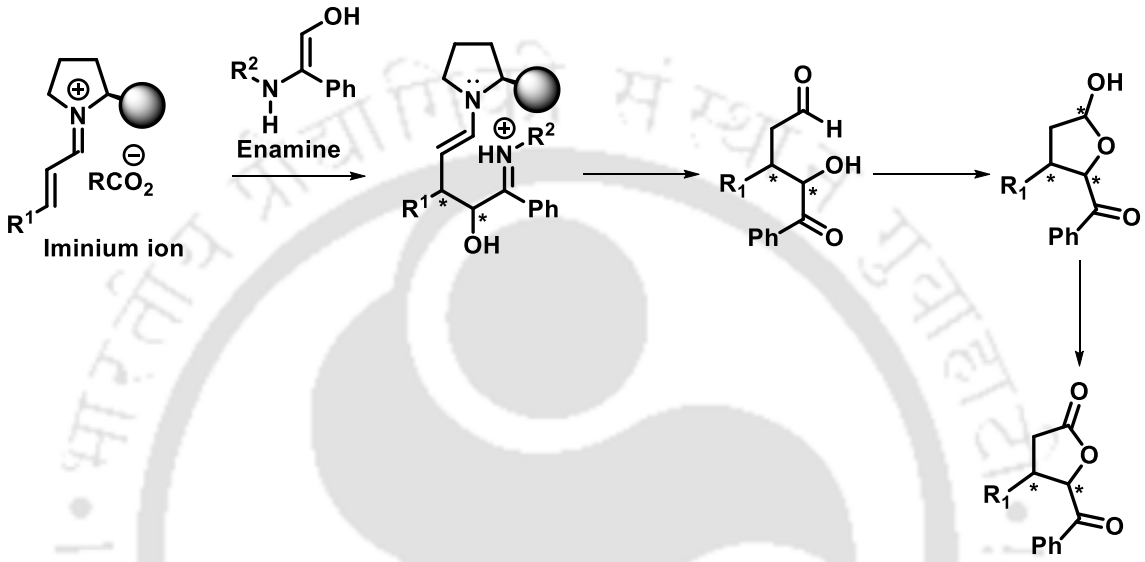


Scheme 9. Catalytic asymmetric domino Michael/hemiacetalization reaction by Chang *et al.*

2.4 Concept

Based on the previously reported literature survey, we examined that the synthesis of chiral *β*,*γ*-disubstituted *γ*-butyrolactone is limited, and no direct asymmetric approach by organocatalysis is still reported. Realizing the importance of chiral *β*,*γ*-disubstituted *γ*-butyrolactone, we thought of developing an asymmetric organocatalytic Michael hemiacetalization reaction of 2-hydroxyacetophenone and cinnamaldehyde followed by PCC oxidation. We envisioned that 2-hydroxyacetophenone can be activated by primary amine catalysis and applied in the organocatalytic Michael-hemiacetalization reaction. We assumed that the combination of a primary amine and a secondary amine catalyst was found to be the best choice for this methodology. It was expected that an iminium

ion would generate from cinnamaldehyde and secondary amine catalyst. Then 2-hydroxyacetophenone would be activated by primary amine catalyst and attack to the iminium ion to deliver an enamine. Then, catalyst controlled intramolecular Michael addition would deliver the hemiacetal followed by PCC oxidation to finally obtain the desired *β,γ*-disubstituted *γ*-butyrolactone (Scheme 10).



Scheme 10. Michael-hemiacetalization reaction between 2-hydroxyacetophenones and cinnamaldehyde.

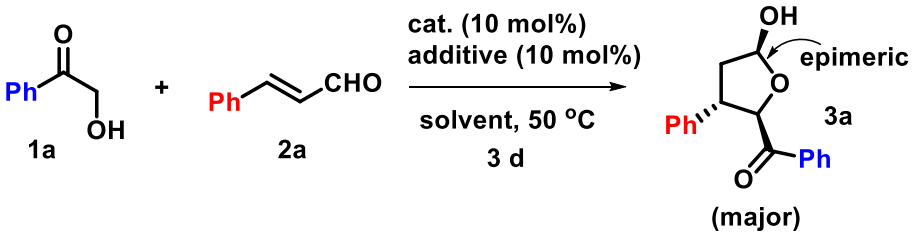
2.5 Results and Discussion

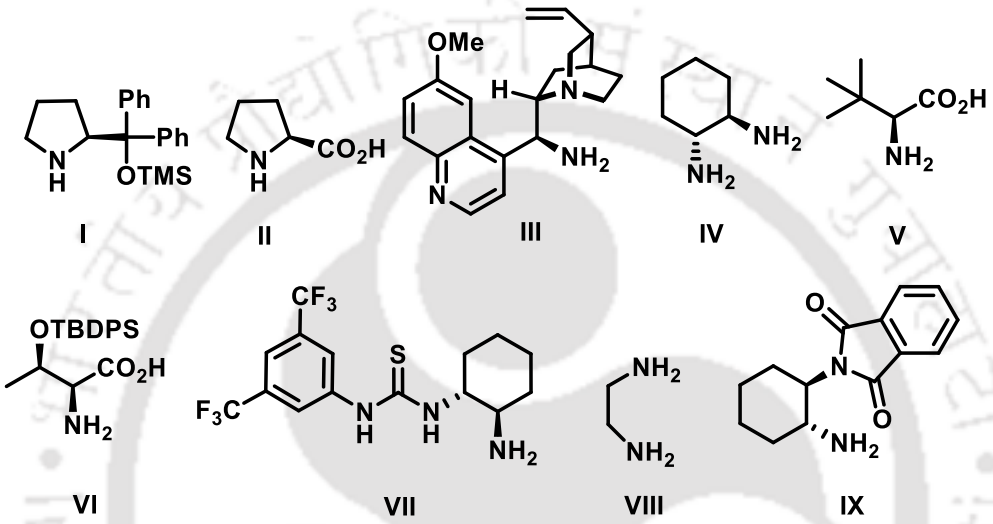
2.5.1 Optimization of catalyst and reaction conditions

Several screenings were taken into account for the optimization of this reaction. We initially screened different primary and secondary amine catalysts, followed by examining the effect of the solvent.

We started our initial experiments by performing the reaction between 2-hydroxyacetophenone and cinnamaldehyde with 10 mol% of Jørgensen-Hayashi catalyst[16] **I** and benzoic acid at 50 ^{o}C, only poor yield of the desired product was observed (Table 1, entry 1). Unfortunately, no trace of the desired product was found with the use of L-proline **II** (Table 1, entry 2).

Table 1. Catalyst screening and optimization of reaction conditions





entry[a]	catalyst	additive	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCO_2H$	$PhCH_3$	<5	n.d	n.d
2	**II**	None	$PhCH_3$	0	-	-
3	**III**	$PhCO_2H$	$PhCH_3$	70	4:1	0
4	**IV**	$PhCO_2H$	$PhCH_3$	<5	n.d	n.d
5	**V**	None	$PhCH_3$	40	4:1	38
6	**VI**	None	$PhCH_3$	44	4:1	32
7	**VII**	$PhCO_2H$	$PhCH_3$	38	4:1	45
8	**I + IV**	$PhCO_2H$	$PhCH_3$	75	3.6:1	93
9	**I + VII**	$PhCO_2H$	$PhCH_3$	85	4:1	96

10	**I + VIII**	$PhCO_2H$	$PhCH_3$	41	3.5:1	95
11	**I + IX**	$PhCO_2H$	$PhCH_3$	60	2:1	90
12	**I + (±)VII**	**$PhCO_2H$**	**$PhCH_3$**	**85**	**4:1**	**96**
13[e]	**I + (±)VII**	$PhCO_2H$	$PhCF_3$	37	4:1	92
14[e]	**I + (±)VII**	$PhCO_2H$	CH_3CN	47	4:1	86
15[e]	**I + (±)VII**	$PhCO_2H$	$CHCl_3$	25	4:1	98
16[e]	**I + (±)VII**	$PhCO_2H$	Xylene	32	4:1	96

[a]Reaction conditions: 0.1 mmol of **1a** with 0.1 mmol of **2a** in 0.2 mL solvent. [b]Isolated combined yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Enantiomeric excesses were determined by HPLC using the stationary phase chiral column of the major diastereomers. [e]Reaction time was 5 d.

Then, we shifted our attention to employ primary amines and primary amino acids in our reaction. With the employment of quinine derived primary amine catalyst **III**, an enhancement in the yield was observed up to 70% with a 4:1 dr ratio with poor enantioselectivity for major diastereomer **3a** (Table 1, entry 3). The poor yield of the desired product was observed with the use of *trans*-cyclohexyl-1,2-diamine **IV** (Table 1, entry 4). Moderate yields and enantioselectivities were obtained with primary amino acids such as L-*tert*-leucine **V** and *O*-TBS-L-threonine **VI** (Table 1, entries 5-6). Improvement of enantioselectivity (45% ee) was achieved with the use of bifunctional primary amine-thiourea catalyst **VII** at the expense of yield (40%) (Table 1, entry 7). Realizing the moderate yields and enantioselectivities due to the lack of simultaneous activation of 2-hydroxyacetophenone and enals by these catalysts, we thought to use a combination of two catalysts in our method. With a combination of two catalysts **I** and **IV,** the enantioselectivity was enhanced to 93% with a 75% yield but with a slight drop in diastereoselectivity (3.6:1) (Table 1, entry 8). Thus, synergistic catalysis[17] became fruitful in our reaction, and excellent enantioselectivity was achieved with the catalyst combination of **I** and **VII** (Table 1, entry 9). High enantioselectivity (95% ee) was also achieved with a catalyst combination of **I** and achiral primary amine **VIII** with poor

yield (Table 1, entry 10). We also screened the catalyst combination of **I** and monamide **IX** with moderate enantioselectivity (90% ee) in 2:1 dr and 60% yield (Table 1, entry 11). Interestingly, the enantioselectivity was retained with catalyst combination of **I** and racemic **VII** and hence illustrates that secondary amine catalyst is responsible for enantioselectivity while the only role of the primary amine is to provide the *E*-enamine from the 2-hydroxyacetophenone (Table 1, entry 12). Different solvents were also screened to improve the diastereoselectivity (Table 1, entries 13-16). However, no beneficial effect could be achieved, and toluene was found to be the best solvent.

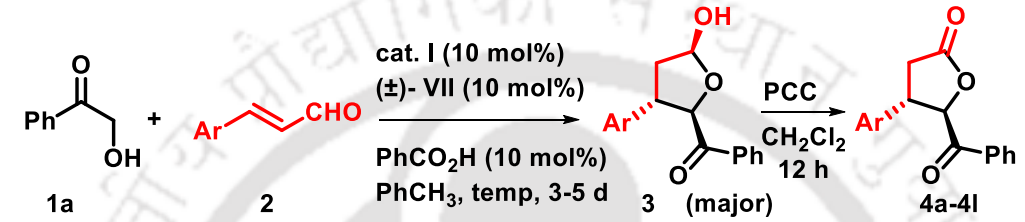
2.5.2 Substrate scope

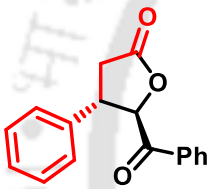
After getting the optimized catalyst and reaction condition in hand, we studied the scope of the Michael-hemiacetalization reaction by varying different substituents on cinnamaldehyde and 2-hydroxyacetophenone.

Initially, the enantioselectivity of unsubstituted lactol **3a** was measured in HPLC, which was found to be 97%. Later, we found that it was challenging to measure the enantioselectivity of other substituted lactols in HPLC due to its instability. Hence, lactol products were oxidized to the corresponding lactone derivatives by pyridinium chlorochromate (PCC).[18] Delightfully, cinnamaldehyde bearing substituents of different electronic properties at the *ortho*, *meta*, and *para* positions gave good to excellent yields and enantioselectivities with >20:1 dr of the desired corresponding lactones (Scheme 11). 4-Methyl substituted enal **2b** provided 60% overall yield and 97% ee of lactone **4b**. It is worth noting that the –OMe substituent at *para*-position of cinnamaldehyde required lower reaction temperature to increase the enantioselectivity of the desired lactone product **4c** from 60% to 96% (Scheme 11, entry 3). The strong electron-withdrawing substituent (-NO_2) at –*para* position of cinnamaldehyde **2e** was well tolerated in our reaction, but a slight drop in yield was observed. Different electron-withdrawing substitutions at –*ortho* position were well endured to give the corresponding lactones in moderate yields with excellent enantio- and diastereoselectivities (Scheme 11). *Ortho*-substitutions were also tolerated, and products **4g** and **4h** were isolated in moderate yields with high enantioselectivities (Scheme 11). 2-Naphthyl group containing enal **2i** underwent the reaction smoothly, delivering product **4i** in 94% ee and >20:1 dr. Enals

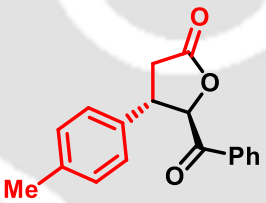
bearing disubstituted aryl rings (**2j-2l)** also gave good results despite being their bulky nature. When the aryl group was substituted by 2-OMe-3-OH group, the desired lactone product was not formed after PCC oxidation because of the interference of –OH group present in the aryl ring and hence lactol product **3m** was isolated with 3.4:1 dr in good yield and high enantioselectivity.

Scheme 11. **Scope of *α,β*-unsaturated aldehydes**[a]

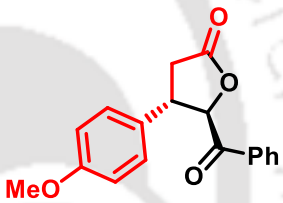




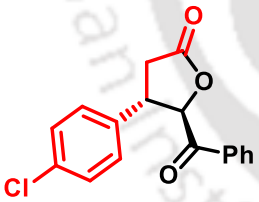
4a, 57%, >20:1 dr,
97% ee, 50 °C



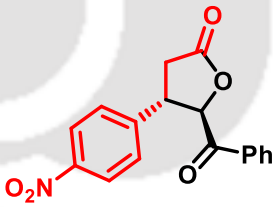
4b, 60%, >20:1 dr
97% ee, 50 °C



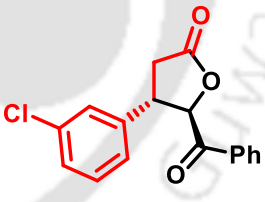
4c, 70%, >20:1 dr
98% ee, rt



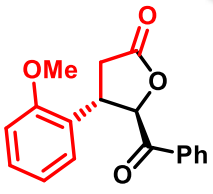
4d, 51%, >20:1 dr
98% ee, rt



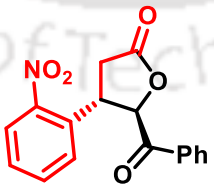
4e, 35%, >20:1 dr
98% ee, rt



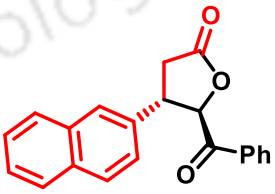
4f, 42%, >20:1 dr
96% ee, rt



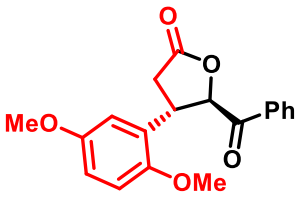
4g, 37%, >20:1 dr
92% ee, 50 °C



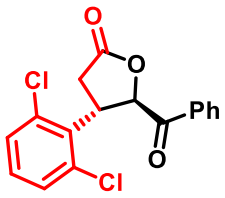
4h, 35%, >20:1 dr
96% ee, 50 °C



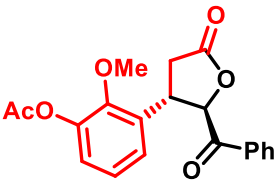
4i, 34%, >20:1 dr
94% ee, rt



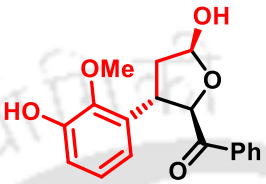
4j, 65%, >20:1 dr,
97% ee, rt



4k, 60%, >20:1 dr
99% ee, rt



4l, 60%, >20:1 dr
91% ee, 50 °C



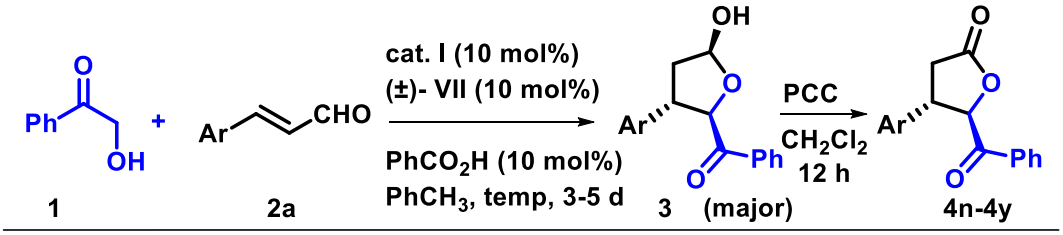
3m, 56%, 3.4:1 dr
94% ee, rt

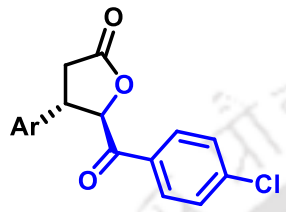
[a]Reaction condition: 0.4 mmol of **1a** with 0.4 mmol of **2** in 0.8 mL $PhCH_3$ for 3-5 d. Isolated combined yield after silica gel column chromatography. The diastereomeric ratio was determined by ^1H NMR. Enantiomeric excess was determined by chiral HPLC using a stationary phase chiral column.

After examining the reaction scope of enals, we shifted our focus to explore a variety of 2-hydroxyacetophenones in the Michael-hemiacetalization reaction, which are shown in Scheme 12. At first, various halogen substituents at *–para* position of the aryl group were reacted, and satisfactory results were obtained with moderate yields and high enantio- and diastereoselectivities (Scheme 12). Different electron-donating and electron-withdrawing substituents were tested at *–meta* position of the aryl ring, and desired lactone product **4r-4t** was formed with good results. Compounds bearing electron-withdrawing and electron-donating substituents at *–ortho* position of the aryl group were also reacted smoothly under the optimized reaction condition. Heteroaromatic hydroxyl ketone **1l** can also be employed, and excellent results were attained. 3,4-disubstituted hydroxy ketone **1m** also delivered the corresponding lactone **4y** with moderate yield and high enantioselectivity.

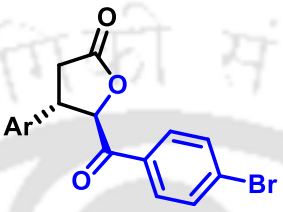
Though a wide range of enals and 2-hydroxyacetophenones with diverse steric and electronic character were well-tolerated, however, this protocol has some limitations as well. Unfortunately, aliphatic substituents did not work in our reaction. Thus, our reaction is limited to various aromatic substitutions only.

Scheme 12. Scope of 2-Hydroxyketones[a]

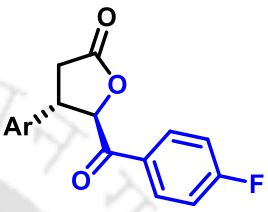




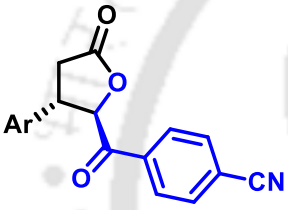
4n, 30%, >20:1 dr,
91% ee, 50 °C



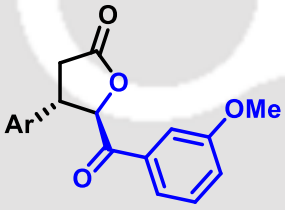
4o, 51%, >20:1 dr
95% ee, 50 °C



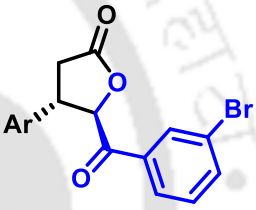
4p, 52%, >20:1 dr
98% ee, rt



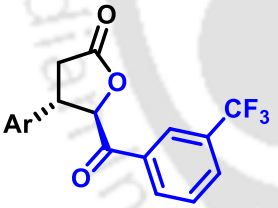
4q, 54%, >20:1 dr
98% ee, rt



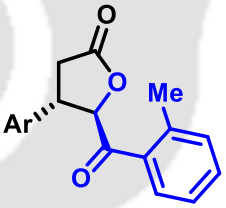
4r, 45%, >20:1 dr
99% ee, rt



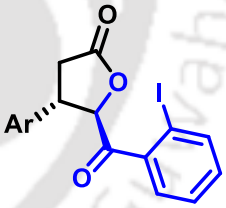
4s, 51%, >20:1 dr
96% ee, rt



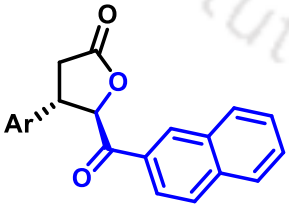
4t, 46%, >20:1 dr
99% ee, rt



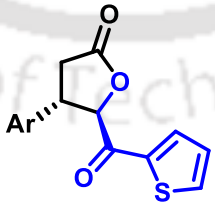
4u, 44%, >20:1 dr
90% ee, 50 °C



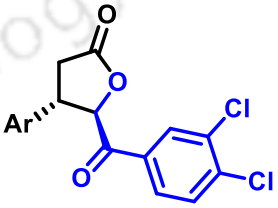
4v, 50%, >20:1 dr
94% ee, 50 °C



4w, 55%, >20:1 dr
91% ee, 50 °C



4x, 45%, >20:1 dr
96% ee, 50 °C

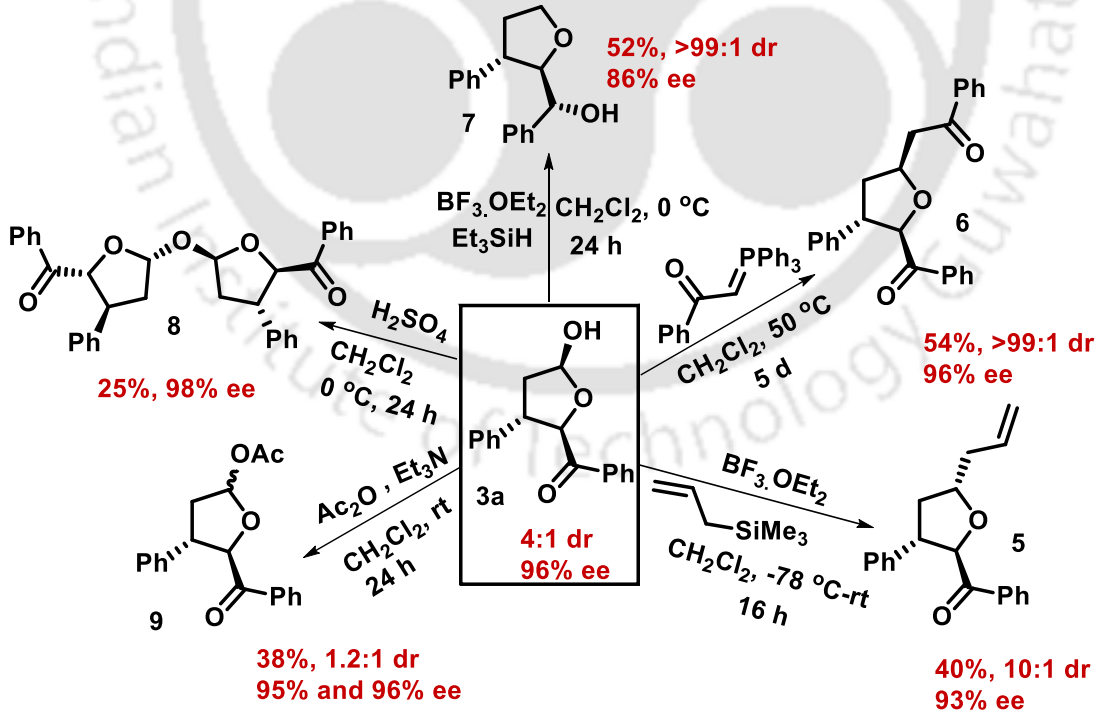


4y, 62%, >20:1 dr
92% ee, 50 °C

[a]Reaction condition: 0.4 mmol of **1** with 0.4 mmol of **2a** in 0.8 mL $PhCH_3$ for 3-5 d. Isolated combined yield after silica gel column chromatography. The diastereomeric ratio was determined by ^1H NMR. Enantiomeric excess was determined by chiral HPLC using a stationary phase chiral column.

2.5.3 Synthetic transformations

To show further the utility of our method, the hemiacetal **3a** was subjected to several useful organic transformations (Scheme 13). Initially, **3a** was treated with allyltrimethyl silane and $BF_3.OEt_2$ to furnish 2,3,5-trisubstituted furan **5** in high diastereo- and enantioselectivity. The relative structure of **5** was confirmed by 2D NMR studies. Similarly, a tandem Wittig-Michael reaction was performed on **3a**, and thus, trisubstituted furan **6** was obtained in moderate yield with perfect diastereoselectivity and without any loss of enantiopurity. Interestingly, the newly generated chiral center at 5-position is in the opposite face to that of **5**. Also, the simultaneous reduction of the hemiacetal group and carbonyl functionality was observed when **3a** was reacted with triethylsilane in the presence of $BF_3.OEt_2$. Thus, **7** was formed as a single diastereomer, and the structure was solved by X-ray crystallography. Lewis acid-catalyzed reversible retro-Michael reaction of **3a** might be responsible for the loss of enantiopurity in **7**. Strong acid like sulphuric acid treatment of **3a** delivered C_2-symmetric bicyclic scaffold **8**, and here also, enantiopurity was perfectly preserved. Then, hemiacetal **3a** was converted to acetates **9** and **9'** with retention of enantioselectivity.



Scheme 13. Synthetic transformations

2.5.4 Determination of product stereochemistry

The absolute configuration of the lactone product **4o** was determined to be (4*S*, 5*R*) by single crystal X-ray crystallography (Figure 2).[19] The absolute configuration of other products is assumed to be same by analogy.

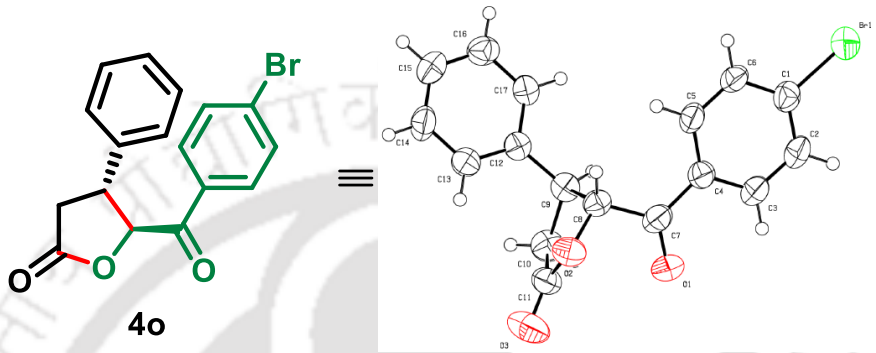


Figure 2. X-ray crystal structure of **4o**

Similarly, the absolute configuration of product **7** was determined to (7*S*, 8*R*, 11*S*) by single crystal X-ray crystallography (Figure 3).[20]

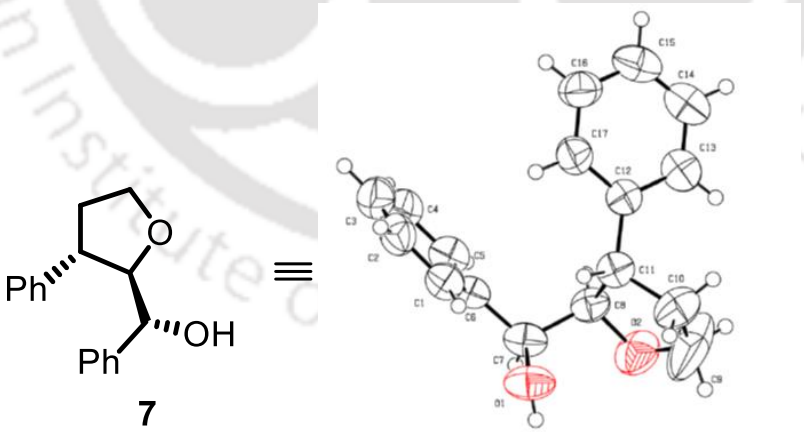
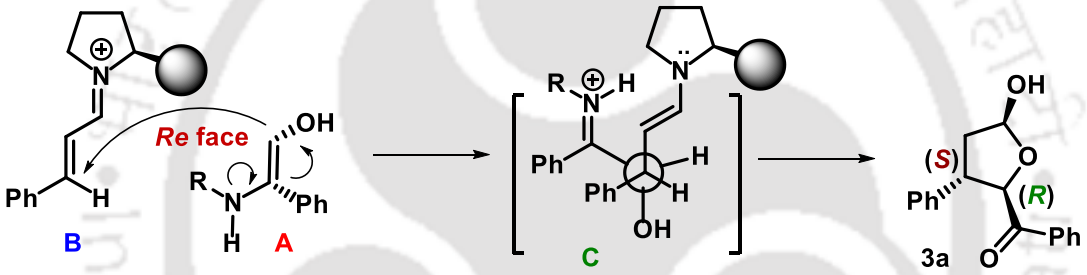


Figure 3. X-ray crystal structure of **7**

2.5.5 The proposed mechanism

The stereochemical outcome of this Michael hemiacetalization reaction can be rationalized using the pre-transition state assembly shown in Scheme 14. From the optimized conditions, it is clear that the chirality of the reaction is monitored by catalyst **I.** We believe that the primary amine thiourea moiety selectively binds with 2-hydroxyacetopheone (**1a**) to provide enamine **A** which then approaches at the *β*-position of the chiral iminium ion **B**. Since the *Si* face of the chiral iminium ion is blocked by bulky diphenylsiloxymethyl group, the addition will take place only from the *Re* face of the iminium ion **B** and *Si* face of enamine **A,** and thus intermediate **C** is formed which leads to the generation of hemiacetal **3a** in (*4S*, *5R*) configuration with high optical purity.



Scheme 14. The proposed mechanism

2.6 Conclusion

This report demonstrates high to excellent enantioselectivities for the first time of the reaction of 2-hydroxyacetophenones in organocatalysis. The methodology also represents rare synergistic catalysis, where both primary and secondary amine catalysts were used concurrently. The *β*,*γ*-disubstituted *γ*-butyrolactol and *γ*-butyrolactone products were obtained in moderate to good yields with high enantioselectivities under mild and simple reaction conditions. Also, selective functionalizations of *γ*-butyrolactol for the synthesis of different trisubstituted and disubstituted tetrahydrofurans are appealing.

2.7 Experimental Section

2.7.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, and Daicel Chiralpak ID Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

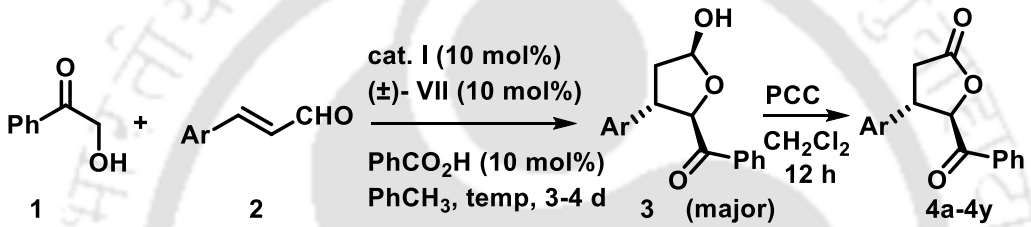
2.7.2 General procedure for the synthesis of *trans*-Cinnamaldehydes and and 2-Hydroxyacetophenones.

trans-Cinnamaldehydes (**2a-m**)[21] and 2-Hydroxyacetophenones (**1b-m**)[22] were synthesized according to the reported procedure.

2.7.3 General Procedure for the Synthesis of Catalyst

The catalyst **VII** was prepared according to reported procedures.[23]

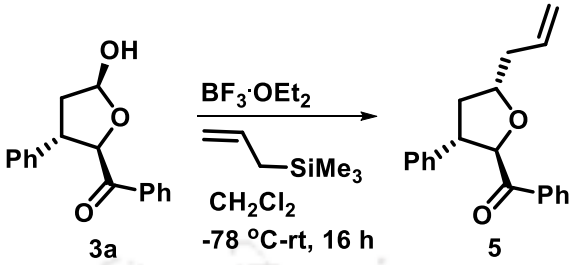
2.7.4 General procedure for the synthesis of compound 4a-4y



In an oven-dried round-bottom flask, 2-hydroxyacetophenones **1** (55 mg, 0.4 mmol), *trans*-cinnamaldehydes **2** (51 µL, 0.4 mmol), 10 mol% of catalyst (**I** and achiral **VII**), and 10 mol% of $PhCO_2H$ were taken. Then, 0.8 mL of $PhCH_3$ was added to the reaction mixture, which was stirred at 50 °C for 3 d. Completion of the reaction was checked by TLC. After the completion of the reaction, the solvent was concentrated, and the reaction mixture was directly subjected to PCC oxidation.

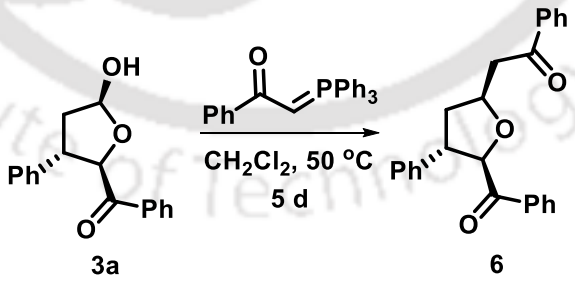
PCC Oxidation of Lactol: To the vacuum-dried reaction mixture, CH_2Cl_2 was added to the reaction mixture as the first step and allowed to stir at 0 °C. Then, 1.5 equiv. of PCC was added; the reaction mixture was slowly warmed to rt and stirred overnight. The progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was concentrated, and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ ethyl acetate (10%) to afford the desired product **4** (61 mg, 57% yield) as a yellow solid.

2.7.5 General procedure for the synthesis of compound 5



In an oven-dried round bottom flask, to a solution of **3a** (54 mg, 0.2 mmol) in dry CH_2Cl_2 (0.4 mL), 2 equivalents of trimethyl allyl silane were added *via* syringe, and the reaction mixture was cooled to -78 ^oC. Then, 3 equiv. of $BF_3{\cdot}Et_2O$ were also added via syringe, and the reaction mixture was allowed to warm up to room temperature over 16 h. The progress of the reaction was monitored by TLC. Water (2 mL/mmol) was added to the reaction mixture and extracted with CH_2Cl_2 (3 X 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (97/3) to afford desired product **5** (23 mg, 40% yield) as a yellow semi-solid. The dr value was found to be 10:1 by ^1H NMR analysis.

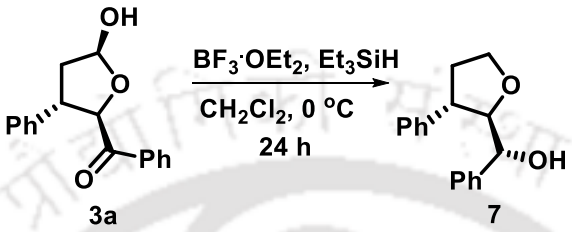
2.7.6 General procedure for the synthesis of compound 6



In an oven-dried round bottom flask, to a solution of **3a** (54 mg, 0.2 mmol) in dry CH_2Cl_2 (16 mL), triphenylphosphorane (76 mg, 0.2 mmol) was added to the reaction mixture and allowed to stir at 50 ^oC for 5 d. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure. The residue was purified by

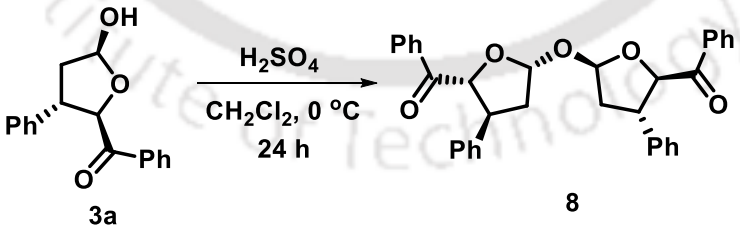
column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford desired product **6** (40 mg, 54% yield) as a light yellow semi-solid. The dr value was found to be >99:1 by ^{1}H NMR analysis.

2.7.7 General procedure for the synthesis of compound 7



In an oven-dried round bottom flask, to a solution of **3a** (54 mg, 0.2 mmol) and triethyl silane (96 µL, 0.6 mmol) in dry CH_2Cl_2 (0.4 mL), 3.3 equivalents of $BF_3{\cdot}Et_2O$ was added *via* syringe, and the reaction mixture was allowed to stir at 0 ^{o}C for 24 h. The progress of the reaction was monitored by TLC. The reaction was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 X 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford desired product **7** (27 mg, 52% yield) as a yellow solid.

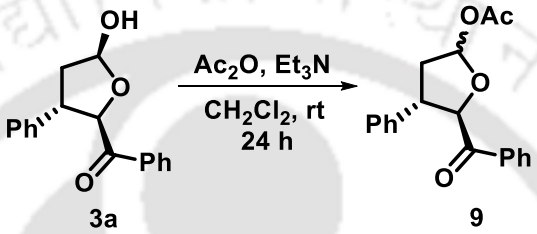
2.7.8 General procedure for the synthesis of compound 8



In an oven-dried round bottom flask, to a solution of one drop of sulfuric acid in 3mL of CH_2Cl_2, **3a** (33 mg, 0.123 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise at 0 ^{o}C, and the reaction mixture was allowed to stir at 0 ^{o}C for 24 h. The progress of the reaction was monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ and extracted

with CH_2Cl_2 (3 X 20 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (95/5) to afford desired product **8** (16 mg, 25% yield) as a white solid.

2.7.9 General procedure for the synthesis of compound 9



In an oven-dried round bottom flask, to a solution of **3a** (54 mg, 0.2 mmol) in dry CH_2Cl_2 (4 mL), 1.5 equiv. of acetic anhydride and 1.5 equiv. of triethylamine were added via syringe and the reaction mixture was allowed to stir at room temperature for 4 d. The progress of the reaction was monitored by TLC. The solvent was concentrated under a vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford the desired product **9** (24 mg, 38% yield) as a light yellow solid. The dr value was found to be 1.2:1 by ^{1}H NMR analysis.

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2.7.10 Crystal structure of compound 4o[19]

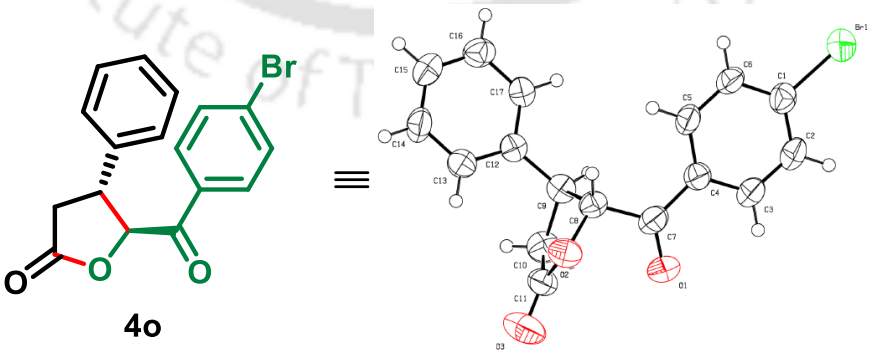


Table 2. Crystal data and structure refinement for compound 4o

Parameters	4o
CCDC No.	1511229
Empirical formula	$C_{17}H_{16}O_3Br$
Formula weight	345.17
Crystal habit, colour	needle/white
Crystal size, mm^3	0.32 × 0.24 × 0.12
Temperature, *T*	296(2) K
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	*' P 21 21 21'*
Unit cell dimensions	a = 5.7218(8) Å b = 5.9498(8) Å c = 42.706(6) Å α = 90.00°, β = 90.00°, γ = 90.00°
Volume, *V* ($Å^3$)	1453.9(3)
Z	4
Calculated density, Mg/m^3	1.577
Absorption coefficient, μ (mm^{-1})	2.834
F(000)	696.0
θ range for data collection	0.95° to 25.23°
Limiting indices	$-6 \le h \le 6, -7 \le k \le 6,$ $-51 \le l \le 49$
Reflection collected/unique	2619/2110
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	2619/0/190

Goodness of fit on F^2	1.067
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0316, wR2 = 0.0762
R indices (all data)	R1 = 0.0494, wR2 = 0.0973

2.7.11 Crystal structure of compound 7[20]

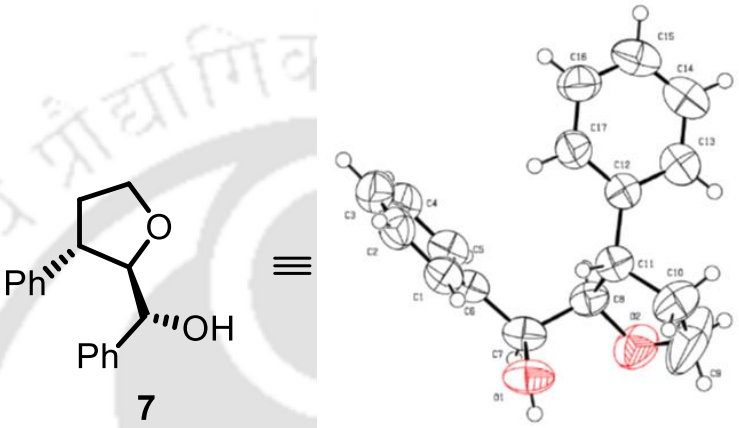
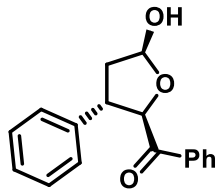


Table 3. Crystal data and structure refinement for compound 7

Parameters	**7**
CCDC No.	1515196
Empirical formula	$C_{17}H_{18}O_2$
Formula weight	254.31
Crystal habit, colour	needle/white
Crystal size, mm^3	0.32× 0.24 × 0.12
Temperature, T	296(2) K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	*' P 21'*

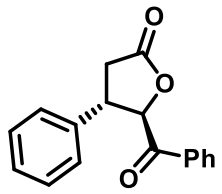
Unit cell dimensions	a = 7.9793(9) Å b = 5.7456(9) Å c = 15.4757(16) Å α = 90.00°, β = 103.111(7)°, γ = 90.00°
Volume, V (Å^3)	691.00(15)
Z	2
Calculated density, Mg/m^3	1.222
Absorption coefficient, μ (mm^{-1})	0.079
F(000)	272.0
θ range for data collection	1.35^o to 24.74^o
Limiting indices	–8 ≤ h ≤ 9, –6 ≤ k ≤ 6, –18 ≤ l ≤ 18
Reflection collected/unique	2131/1360
Max. and min. transmission	0.991/ 0.978
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	2131/1/172
Goodness of fit on F^2	1.083
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0562, wR2 = 0.1209
R indices (all data)	R1 = 0.0910, wR2 = 0.1343

2.8 Characterization Data of Products



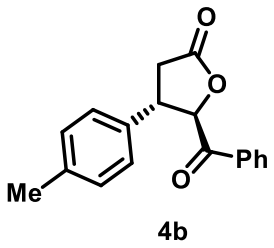
3a

((2S,4S,5R,)-5-hydroxy-3-phenyltetrahydrofuran-2-yl) (phenyl)methanone (3a) was obtained as a light yellow solid in 85% yield (23 mg) after column chromatography**.** The dr value was found to be 4:1 by ^{1}H NMR analysis. M.P. = 126-128 ^{o}C. **IR:** ν 3396(broad), 3025, 2938, 1687, 1578, 1447, 1237, 947, 693 cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77 (t, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.41 – 7.31 (m, 5H), 7.27 (q, *J* = 7.1 Hz, 4H), 5.92 (d, *J* = 2.7 Hz, 0.2H), 5.85 (s, 1H), 5.52 (dd, *J* = 6.6, 3.9 Hz, 1.2H), 3.74 (dd, *J* = 13.5, 8.0 Hz, 1H), 3.65 (dd, *J* = 17.7, 6.8 Hz, 0.3H), 2.80 – 2.71 (m, 0.3H), 2.47 – 2.32 (m, 2H), 2.22 – 2.15 (m, 0.3H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 200.0, 141.9, 134.5, 134.1, 133.6, 129.2, 129.2, 129.0, 128.8, 128.6, 128.3, 127.5, 127.5, 127.2, 101.0, 100.0, 87.7, 85.9, 47.8, 47.1, 44.2, 42.2. **HPLC Analysis:** ee = 96%, Chiralpak OD Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.7 min, t_{minor} = 15.4 min). **ESI HRMS**: calcd. For $C_{17}H_{16}NaO_3$ $[M+Na]^+$ 291.0997, found 291.0997. The optical rotation of **3a** was found to be $[\alpha]^{21}_{D}$ = -113.2 (c 0.02, $CHCl_3$).



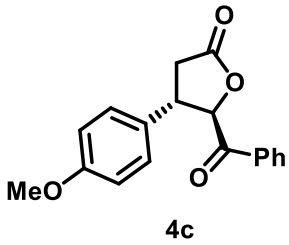
4a

(4S,5R)-5-benzoyl-4-phenyldihydrofuran-2(3H)-one (4a) was obtained as a light yellow solid in 57% combined yield (60 mg) after column chromatography**.** M.P. = 97-99 ^{o}C. **IR:** ν 3375, 3029, 2923, 1776, 1695, 1593, 1448, 1199, 1063, 976, 686 cm^{-1}. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.62 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.30 – 7.26 (m, 2H), 5.77 (d, *J* = 3.9 Hz, 1H), 3.92 – 3.85 (m, 1H), 3.08 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.69 (dd, *J* = 18.0, 4.6 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 193.6, 175.7, 140.7, 134.6, 133.7, 129.6, 129.2, 129.0, 128.3, 126.9, 84.5, 43.3, 35.4. **HPLC Analysis:** ee = 97%, Chiralpak OD Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 29.7 min, t_{minor} = 35.6 min). **ESI HRMS**: calcd. For $C_{17}H_{15}O_3$ $[M+H]^+$ 267.1021, found 267.1026. The optical rotation of **4a** was found to be $[\alpha]^{24}_{D}$ = -104.0 (c 0.02, $CHCl_3$).



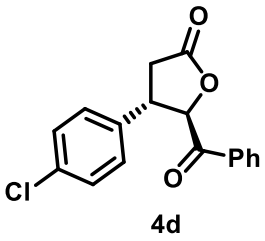
4b

(4S,5R)-5-benzoyl-4-(p-tolyl)dihydrofuran-2(3H)-one (4b) was obtained as a light yellow semi-solid in 60% combined yield (67 mg) after column chromatography**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.18 (q, *J* = 8.1 Hz, 4H), 5.76 (d, *J* = 3.8 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.05 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.66 (dd, *J* = 18.0, 4.5 Hz, 1H), 2.36 (s, 3H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 193.7, 175.8, 138.0, 137.7, 134.5, 133.7, 130.2, 129.1, 129.0, 126.7, 84.6, 43.0, 35.4, 21.2. **HPLC Analysis:** ee = 97%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 29.2 min, t_{minor} = 24.4 min). **ESI HRMS**: calcd. For $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1178, found 281.1181. The optical rotation of **4b** was found to be $[\alpha]^{27}_D$ = -97.0 (c 0.02, $CHCl_3$).



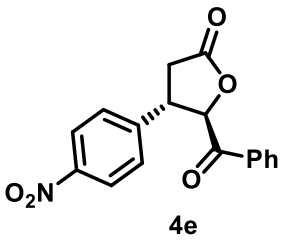
4c

(4S,5R)-5-benzoyl-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one (4c) was obtained as a yellow semi-solid in 70% combined yield (78 mg) after column chromatography**. ^{1}H NMR (400 MHz, $CDCl_3$)** 7.89 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.74 (d, *J* = 3.9 Hz, 1H), 3.81 (s, 3H), 3.05 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.65 (dd, *J* = 18.0, 4.7 Hz, 1H).**^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 193.7, 175.8, 159.5, 134.6, 133.7, 132.7, 129.2, 129.0, 128.0, 114.9, 84.8, 55.5, 42.7, 35.5, 29.8. **HPLC Analysis:** ee = 98%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 34.6 min, t_{minor} = 31.1 min). **ESI HRMS**: calcd. For $C_{18}H_{17}O_4$ $[M+H]^+$ 297.1127, found 297.1126. The optical rotation of **4c** was found to be $[\alpha]^{25}_D$ = -74.0 (c 0.02, $CHCl_3$).



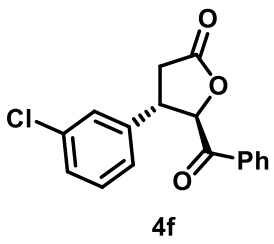
4d

(4S,5R)-5-benzoyl-4-(4-chlorophenyl)dihydrofuran-2(3H)-one (4d) was obtained as a yellow semi-solid in 51% combined yield (61 mg) after column chromatography**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.72 (d, *J* = 4.0 Hz, 1H), 3.89 (dt, *J* = 9.1, 4.4 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.66 (dd, *J* = 18.0, 4.8 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 193.3, 175.3, 139.0, 134.7, 134.2, 133.6, 129.8, 129.1, 129.1, 128.3, 84.2, 42.6, 35.3. **HPLC Analysis:** ee = 98%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 28.0 min, t_{minor} = 24.9 min). **ESI HRMS**: calcd. For $C_{17}H_{14}ClO_3$ $[M+H]^+$ 301.0631, found 301.0631. The optical rotation of **4d** was found to be $[\alpha]^{25}_D$ = -50.5 (c 0.05, $CHCl_3$).



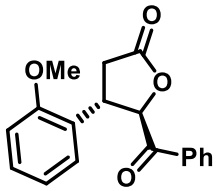
4e

(4S,5R)-5-benzoyl-4-(4-nitrophenyl)dihydrofuran-2(3H)-one (4e) was obtained as a yellow semi-solid in 35% combined yield (43 mg) after column chromatography**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.26 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.51 (dd, *J* = 8.2, 6.1 Hz, 4H), 5.75 (d, *J* = 4.4 Hz, 1H), 4.12 (dt, *J* = 9.6, 4.9 Hz, 1H), 3.16 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.74 (dd, *J* = 18.0, 5.4 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 192.8, 174.3, 147.5, 135.0, 129.3, 129.2, 128.1, 124.9, 83.6, 42.6, 35.1. **HPLC Analysis:** ee = 98%, Chiralpak IB Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 61.5 min, t_{minor} = 56.5 min). **ESI HRMS**: calcd. For $C_{17}H_{14}NO_5$ $[M+H]^+$ 312.0872, found 312.0879. The optical rotation of **4e** was found to be $[\alpha]^{27}_D$ = -52.8 (c 0.01, $CHCl_3$).



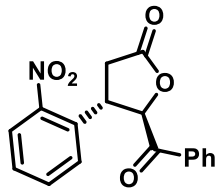
4f

(4S,5R)-5-benzoyl-4-(3-chlorophenyl)dihydrofuran-2(3H)-one (4f) was obtained as a yellow semi-solid in 42% combined yield (50 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.34 – 7.30 (m, 2H), 7.27 (s, 1H), 7.18 (d, *J* = 6.5 Hz, 1H), 5.73 (d, *J* = 4.0 Hz, 1H), 3.91 (dt, *J* = 9.1, 4.4 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.68 (dd, *J* = 18.1, 4.9 Hz, 1H).**13C {1H} NMR (150 MHz, $CDCl_3$)** δ 193.3, 175.0, 142.6, 135.5, 134.7, 133.7, 131.0, 129.3, 129.1, 128.5, 127.2, 125.1, 84.0, 42.7, 35.2. **HPLC Analysis:** ee = 96%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 26.4 min, t_{minor} = 23.8 min). **ESI HRMS**: calcd. For $C_{17}H_{14}ClO_3$ $[M+H]^+$ 301.0631, found 301.0638. The optical rotation of **4f** was found to be $[\alpha]^{27}_D$ = -74.3 (c 0.03, $CHCl_3$).



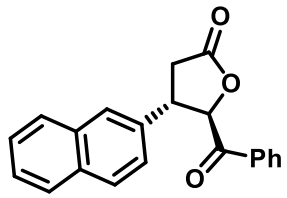
4g

(4S,5R)-5-benzoyl-4-(2-methoxyphenyl)dihydrofuran-2(3H)-one (4g) was obtained as a light yellow semi-solid in 37% combined yield (44 mg) after column chromatography**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.2 Hz, 2H), 5.79 (d, *J* = 4.0 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.81 (s, 3H), 2.99 (dd, *J* = 17.9, 10.1 Hz, 1H), 2.78 (dd, *J* = 17.9, 4.5 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 194.5, 176.5, 157.1, 134.3, 129.5, 129.1, 129.0, 129.0, 128.3, 121.2, 111.3, 83.3, 55.3, 39.7, 33.8, 29.9. **HPLC Analysis:** ee = 92%, Chiralpak OD Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 28.0 min, t_{minor} = 32.0 min). **ESI HRMS**: calcd. For $C_{18}H_{20}NO_4$ $[M+NH_4]^+$ 314.1392, found 314.1399. The optical rotation of **4g** was found to be $[\alpha]^{26}_D$ = -25.1 (c 0.01, $CHCl_3$).



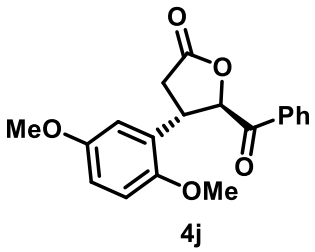
4h

(4S,5R)-5-benzoyl-4-(2-nitrophenyl)dihydrofuran-2(3H)-one (4h) was obtained as a yellow semi-solid in 35% combined yield (43 mg) after column chromatography**.** **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (t, *J* = 8.7 Hz, 3H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 (dd, *J* = 11.8, 8.0 Hz, 2H), 7.50 (dd, *J* = 14.0, 6.4 Hz, 2H), 5.85 (d, *J* = 2.5 Hz, 1H), 4.51 (dt, *J* = 9.6, 2.7 Hz, 1H), 3.29 (dd, *J* = 18.3, 9.6 Hz, 1H), 2.71 (dd, *J* = 18.3, 2.9 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 193.2, 175.1, 135.7, 134.8, 134.4, 133.7, 129.3, 129.2, 127.8, 125.5, 83.1, 38.1, 35.1, 29.9. **HPLC Analysis:** ee = 96%, Chiralpak OD Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 68.8 min, t_{minor} = 75.3 min). **ESI HRMS**: calcd. For $C_{17}H_{14}NO_5$ $[M+H]^+$ 312.0872, found 312.0871. The optical rotation of **4h** was found to be $[\alpha]^{25}_D$ = -12.4 (c 0.007, $CHCl_3$).



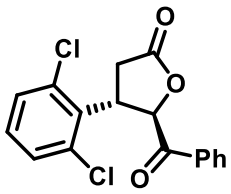
4i

(4S,5R)-5-benzoyl-4-(naphthalen-2-yl)dihydrofuran-2(3H)-one (4i) was obtained as a yellow solid in 34% combined yield (43 mg) after column chromatography**.** M.P. = 149-151 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.2 Hz, 3H), 7.86 (dd, *J* = 14.6, 8.1 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.47 (m, 4H), 7.45 (t, *J* = 7.8 Hz, 2H), 5.99 (d, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 9.4 Hz, 1H), 3.25 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.75 (dd, *J* = 18.0, 2.6 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 194.2, 175.8, 136.5, 134.7, 134.4, 133.7, 130.8, 129.5, 129.2, 129.2, 128.9, 127.1, 126.4, 125.9, 123.1, 122.5, 83.6, 38.2, 35.1. **HPLC Analysis:** ee = 94%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 51.1 min, t_{minor} = 33.4 min). **ESI HRMS**: calcd. For $C_{21}H_{17}O_3$ $[M+H]^+$ 317.1178, found 317.1178. The optical rotation of **4i** was found to be $[\alpha]^{27}_D$ = -28.3 (c 0.01, $CHCl_3$).



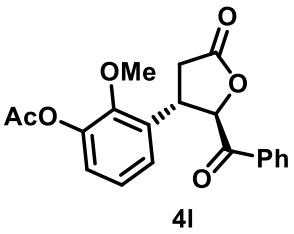
4j

(4S,5R)-5-benzoyl-4-(2,5-dimethoxyphenyl)dihydrofuran-2(3H)-one (4j) was obtained as a yellow semi-solid in 65% combined yield (85 mg) after column chromatography**.** **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 6.88 – 6.80 (m, 2H), 6.71 (s, 1H), 5.78 (d, *J* = 4.2 Hz, 1H), 3.95 (dt, *J* = 8.6, 4.4 Hz, 1H), 3.74 (s, 6H), 2.97 (dd, *J* = 17.9, 10.1 Hz, 1H), 2.76 (dd, *J* = 17.9, 4.7 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 194.4, 176.4, 153.8, 151.2, 134.3, 133.9, 129.2, 129.1, 128.9, 115.3, 113.3, 112.0, 83.2, 55.9, 55.7, 39.7, 33.8. **HPLC Analysis:** ee = 97%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 25.9 min, t_{minor} = 22.9 min). **ESI HRMS**: calcd. For $C_{19}H_{19}O_5$ $[M+H]^+$ 327.1232, found 327.1231. The optical rotation of **4j** was found to be $[\alpha]^{24}_D$ = -22.0 (c 0.01, $CHCl_3$).



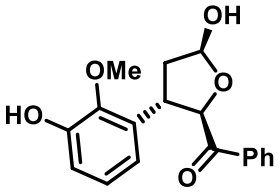
4k

(4S,5R)-5-benzoyl-4-(2,6-dichlorophenyl)dihydrofuran-2(3H)-one (4k) was obtained as a yellow solid in 60% combined yield (80 mg) after column chromatography**.** M.P. = 148-150 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.18 (m, 1H), 6.03 (d, *J* = 6.7 Hz, 1H), 4.97 (dt, *J* = 11.7, 7.2 Hz, 1H), 3.07 (ddd, *J* = 30.3, 18.6, 9.7 Hz, 2H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 193.9, 175.0, 135.9, 134.4, 134.2, 129.8, 129.2, 128.9, 81.5, 37.5, 33.2. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.6 min, t_{minor} = 14.4 min). **ESI HRMS**: calcd. For $C_{17}H_{13}Cl_2O_3$ $[M+H]^+$ 335.0242, found 335.0247. The optical rotation of **4k** was found to be $[\alpha]^{23}_D$ = -26.1 (c 0.007, $CHCl_3$).



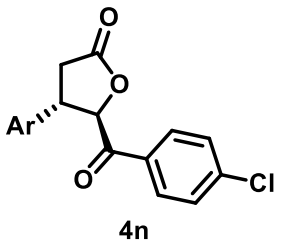
4l

3-((2R,3S)-2-benzoyl-5-oxotetrahydrofuran-3-yl)-2-methoxyphenyl acetate (4l) was obtained as a light yellow semi-solid in 60% combined yield (85 mg) after column chromatography**. ^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.41 (t, *J* = 7.1 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.74 (m, 2H), 5.72 (s, 1H), 3.73 (s, 3H), 3.02 – 2.93 (m, 2H), 2.63 (dd, *J* = 17.9, 2.9 Hz, 1H), 2.24 (s, 3H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 193.5, 175.5, 169.1, 151.8, 139.4, 134.6, 133.6, 129.0, 123.7, 118.8, 111.0, 84.2, 56.0, 51.2, 43.1, 35.2, 22.8, 20.7. **HPLC Analysis:** ee = 91%, Chiralpak OD Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 53.3 min, t_{minor} = 61.8 min). **ESI HRMS**: calcd. For $C_{20}H_{19}O_6$ $[M+H]^+$ 355.1182, found 355.1188. The optical rotation of **4l** was found to be $[\alpha]^{24}_D$ = -46.3 (c 0.06, $CHCl_3$).



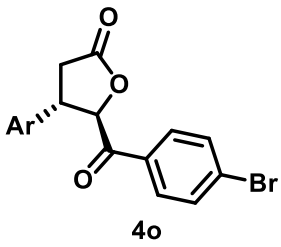
3m

((2R,3S)-5-hydroxy-3-(3-hydroxy-2-methoxyphenyl) tetrahydrofuran-2-yl)(phenyl)methanone (3m) was obtained as a yellow solid in 56% yield (18 mg) after column chromatography**.** M.P. = 155-157 ^{o}C. The dr value was found to be 3.4:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.76 (t, *J* = 6.6 Hz, 2H), 7.54 (dd, *J* = 16.1, 8.6 Hz, 1H), 7.41 – 7.32 (m, 3H), 6.87 (ddd, *J* = 11.5, 9.4, 1.8 Hz, 2H), 6.74 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 5.91 (dd, *J* = 5.4, 2.6 Hz, 0.29H), 5.82 (dd, *J* = 4.6, 1.5 Hz, 1H), 5.47 (dd, *J* = 6.7, 3.3 Hz, 1H), 3.82 (s, 3H), 3.65 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.45 – 2.27 (m, 2H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 200.2, 147.0, 144.9, 134.5, 134.1, 133.5, 129.2, 128.8, 128.6, 120.1, 114.9, 110.0, 100.9, 87.8, 56.1, 47.6, 44.3. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 16.8 min, t_{minor} = 11.9 min). **ESI HRMS**: calcd. For $C_{18}H_{18}NaO_5$ $[M+Na]^+$ 337.1052, found 337.1055. The optical rotation of **3m** was found to be $[\alpha]^{26}_D$ = -113.3 (c 0.005, $CHCl_3$).



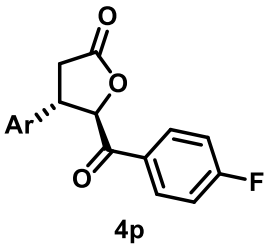
4n

(4S,5R)-5-(4-chlorobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4n) was obtained as a yellow semi-solid in 30% combined yield (36 mg) after column chromatography**.** **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.47 – 7.34 (m, 5H), 7.29 – 7.25 (m, 2H), 5.70 (d, *J* = 4.2 Hz, 1H), 3.90 (dt, *J* = 9.4, 4.7 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.72 (dd, *J* = 18.0, 5.1 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 192.5, 175.4, 141.1, 140.4, 132.1, 130.5, 129.7, 129.5, 128.4, 126.9, 84.4, 43.1, 35.4. **HPLC Analysis:** ee = 91%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 24.5 min, t_{minor} = 26.4 min). **ESI HRMS**: calcd. For $C_{17}H_{14}ClO_3$ $[M+H]^+$ 301.0631, found 301.0657. The optical rotation of **4n** was found to be $[\alpha]^{24}_D$ = -78.5 (c 0.009, $CHCl_3$).



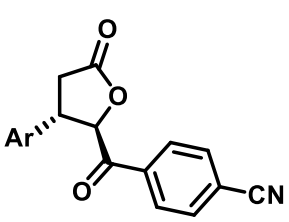
4o

(4S,5R)-5-(4-bromobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4o) was obtained as a light yellow solid in 51% combined yield (70 mg) after column chromatography. M.P. = 114-116 ^{o}C. CCDC number assigned to structure 4o is 1511229. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.43 – 7.34 (m, 3H), 7.27 (d, *J* = 7.5 Hz, 2H), 5.70 (d, *J* = 4.3 Hz, 1H), 3.89 (dt, *J* = 9.4, 4.8 Hz, 1H), 3.07 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.72 (dd, *J* = 18.0, 5.1 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 192.7, 175.3, 140.3, 132.5, 130.5, 130.1, 129.7, 128.3, 126.9, 84.4, 43.1, 35.4. **HPLC Analysis:** ee = 95%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 33.8 min, t_{minor} = 36.8 min). **ESI HRMS**: calcd. For $C_{17}H_{14}BrO_3$ $[M+H]^+$ 345.0126, found 345.0129. The optical rotation of **4o** was found to be $[\alpha]^{25}_D$ = -106.3 (c 0.006, $CHCl_3$).



4p

(4S,5R)-5-(4-fluorobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4p) was obtained as a yellow semi-solid in 52% combined yield (59 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93 (s, 2H), 7.39 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.1 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 2H), 5.70 (s, 1H), 3.90 (d, *J* = 4.0 Hz, 1H), 3.07 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.71 (d, *J* = 18.1 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 192.1, 175.4, 167.4, 165.7, 140.4, 131.9, 131.9, 130.3, 129.6, 128.3, 126.9, 116.5, 116.3, 84.4, 43.1, 35.4. **HPLC Analysis:** ee = 98%, Chiralpak IB Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.9 min, t_{minor} = 15.4 min). **ESI HRMS**: calcd. For $C_{17}H_{14}FO_3$ $[M+H]^+$ 285.0927, found 285.0946. The optical rotation of **4p** was found to be $[\alpha]^{24}_D$ = -107.2 (c 0.04, $CHCl_3$).



4q

4-((2R,3S)-5-oxo-3-phenyltetrahydrofuran-2-carbonyl)benzonitrile (4q) was obtained as a yellow semi solid in 54% combined yield (63 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.29 – 7.25 (m, 2H), 5.68 (d, *J* = 4.8 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.08 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.76 (dd, *J* = 18.1, 5.9 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 192.6, 174.8, 139.8, 136.9, 132.9, 129.7, 129.6, 128.5, 127.0, 117.7, 117.7, 84.6, 42.9, 35.5. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 35.9 min, t_{minor} = 55.1 min). **ESI HRMS**: calcd. For $C_{18}H_{14}NO_3$ $[M+H]^+$ 292.0974, found 292.0974. The optical rotation of **4q** was found to be $[\alpha]^{25}_D$ = -83.1 (c 0.04, $CHCl_3$).

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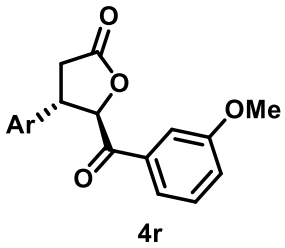
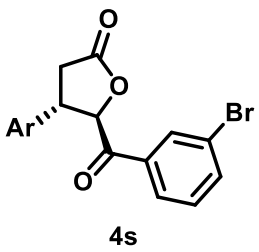


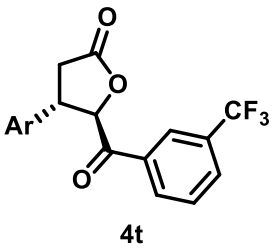
4r

(4S,5R)-5-(3-methoxybenzoyl)-4-phenyldihydrofuran-2(3H)-one (4r) was obtained as a yellow semi-solid in 45% combined yield (53 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.45 – 7.43 (m, 1H), 7.39 (dt, *J* = 13.5, 6.7 Hz, 3H), 7.37 – 7.32 (m, 2H), 7.29 – 7.26 (m, 2H), 7.16 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.76 (d, *J* = 3.8 Hz, 1H), 3.86 – 3.83 (m, 1H), 3.81 (s, 3H), 3.07 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.68 (dd, *J* = 18.0, 4.5 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 193.5, 175.7, 160.2, 140.8, 134.9, 130.1, 129.6, 128.3, 126.8, 121.5, 121.4, 112.9, 84.5, 55.6, 43.4, 35.3. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 14.8 min, t_{minor} = 16.0 min). **ESI HRMS**: calcd. For $C_{18}H_{17}O_4$ $[M+H]^+$ 297.1127, found 297.1125. The optical rotation of **4r** was found to be $[\alpha]^{23}_D$ = -111.9 (c 0.03, $CHCl_3$).



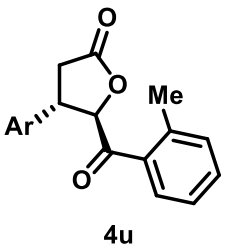
4s

(4S,5R)-5-(3-bromobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4s) was obtained as a yellow semi solid in 51% combined yield (70 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.29 – 7.25 (m, 2H), 5.67 (d, *J* = 4.4 Hz, 1H), 3.91 (dt, *J* = 9.6, 4.9 Hz, 1H), 3.07 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.74 (dd, *J* = 18.1, 5.3 Hz, 1H).**^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 192.4, 175.2, 140.2, 137.4, 135.5, 132.1, 130.7, 129.7, 128.4, 127.6, 126.9, 123.5, 84.5, 43.1, 35.4, 29.8. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.9 min, t_{minor} = 14.0 min). **ESI HRMS**: calcd. For $C_{17}H_{14}BrO_3$ $[M+H]^+$ 345.0126, found 345.0121. The optical rotation of **4s** was found to be $[\alpha]^{24}_D$ = -69.0 (c 0.02, $CHCl_3$).



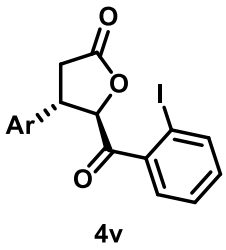
4t

(4S,5R)-4-phenyl-5-(3-(trifluoromethyl)benzoyl) dihydrofuran-2(3H)-one (4t) was obtained as a yellow semi solid in 46% combined yield (62 mg) after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.28 (dd, *J* = 12.2, 5.1 Hz, 2H), 5.72 (d, *J* = 4.7 Hz, 1H), 3.99 – 3.90 (m, 1H), 3.09 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.77 (dd, *J* = 18.1, 5.7 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 192.5, 175.1, 140.0, 134.4, 132.2, 131.7, 130.9, 129.9, 129.7, 128.5, 126.9, 126.0, 84.6, 43.0, 35.4. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.9 min, t_{minor} = 11.4 min). **ESI HRMS**: calcd. For $C_{18}H_{14}F_3O_3$ $[M+H]^+$ 335.0895, found 335.0896. The optical rotation of **4t** was found to be $[\alpha]^{27}_D$ = -56.0 (c 0.04, $CHCl_3$).



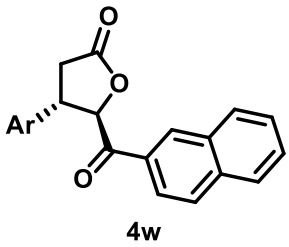
4u

(4S,5R)-5-(2-methylbenzoyl)-4-phenyldihydrofuran-2(3H)-one (4u) was obtained as a yellow semi solid in 44% combined yield (49 mg) after column chromatography. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.55 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.44 (td, *J* = 7.5, 1.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.21 (m, 3H), 5.69 (d, *J* = 4.0 Hz, 1H), 3.83 (dt, *J* = 9.1, 4.4 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.69 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.57 (s, 3H). **^{13}C {1H} NMR (126 MHz, $CDCl_3$)** δ 196.6, 175.7, 140.7, 140.6, 133.5, 133.0, 132.7, 129.6, 129.5, 128.2, 126.8, 126.1, 85.5, 43.5, 35.5, 21.9. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.9 min, t_{minor} = 12.6 min). **ESI HRMS**: calcd. For $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1178, found 281.1173. The optical rotation of **4u** was found to be $[\alpha]^{25}_D$ = -114.0 (c 0.02, $CHCl_3$).



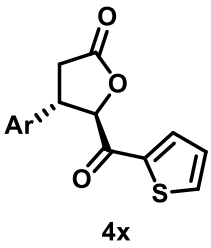
4v

(4S,5R)-5-(2-iodobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4v) was obtained as a yellow semi solid in 50% combined yield (79 mg) after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 2H), 7.36 (dt, *J* = 22.1, 7.9 Hz, 4H), 7.27 – 7.20 (m, 3H), 5.65 (d, *J* = 4.5 Hz, 1H), 3.96 (dt, *J* = 9.5, 4.8 Hz, 1H), 3.16 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.76 (dd, *J* = 18.0, 5.2 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 197.9, 175.1, 133.1, 129.5, 129.2, 128.3, 128.2, 126.8, 92.7, 85.9, 43.2, 35.5. **HPLC Analysis:** ee = 94%, Chiralpak IB Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 41.3 min, t_{minor} = 56.4 min). **ESI HRMS**: calcd. For $C_{17}H_{14}IO_3$ $[M+H]^+$ 392.9982, found 392.9986. The optical rotation of **4v** was found to be $[\alpha]^{24}_D$ = -93.2 (c 0.01, $CHCl_3$).



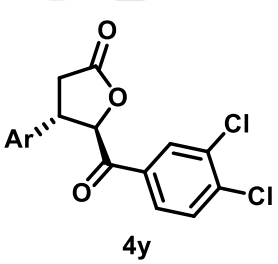
4w

(4S,5R)-5-(2-naphthoyl)-4-phenyldihydrofuran-2(3H)-one (4w) was obtained as a yellow solid in 55% combined yield (70 mg) after column chromatography. M.P. = 110-112 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.92 – 7.81 (m, 3H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.31 (d, *J* = 7.2 Hz, 2H), 5.92 (d, *J* = 4.0 Hz, 1H), 3.94 (dt, *J* = 9.1, 4.4 Hz, 1H), 3.12 (dd, *J* = 18.0, 9.5 Hz, 1H), 2.75 (dd, *J* = 18.0, 4.8 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 193.5, 175.7, 140.7, 136.2, 132.4, 131.4, 131.0, 129.9, 129.6, 129.4, 129.1, 128.2, 128.0, 127.3, 126.9, 123.9, 84.6, 43.5, 35.4. **HPLC Analysis:** ee = 91%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 18.3 min, t_{minor} = 20.0 min). **ESI HRMS**: calcd. For $C_{21}H_{17}O_3$ $[M+H]^+$ 317.1178, found 317.1177. The optical rotation of **4w** was found to be $[\alpha]^{26}_D$ = -51.1 (c 0.02, $CHCl_3$).



4x

(4S,5R)-5-(furan-2-carbonyl)-4-phenyldihydrofuran-2(3H)-one (4x) was obtained as a yellow solid in 45% combined yield (46 mg) after column chromatography. M.P. = 107-110 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.64 (d, *J* = 0.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.32 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 3.4 Hz, 1H), 5.53 (d, *J* = 4.1 Hz, 1H), 3.88 (dt, *J* = 9.1, 4.5 Hz, 1H), 3.08 (dd, *J* = 18.0, 9.4 Hz, 1H), 2.71 (dd, *J* = 18.0, 4.9 Hz, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 182.8, 175.6, 150.3, 148.2, 140.4, 129.5, 128.2, 126.8, 120.6, 113.1, 84.7, 43.6, 35.1, 29.8. **HPLC Analysis:** ee = 96%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 32.1 min, t_{minor} = 36.0 min). **ESI HRMS**: calcd. For $C_{15}H_{13}O_4$ $[M+H]^+$ 257.0814, found 257.0815. The optical rotation of **4x** was found to be $[\alpha]^{26}_D$ = -35.5 (c 0.01, $CHCl_3$).



4y

(4S,5R)-5-(3,4-dichlorobenzoyl)-4-phenyldihydrofuran-2(3H)-one (4y) was obtained as a yellow semi solid in 62% combined yield (83 mg) after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.29 – 7.25 (m, 2H), 5.62 (d, *J* = 4.7 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.07 (dd, *J* = 18.1, 9.5 Hz, 1H), 2.75 (dd, *J* = 18.1, 5.8 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 191.6, 175.0, 139.9, 139.4, 134.0, 133.4, 131.2, 131.1, 129.7, 128.4, 128.0, 127.0, 84.5, 43.0, 35.4. **HPLC Analysis:** ee = 92%, Chiralpak IB Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 53.6 min, t_{minor} = 56.5 min). **ESI HRMS**: calcd. For $C_{17}H_{16}Cl_2NO_3$ $[M+H]^+$ 352.0507, found 352.0503. The optical rotation of **4y** was found to be $[\alpha]^{25}_D$ = -28.6 (c 0.002, $CHCl_3$).

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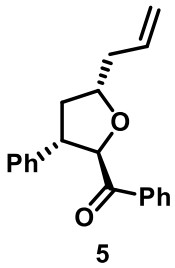
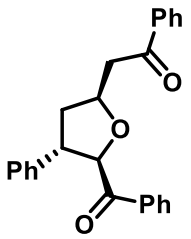


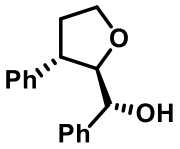
5

((2R,3S,5S)-5-allyl-3-phenyltetrahydrofuran-2-yl)(phenyl) methanone (5): Purified by column chromatography on silica gel eluting with hexane/ethyl acetate (97/3) to afford desired product **5** (23 mg, 40% yield) as a yellow semi-solid. The dr value was found to be 10:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.30 (m, 5H), 7.25 (dd, *J* = 8.6, 4.9 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.31 (d, *J* = 4.9 Hz, 1H), 5.08 (dd, *J* = 31.2, 13.7 Hz, 2H), 4.44 (p, *J* = 6.7 Hz, 1H), 3.80 (dd, *J* = 12.9, 5.1 Hz, 1H), 2.57 (dt, *J* = 13.6, 6.7 Hz, 1H), 2.38 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.18 – 2.13 (m, 2H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 197.9, 142.6, 135.4, 134.8, 133.4, 129.1, 129.0, 128.6, 127.6, 127.0, 117.3, 86.7, 80.5, 47.5, 40.4, 39.4. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.0 min, t_{minor} = 6.7 min). **ESI HRMS**: calcd. For $C_{20}H_{21}O_2$ $[M+H]^+$ 293.1542, found 293.1541. The optical rotation of **5** was found to be $[\alpha]^{25}_D$ = -69.0 (c 0.03, $CHCl_3$).



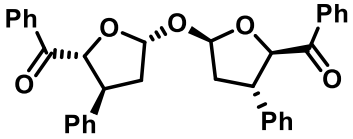
6

2-((2S,4S,5R)-5-benzoyl-4-phenyltetrahydrofuran-2-yl)-1-phenylethan-1-one (6): Purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford desired product **6** (40 mg, 54% yield) as a light yellow semi-solid. The dr value was found to be >99:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.50 (dd, *J* = 15.5, 8.9 Hz, 1H), 7.42 (q, *J* = 8.6 Hz, 3H), 7.29 – 7.18 (m, 7H), 5.22 (d, *J* = 6.8 Hz, 1H), 4.79 – 4.70 (m, 1H), 3.72 (dd, *J* = 17.3, 7.5 Hz, 1H), 3.62 (dd, *J* = 16.4, 4.9 Hz, 1H), 3.23 (dd, *J* = 16.4, 7.7 Hz, 1H), 2.79 – 2.71 (m, 1H), 1.90 (dd, *J* = 22.4, 10.0 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 198.2, 197.9, 142.0, 137.1, 135.2, 133.5, 133.4, 129.2, 129.0, 128.8, 128.6, 128.4, 127.7, 127.2, 86.4, 77.6, 48.6, 44.3, 42.4, 29.9. **HPLC Analysis:** ee = 96%, Phenomenex LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 20.4 min, t_{minor} = 18.0 min). **ESI HRMS**: calcd. For $C_{25}H_{23}O_3$ $[M+H]^+$ 371.1647, found 371.1648. The optical rotation of **6** was found to be $[\alpha]^{25}_D$ = -41.6 (c 0.02, $CHCl_3$).



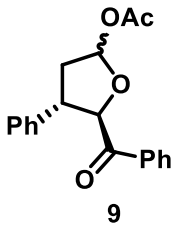
7

(R)-phenyl((2R,3S)-3-phenyltetrahydrofuran-2-yl)methanol (7): Purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford desired product **7** (27 mg, 52% yield) as a yellow solid. CCDC number assigned to structure 7 is 1515196. M.P. = 59-61 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 (d, *J* = 7.1 Hz, 2H), 7.17 (ddt, *J* = 24.9, 14.4, 7.1 Hz, 6H), 6.96 (d, *J* = 7.0 Hz, 2H), 4.87 (d, *J* = 3.8 Hz, 1H), 4.27 (dd, *J* = 7.3, 4.0 Hz, 1H), 4.08 (dd, *J* = 14.7, 6.9 Hz, 1H), 3.96 (dd, *J* = 15.4, 7.1 Hz, 1H), 3.21 (dd, *J* = 15.8, 7.8 Hz, 1H), 2.63 (s, 1H), 2.28 (dt, *J* = 14.2, 7.6 Hz, 1H), 2.03 (td, *J* = 14.8, 7.5 Hz, 1H). **^{13}C {1H} NMR (100 MHz, $CDCl_3$)** δ 143.0, 140.0, 128.6, 128.3, 127.7, 127.6, 126.7, 126.3, 89.4, 74.7, 69.2, 45.5, 36.7. **HPLC Analysis:** ee = 86%, Chiralpak IE Column, n-Hexane/i-PrOH = 99/1, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 46.7 min, t_{minor} = 52.4 min). **ESI HRMS**: calcd. For $C_{17}H_{17}O$ [M-OH] $^{+}$ 237.1279, found 237.1279. The optical rotation of **7** was found to be $[\alpha]^{24}_{D}$ = -18.4 (c 0.03, $CHCl_3$).



8

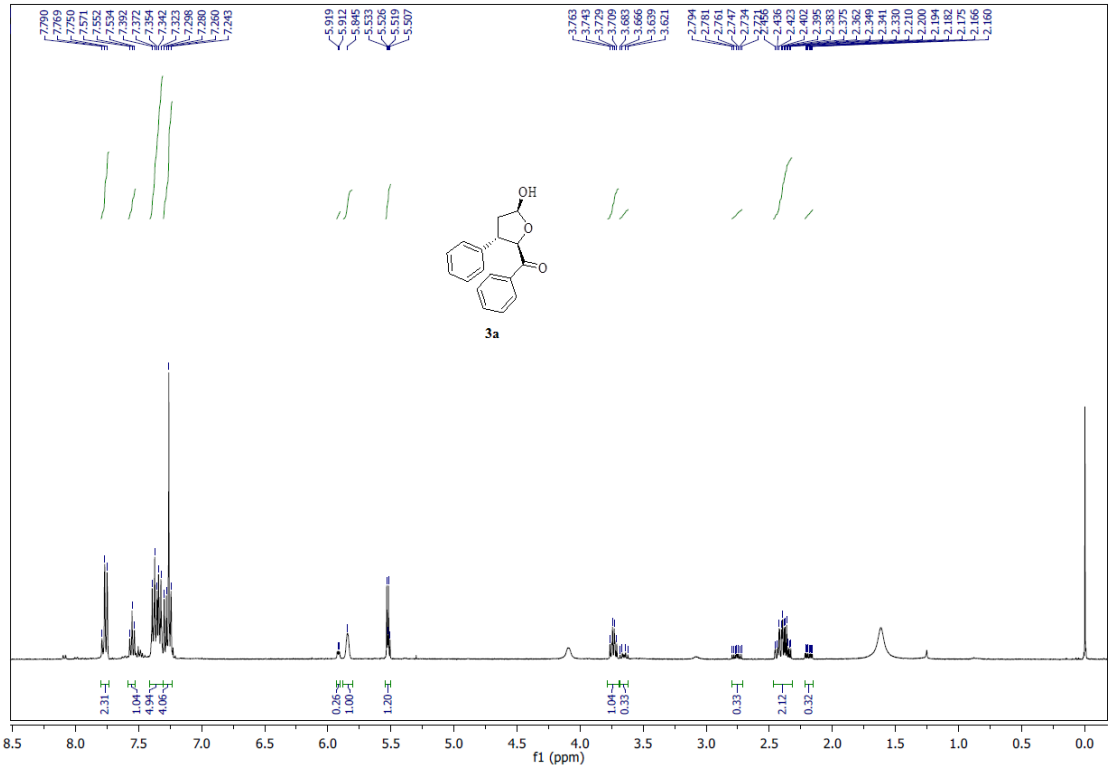
((2R,2'R,3S,3'S,5R,5'R)-oxybis(3-phenyltetrahydrofuran-5,2-diyl))bis(phenylmethanone)(8): Purified by column chromatography on silica gel eluting with hexane/ethyl acetate (95/5) to afford desired product **8** (16 mg, 25% yield) as a white solid. M.P. = 85-87 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.20 (m, 6H), 5.38 (d, *J* = 4.9 Hz, 1H), 5.13 (d, *J* = 6.4 Hz, 1H), 4.10 (dd, *J* = 16.1, 8.1 Hz, 1H), 2.18 (dd, *J* = 13.0, 8.1 Hz, 1H), 2.05 – 1.98 (m, 1H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 198.2, 142.4, 135.7, 133.1, 129.4, 128.9, 128.4, 127.8, 127.0, 100.7, 88.1, 44.3, 41.7, 29.9. **HPLC Analysis:** ee = 98%, Chiralpak IC Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.0 min, t_{minor} = 8.6 min). **ESI HRMS:** calcd. For $C_{34}H_{31}O_5$ [M+H] $^{+}$ 519.2171, found 519.2172. The optical rotation of **8** was found to be $[\alpha]^{25}_{D}$ = -64.0 (c 0.02, $CHCl_3$).

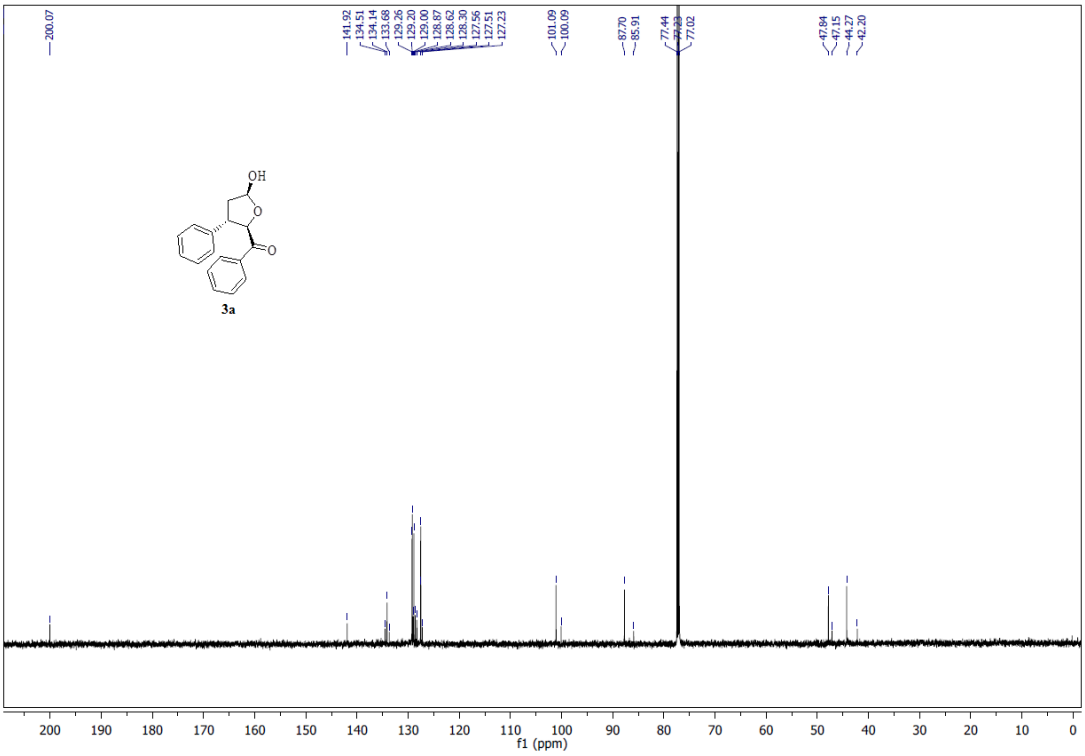


9

(4S,5R)-5-benzoyl-4-phenyltetrahydrofuran-2-yl acetate (9): Purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90/10) to afford desired product **9** (24 mg, 38% yield) as a light yellow solid. M.P. = 118-120 ^{o}C. The dr value was found to be 1.2:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.86 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.81 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.51 (td, *J* = 7.4, 3.3 Hz, 2H), 7.40 – 7.29 (m, 12H), 7.27 – 7.23 (m, 2H), 6.63 (dd, *J* = 5.8, 1.9 Hz, 1H), 6.54 (d, *J* = 4.8 Hz, 1H), 5.49 (d, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 7.1 Hz, 1H), 4.15 (dd, *J* = 17.7, 7.5 Hz, 1H), 3.78 – 3.73 (m, 1H), 2.88 (ddd, *J* = 14.3, 10.7, 5.8 Hz, 1H), 2.53 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.49 – 2.43 (m, 1H), 2.28 (ddd, *J* = 14.3, 5.6, 1.9 Hz, 1H), 2.16 (s, 3H), 1.93 (s, 3H). **^{13}C {1H} NMR (150 MHz, $CDCl_3$)** δ 196.8, 195.6, 170.5, 170.1, 140.9, 140.7, 135.3, 135.0, 133.8, 133.5, 129.4, 129.2, 129.1, 129.0, 128.7, 128.5, 128.1, 127.8, 127.4, 127.4, 99.7, 98.9, 88.3, 87.2, 46.3, 44.4, 41.1, 40.6, 29.8, 29.8, 21.5, 21.2. **HPLC Analysis:** ee = 95%, 96%, Phenomenex LUX C4 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 18.2 min, 38.9 min, t_{minor} = 20.1 min, 24.4min). **ESI HRMS:** calcd. For $C_{19}H_{22}NO_4$ $[M+NH_4]^+$ 328.1549, found 328.1545. The optical rotation of **9** was found to be $[\alpha]^{24}_D$ = -63.6 (c 0.02, $CHCl_3$).

2.9 Selected NMR and HPLC spectra of products





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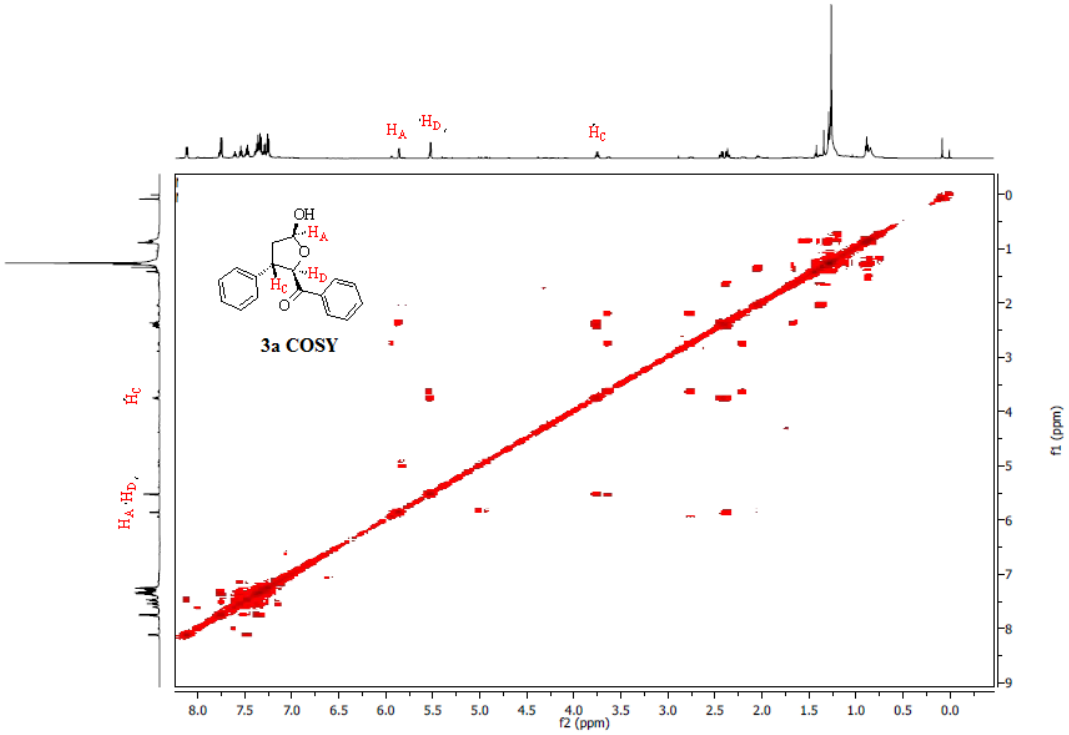
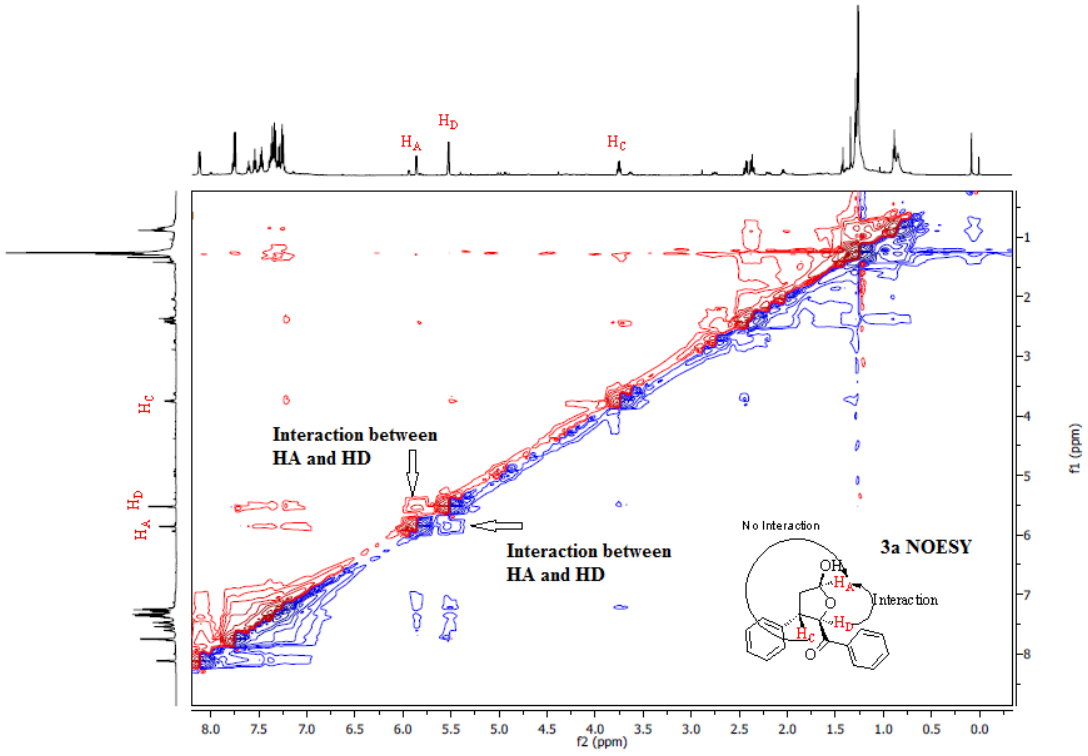
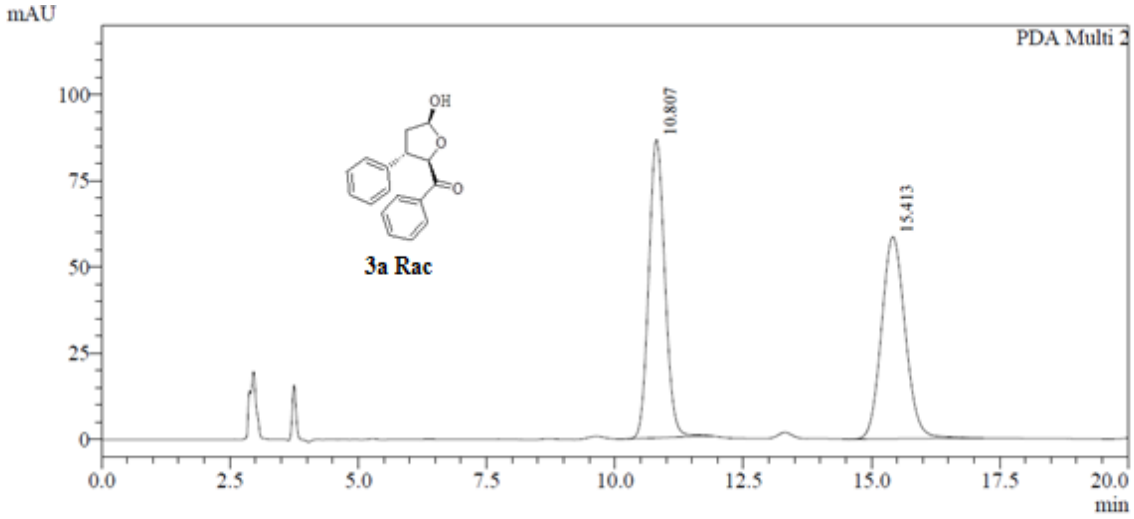


NOESY spectra of compound **3a:**





PeakTable

PDA Ch2 210nm 4nm

Peak#	Ret. Time	Area	Area %
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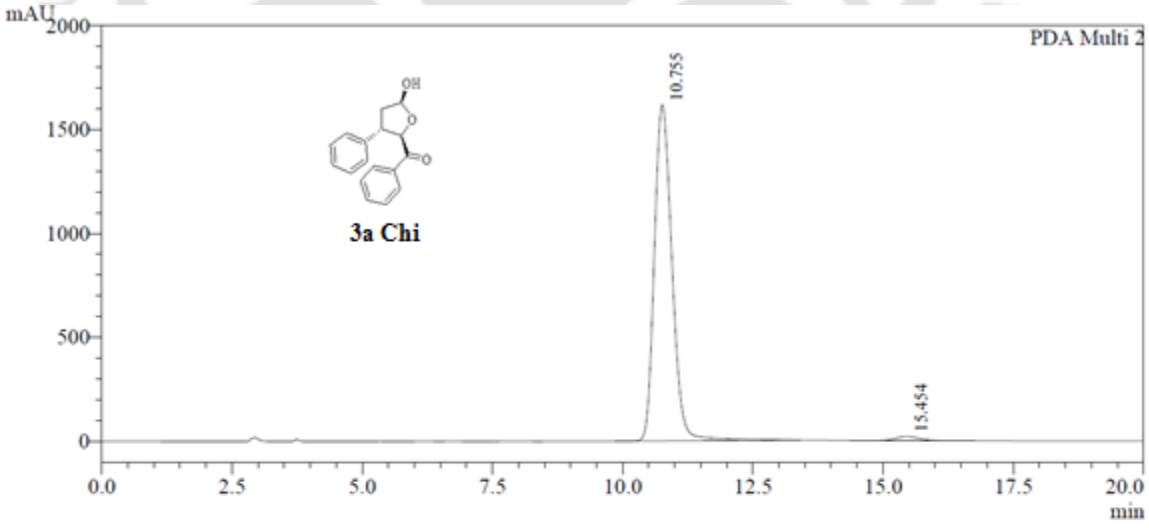
2	15.413	1886805	49.917
Total		3779881	100.000



PeakTable

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Peak#	Ret. Time	Area	Area %
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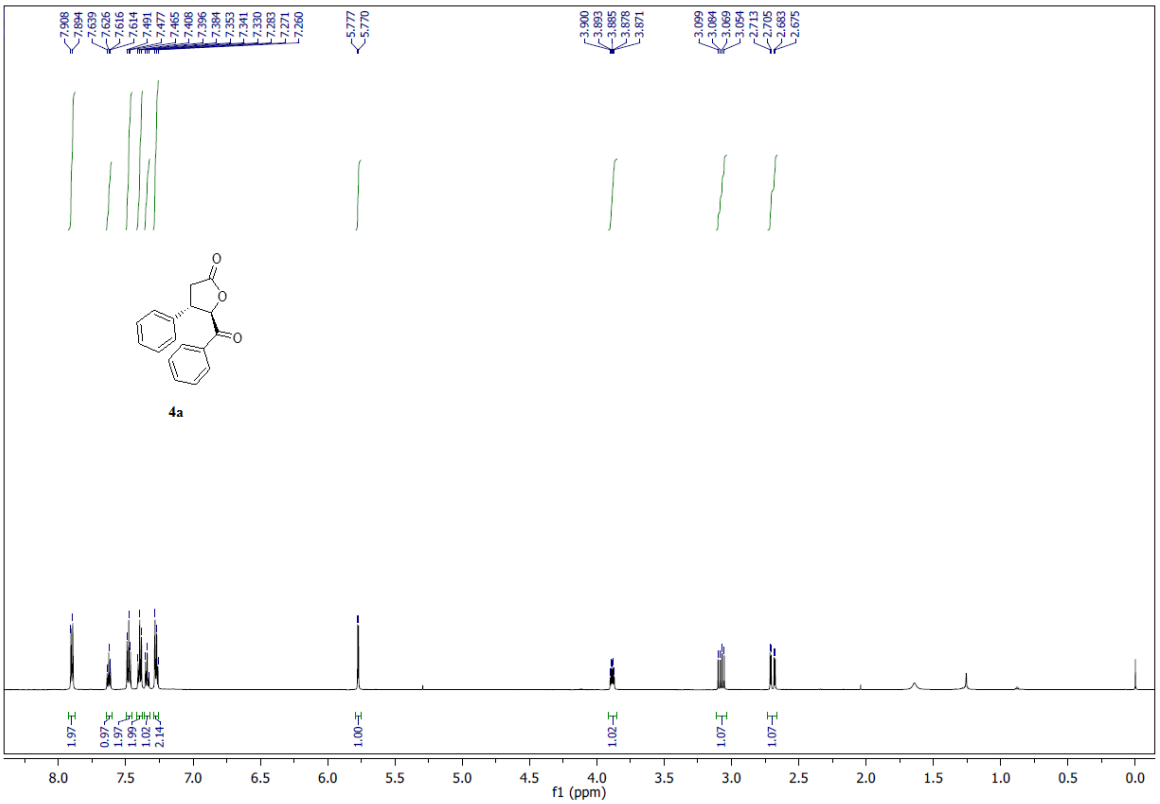
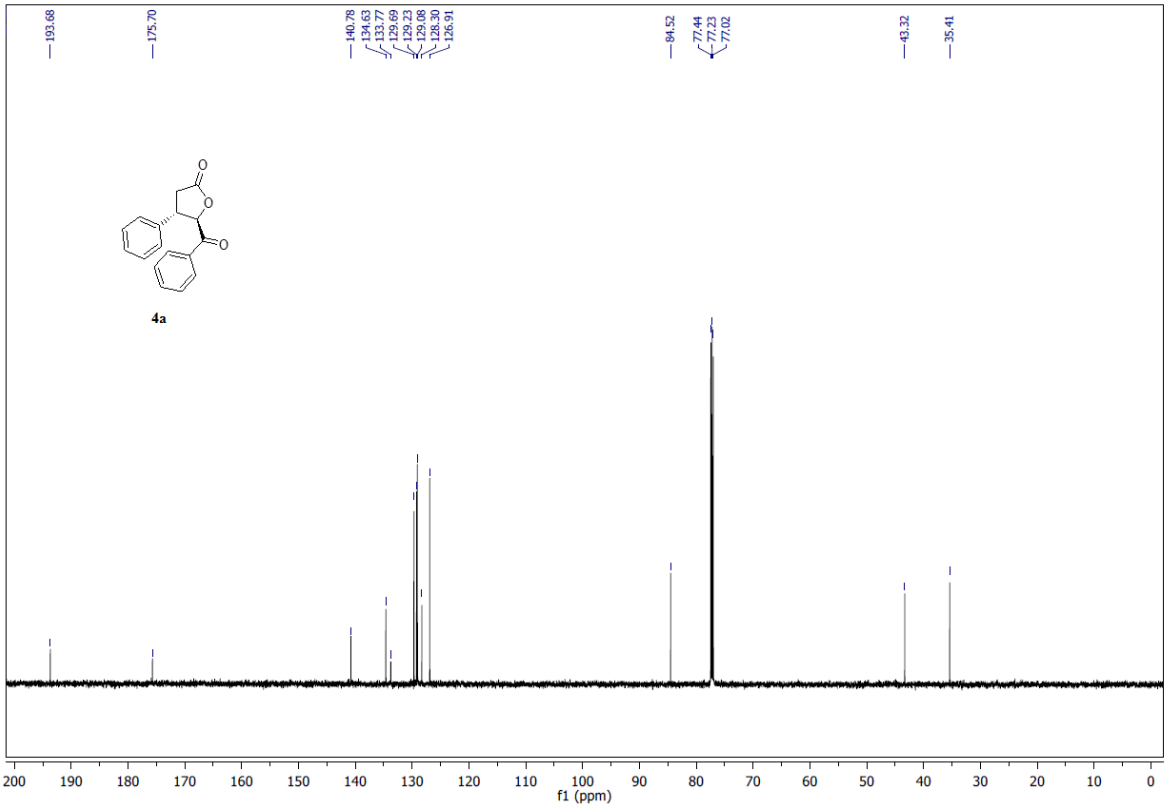
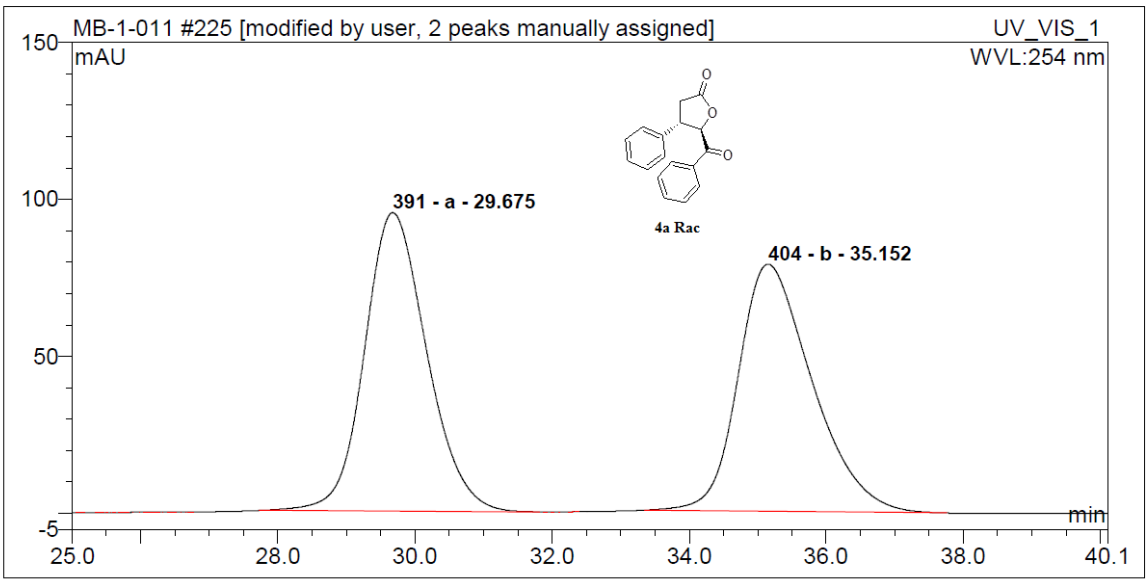
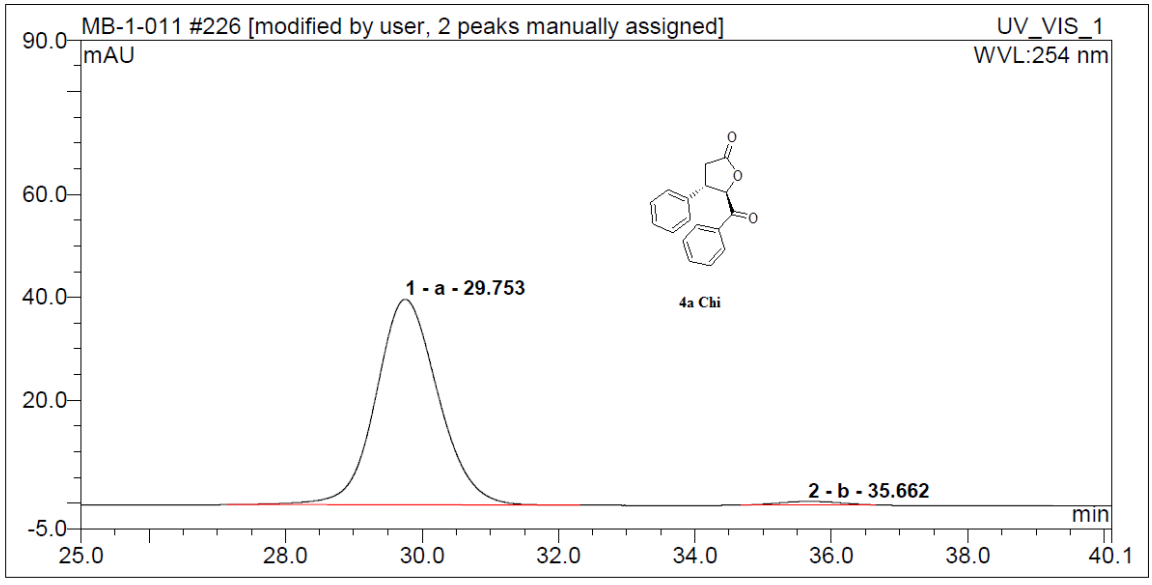


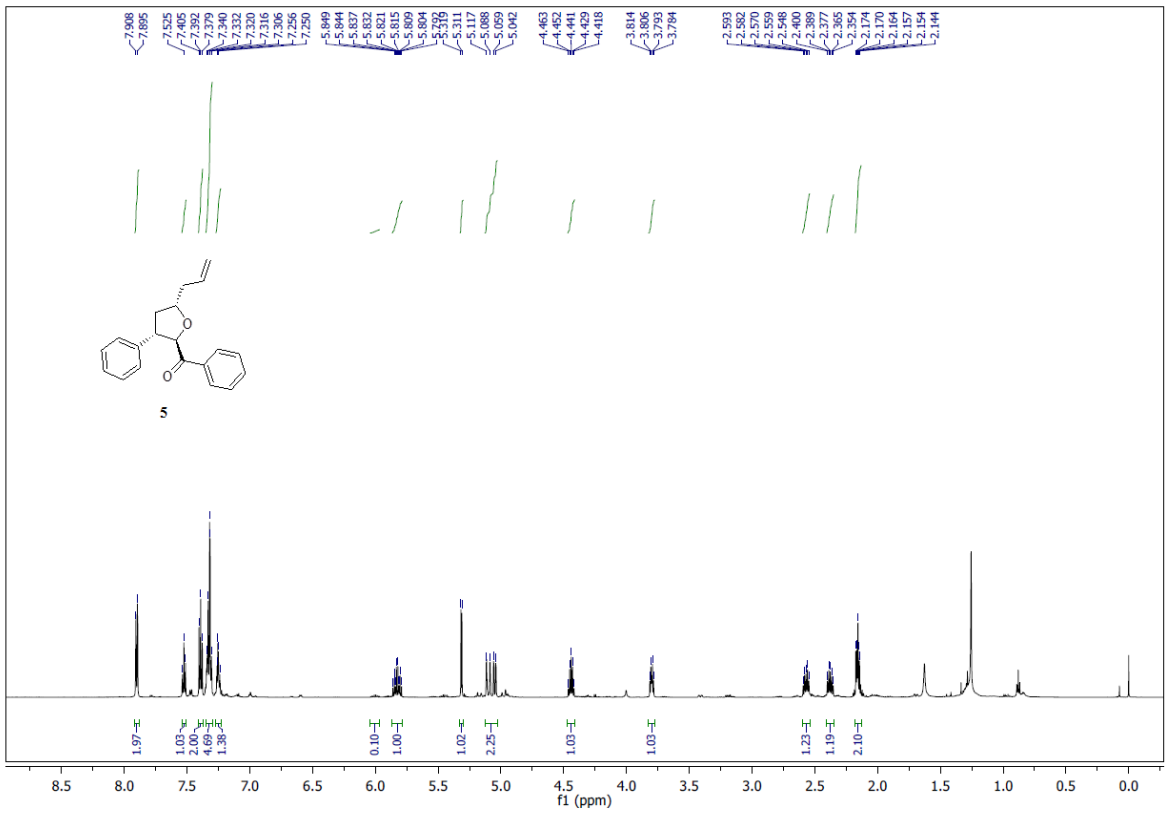


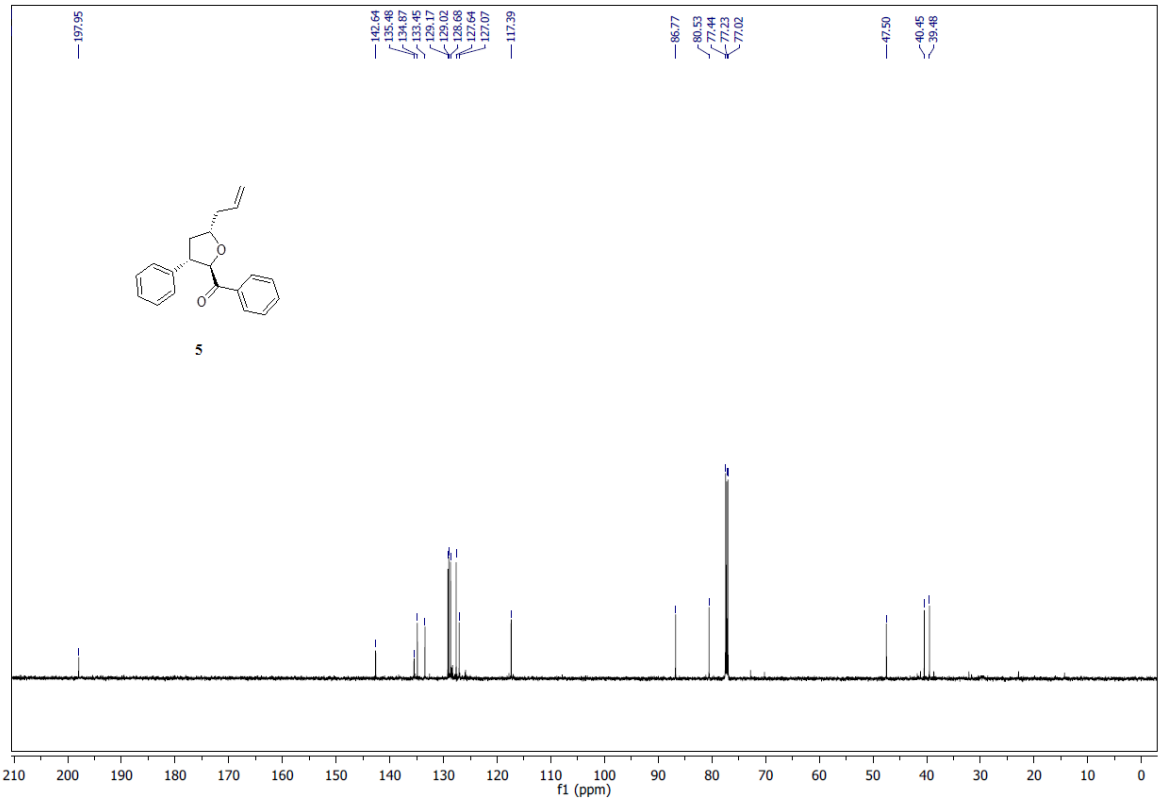


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
391	a	29.68	99.94931	50.41093327	94.98738	n.a.
404	b	35.15	98.320	49.58904435	78.648	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	29.75	42.39513	98.31651009	40.01889	n.a.
2	b	35.66	0.726	1.683489912	0.706	n.a.





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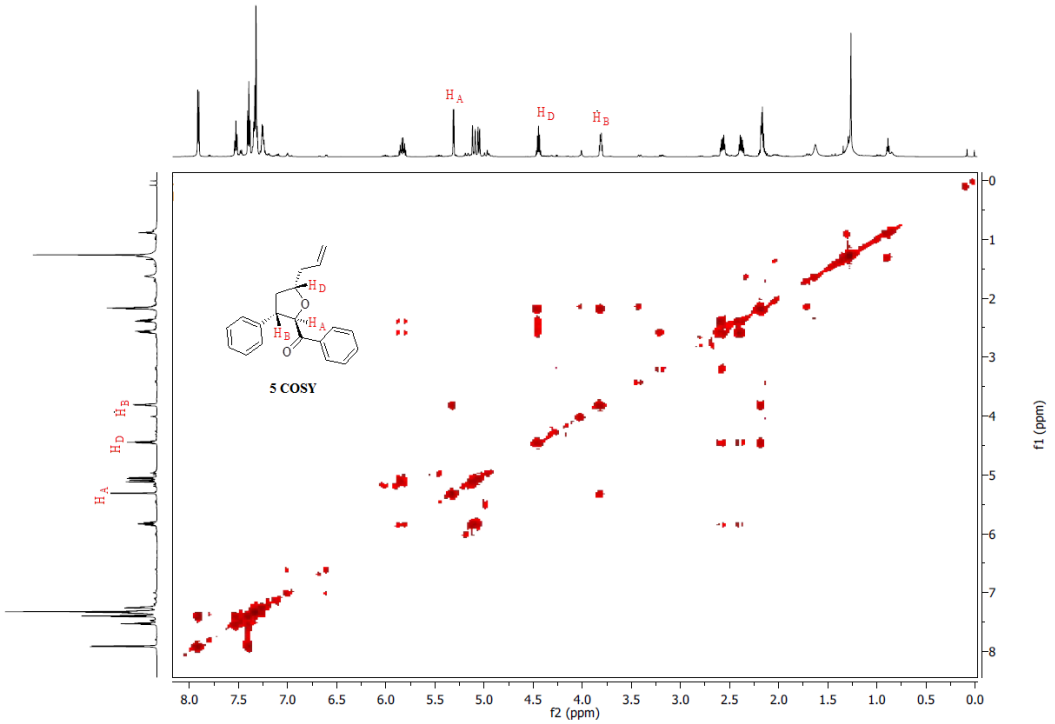

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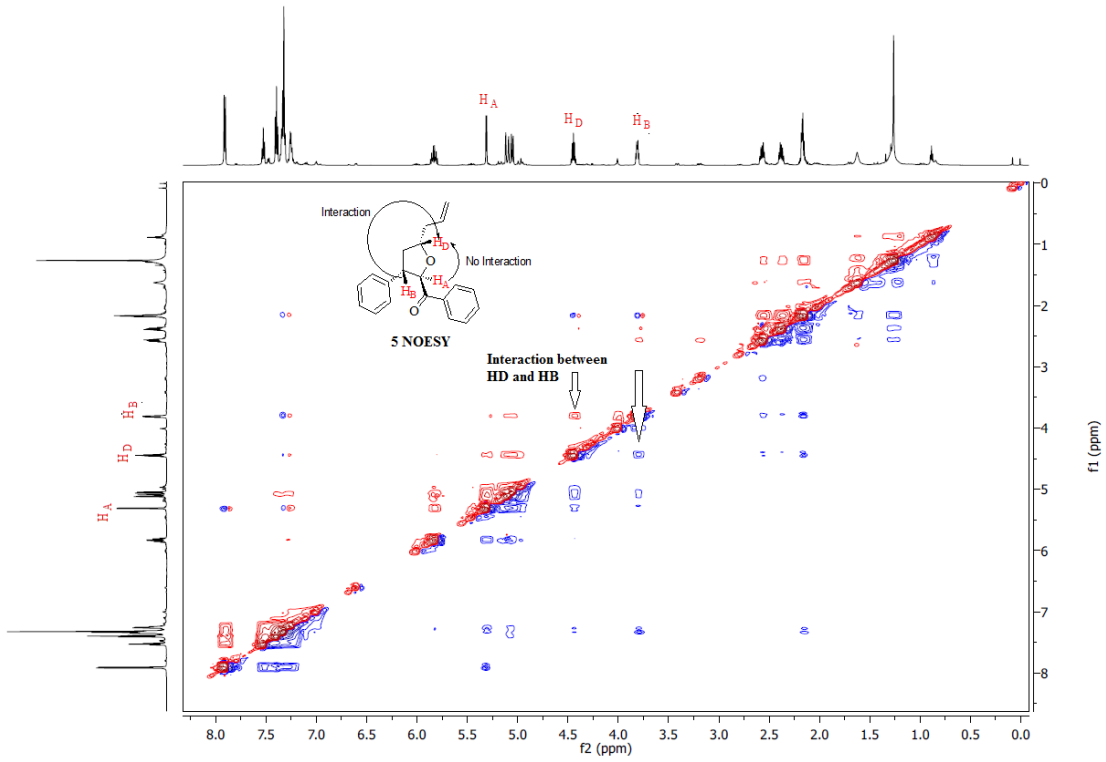
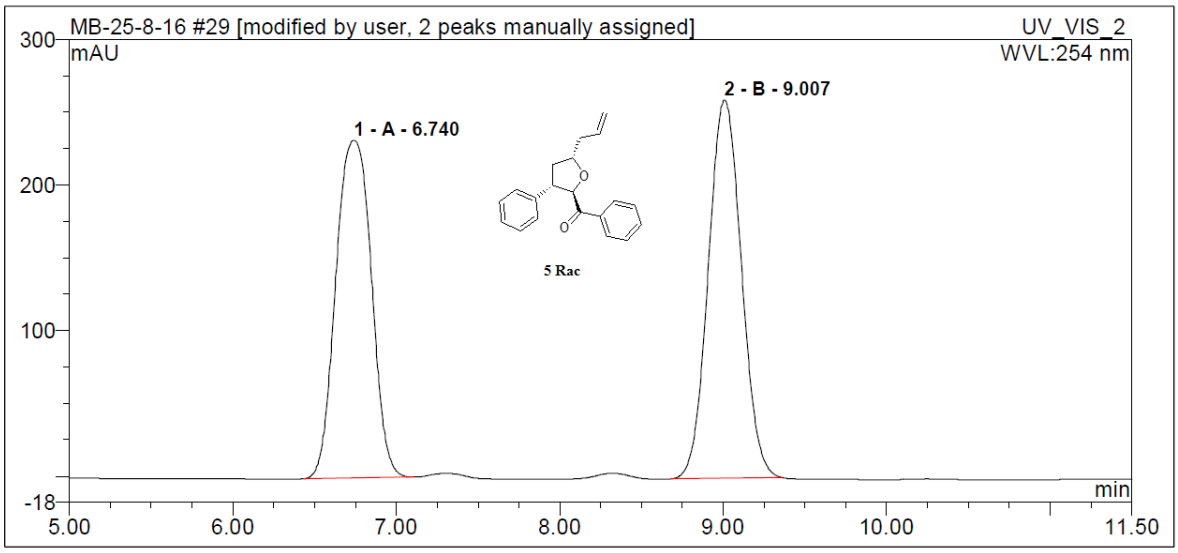
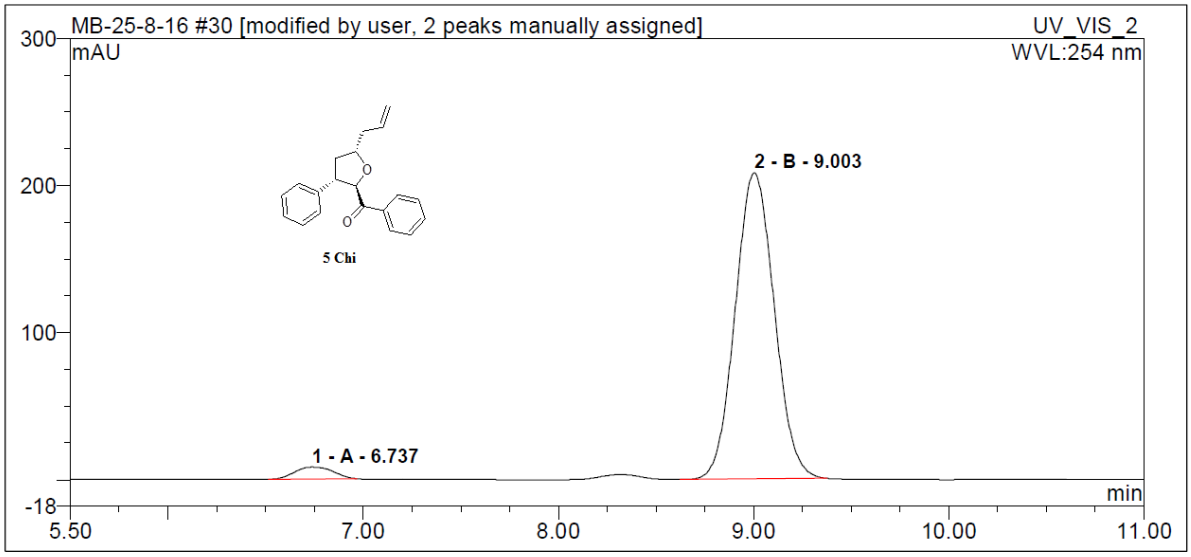
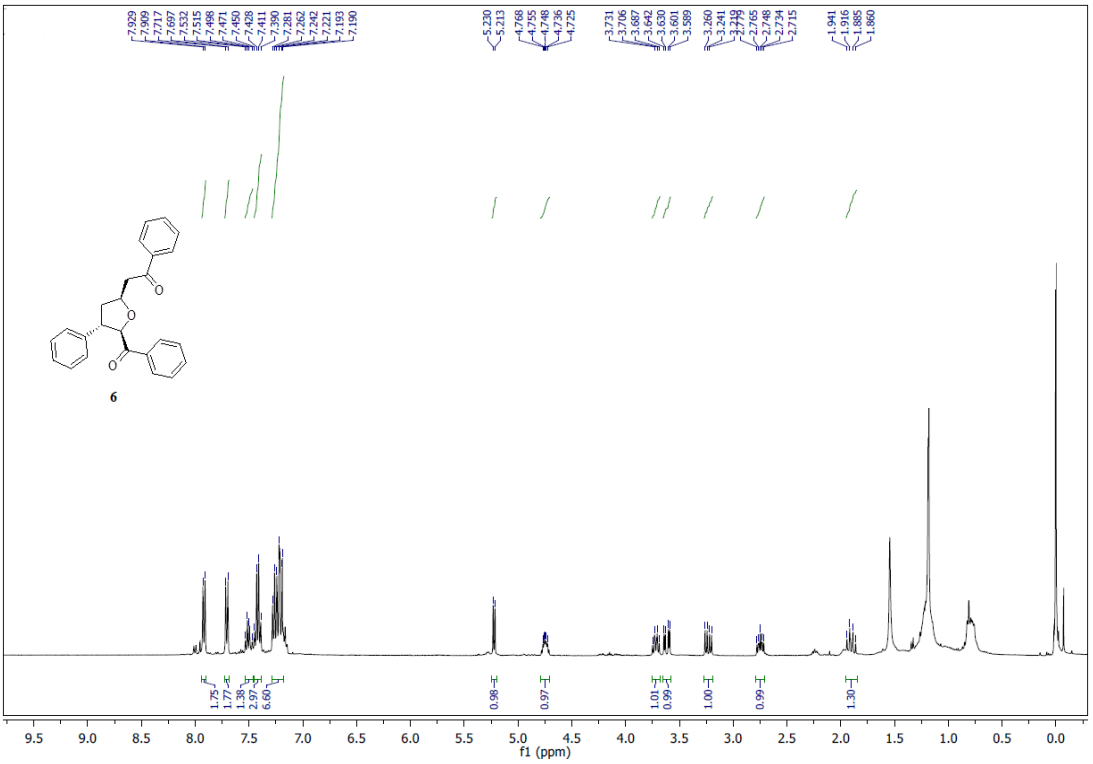


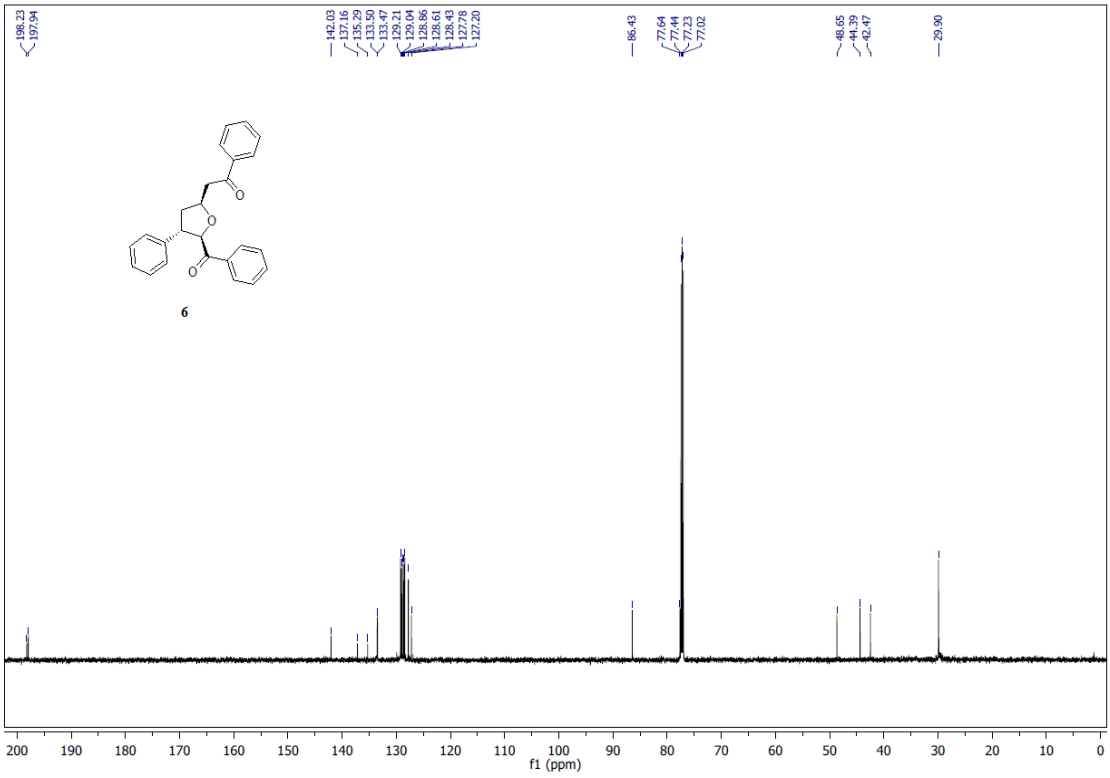


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.74	58.41951	48.99512401	231.9066	n.a.
2	B	9.01	60.816	51.00487599	259.867	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.74	1.833884	3.662965885	8.13691	n.a.
2	B	9.00	48.232	96.33703411	208.043	n.a.





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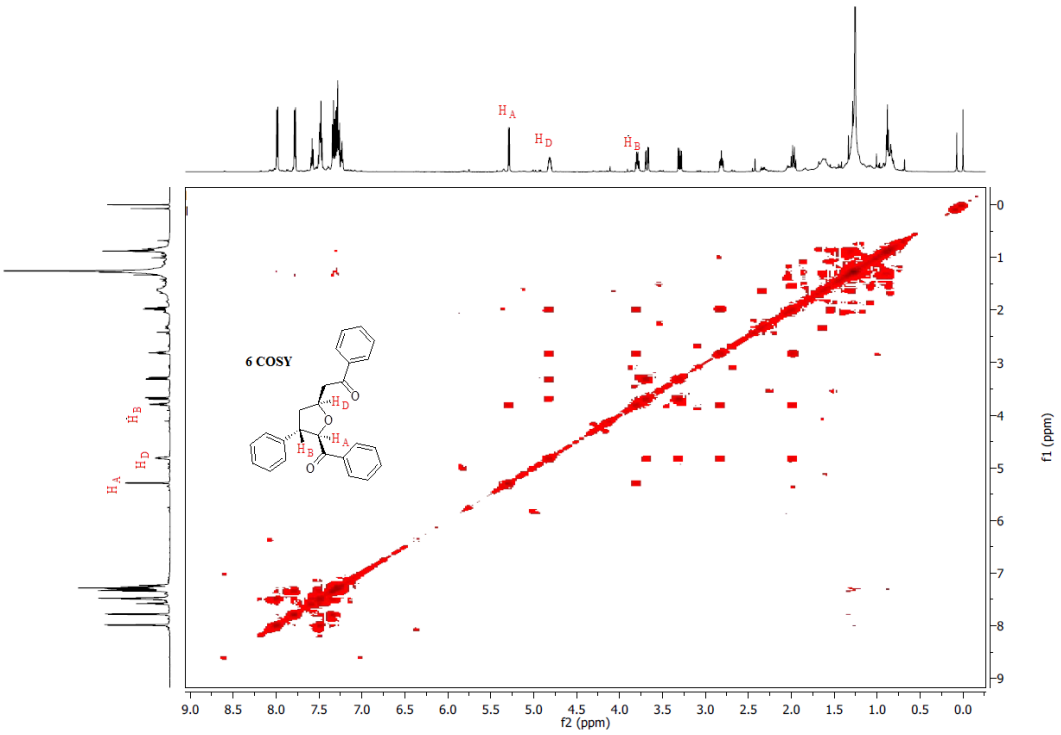

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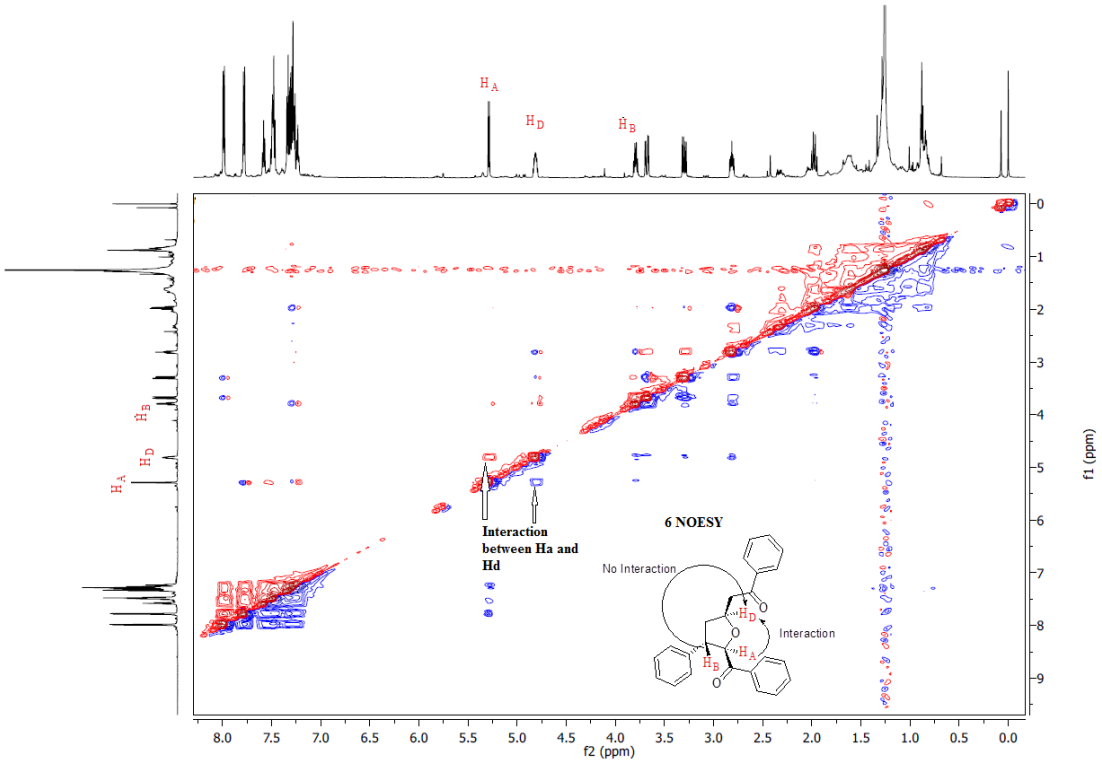
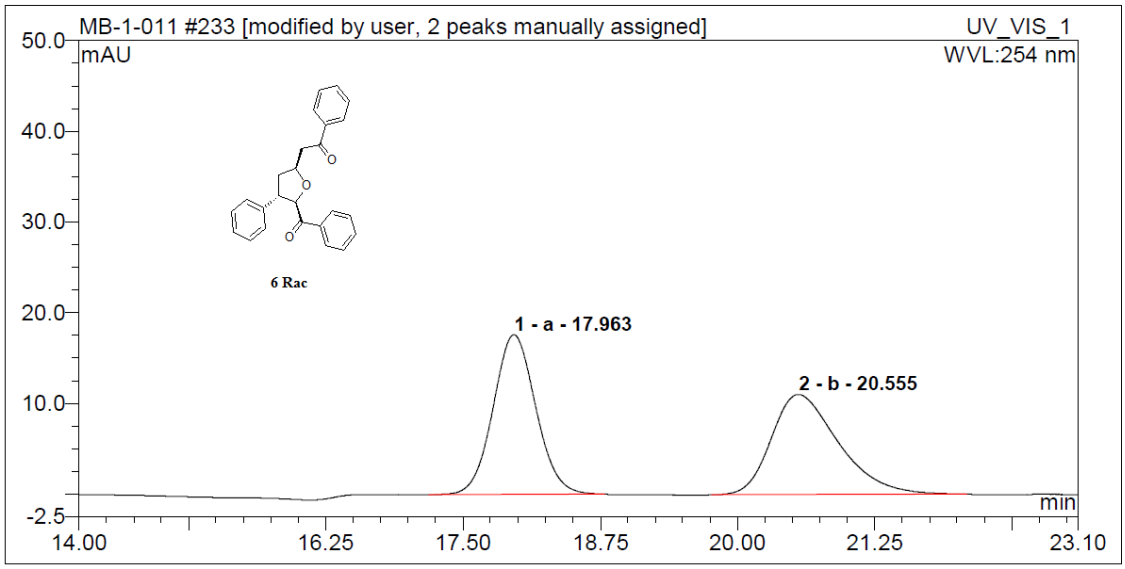
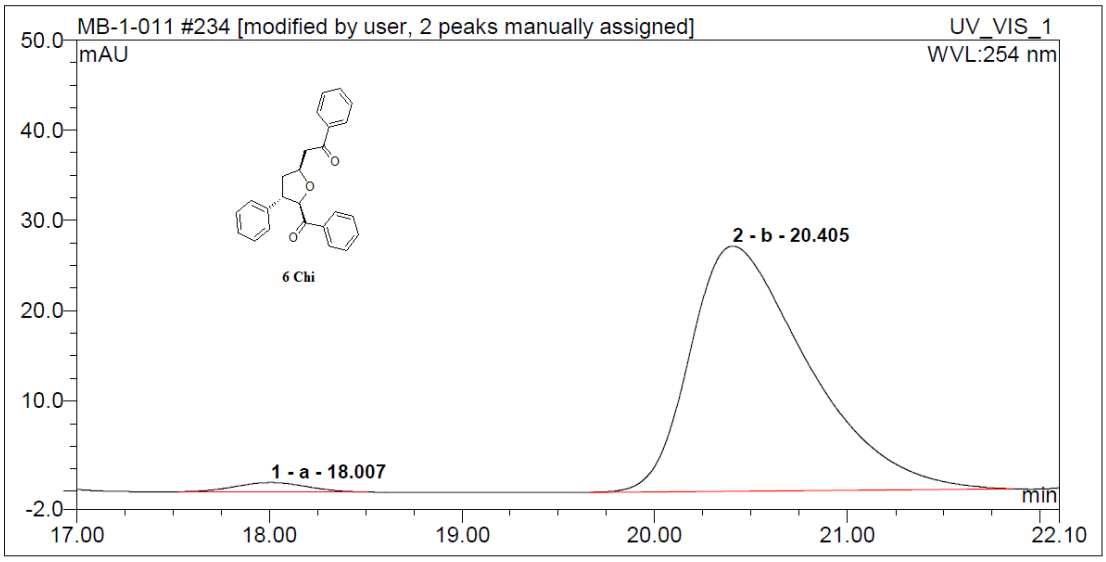
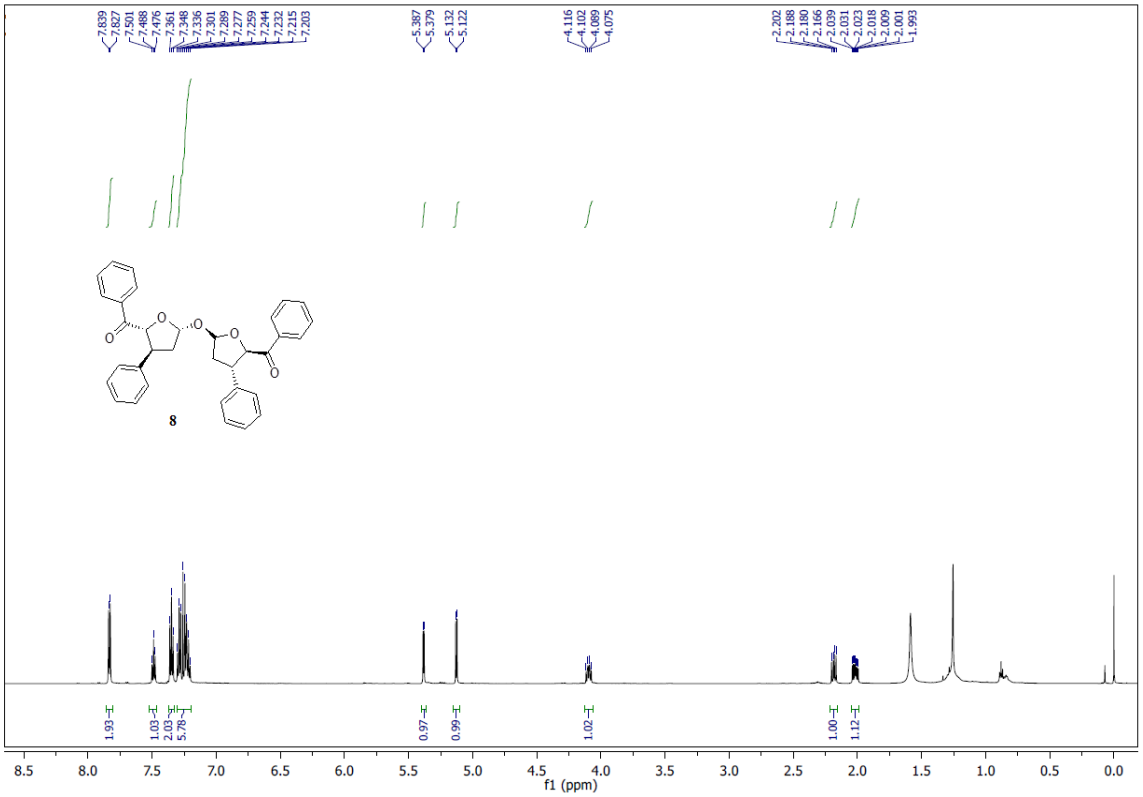


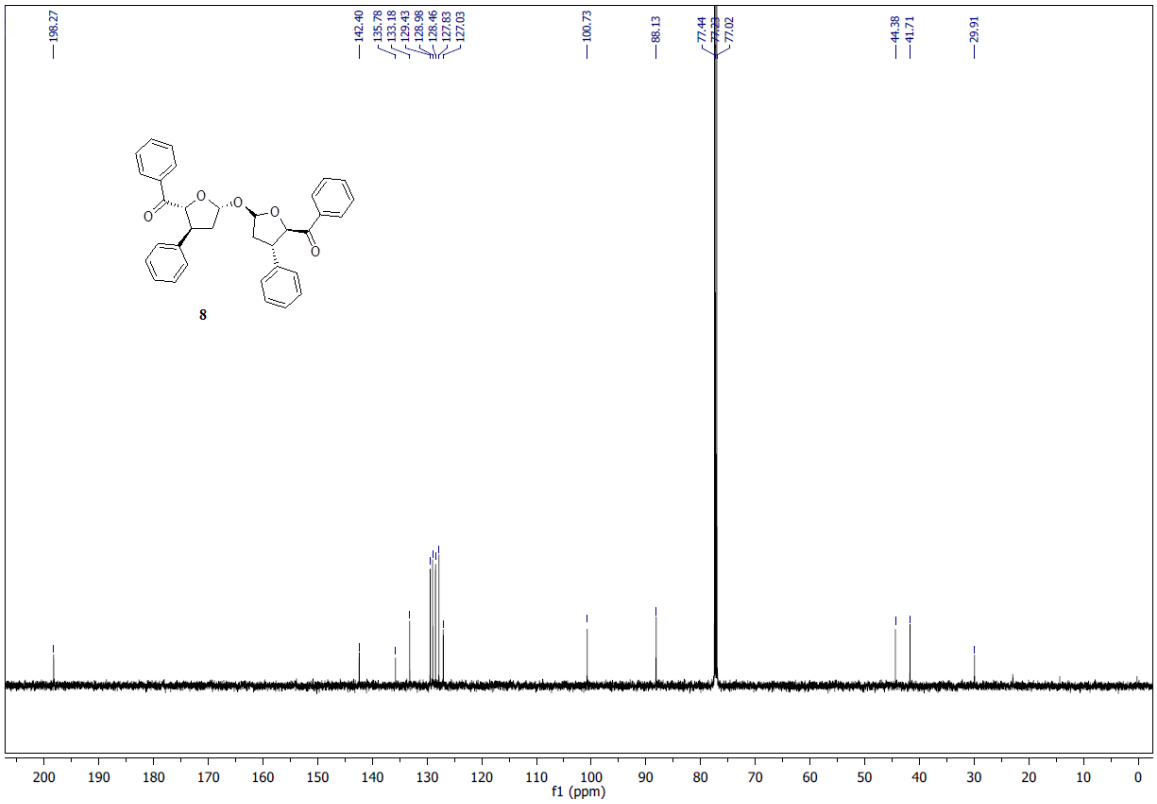


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	17.96	7.942766	50.30993227	17.61185	n.a.
2	b	20.56	7.845	49.69006773	11.050	n.a.

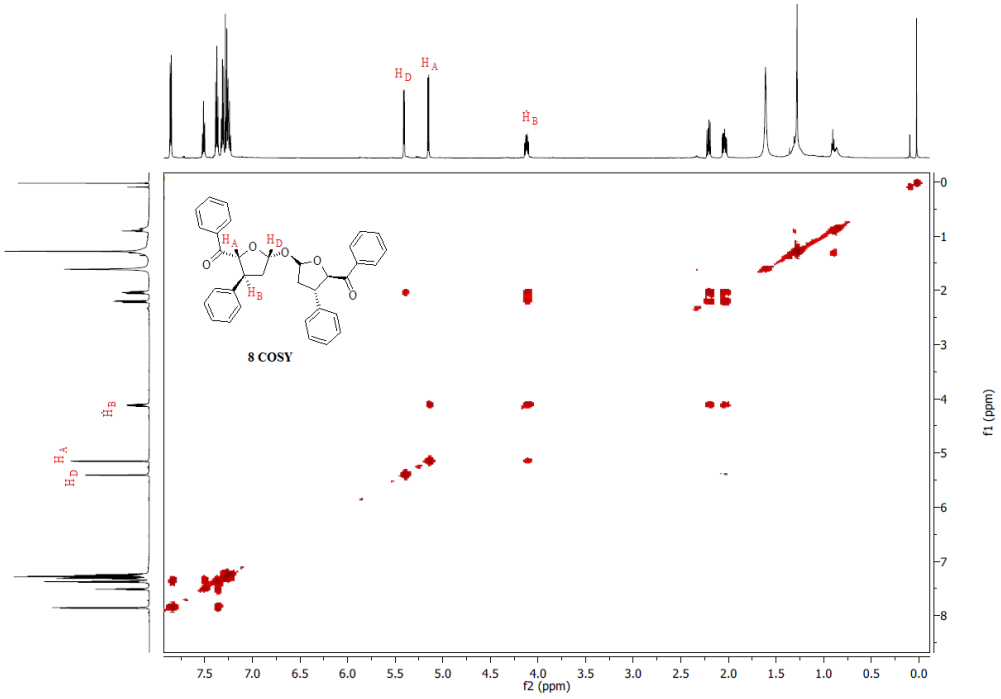


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.01	0.445667	2.262511532	1.04063	n.a.
2	b	20.41	19.252	97.73748847	27.170	n.a.





COSY spectra of compound **8:**



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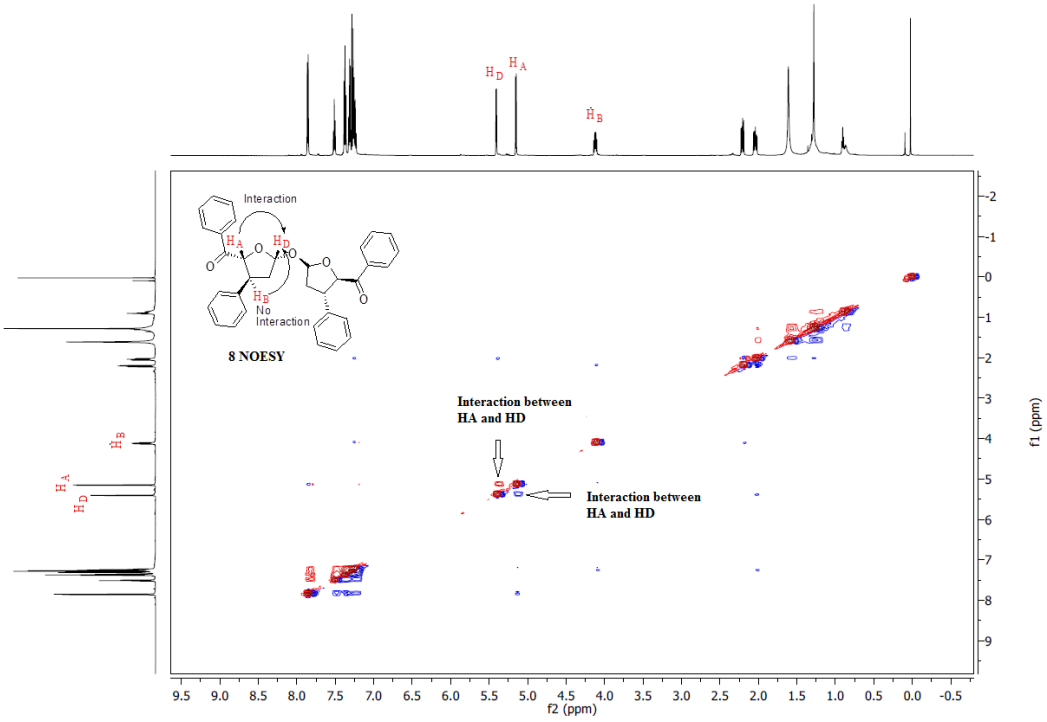
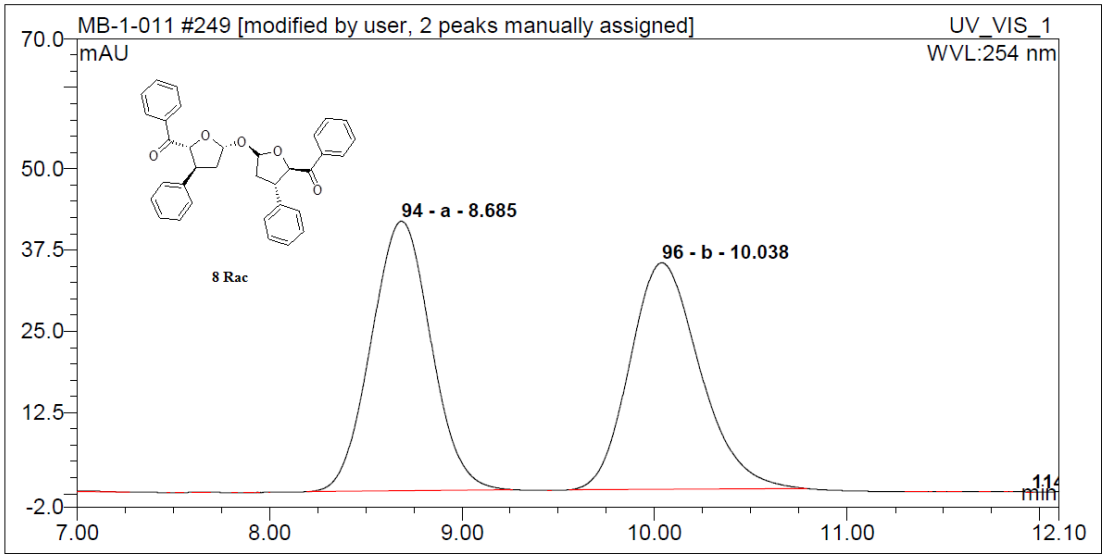
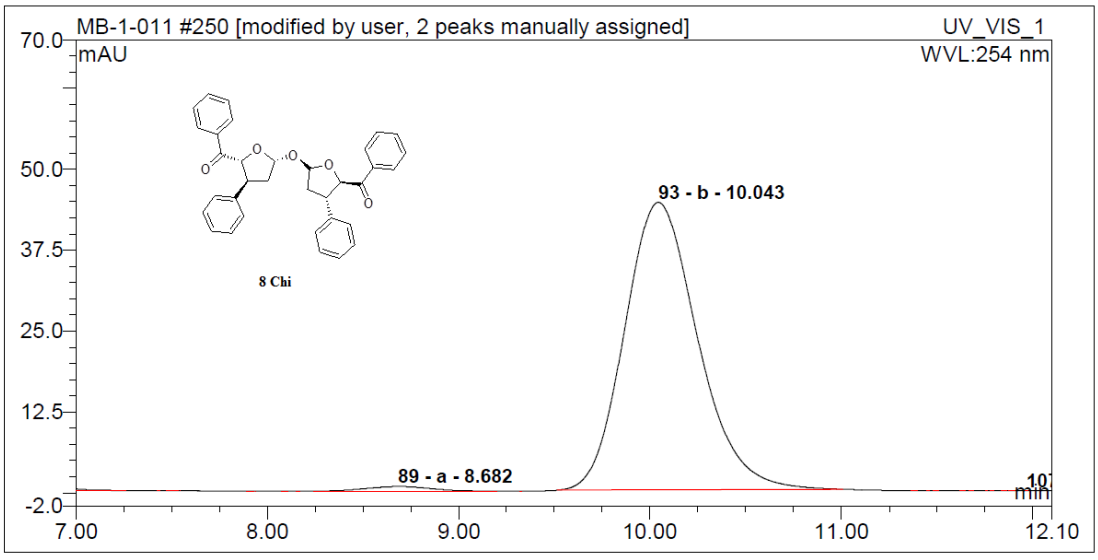




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
94	a	8.69	14.93028	50.33792702	41.46754	n.a.
96	b	10.04	14.730	49.66174201	34.851	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
89	a	8.68	0.27468	1.378520679	0.70978	n.a.
93	b	10.04	19.651	98.6213063	44.447	n.a.

2.10 References

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18. PCC is a mild oxidant used earlier in the oxidation of hemiacetals to lactones. For examples, see ref (a) Enders, D.; Grossmann, A.; Gieraths, B.; Düzdemir, M.; Merkens, C. *Org. Lett.* **2012**, *14*, 4254. (b) Yao, W.; Pan, L.; Wu, Y.; Ma, C. *Org. Lett.* **2010**, *12*, 2422. (c) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 2561.

19. CCDC 1511229 contains the crystallographic data for compound **4o**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.

20. CCDC 1515196 contains the crystallographic data for compound **7**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.

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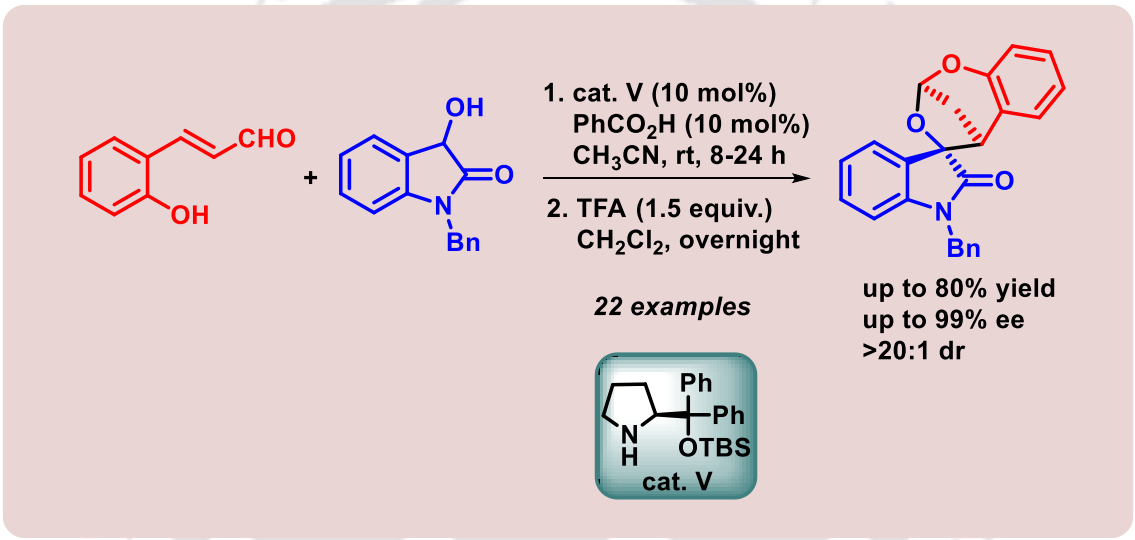
Chapter 3

Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton



J. Org. Chem. **2018**, *83*, 14703-14712.

3.1 Introduction

Cyclic acetals are privileged structural motif commonly encountered in many natural products and pharmaceuticals and exhibit a wide range of significant bioactivities.[1] Bridged acetals, especially methanobenzodioxepine, are useful scaffolds as they are used in the treatment of neurodegenerative disease.[2] Although they are useful scaffolds with the potential application, still strategies for the formation of bridged acetals are less explored.[3] Such skeleton is present in procyanidin A1,[4] epicoccolide A,[5] cholinesterase inhibitor,[6] and other bioactive compounds which are shown in Figure 1.[7]

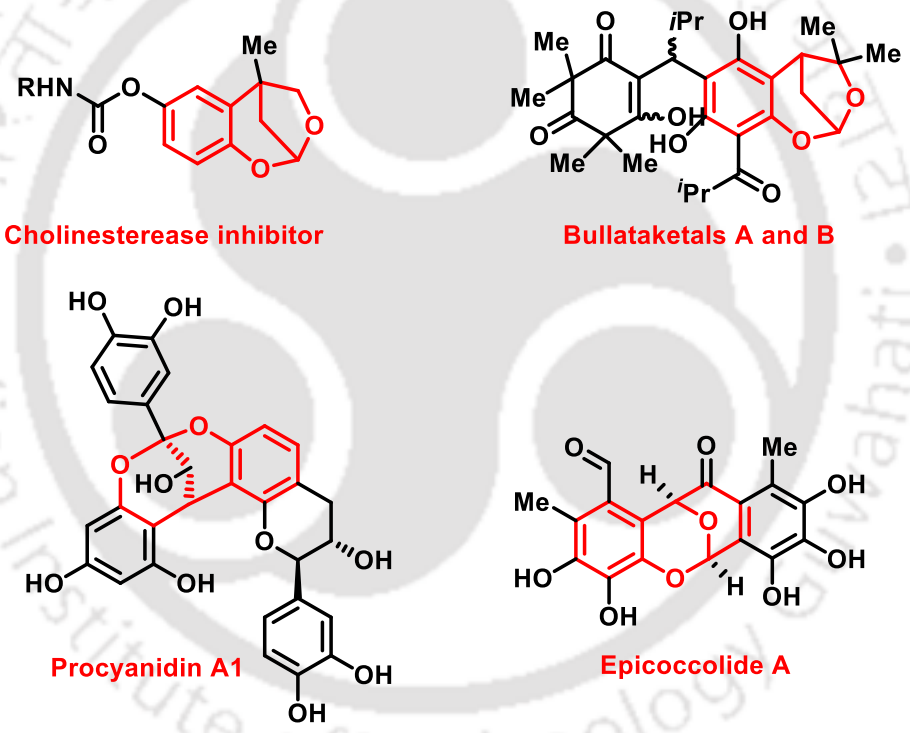


Figure 1. Biologically active compounds containing methanobenzodioxepine scaffolds

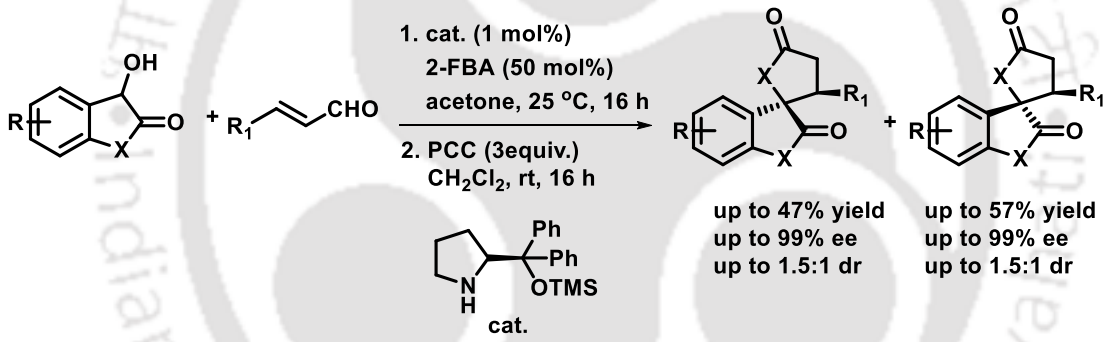
Due to the importance of the bridged acetal framework, it has received significant attention. Though a variety of asymmetric cyclic acetals,[8] fused acetals,[9] and spiro acetals[10] have been developed in recent years, there are only three examples for the asymmetric synthesis of bridged acetals; and surprisingly there is no report for the asymmetric synthesis of bridged acetals with the additional heterocyclic skeleton. Thus,

the development of highly efficient methods for the preparation of optically active bridged acetals with additional heterocyclic skeleton would be of great utility for the discovery of new chiral drugs.

3.2 Known strategies for the employment of dioxindoles in asymmetric reactions:

3.2.1 Asymmetric Michael addition reaction of Dioxindole

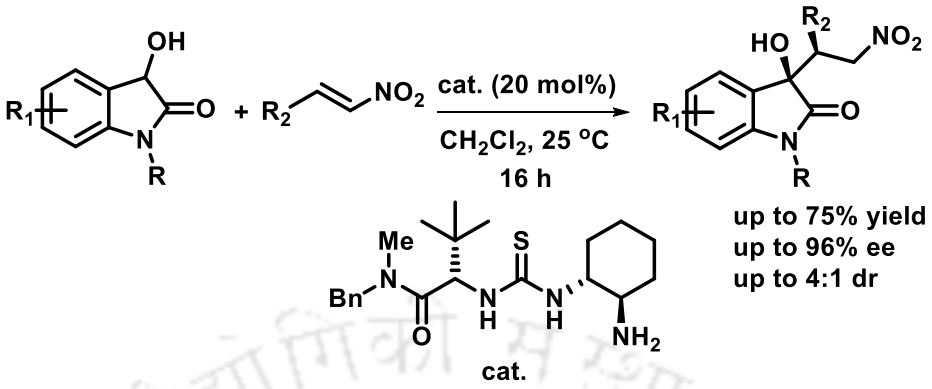
In 2012, Melchiorre *et al*. reported a highly efficient conjugate addition reaction between 3-hydroxyoxindole and *β*-substituted enals using prolinol TMS ether catalyst. This protocol allowed efficient synthesis of enantioenriched spiro-oxindole products with good yields and excellent enantioselectivities (Scheme 1).[11]



Scheme 1. Synthesis of enantioenriched 3-substituted 3-hydroxyoxindole by Melchiorre *et al.*

3.2.2 Organocatalytic asymmetric synthesis of 3-substituted 3-hydroxy-2-oxindoles

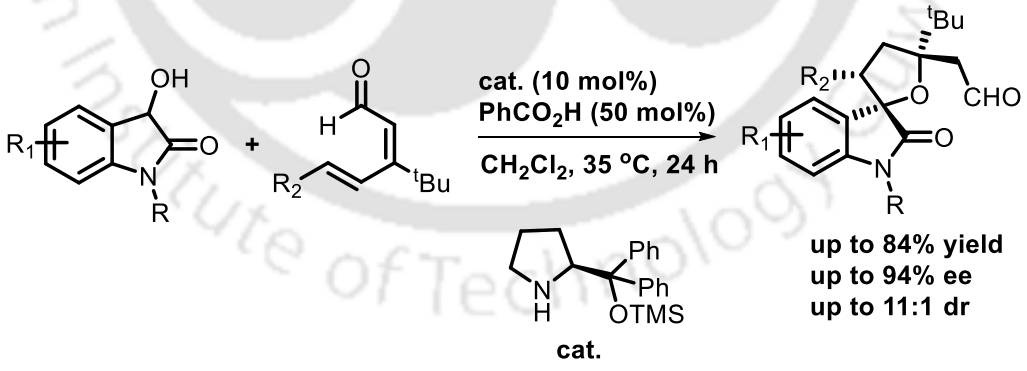
The same group reported a catalytic asymmetric 1,4-addition of 3-substituted oxindoles to nitroalkenes. 3-Substituted 3-hydroxyoxindole derivatives with high stereocontrol were obtained using the bifunctional primary amine-thiourea utilizing a non-covalent-based mode of catalysis (Scheme 2).[12]



Scheme 2. Asymmetric 1,4-addition of 3-substituted oxindoles by Melchiorre *et al.*

3.2.3 Aminocatalytic vinylogous cascade reaction of dioxindole

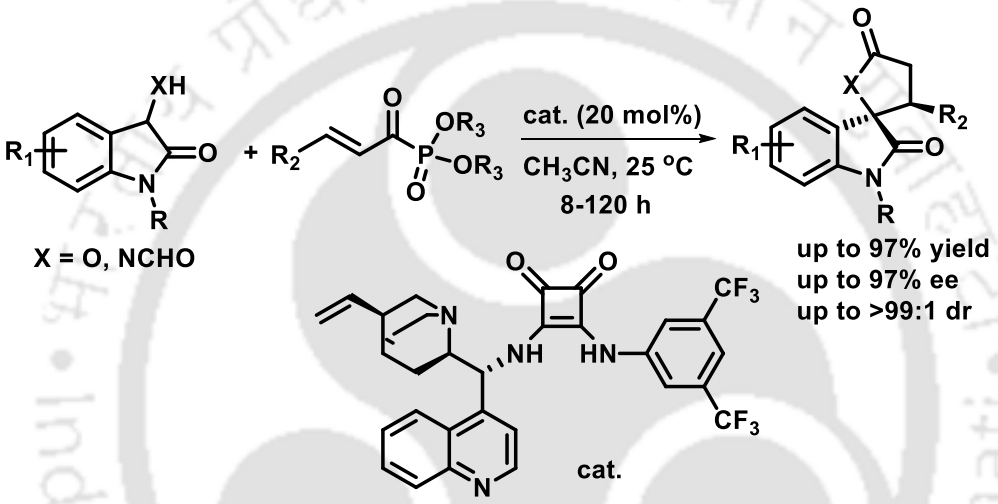
In 2013, Melchiorre and co-workers developed a novel aminocatalytic vinylogous cascade reaction of 2,4-dienals and dioxindole for the synthesis of tetrahydrofuran spirooxindole derivatives. This protocol shows the asymmetric 1,6-addition to linear 2,4-dienals proceeding with high δ-site and stereoselectivity. By using prolinol catalyst, this reaction delivered desired products in good yields with moderate diastereoselectivities and excellent enantioselectivities (Scheme 3).[13]



Scheme 3. Synthesis of tetrahydrofuran spirooxindole derivatives by Melchiorre *et al.*

3.2.4 Organocatalytic asymmetric Michael/cyclization cascade reactions of 3‑Hydroxyoxindoles/3-aminooxindoles

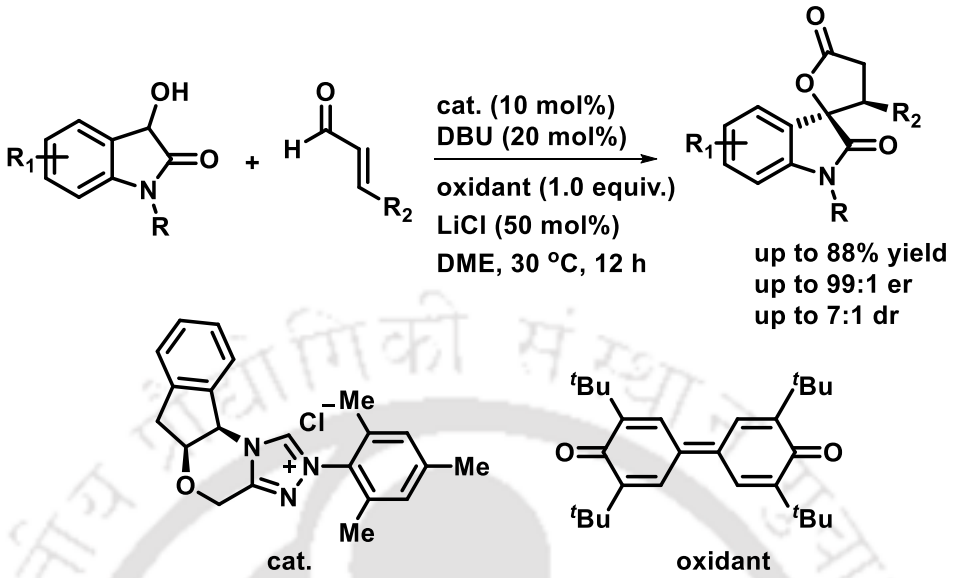
Yuan *et al.* developed a highly enantioselective Michael/cyclization cascade reaction of 3-hydroxyoxindoles/3-aminooxindoles with *α*,*β*-unsaturated acyl phosphonates catalyzed by a cinchonine derived squaramide catalyst in 2015. This reaction delivered a variety of spirocyclic oxindole-*γ*-lactones/lactams in moderate to excellent yields with good to excellent diastereo- and enantioselectivities under mild reaction conditions (Scheme 4).[14]



Scheme 4. Synthesis of chiral spirocyclic oxindole-*γ*-lactone/lactam derivatives by Yuan *et al.*

3.2.5 Enantioselective NHC-catalyzed annulation of enals with 3-hydroxy oxindoles

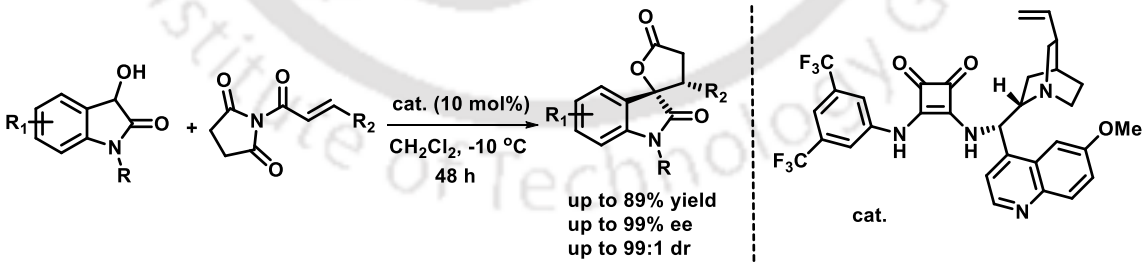
In 2017, Biju *et al.* reported the enantioselective *N*-heterocyclic carbene (NHC)-catalyzed annulation of enals with 3-hydroxy oxindoles for the synthesis of spiro *γ*-butyrolactone derivatives in good yields with moderate diastereo- and enantioselectivities. The reaction proceeded *via* the generation of a chiral *α*,*β*-unsaturated acyl azolium intermediate, followed by its interception with 3-hydroxy oxindoles in a formal [3 + 2] cyclization to give desired spiro compounds (Scheme 5).[15]



Scheme 5. Synthesis of spiro *γ*-butyrolactone derivatives by Biju *et al.*

3.2.6 Organocatalytic synthesis of spirooxindole lactone

In 2017, Du group developed an asymmetric cascade Michael/cyclization reaction of 3-hydroxyoxindoles with *α,β*-unsaturated *N*-acylated succinimides using a bifunctional quinine-derived squaramide catalyst. This strategy allowed the synthesis of spirooxindole lactone derivatives in good yields with high to excellent stereoselectivities (Scheme 6).[16]

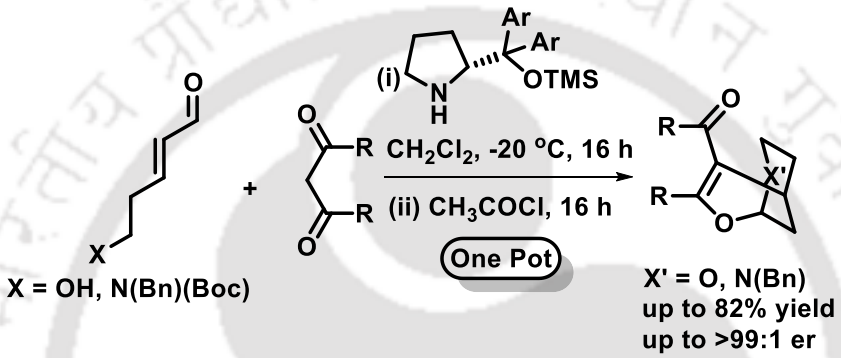


Scheme 6. Asymmetric cascade Michael/cyclization reaction of 3-hydroxyoxindoles with *α,β*-unsaturated *N*-acylated succinimides by Du *et al.*

3.3 Known strategies for the asymmetric synthesis of bridged acetals

3.3.1 Enantioselective formation of *O,O*- and *N,O*- Acetals

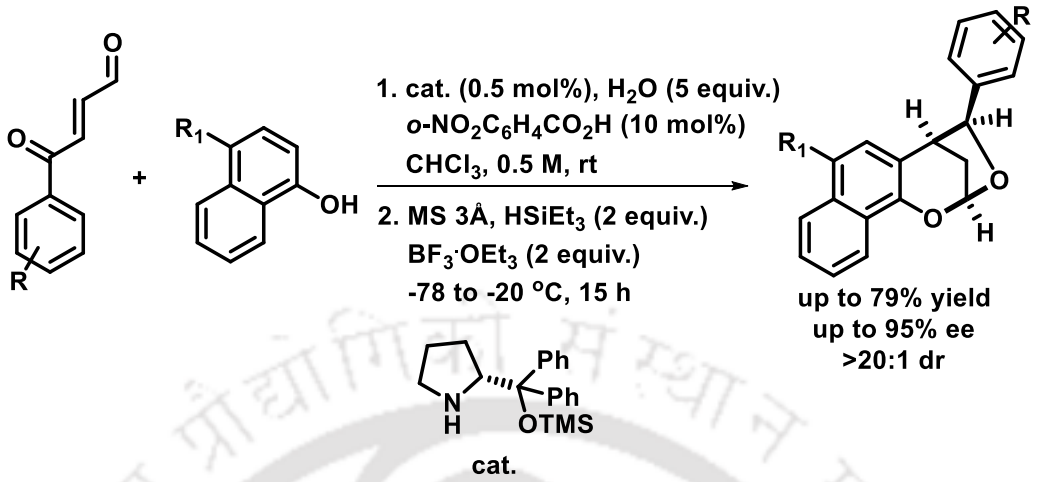
In 2013, the Franzén group reported an asymmetric catalytic one-pot *O,O* and *N,O*-acetalization cascade reaction for the efficient synthesis of functionalized dioxabicyclo- and oxaazabicyclo[3.3.1]nonane derivatives. Dioxabicyclo- and oxaazabicyclo[3.3.1]nonane skeletons are prepared in 63-80% yield with good enantioselectivities (Scheme 7).[17]



Scheme 7. Synthesis of *O,O*- and *N,O*- Acetals by Franzén *et al.*

3.3.2 Enantioselective formation of Methanobenzodioxepine

In 2016, Jørgensen and co-workers reported an organocatalytic enantioselective synthesis of methanobenzodioxepine scaffolds. 5,6-Bridged methanobenzodioxepine scaffolds with three stereocenters were isolated in moderate to good yields and up to 95% ee. This reaction provided the highest known turnover numbers in iminium ion catalysis with 0.25 mol% catalyst loading (Scheme 8).[18]

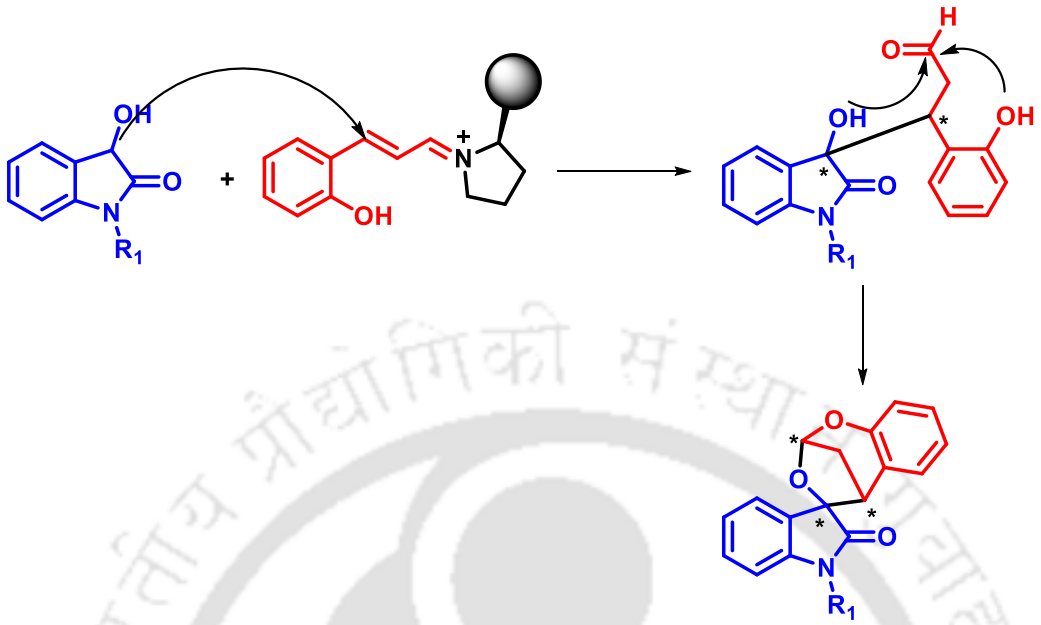


Scheme 8. Construction of methanobenzodioxepine by Jørgensen *et al.*

3.4 Concept

Considering the importance of a 3-substituted-3-hydroxy oxindole scaffold in many biologically active molecules and due to its wide applicability, we thought to develop a useful strategy for the synthesis of spirooxindoles. Over the past few years, spirooxindoles have received special attention due to their potential biological significance. Despite so many methods, synthesis of chiral methanobenzodioxepine spirooxindoles is confined. To the extent of our knowledge, no direct asymmetric organocatalytic approach for the synthesis of bridged acetals with an additional heterocyclic skeleton was reported; thus, we thought of developing an organocatalytic reaction for the synthesis of bridged acetal spirooxindoles.

Our plan was to accomplish the catalytic asymmetric Michael addition/cyclization reaction of 2-hydroxycinnamaldehyde with 3-hydroxy oxindole using prolinol TMS ether catalyst (Scheme 9). It was expected that the first iminium ion would generate from 2-hydroxycinnamaldehyde and prolinol catalyst. Then, dioxindole would attack to iminium ion followed by acid-catalyzed acetalization reaction.



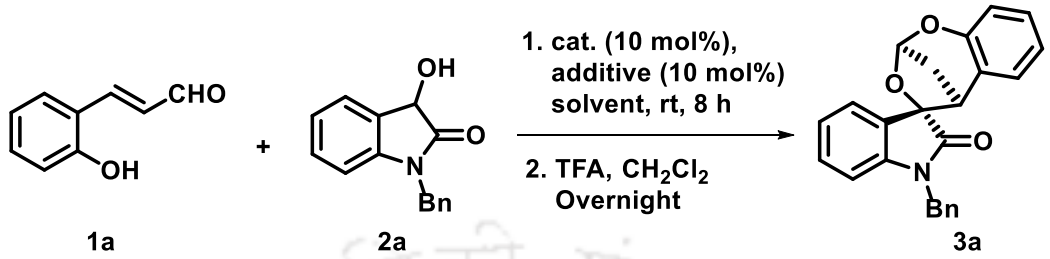
Scheme 9. Catalytic asymmetric Michael addition/cyclization reaction of 2-hydroxycinnamaldehyde with 3-hydroxy oxindole

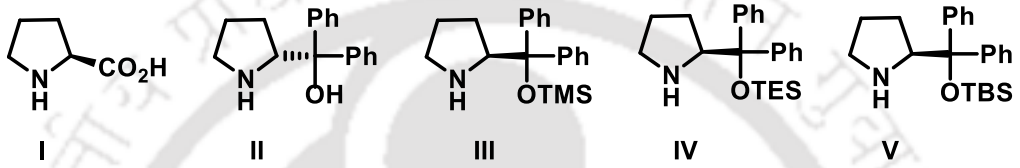
3.5 Results and discussion

3.5.1 Optimization of catalyst and reaction conditions

We began our investigation by conducting a model reaction between 2-hydroxycinnamaldehyde (**1a**) and 3-hydroxy oxindole (**2a**) with L-proline **I** in toluene. However, no product formation was detected (Table 1, entry 1). Interestingly, when we placed the reaction with diphenyl prolinol **II** in combination with benzoic acid, hemiacetal formation was observed. After the first step, the intermediate was directly subjected to TFA in CH_2Cl_2 for sequential transformations, which led to the formation of **3a** as a single diastereomer in 55% yield with moderate enantioselectivity (60%) (Table 1, entry 2). Encouraged by this result, a series of secondary amine catalysts were screened. Gratifyingly, the enantioselectivity got increased to 93% ee with Jørgensen−Hayashi catalyst **III** (Table 1, entry 3).[19] Enantioselectivity of the desired product remained same with catalyst **IV** (Table 1, entry 4).

Table 1. Catalyst screening and optimization of reaction conditions





entry[a]	catalyst	additive	solvent	yield(%)[b]	dr[c]	ee (%)[d]
1	**I**	-	$PhCH_3$	0	-	-
2	**II**	$PhCO_2H$	$PhCH_3$	55	>20:1	60
3	**III**	$PhCO_2H$	$PhCH_3$	70	>20:1	93
4	**IV**	$PhCO_2H$	$PhCH_3$	68	>20:1	93
5	**V**	$PhCO_2H$	$PhCH_3$	78	>20:1	96
6	**V**	$PhCO_2H$	CH_2Cl_2	20	>20:1	89
7	**V**	$PhCO_2H$	$PhCF_3$	65	>20:1	97
8	**V**	$PhCO_2H$	MTBE	25	>20:1	95
9	**V**	**$PhCO_2H$**	CH_3CN	**79**	**>20:1**	**98**
10	**V**	3-NO_2-$PhCO_2H$	CH_3CN	78	>20:1	97
11	**V**	2-Br-$PhCO_2H$	CH_3CN	60	>20:1	96

12	**V**	3,4-diOMe-$PhCO_2H$	CH_3CN	63	>20:1	98
13	**V**	CH_3CO_2H	CH_3CN	56	>20:1	98

[a]Unless otherwise mentioned, reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2a** in 0.5 mL of solvent. [b]Isolated yield by two steps after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

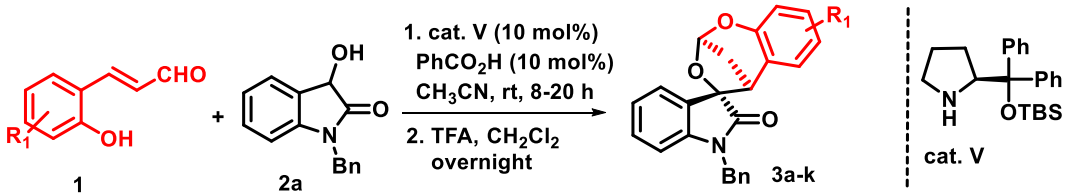
We were glad to find that excellent enantioselectivity (96%) of the desired product in high yield was obtained with the use of catalyst **V** (Table 1, entry 5). Solvents were further screened to improve the enantioselectivity and yield of the desired product. Halogenated solvents such as dichloromethane were not good for this reaction as the poor conversion was seen (Table 1, entry 6). Gratifyingly, slight enhancement in enantioselectivity was observed in *α,α,α*- trifluorotoluene, albeit less yield (Table 1, entry 7). Less conversion was also observed in ether solvent such as MTBE (Table 1, entry 8). Finally, acetonitrile was found to be the best solvent, provided the desired product in 79% yield with 98% enantioselectivity (Table 1, entry 9). Next, we turned our attention to investigate other acid additives, but benzoic acid was found to be the best acid additive (Table 1, entries 10-13).

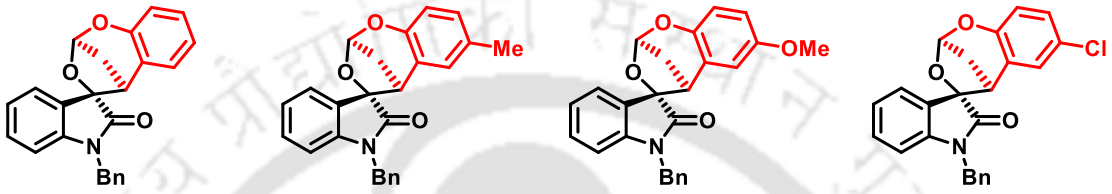
3.5.2 Substrate scope

With the optimized catalyst and reaction condition in hand, we set out to elucidate the scope of this Michael reaction concerning *o*-hydroxyaromatic *α,β*-unsaturated aldehydes, as well as 3-hydroxy oxindole. To our delight, high enantioselectivities were obtained in all the cases, and excellent diastereoselectivities were maintained.

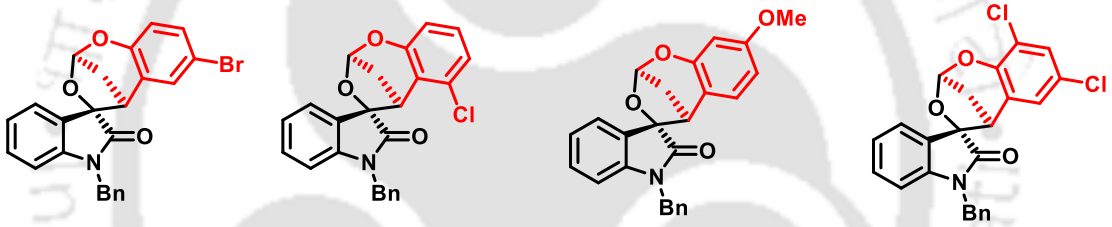
We first examined the scope of *o*-hydroxyaromatic *α,β*-unsaturated aldehydes by varying different substituents. It can be seen from Scheme 10, the desired corresponding products were obtained in moderate yields with excellent enantioselectivities. Delightfully, a single diastereomer was formed in all cases. Without any substitution, product **3a** was obtained in 79% yield with 98% enantiomeric excess.

Scheme 10. Scope of *o*-hydroxyaromatic *α,β*-unsaturated aldehydes[a]

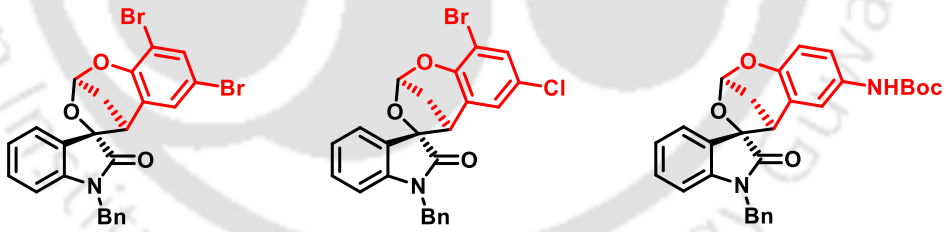




3a, 79%, >20:1 dr, 98% ee | 3b, 64%, >20:1 dr, 97% ee | 3c, 51%, >20:1 dr, 98% ee | 3d, 66%, >20:1 dr, 97% ee



3e, 57%, >20:1 dr, 98% ee | 3f, 61%, >20:1 dr, 99% ee | 3g, 62%, >20:1 dr, 97% ee | 3h, 34%, >20:1 dr, 94% ee



3i, 23%, >20:1 dr, 95% ee | 3j, 32%, >20:1 dr, 95% ee | 3k, 47%, >20:1 dr, 98% ee

[a]All reactions were carried out with 0.12 mmol of **1** with 0.1 mmol of **2a** in 0.5 mL CH_3CN. Yield corresponds to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees was determined by chiral HPLC using a stationary phase chiral column.

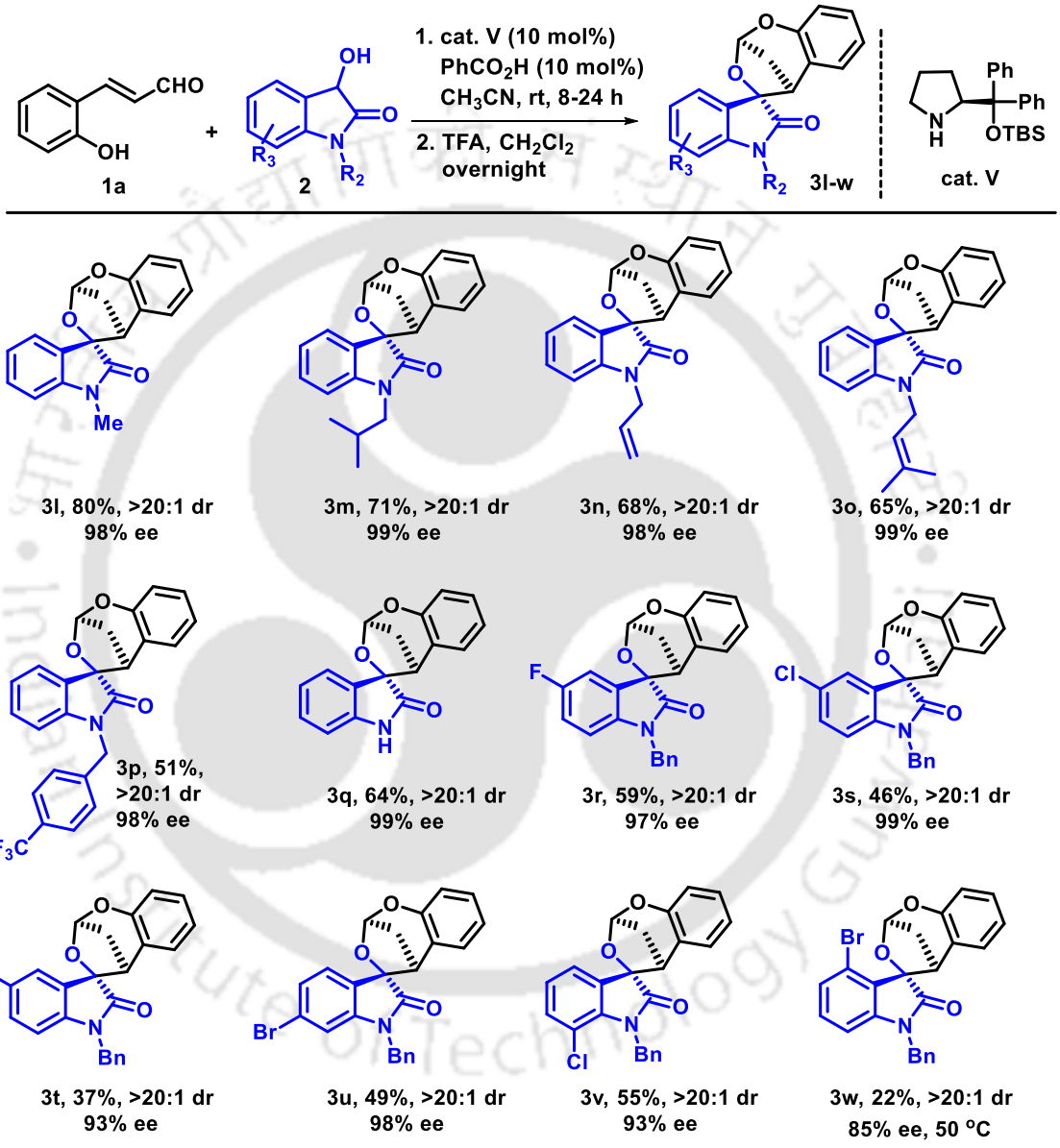
o-Hydroxy-cinnamaldehyde having electron-donating substituents at the–*para* position **1b-c** were screened, and the desired products (**3b-3c)** were obtained in acceptable yields with excellent stereoselectivities (Scheme 10). 4-Halo substituted enals (**1c-1d**) were also

well-tolerated in our reaction conditions and furnished the desired products (**3c-3d**) in moderate yields with excellent enantioselectivities (Scheme 10). Then 3-chloro and 5-methoxy substituted enals **1f** and **1g** were employed in the reaction, and high enantioselectivities were achieved for the corresponding products. In particular, 99% ee was observed for product **3f** having 3-chloro substitution. Our methodology is also suitable for 4,6-disubstituted enals (**1h-1j**), and high diastereo- and enantioselectivities were observed, albeit moderate yields were detected (Scheme 10). To our delight, substrate **1k** having a 4-NHBoc group could also be employed in our methodology, delivering product **3k** in excellent enantioselectivity (Scheme 10).

After examining the scope of *o*-hydroxyaromatic *α,β*-unsaturated aldehydes, we turned our attention to various 3-hydroxy oxindoles, summarized in Scheme 11. *N*-substitutions were checked, and gratifyingly here also excellent results were achieved, preserving high diastereomeric ratio. For example, 80% yield and 98% enantiomeric excess were obtained for product **3l** having *N*-methyl substitution, and 99% ee was observed for product **3m** having *N*-^{i}Bu substitution (Scheme 11). Dioxindole **2d** having *N*-allyl group and **2e** having *N*-prenyl group also participated in the reaction, delivering products **3n** and **3o,** respectively, in excellent enantioselectivities. Then dioxindole **2f** having *N*-4-CF_3benzyl group was employed in the reaction, and smooth conversion was observed for **3p** with 98% ee. Moreover, our methodology was also suitable for *N*-unsubstituted oxindole **2g**, delivering the product **3q** in 99% ee (Scheme 11). We next investigated the aromatic part of the oxindole motif, and here also, the results were unaffected. Initially, 5-halo substituted *N*-benzyl dioxindoles **2h−2j** were prepared and engaged in the reaction. The desired products **3r−3t** were isolated in acceptable yields with excellent enantioselectivities. The reaction with dioxindole **2k** and **2l** having 6-bromo and 7-chloro substitutions, respectively, also gave satisfactory results. Finally, 4-bromo substituted oxindole **2m** participated in the reaction, but the acetal formation was slow, and only after heating at 40 °C, the moderate yield was detected with prolonged reaction time.

Nevertheless these products having halo substitutions are important as they can be elaborated easily by cross-coupling reactions.

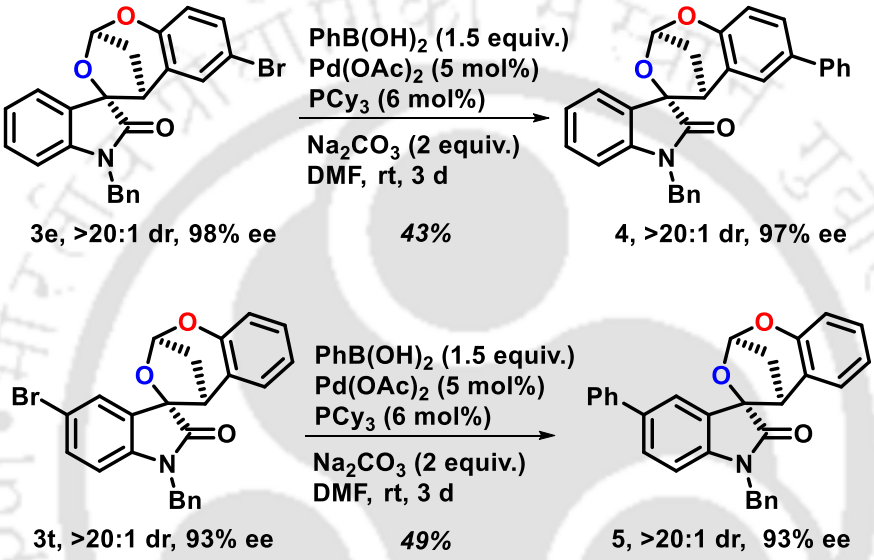
Scheme 11. Scope of dioxindoles[a]



[a]All reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2** in 0.5 mL CH_3CN. Yield corresponds to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees was determined by chiral HPLC using stationary phase chiral column.

3.5.3 Synthetic transformations

The synthetic utility of our method was demonstrated by performing Suzuki coupling reactions on **3e** and **3t** (Scheme 12). Thus, when phenylboronic acid was treated with **3e** and **3t** in the presence of palladium acetate and tricyclohexyl phosphine under basic conditions, the corresponding products **4** and **5** were formed in moderate yields. Delightfully, the enantiopurity was preserved for both products.



Scheme 12. Synthetic transformations

3.5.4 Determination of product stereochemistry

The absolute structure of product **3s** was solved by X-ray crystallography[20] and was found to be (2*R*,3'*S*,5*S*). The configuration of other products is expected to be the same by analogy (Figure 2).

Figure 2. X-ray crystal structure of **3s**

3.5.5 The proposed mechanism

Based on the configuration, a plausible mechanism has been shown in Figure 3. It is believed that catalyst **V** reacts with **1a** in the presence of benzoic acid to provide aminal **A**[21] whose presence was detected by NMR by stoichiometric mixing of **V** and **1a**. Interestingly, intermediate **A** is nucleophilic in nature, and it must be in equilibrium with iminium ion **B,** which is electrophilic and thus the active intermediate for our reaction. Since the *Si* face of the chiral iminium ion is blocked by the bulky OTBS group, the conjugate addition of dioxindole **2a** takes place from the *Re* face to generate intermediate **6** after hydrolysis. A Newman projection **C** was drawn to understand the diastereoselectivity of the reaction. The enamine group and the CONAr group orients in *anti*-fashion, possibly due to steric interaction. Intermediate **6** then undergoes acetalization reaction diastereoselectively in the presence of TFA to deliver product **3a**.

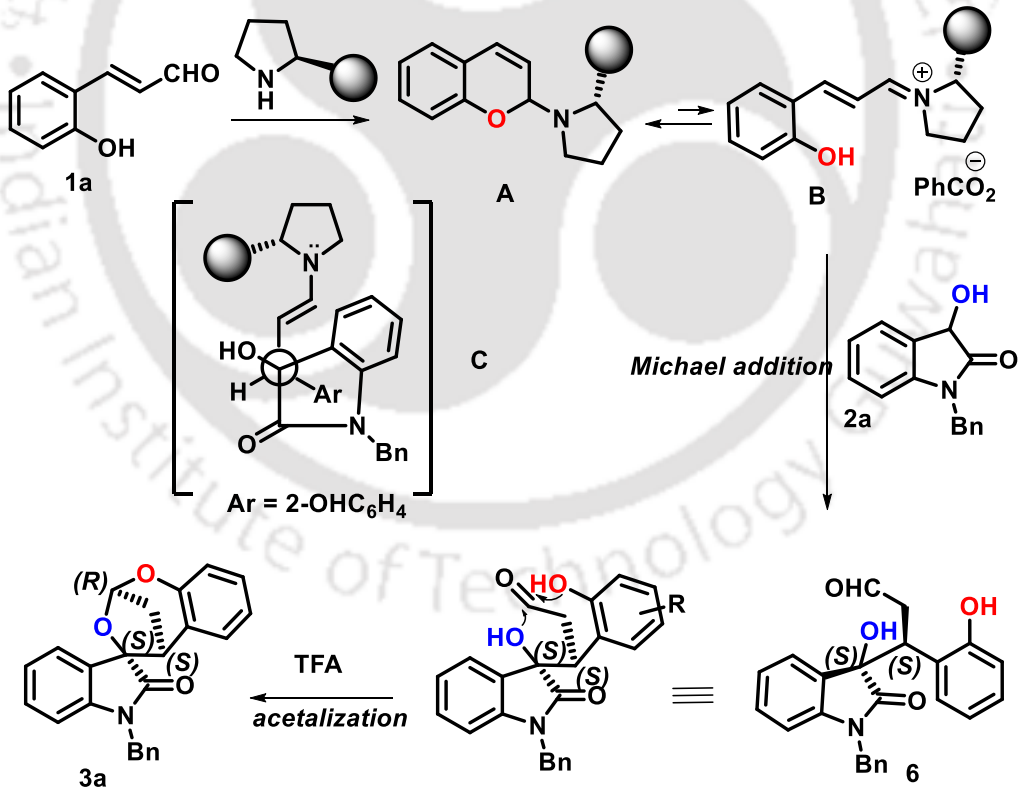


Figure 3. The proposed mechanism

3.6 Conclusion

In summary, this report demonstrates the first catalytic asymmetric synthesis of bridged *O,O*-acetal with spirooxindole skeleton. The methodology involves amine catalyzed conjugate addition followed by diastereoselective acetalization with TFA. The desired spirooxindole products were obtained in good to high yields with high diastereo- and enantioselectivities in operationally simple reaction conditions. Also, few products have been further functionalized via Suzuki coupling reaction. Given the high pharmaceutical significance of spirooxindoles and bridged acetals, our products might be bioactive.

3.7 Experimental Section

3.7.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz, and 600 MHz spectrometers. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz, and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Phenomenex LUX C1 Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using

SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

3.7.2 General procedure for the synthesis of *ortho*-hydroxy-cinnamaldehydes

Ortho-hydroxy-cinnamaldehydes (**1a-1k**) were prepared according to reported procedures.[22]

In an oven-dried round bottom flask, (triphenylphosphoranylidene)acetaldehyde (2 mmol, 1.0 equiv.) was added to the stirred solution of salicylaldehyde (2 mmol) in dry THF (2 mL) and the resulting solution was heated at reflux overnight. Completion of the reaction was checked by TLC (6–12 h). After completion of the reaction, the solvent was evaporated, and the reaction mixture was purified by flash column chromatography on silica gel eluting with hexane/ethyl acetate to afford desired products **1a-k**.

3.7.3 General procedure for the synthesis of dioxindoles

Dioxindoles (**2a-2m**) were prepared according to reported procedures.[23]

In an oven-dried round bottom flask, a solution of isatin (10 mmol) was slowly added to K_2CO_3 (25 mmol, 2.5 equiv.) under an argon atmosphere at 0 ºC. The reaction mixture was allowed to stir at 0 ºC for 10 min. Then, alkyl halide or benzyl halide (20 mmol, 2.0 equiv.) was added to the reaction mixture and allowed to stir at rt for 12 h. The reaction mixture was filtered through Celite with about 50 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. Water was added until precipitation of the *N*-protected isatin. Crystallization from hexane/ethyl acetate afforded the pure product.

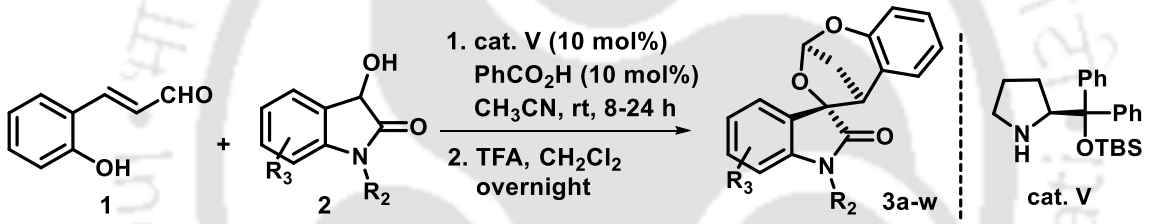
N-protected isatins (10 mmol) were added in small portions to a stirred suspension of sodium borohydride (15 mmol, 1.5 equiv.) in 60 mL of 1:1 CH_2Cl_2/EtOH mixture at 0

ºC. The mixture was vigorously stirred at this temperature until the suspension became colorless (about 5 min). Then, water (1.0 mL) was added, and the reaction mixture was stirred until the bubbling stops. The mixture was extracted with CH_2Cl_2 (3 ×50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was used without further purification.

3.7.4 General procedure for the synthesis of catalyst

The catalyst (**III, IV,** and **V**) was prepared according to reported procedures.[24, 25]

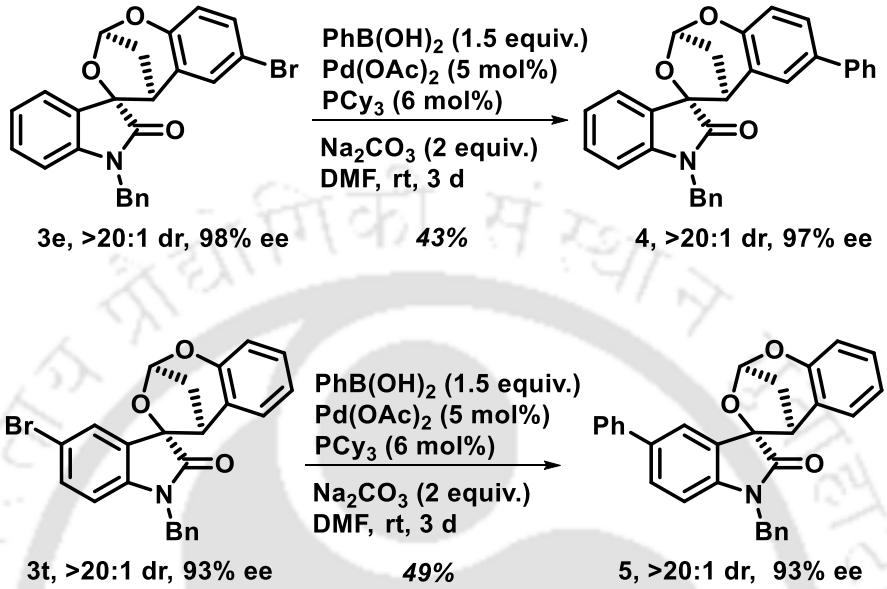
3.7.5 General procedure for the synthesis of products 3a-3w



In an oven-dried round bottom flask, **1** (17.7 mg, 0.12 mmol), **2** (23.9 mg, 0.1 mmol), 10 mol% of cat. **V** and 10 mol% of $PhCO_2H$ were taken. 0.5 mL of CH_3CN was added to the reaction mixture and stirred at rt for 8-20 h. Completion of the reaction was checked by TLC. After completion of the reaction, the solvent was concentrated, and the reaction mixture was directly subjected to TFA.

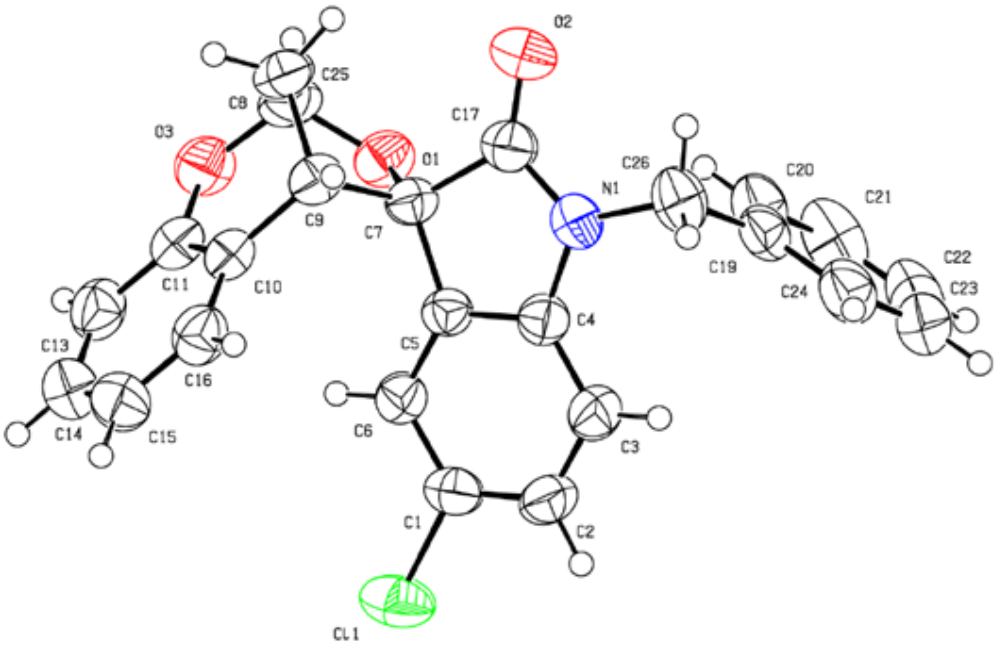
Second step: To the vacuum dried reaction mixture, CH_2Cl_2 was added to the reaction mixture of the first step and allowed to stir at rt. 1.5 equiv. of TFA was added; the reaction mixture was allowed to stir overnight. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was concentrated, and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10 %) to afford the desired product **3a-w**.

3.7.6 General procedure for the preparation of compound 4/5



In an oven-dried round bottom flask, compound **3e/3t** (44.8 mg, 0.1 mmol), phenylboronic acid (1.5 equiv.), palladium (II) acetate (0.05equiv.), tricyclohexylphosphine (0.06 equiv.) and Na_2CO_3 (2 equiv.) were taken, flushed with argon and then dry DMF (0.1 mL) was added. The reaction mixture was allowed to stir for 3 d under the argon atmosphere. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography using EtOAc-Hexane (1-2%) as eluent to afford the compound **4/5**.

3.7.7 Crystal structure of compound 3s[20]



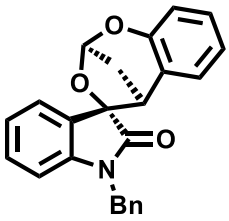
ORTEP crystal structure

Table 2. Crystal data and structure refinement for compound 3s

Parameters	3s
CCDC No.	1843516
Empirical formula	$C_{24}H_{18}NO_3Cl$
Formula weight	403.84
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.36×0.33×0.33
Temperature, *T*	296 K
Wavelength, λ (Å)	0.71073

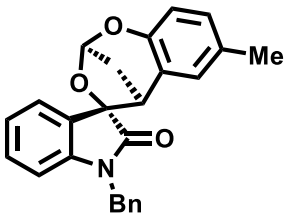
Crystal system	Monoclinic
Space group	*'P 21'*
Unit cell dimensions	a = 5.5810 (4) Å b = 18.9438 (14) Å c = 9.1233 (7) Å α = 90°, β = 93.554 (5)°, γ = 90°
Volume, V (Å^3)	962.71 (12)
Z	2
Calculated density, Mg/m^3	1.393
Absorption coefficient, μ (mm^{-1})	0.225
F(000)	420
θ range for data collection	2.150° to 25.040°
Limiting indices	$-6 \le h \le 6$, $-21 \le k \le 22$, $-10 \le l \le 10$
Reflection collected/unique	3340/2998
Refinement method	'SHELXL–2014/7 (Sheldrick, 2014)'
Data/restraints/parameters	3340/1/262
Goodness of fit on F^2	1.1430
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0310, wR2 = 0.0561
R indices (all data)	R1 = 0.0353, wR2 = 0.0573

3.8 Characterization data of products



3a

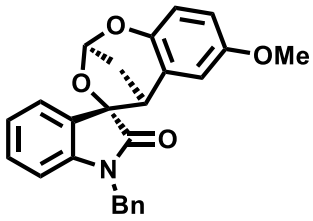
((2'R,3S,5'S)-1-benzyl-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3a) was obtained as a light yellow solid in 79% yield (29.2 mg) after column chromatography. M.P. = 128-130 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.32 – 7.18 (m, 6H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.3 Hz, 2H), 6.55 (d, *J* = 7.4 Hz, 1H), 6.04 (d, *J* = 3.5 Hz, 1H), 5.84 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 175.5, 151.8, 143.0, 135.6, 130.1, 129.7, 129.0, 128.9, 127.9, 127.4, 125.9, 125.7, 125.5, 122.6, 120.8, 116.5, 109.1, 101.3, 90.8, 45.1, 43.9, 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.0 min, t_{minor} = 21.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{20}NO_3[M+H]^+$ 370.1438, found 370.1439.



3b

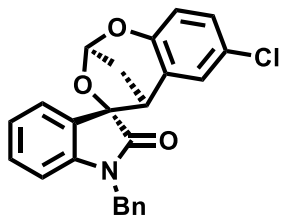
((2'R,3S,5'S)-1-benzyl-7'-methyl-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3b) was obtained as light yellow semi solid in 64% (24.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.30 – 7.20 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.62 (t, *J* = 6.6 Hz, 2H), 6.36 (s, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 5.86 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 3.60 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.19 (d, *J* = 3.9 Hz, 1H), 2.39 (d, *J* = 11.6 Hz, 1H), 2.11 (s, 3H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.6, 149.6, 143.1, 135.7, 130.1, 130.1, 130.1, 129.4, 129.0, 127.9, 127.5, 126.1, 125.8, 125.2, 122.6, 116.2, 109.0, 101.3, 90.7, 45.1, 43.9, 31.6, 20.5. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-

PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.9 min, t_{minor} = 15.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{22}NO_3$ $[M+H]^+$ 384.1594, found 384.1603.



3c

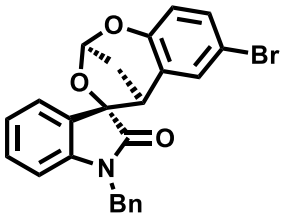
((2'R,3S,5'S)-1-benzyl-7'-methoxy-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3c) was obtained as a yellow sticky solid in 51% (20.4 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.31 – 7.20 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.68 – 6.59 (m, 2H), 6.12 (d, *J* = 2.9 Hz, 1H), 6.01 (d, *J* = 3.5 Hz, 1H), 5.91 (d, *J* = 7.2 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.65 – 3.55 (m, 4H), 3.18 (d, *J* = 3.9 Hz, 1H), 2.38 (d, *J* = 11.6 Hz, 1H). **^{13}C{1H} NMR (101 MHz, Chloroform-*d*)** δ 175.5, 153.7, 145.7, 143.0, 135.7, 130.1, 129.0, 127.9, 127.5, 126.0, 125.7, 122.8, 117.0, 114.9, 114.6, 109.1, 101.2, 90.6, 76.9, 56.1, 45.3, 43.9, 31.6. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.1 min, t_{minor} = 23.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{22}NO_4$ $[M+H]^+$ 400.1543, found 400.1540.



3d

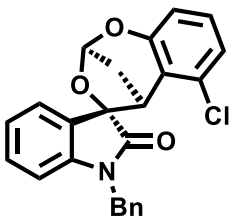
((2'R,3S,5'S)-1-benzyl-7'-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3d) was obtained as a white semi solid in 66% (26.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.28 (dt, *J* = 15.3, 7.1 Hz, 5H), 7.17 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.0 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.64 (dt, *J* = 11.8, 3.9 Hz, 1H), 3.22 (d, *J* = 3.9 Hz, 1H), 2.37 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.2, 150.5, 143.1, 135.5,

130.4, 129.5, 129.1, 128.5, 128.0, 127.4, 127.0, 125.7, 125.7, 125.3, 122.9, 117.8, 109.3, 101.3, 90.7, 44.9, 44.0, 31.2. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.3 min, t_{minor} = 21.6 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1055.



3e

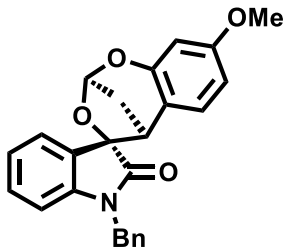
((2'R,3S,5'S)-1-benzyl-7'-bromo-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3e) was obtained as a light yellow sticky solid in 57% (25.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 – 7.27 (m, 3H), 7.27 – 7.21 (m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.64 (dt, *J* = 11.8, 3.9 Hz, 1H), 3.22 (d, *J* = 3.9 Hz, 1H), 2.37 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.2, 151.0, 143.1, 135.5, 132.5, 131.4, 130.5, 129.1, 128.0, 127.4, 125.8, 125.3, 122.9, 118.3, 112.9, 109.3, 101.3, 90.7, 44.9, 44.0, 31.2. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.9 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0542.



3f

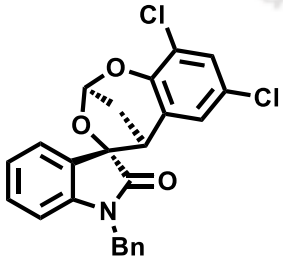
((2'R,3S,5'S)-1-benzyl-6'-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3f) was obtained as a light yellow semi solid in 61% (24.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 – 7.22 (m, 5H), 7.18 – 7.07 (m, 2H), 6.83 (dd, *J* = 10.5, 8.1 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 4.78 (d, *J* = 15.9 Hz, 1H), 3.89 (d, *J* = 4.1 Hz, 1H), 3.62 (dt, *J* = 11.8, 3.9 Hz, 1H),

2.36 (d, *J* = 11.8 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.2, 152.9, 142.9, 135.5, 133.5, 130.2, 129.8, 129.0, 127.8, 127.1, 125.3, 124.8, 123.8, 122.8, 121.6, 115.2, 109.3, 101.2, 90.8, 43.8, 42.0, 30.7. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.8 min, t_{minor} = 21.5 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1051.



3g

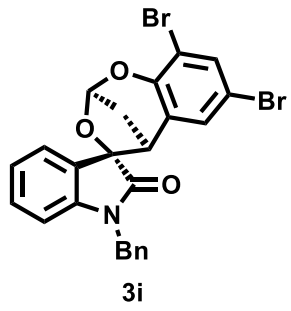
((2'R,3S,5'S)-1-benzyl-8'-methoxy-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3g) was obtained as a light yellow sticky solid in 62% (24.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.30 (ddd, *J* = 17.5, 12.7, 6.0 Hz, 6H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.64 (m, 2H), 6.55 – 6.47 (m, 2H), 6.35 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.07 (d, *J* = 3.5 Hz, 1H), 5.98 (d, *J* = 7.5 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.81 (s, 3H), 3.65 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.7, 161.0, 152.8, 143.2, 135.8, 130.2, 129.5, 129.2, 128.0, 127.6, 126.2, 126.0, 122.8, 118.0, 109.2, 106.7, 102.2, 101.4, 91.1, 55.7, 44.7, 44.0, 32.0. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.9 min, t_{minor} = 20.1 min). **HRMS (+ESI-TOF):** calcd. For $C_{25}H_{22}NO_4$ $[M+H]^+$ 400.1543, found 400.1548.



3h

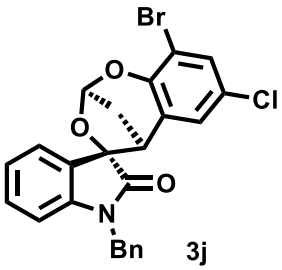
((2'S,3S,5'S)-1-benzyl-7',9'-dichloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3h) was obtained as a yellow sticky solid in 34% (15.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 (d, *J* = 2.4 Hz, 2H), 7.33 (s, 1H), 7.29 (d, *J* = 7.0 Hz, 3H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.01 (d, *J* = 7.5 Hz, 1H), 4.93 (d, *J* =

15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.73 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9 , 146.8 , 143.1 , 135.4 , 130.6 , 129.9 , 129.1 , 128.0 , 128.0 , 127.5 , 127.1 , 125.7 , 125.6 , 124.8 , 123.0 , 122.4 , 109.5 , 101.7 , 90.7 , 45.0 , 44.1 , 31.1 , 29.9. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.0 min, t_{minor} = 19.5 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}Cl_2NO_3$ $[M+H]^+$ 438.0658, found 438.0655.



3i

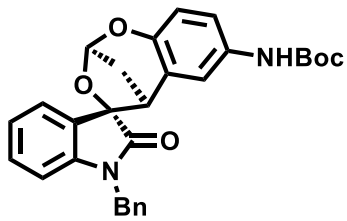
((2'S,3S,5'S)-1-benzyl-7',9'-dibromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3i) was obtained as a light yellow semi solid in 23% (12.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.28 (d, *J* = 16.5 Hz, 4H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.74 – 6.67 (m, 2H), 6.20 (d, *J* = 3.3 Hz, 1H), 6.00 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.41 (d, *J* = 11.8 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9, 148.4, 143.1, 135.4, 130.7, 130.6, 129.1, 128.4, 128.0, 127.5, 125.8, 124.8, 123.0, 112.8, 109.5, 101.8, 90.7, 45.0, 44.0, 31.1, 29.9. **HPLC Analysis:** ee = 95%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.5 min, t_{minor} = 19.6 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}Br_2NO_3$ $[M+H]^+$ 525.9648, found 525.9647.



3j

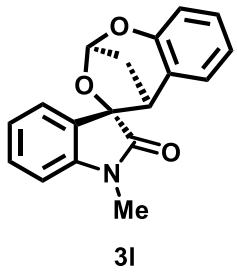
((2'S,3S,5'S)-1-benzyl-9'-bromo-7'-chloro-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3j) was obtained as a light yellow semi solid in 32% (15.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.50 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.32 (m, 2H),

7.28 (d, *J* = 16.3 Hz, 4H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.00 (d, *J* = 7.0 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.28 (d, *J* = 3.8 Hz, 1H), 2.41 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 174.9, 147.8, 143.0, 135.4, 132.7, 130.6, 129.1, 128.0, 127.8, 127.4, 126.0, 125.7, 123.0, 110.9, 109.5, 101.8, 90.6, 45.0, 44.0, 31.1. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.8 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}BrClNO_3$ $[M+H]^+$ 482.0153, found 482.0157.



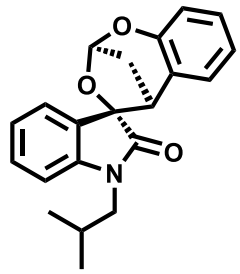
3k

(tert-butyl((2'R,3S,5'S)-1-benzyl-2-oxo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-7'-yl)carbamate) (3k) was obtained as a dark yellow semi solid in 47% (22.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.36 – 7.27 (m, 5H), 7.18 (d, *J* = 6.6 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.72 – 6.64 (m, 3H), 6.05 (d, *J* = 3.5 Hz, 1H), 6.00 (d, *J* = 6.9 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.64 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.26 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H), 1.45 (s, 9H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.5, 147.7, 143.1, 135.6, 131.5, 130.2, 129.1, 127.9, 127.4, 125.9, 125.8, 125.7, 122.8, 116.7, 109.2, 101.3, 90.6, 45.1, 44.0, 31.6, 28.5. **HPLC Analysis:** ee = 98%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.4 min, t_{minor} = 9.5 min). **HRMS (+ESI-TOF):** calcd. For $C_{29}H_{28}N_2NaO_5$ $[M+Na]^+$ 507.1890, found 507.1876.



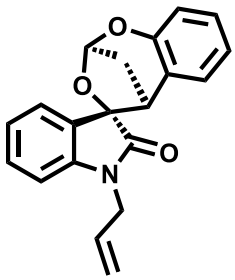
3l

((2'R,3S,5'S)-1-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3l) was obtained as a yellow sticky solid in 80% (23.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.38 – 7.32 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 13.3, 7.5 Hz, 2H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 3.28 – 3.25 (m, 1H), 3.09 (s, 3H), 2.93 (dt, *J* = 11.8, 3.8 Hz, 1H), 2.50 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.1, 151.7, 143.2, 130.3, 129.5, 129.4, 126.9, 125.2, 123.4, 122.7, 121.0, 115.9, 108.6, 100.7, 90.7, 46.9, 33.1, 26.7. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.2 min, t_{minor} = 17.3 min). **HRMS (+ESI-TOF):** calcd. For $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1125, found 294.1131.



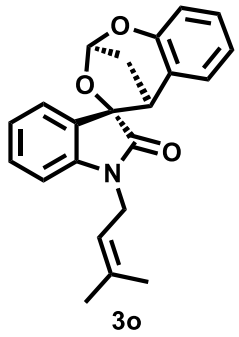
3m

((2'R,3S,5'S)-1-isobutyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3m) was obtained as a white semi solid in 71% (23.8 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.25 (dd, *J* = 10.6, 4.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.88 (d, *J* = 7.5 Hz, 1H), 3.63 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.54 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.39 (dd, *J* = 13.9, 7.3 Hz, 1H), 3.22 (d, *J* = 4.0 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 2.19 – 2.10 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 6H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.6, 151.9, 143.7, 130.1, 129.6, 128.9, 125.9, 125.8, 125.6, 122.3, 120.8, 116.5, 108.6, 101.3, 90.7, 47.5, 45.2, 31.4, 27.1, 20.4. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.8 min, t_{minor} = 8.7 min). **HRMS (+ESI-TOF)**: calcd. For $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1598.



3n

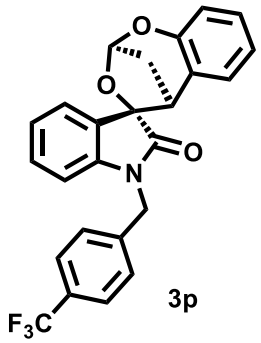
((2'R,3S,5'S)-1-allyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo [d][1,3]dioxepin]-2-one) (3n) was obtained as a light yellow semi solid in 68% (21.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.25 (dd, *J* = 9.9, 5.7 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 13.5, 7.6 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.84 (ddd, *J* = 15.7, 12.0, 6.7 Hz, 2H), 5.30 – 5.22 (m, 2H), 4.35 (dd, *J* = 16.3, 5.3 Hz, 1H), 4.23 (dd, *J* = 16.3, 5.3 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 4.0 Hz, 3H), 2.43 (d, *J* = 11.6 Hz, 1H**). ^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.1, 151.8, 143.1, 131.3, 130.1, 129.7, 128.9, 125.9, 125.7, 125.5, 122.6, 120.8, 118.0, 116.5, 108.9, 101.3, 90.8, 45.1, 42.5, 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.0 min, t_{minor} = 11.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{20}H_{18}NO_3$ $[M+H]^+$ 320.1281, found 320.1274.



3o

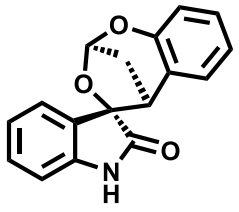
(2'R,3S,5'S)-1-(3-methylbut-2-en-1-yl)-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one (3o) was obtained as a light yellow semi solid in 65% (22.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.28 – 7.21 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.05 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.18 (t, *J* = 6.1 Hz, 1H), 4.31 (dd, *J* = 15.4, 6.4 Hz, 1H), 4.22 (dd, *J* = 15.5, 6.8 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.24 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 1.83 (s, 3H), 1.73 (s, 3H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9, 151.9, 143.3, 137.1, 130.1, 129.6, 128.9, 125.9, 125.6, 122.4, 120.7, 118.1, 116.5, 108.8, 101.3, 90.9, 44.9, 38.3, 31.4, 25.8, 18.3. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0

mL/min, λ = 254 nm (t_{major} = 6.7 min, t_{minor} = 12.4 min). **HRMS (+ESI-TOF)**: calcd. For $C_{22}H_{22}NO_3$ [M+H] $^+$ 348.1594, found 348.1596.



3p

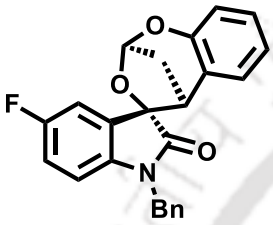
(2'R,3S,5'S)-1-(4-(trifluoromethyl)benzyl)-5'H-spiro[indoline-3,4'[2,5]methanobenzo [d][1,3]dioxepin]-2-one (3p) was obtained as a green semi solid in 51% (22.3 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.64 – 6.58 (m, 2H), 6.09 (d, *J* = 3.5 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 4.91 (q, *J* = 16.0 Hz, 2H), 3.64 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.48 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.6, 151.9, 142.7, 139.7, 130.2, 130.2(q, J_{C-F} = 32.33 Hz), 129.8, 128.9, 127.7, 126.2, 126.1(q, J_{C-F} = 3.03 Hz), 125.8, 125.5, 125.3, 124.1(q, J_{C-F} = 272.70 Hz) 123.0, 120.9 116.6, 108.8, 101.3, 90.8, 45.2, 43.5, 31.5. **HPLC Analysis:** ee = 98%, Chiralpak IA Column Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.1 min, t_{minor} = 19.4 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{19}F_3NO_3$ [M+H] $^+$ 438.1312, found 438.1312.



3q

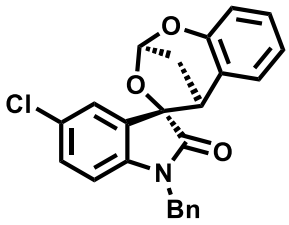
(2'R,3S,5'S)-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3q) was obtained as a light pink solid in 64% (17.9 mg) yield after column chromatography. M.P. = 115-117 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.29 (s, 1H), 7.25 (dd, *J* = 9.5, 6.0 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 13.7, 7.4 Hz, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 3.55 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.31 (d, *J* = 3.9 Hz, 1H), 2.44 (d, *J* = 11.6 Hz, 1H).

^{13}C {1H} NMR (101 MHz, Chloroform-*d*) δ 177.8, 151.8, 140.9, 130.2, 129.7, 128.9, 126.2, 126.2, 125.4, 122.6, 120.8, 116.5, 110.1, 101.3, 91.2, 44.9, 31.2. **HPLC Analysis:** ee = 99%, Chiralpak IA Column n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 16.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{17}H_{14}NO_3$ $[M+H]^+$ 280.0968, found 280.0970.



3r

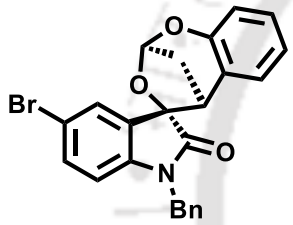
(2'*R*,3*S*,5'*S*)-1-benzyl-5-fluoro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3r) was obtained as a light grey semi solid in 59% (22.9 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 – 7.29 (m, 2H), 7.25 (dd, *J* = 12.0, 4.1 Hz, 4H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.54 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.55 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 3.63 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.45 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.3, 158.9 (d, J_{C-F} = 241.39 Hz), 151.7, 138.9, 138.9, 135.3, 130.0, 129.1, 128.9, 128.1, 127.6 (d, J_{C-F} = 8.08 Hz), 127.4, 127.4, 124.9, 121.0, 116.7, 116.4 (d, J_{C-F} = 24.24 Hz), 114.1 (d, J_{C-F} = 26.26 Hz), 109.6 (d, J_{C-F} = 8.08 Hz), 101.4, 90.8, 90.7, 45.2, 44.1, 31.4. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.9 min, t_{minor} = 23.6 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}FNO_3$ $[M+H]^+$ 388.1343, found 388.1346.



3s

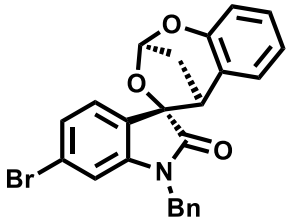
(2'R,3S,5'S)-1-benzyl-5-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3s) was obtained as a light brown solid in 46% (18.6 mg) yield after column chromatography. M.P. = 167-170 ^oC. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.34 (t, *J* = 7.3 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.84 (td,

J = 7.5, 1.0 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.09 (d, *J* = 3.5 Hz, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.7 Hz, 1H), 3.62 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.29 (d, *J* = 3.9 Hz, 1H), 2.50 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 175.0, 151.7, 141.4, 135.2, 130.0, 129.9, 129.1, 128.9, 128.1, 128.1, 127.5, 127.4, 126.5, 124.9, 121.0, 116.7, 110.0, 101.4, 90.7, 45.2, 44.0, 31.3. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 25.1 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1049.



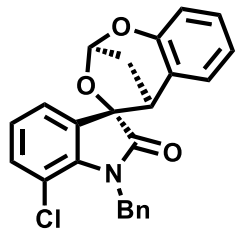
3t

(2'R,3S,5'S)-1-benzyl-5-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3t) was obtained as a light yellow sticky solid in 37% (16.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.27 (dd, *J* = 14.8, 7.2 Hz, 3H), 7.21 (t, *J* = 5.0 Hz, 3H), 7.16 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.82 (d, *J* = 2.0 Hz, 1H), 4.82 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 3.56 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.23 (d, *J* = 3.9 Hz, 1H), 2.44 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9, 151.7, 141.9, 135.1, 132.8, 130.0, 129.3, 129.1, 128.9, 128.1, 127.8, 127.4, 124.9, 121.0, 116.8, 115.5, 110.5, 101.4, 90.7, 45.3, 44.0, 31.3. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.5 min, t_{minor} = 26.0 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0544.



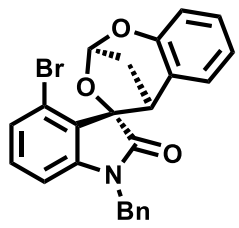
3u

(2'R,3S,5'S)-1-benzyl-6-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3u) was obtained as a light brown semi solid in 49% (22.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.84 – 7.78 (m, 2H), 7.78 – 7.67 (m, 4H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 6.16 (d, *J* = 8.6 Hz, 1H), 5.35 (d, *J* = 15.7 Hz, 1H), 5.20 (d, *J* = 15.7 Hz, 1H), 4.07 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.72 (d, *J* = 3.9 Hz, 1H), 2.91 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175., 151.7, 144.3, 135.1, 129.9, 129.2, 128.9, 128.2, 127.4, 127.2, 125.6, 125.1, 124.7, 124.0, 121.0, 116.6, 112.5, 101.3, 90.4, 45.1, 44.0, 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.7 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0546.



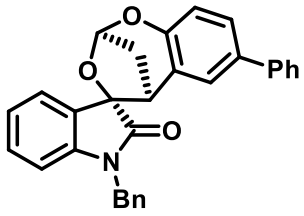
3v

(2'R,3S,5'S)-1-benzyl-7-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one (3v) was obtained as a brown semi solid in 55% (22.2 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (dd, *J* = 14.3, 6.0 Hz, 5H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.64 – 6.56 (m, 2H), 6.08 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.32 (s, 2H), 3.64 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.46 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 176.2, 151.8, 139.0, 137.2, 132.7, 129.9, 129.0, 128.8, 128.8, 127.5, 126.6, 125.1, 124.5, 123.5, 120.9, 116.5, 115.4, 101.4, 90.2, 45.6, 45.1, 31.4. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 15.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1046.



3w

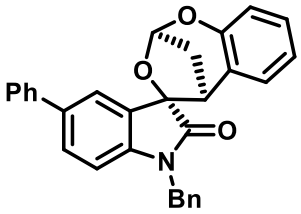
(2'*R*,3*S*,5'*S*)-1-benzyl-4-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3w) was obtained as a yellow semi solid in 22% (10.0 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 15.2, 7.4 Hz, 3H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.95 – 6.93 (m, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.63 (dd, *J* = 8.6, 4.9 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 3.6 Hz, 1H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.7 Hz, 1H), 3.71 (dt, *J* = 11.7, 3.8 Hz, 1H), 3.21 (d, *J* = 3.7 Hz, 1H), 2.24 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 176.4, 153.4, 144.5, 135.3, 130.6, 130.2, 129.2, 128.5, 128.4, 128.1, 127.4, 125.9, 123.9, 121.5, 120.8, 117.0, 108.3, 102.3, 94.3, 47.2, 44.2, 29.8. **HPLC Analysis:** ee = 85%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 23.0 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0547.



4

(2'R,3S,5'S)-1-benzyl-7'-phenyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (4) was obtained as a light yellow sticky solid in 43% (19.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.40 – 7.26 (m, 11H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.66 (dd, *J* = 17.4, 7.8 Hz, 2H), 6.13 (d, *J* = 3.5 Hz, 1H), 5.97 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.35 (d, *J* = 3.9 Hz, 1H), 2.51 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 175.4, 151.4, 143.0, 140.7, 135.6, 134.2, 130.3, 129.1, 128.8, 128.4, 127.9, 127.7, 127.5, 127.0, 126.9, 126.0, 125.7, 125.6, 122.7, 116.8, 109.2, 101.4, 90.8, 45.3, 44.0, 31.5. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.2

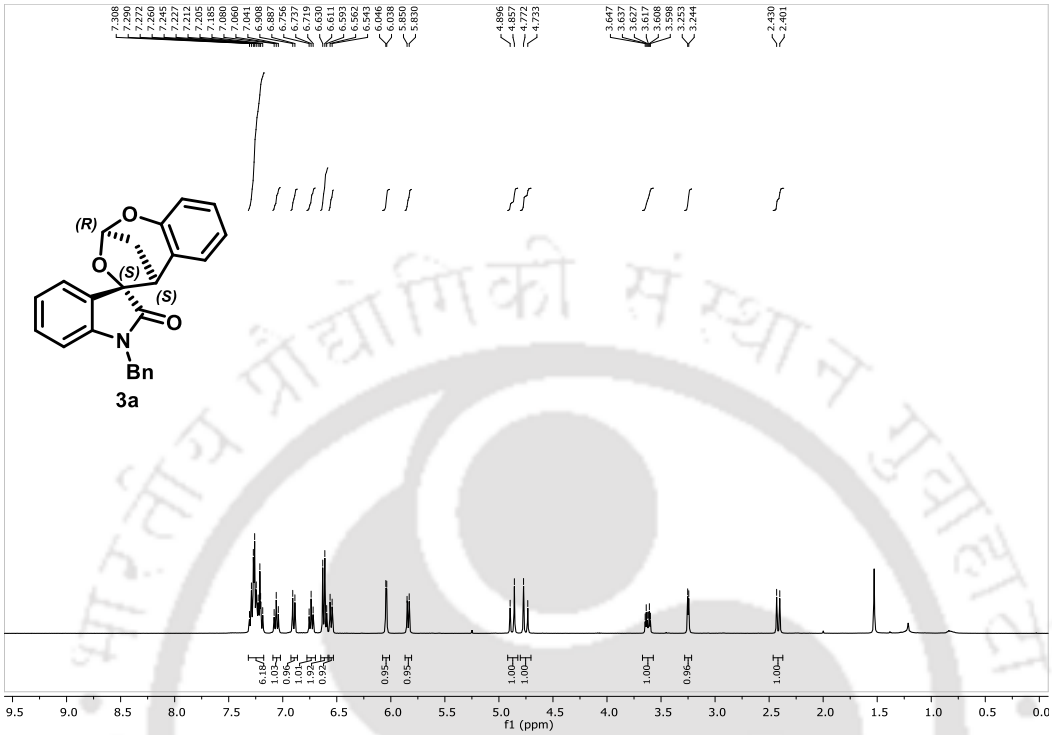
min, t_{minor} = 20.1 min). **HRMS (+ESI-TOF)**: calcd. For $C_{30}H_{24}NO_3$ $[M+H]^+$ 446.1751, found 446.1750.

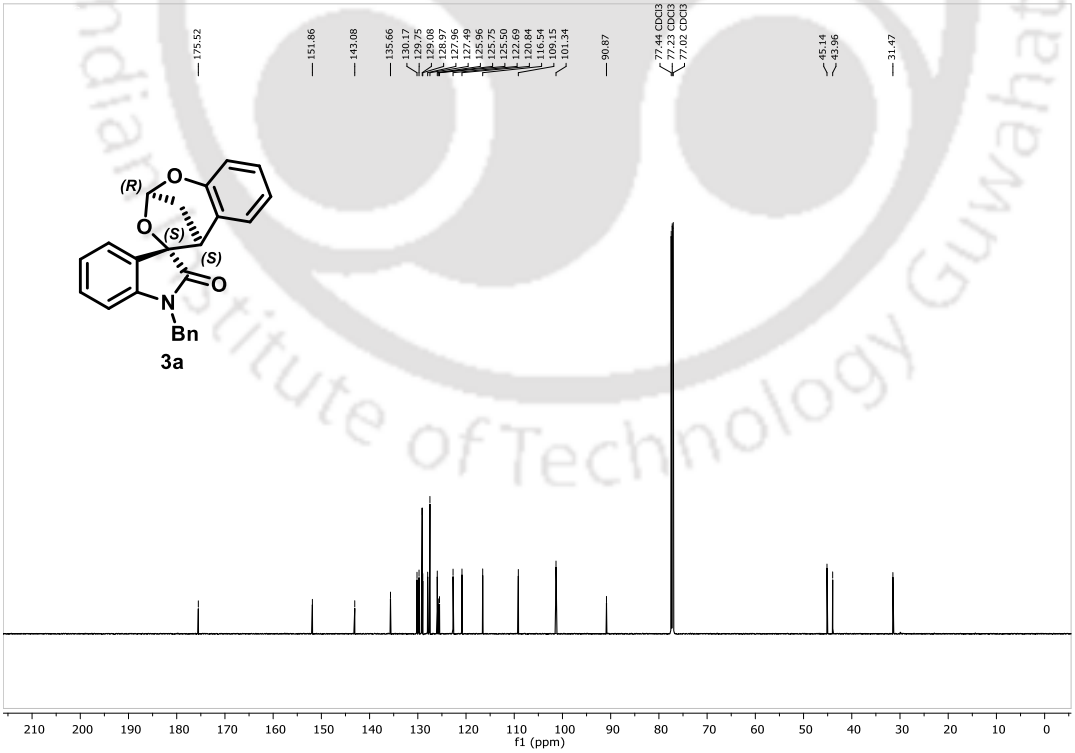


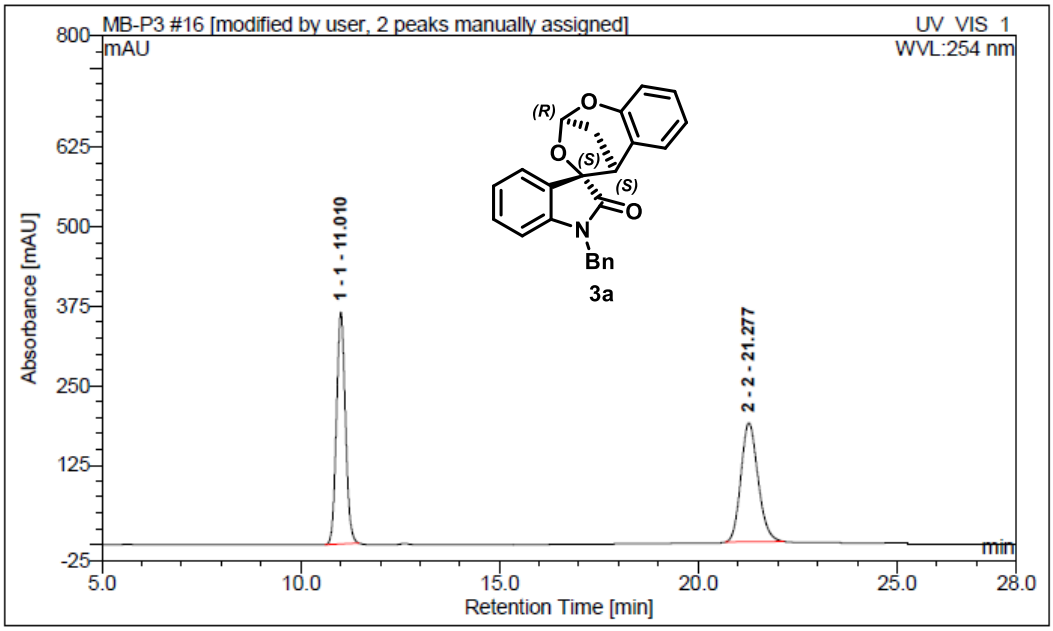
5

(2'*R*,3*S*,5'*S*)-1-benzyl-5-phenyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (5) was obtained as a light yellow semi solid in 49% (21.8 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.37 – 7.31 (m, 6H), 7.31 – 7.25 (m, 4H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.18 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 3.5 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 3.67 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.36 (d, *J* = 4.0 Hz, 1H), 2.52 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 175.5, 152.0, 142.2, 140.4, 135.8, 135.6, 129.7, 129.1, 129.1, 128.7, 128.6, 128.0, 127.5, 127.0, 126.7, 126.2, 125.6, 124.9, 121.0, 116.8, 109.3, 101.4, 90.7, 45.2, 44.1, 29.9. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 20.6 min, t_{minor} = 30.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{30}H_{24}NO_3$ $[M+H]^+$ 446.1751, found 446.1756.

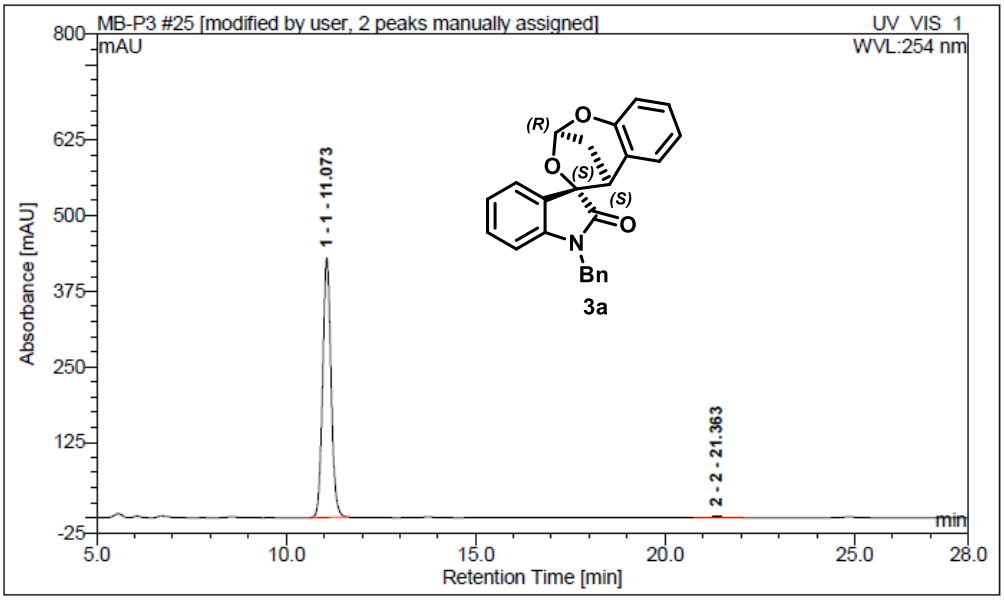
3.9 Selected NMR and HPLC spectra of products







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.01	95.15809	50.40367906	364.9188	n.a.
2	2	21.28	93.634	49.59632094	187.320	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.07	110.4171	98.92151554	429.0864	n.a.
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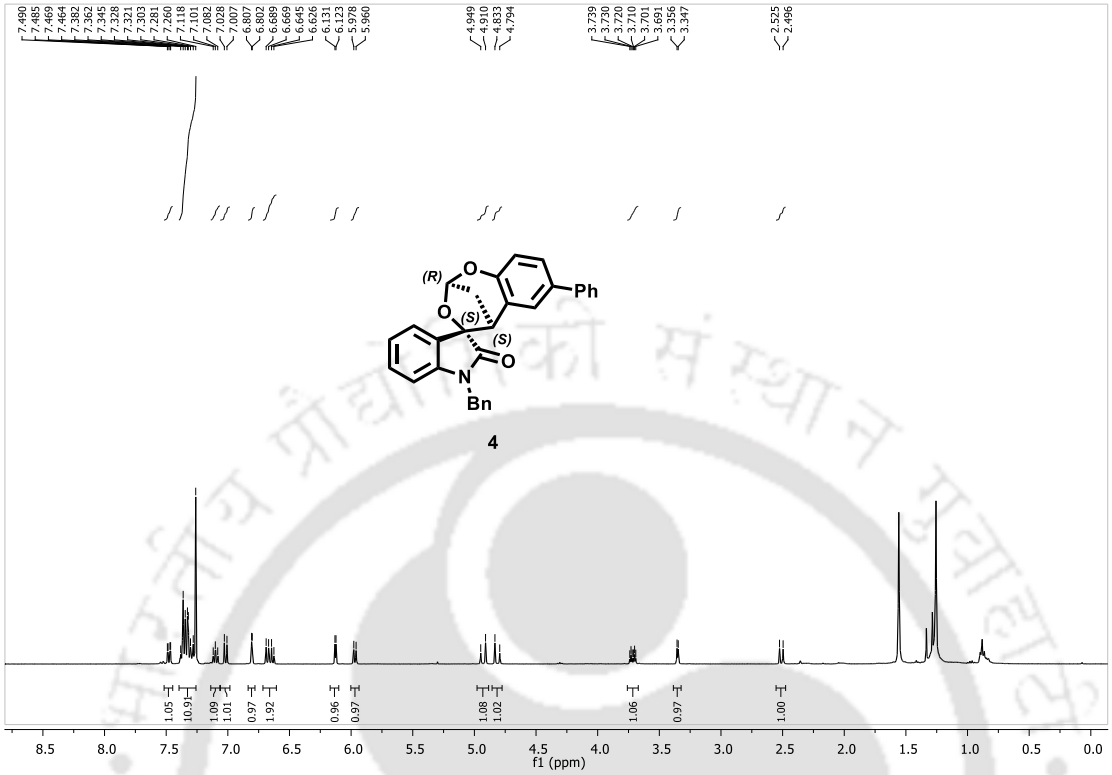
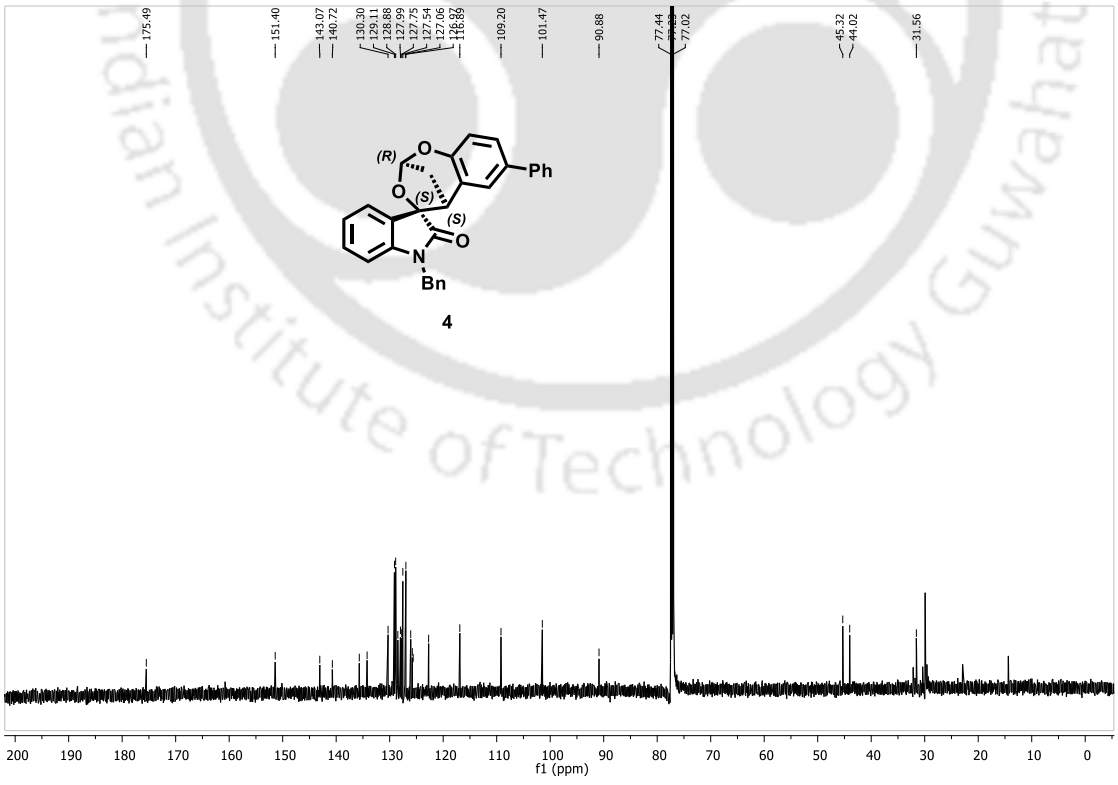
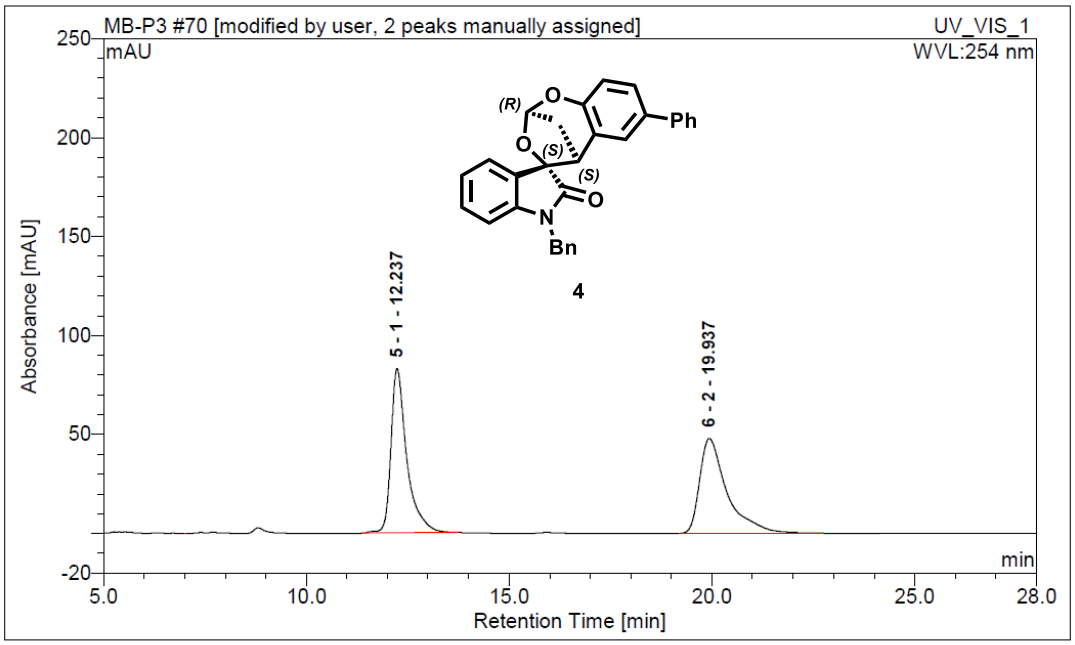
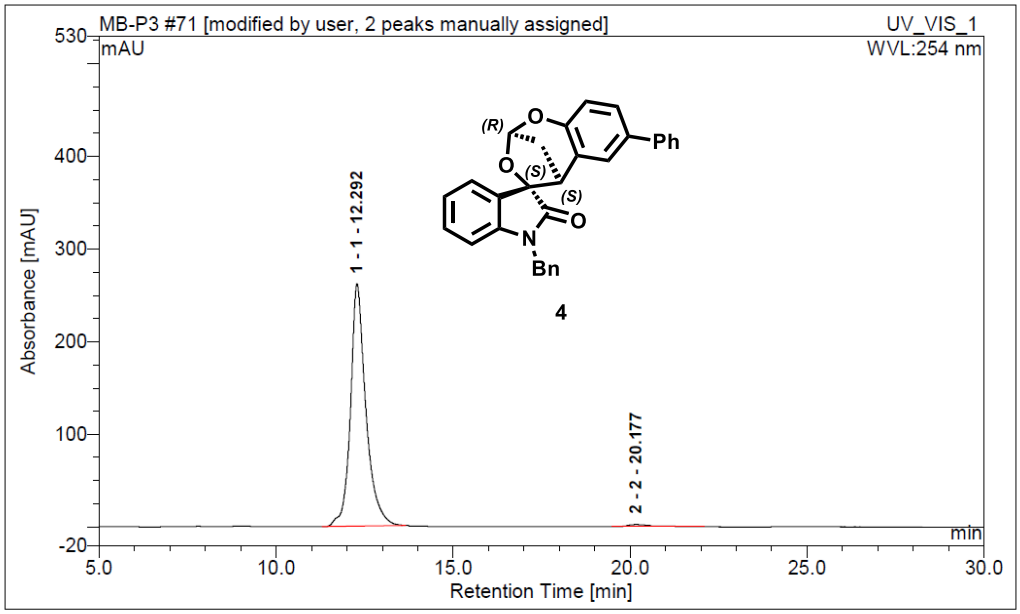


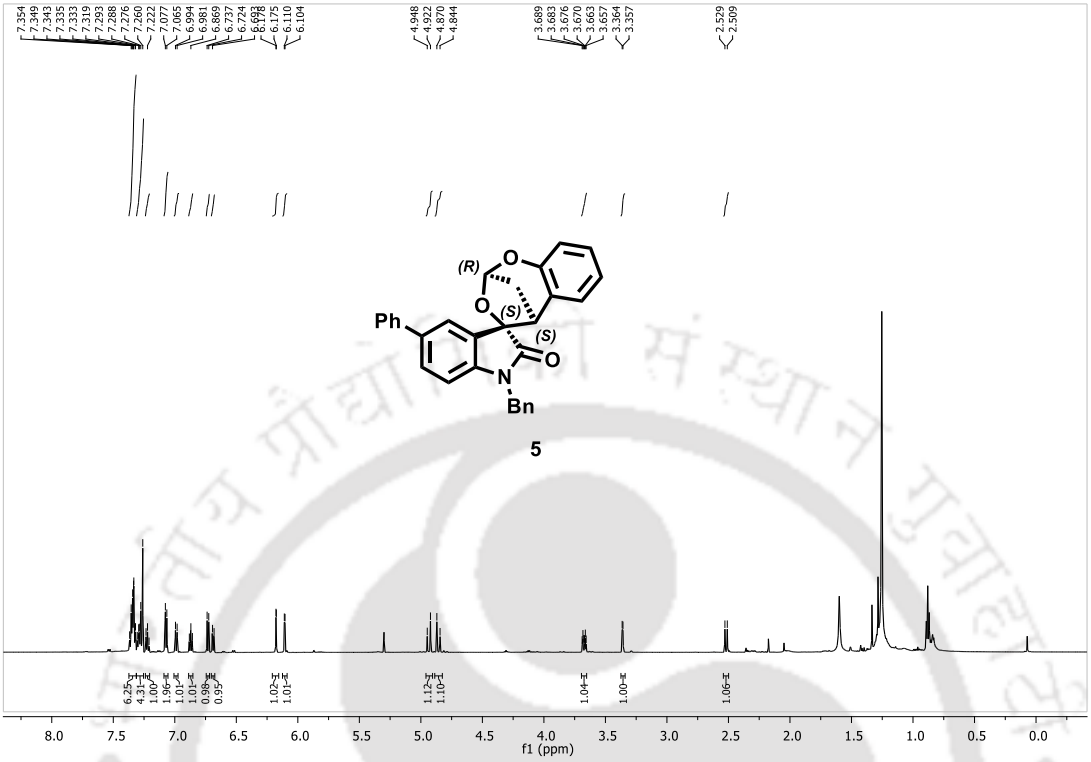


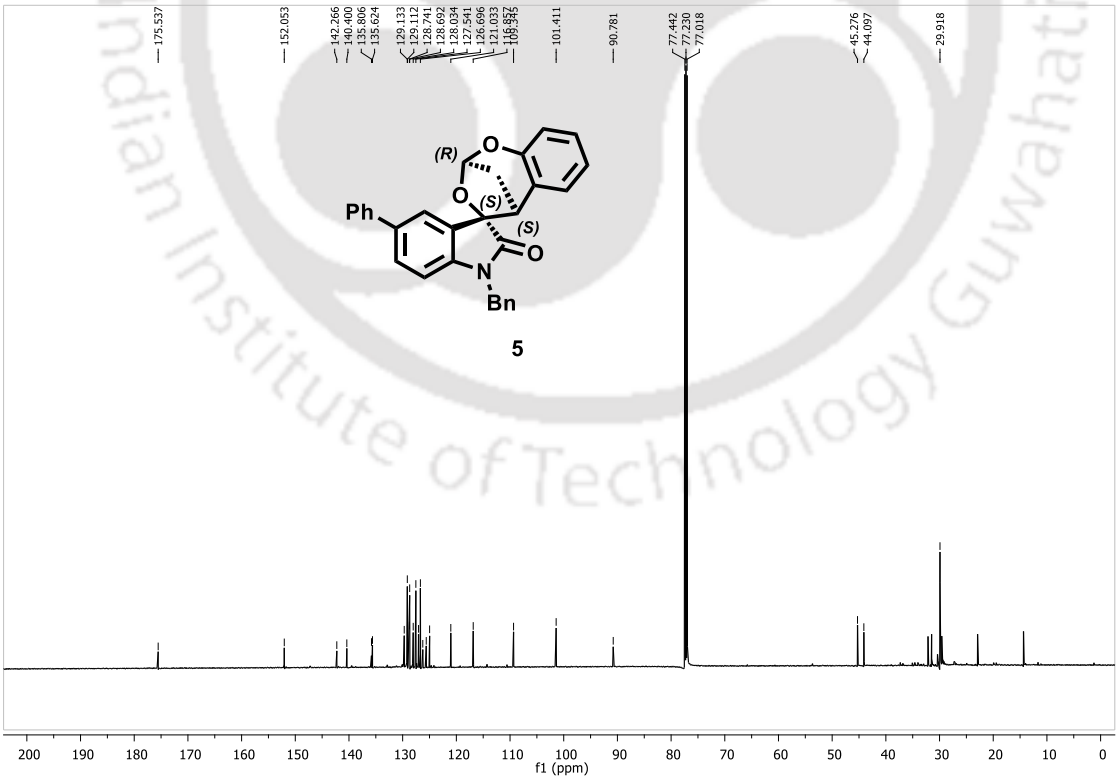


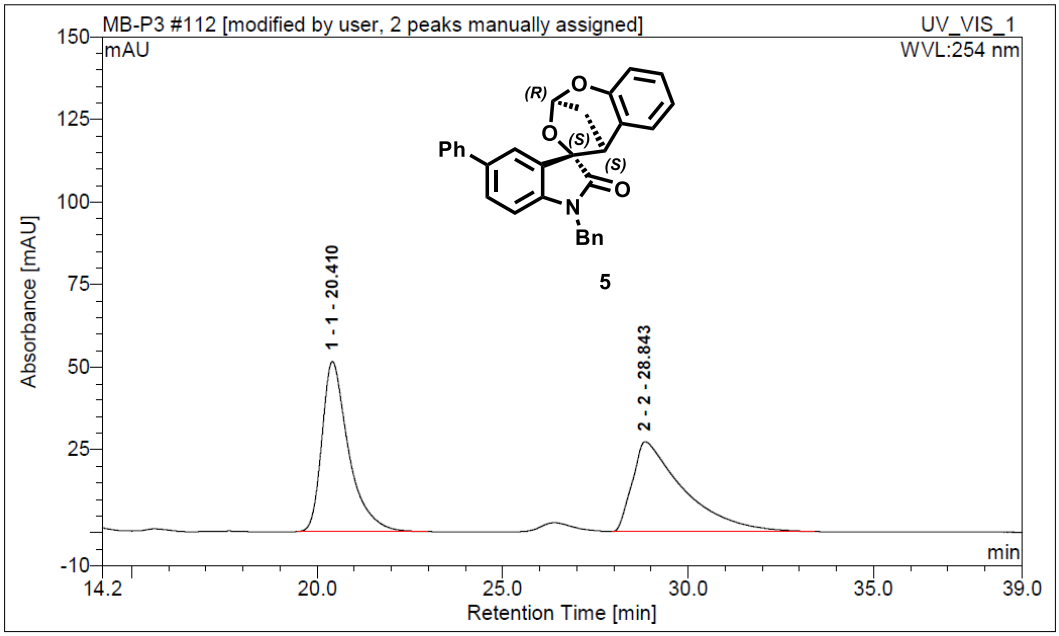
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
5	1	12.24	37.7215	50.22427187	83.01616	n.a.
6	2	19.94	37.385	49.77572813	47.864	n.a.



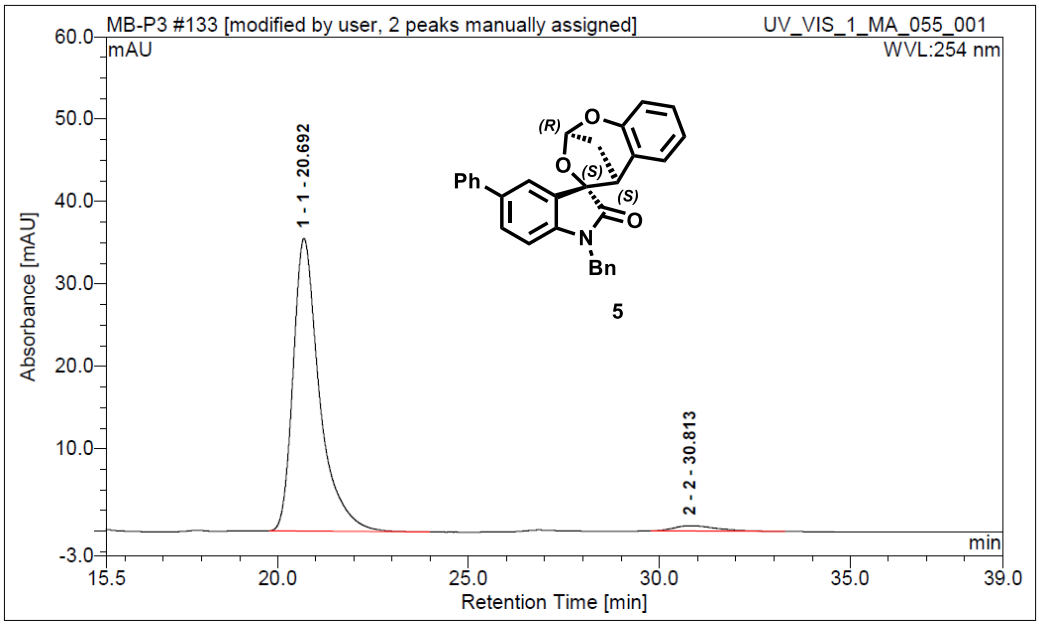
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	12.29	132.5096	98.48614064	261.7411	n.a.
2	2	20.18	2.037	1.513859363	2.321	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.41	42.87061	49.8011577	51.45814	n.a.
2	2	28.84	43.213	50.1988423	27.146	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.69	28.54026	97.11895787	35.54597	n.a.
2	2	30.81	0.847	2.881042128	0.648	n.a.

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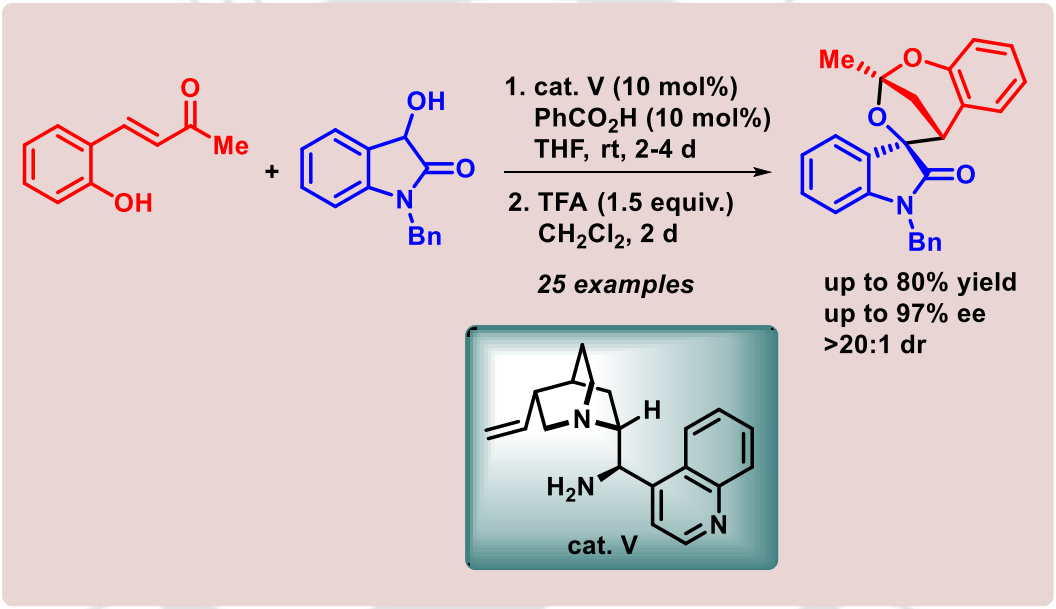
Chapter 4

Organocatalytic Asymmetric Synthesis of Bridged O,O-Ketal with Spirooxindole Motif



Eur. J. Org. Chem. **2019**, 2552-2559.

4.1 Introduction

Chiral *O,O*-acetals and ketals are prevalent in many natural products, and pharmaceuticals and a wide range of bioactivities are associated with them.[1] The asymmetric synthesis of bridged *O,O*-acetals and ketals has been less studied despite their presence in ephedrannin B,[2] procyanidin A2,[3] diinsiniol,[4] and other bioactive compounds which are shown in (Figure 1).[5]

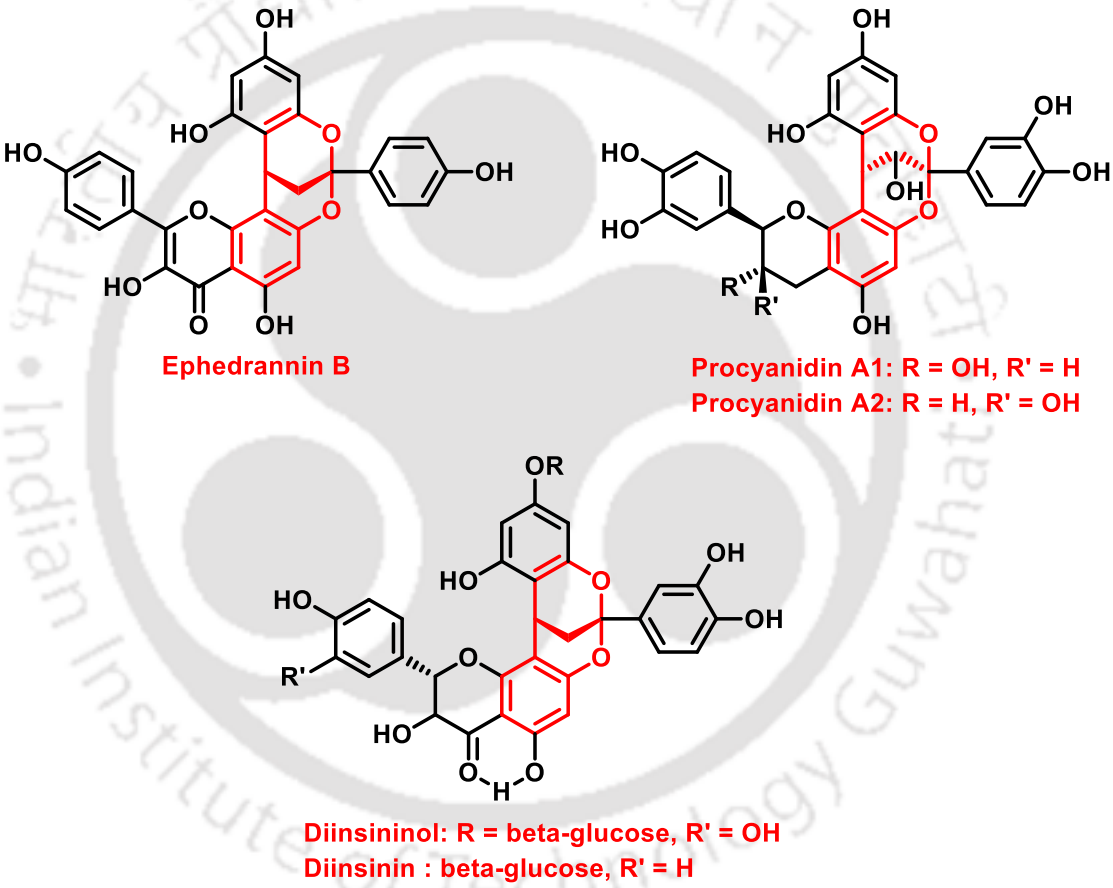


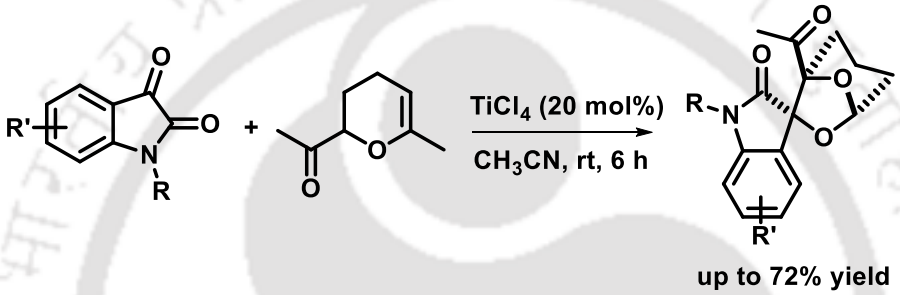
Figure 1. Biologically active compounds containing methanobenzodioxepine scaffold

Spirocyclic oxindole frameworks have shown significant biological activities associated with them.[6] Thus, developing a method for the preparation of enantiopure spirocyclic oxindoles would be of great importance.

4.2 Known strategies for the synthesis of bridged ketal spirooxindole

4.2.1 $TiCl_4$ catalyzed tandem reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with isatin

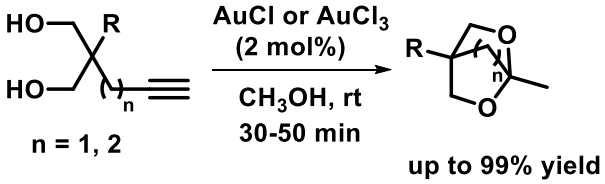
In 2005, Basavaiah *et al.* developed a one-pot atom economical stereoselective synthesis of spiro-oxindoles. This methodology involved the coupling (aldol reaction) of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with various isatin derivatives catalyzed by titanium tetrachloride. Under the optimized reaction conditions, the desired spiro-oxindoles products were isolated in good yields (Scheme 1).[7]



Scheme 1 Stereoselective synthesis of spiro-oxindoles by Basavaiah *et al.*

4.2.2 Gold-catalyzed cycloisomerization of bis-homopropargylic diols for the synthesis of strained bicyclic ketals

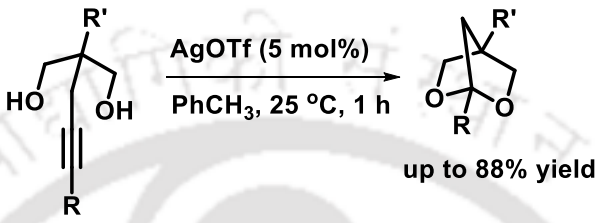
In 2005, Genêt *et al.* reported a highly efficient cycloisomerization of bis-homopropargylic diols for the synthesis of dioxabicyclo[2.2.1], [2.2.2], and [3.2.1] ketals. This reaction was catalyzed by gold, and strained bicyclic ketals were obtained in excellent yields. The reaction mechanism of this reaction involves Lewis acid-type activation, followed by two intramolecular cyclizations (Scheme 2).[8]



Scheme 2 Synthesis of strained bicyclic ketals by Genêt *et al.*

4.2.3 Silver-catalyzed intramolecular oxycyclization for the synthesis of bridged bicyclic ketals

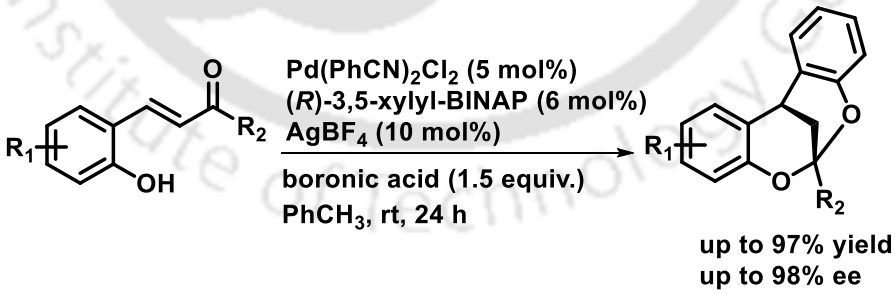
In 2007, Oh *et al.* reported a silver triflate catalyzed intramolecular oxycyclization of structurally diverse homopropargylic diols and related compounds. This methodology allowed the synthesis of bicyclic ketals in good yields (Scheme 3).[9]



Scheme 3. Synthesis of bridged bicyclic ketals by Oh *et al.*

4.2.4 Pd(II)-catalyzed asymmetric approach toward chiral [3.3.1]-bicyclic ketals

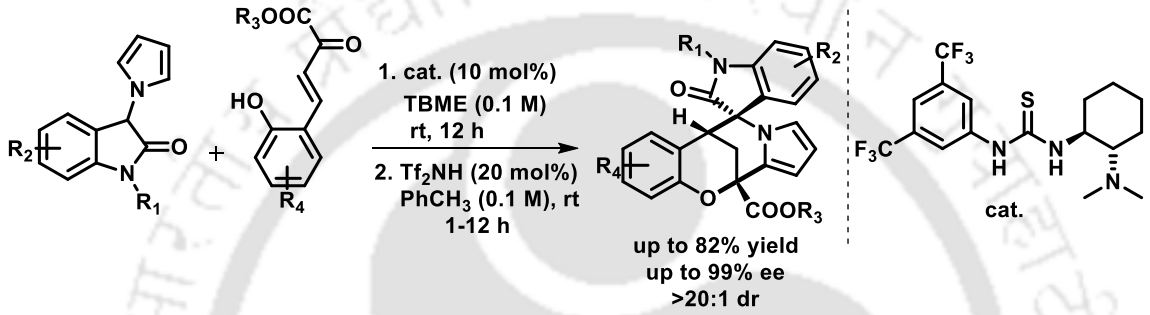
In 2013, Shi and group reported an enantioselective Pd(II)-catalyzed construction of [3.3.1]-bicyclic ketals from 2-hydroxyphenylboronic acid and enone. 2-Hydroxyphenyl palladium complex acts as a bis(nucleophile) generated *in situ* from the transmetalation of 2-hydroxyphenylboronic acid. [3.3.1]-Bicyclic ketals were obtained in good yields with excellent enantioselectivities (Scheme 4).[10]



Scheme 4. Synthesis of [3.3.1]-bicyclic ketals by Shi *et al.*

4.2.5 Organocatalyzed asymmetric Michael-hemiketalization-oxa-Pictet-Spengler cyclization for bridged and spiro heterocyclic skeleton

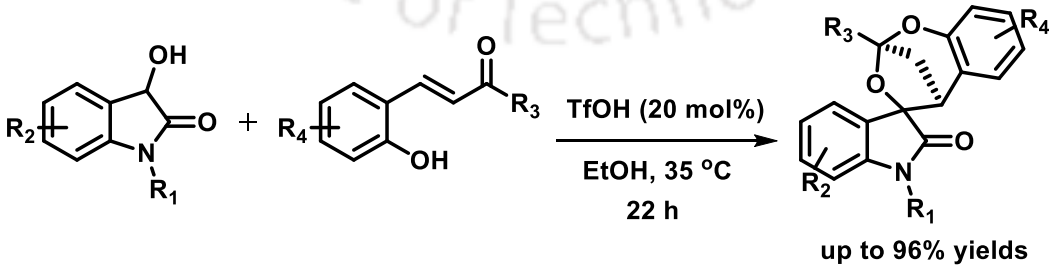
Wang *et al.* reported the Michael-hemiketalization-oxa-Pictet-Spengler cyclization between 3-pyrrolyloxindole and *(E)*-2-hydroxyaryl-2-oxobut-3-enoates in 2017. The strategy allowed the construction of chiral bridged and spiro heterocyclic skeletons with one spiro stereogenic carbon and two bridged carbon centers in high yields with excellent diastereoselectivities and enantioselectivities. Moreover, an oxocarbenium ion acts as a key intermediate for this cyclization reaction (Scheme 5).[11]



Scheme 5. Construction of chiral bridged and spiro heterocyclic skeletons by Wang *et al.*

4.2.6 Metal-free diastereoselective construction of bridged ketal spirooxindoles

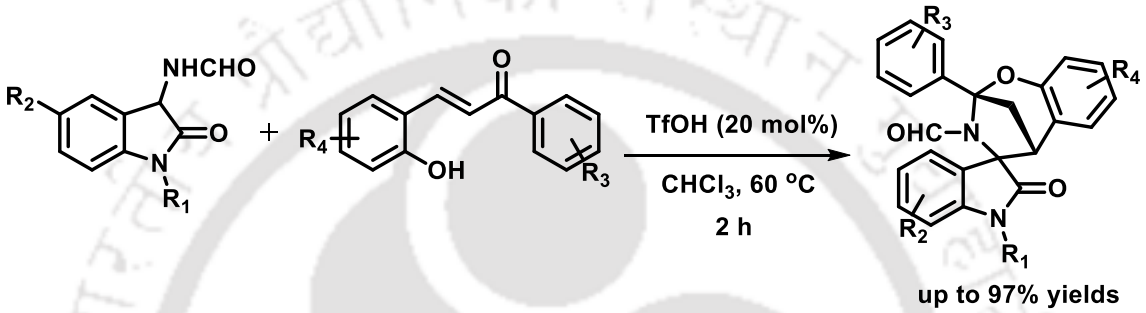
In 2017, the Bu group reported a TfOH-catalyzed Michael addition/ketalization sequence of 3-hydroxyoxindoles and *ortho*-hydroxychalcones. This method resulted in the formation of methanobenzodioxepine spirooxindoles with simultaneous construction of two new rings, one of which is a bridged ring. Under the optimized conditions, the desired spirooxindoles were formed in outstanding yields with excellent diastereoselectivities. (Scheme 6).[12]



Scheme 6. Synthesis of bridged ketal spirooxindole by Bu *et al.*

4.2.7 Michael addition/*N*,*O*-ketalization sequence for the synthesis of bridged cyclic *N*,*O*-ketal spirooxindole

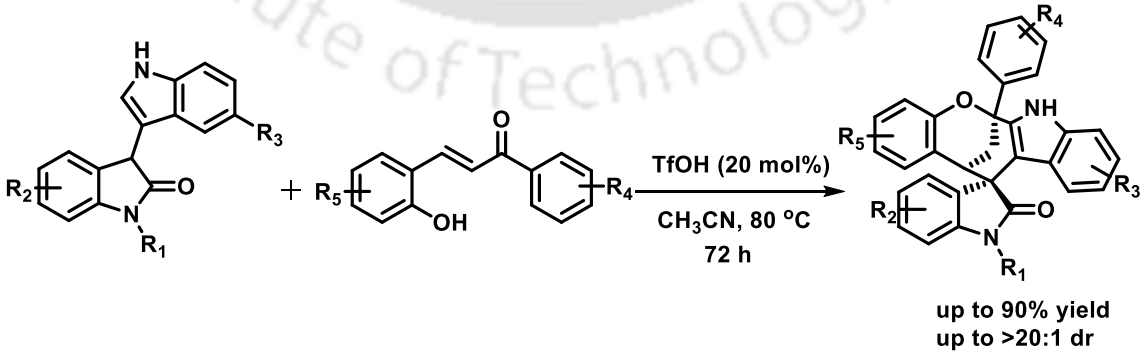
In 2018, the same group reported a Michael addition/*N*,*O*-ketalization of 3-aminooxindoles and *ortho*-hydroxychalcones for the construction of bridged cyclic *N*,*O*-ketal spirooxindole. A wide range of bridged cyclic *N*,*O*-ketal spirooxindole with complex and strained structures was formed in good yields. For demonstrating the synthetic value, a gram scale experiment was also conducted (Scheme 7).[13]



Scheme 7. Construction of *N*,*O*-ketal spirooxindole by Bu *et al.*

4.2.8 Diastereoselective construction of indole-bridged chroman spirooxindoles

In 2018, Bu and co-workers reported a highly diastereoselective synthesis of polycyclic indole-bridged chroman spirooxindoles by a TfOH-catalyzed Michael addition-inspired triple cascade reaction. Under the optimized reaction conditions, a wide range of polycyclic indole-bridged chroman spirooxindoles were obtained in moderate to excellent yields with high diastereoselectivities (Scheme 8).[14]

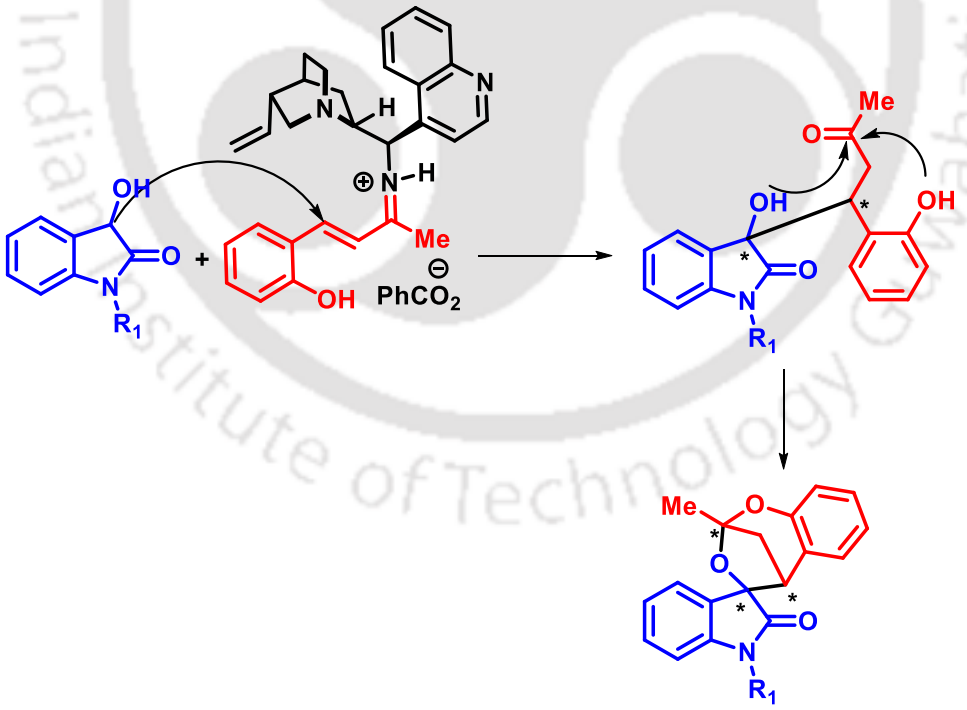


Scheme 8. Synthesis of polycyclic indole-bridged chroman spirooxindoles by Bu *et al.*

4.3 Concept

Spirocyclic oxindole frameworks are ubiquitous in many natural and unnatural compounds and showed significant biological activities associated with them.[15] Thus, a considerable number of methods have been developed for the preparation of enantiopure spirocyclic oxindoles during recent years. However, from the literature survey, it was found that most of the methods reported the construction of spirooxindoles having monocyclic or fused scaffolds.[16] The preparation of chiral spiro oxindoles having multi rings is a challenging task, and only a few examples were reported. Thus, we became interested in the synthesis of bridged *O*,*O*-ketals with spirooxindole skeleton.

Our plan was to accomplish the catalytic asymmetric Michael addition/cyclization reaction of 2-hydroxybenzylidene acetone[17] with 3-hydroxy oxindole[18] using primary amine catalysts. It was expected that the first iminium ion would generate from 2-hydroxybenzylidene acetone and primary amine catalyst. Then, dioxindole would attack to iminium ion, followed by acid-catalyzed ketalization reaction (Scheme 9).



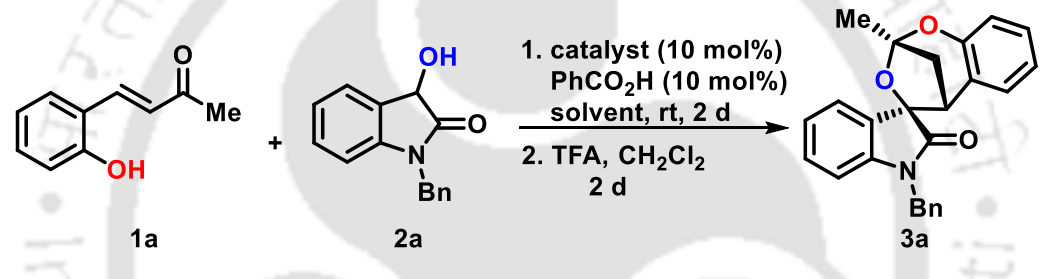
Scheme 9. 3-Hydroxy oxindole in asymmetric Michael reaction

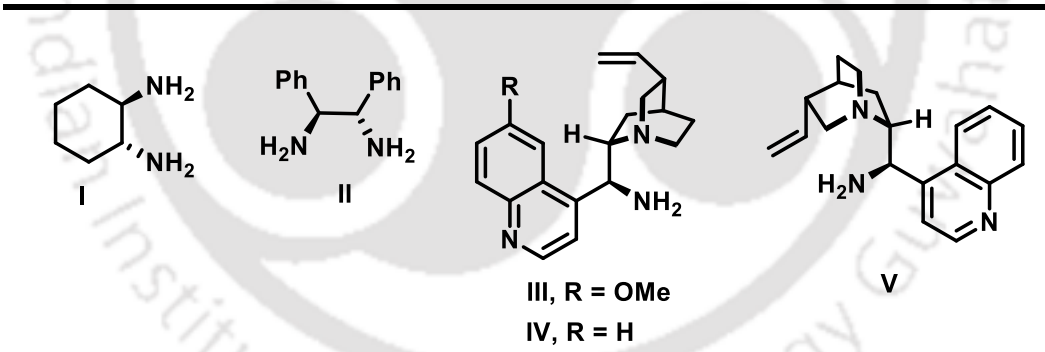
4.4 Results and discussion

4.4.1 Optimization of catalyst and reaction conditions

We began our investigation by carrying out a reaction between *ortho*-hydroxybenzylidene acetone (**1a**) and *N*-benzyl dioxindole (**2a**) with *trans*-1,2-diaminocyclohexane **I** and benzoic acid in toluene at room temperature (Table 1). After stirring for 2 days, the formation of a hemiketal was observed, and further treatment with trifluoroacetic acid led to the desired ketal **3a**. Though the yield and enantioselectivity of **3a** were moderate but excellent diastereomeric excess of **3a** was obtained (entry 1).

Table 1. **Catalyst screening and optimization of reaction conditions**





entry[a]	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCH_3$	20	>20:1	50
2	**II**	$PhCH_3$	12	>20:1	56
3	**III**	$PhCH_3$	62	>20:1	20
4	**IV**	$PhCH_3$	55	>20:1	76

5	**V**	$PhCH_3$	72	>20:1	80
6	**V**	Et_2O	78	>20:1	91
7	**V**	MTBE	67	>20:1	92
8	**V**	1,4-dioxane	58	>20:1	93
9	**V**	CH_2Cl_2	56	>20:1	82
10	**V**	**THF**	**80**	**>20:1**	**96**

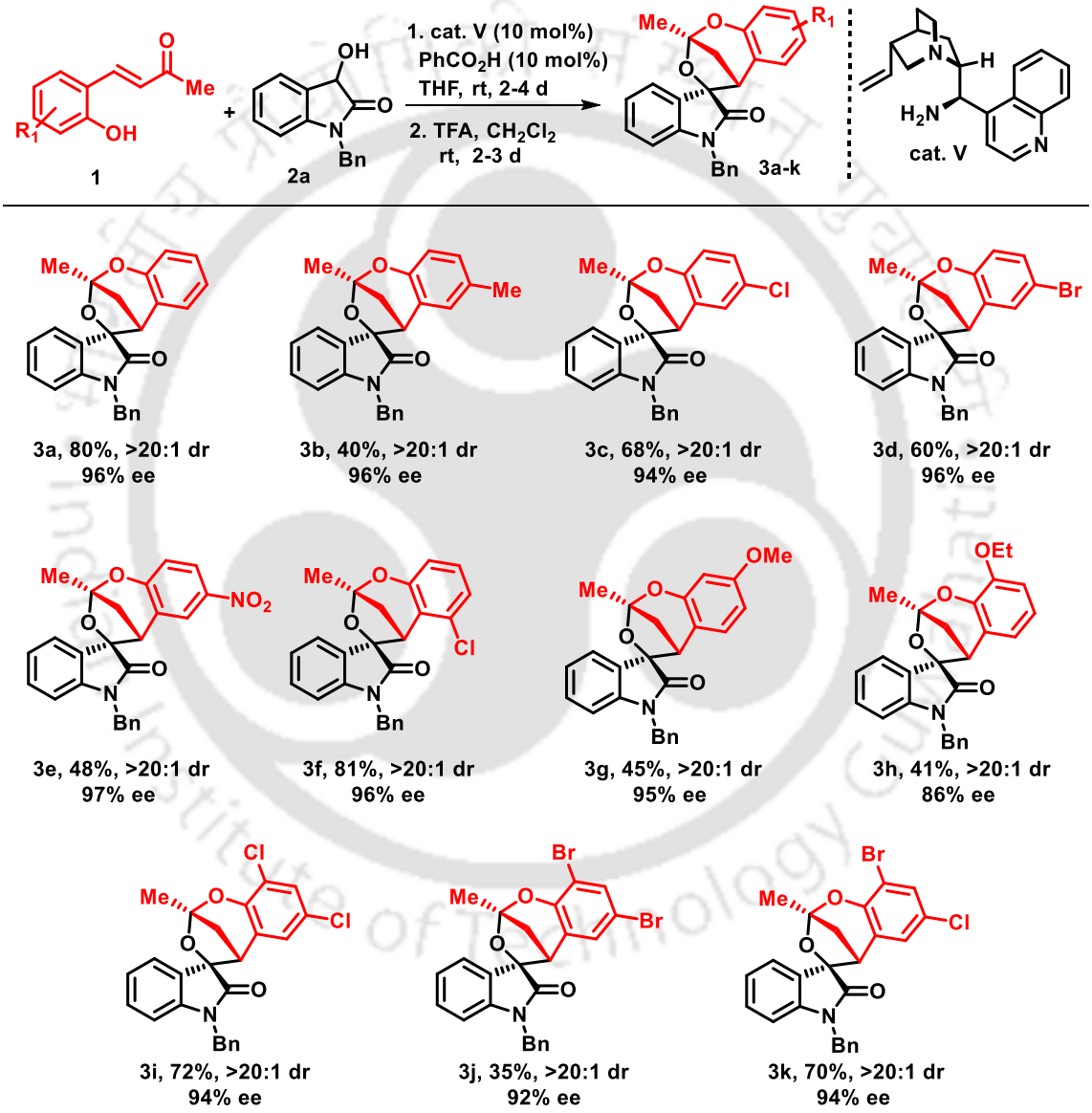
[a]All reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2a** in 0.5 mL of solvent at room temperature and 1.5 equiv. of TFA and 2 mL of CH_2Cl_2. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC using stationary phase chiral column.

Inspired by this result, different primary amine catalysts were screened. The enantioselectivity got slightly enhanced to 56% ee with *trans*-1,2-diphenylethylenediamine **II,** but poor yield was detected (entry 2). Then cinchona alkaloid derived primary amines were employed in our reaction, and interestingly these catalysts provided mixed results. Though poor enantioselectivity was achieved with quinine derived primary amine **III**, a significant enhancement in enantioselectivity was observed with cinchonidine derived primary amine **IV** (entries 3–4). Finally, the best catalyst turned out to be cinchonine derived primary amine **V**, which afforded 80% ee of **3a** (entry 5). To further increase the enantioselectivity, different solvents were screened, and gratifyingly, this turned out to be beneficial. For example, both the yield and enantioselectivity got enhanced in diethyl ether (entry 6). Slight enhancements in enantioselectivity were observed in methyl-*tert*-butyl ether and 1,4-dioxane (entries 7–8). Halogenated solvent such as dichloromethane was not a good choice for this reaction (entry 9). Delightfully, THF emerged as the best solvent, and product **3a** was isolated in 80% yield with 96% ee (entry 10).

4.4.2 Substrate scope

After the reaction conditions got established, a variety of *ortho*-hydroxybenzylidene acetones **1** having substitutions on the aryl ring were subjected to the catalytic system and the results are shown in Scheme 10. Gratifyingly, the desired products were obtained

Scheme 10. Scope of *o*-Hydroxybenzylidene acetones[a]

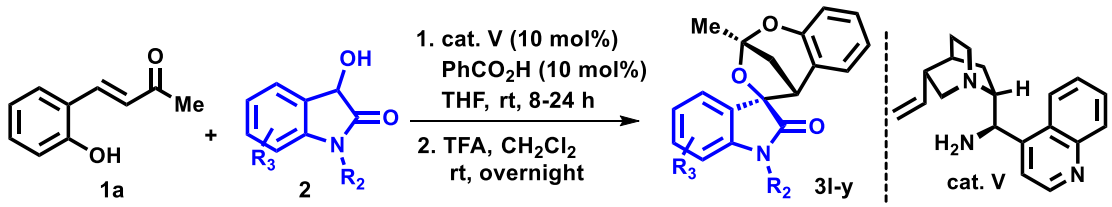


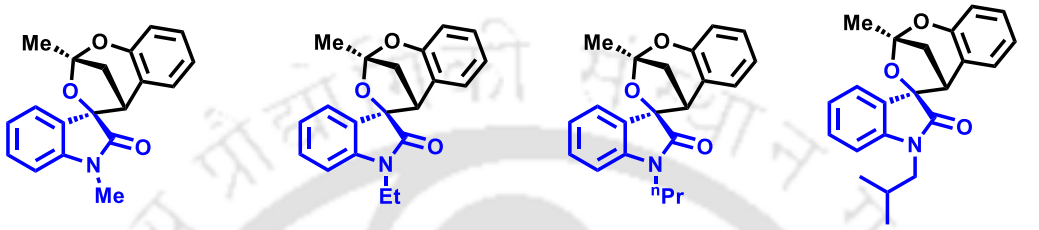
[a]All reactions were carried out with 0.12 mmol of **1** with 0.1 mmol of **2a** in 0.5 mL of THF and 1.5 equiv. of TFA and 2.0 mL of CH_2Cl_2. Yield corresponds to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees was determined by chiral HPLC.

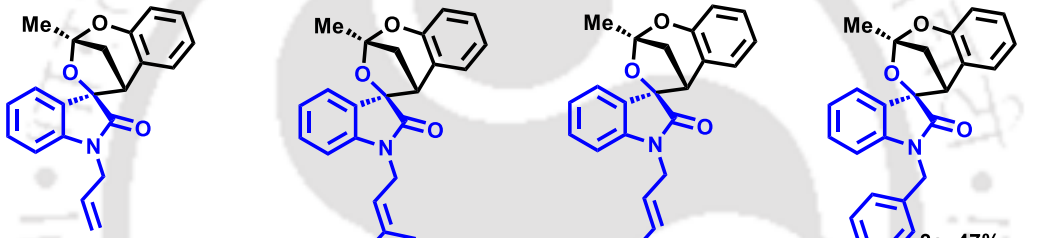
in high enantio- and diastereoselectivities in almost all of the cases. At first, different 4-substituted benzylidene acetones **1b**–**1e** were employed to afford products in moderate to good yields and with excellent stereoselectivities. Both alkyl and halo substituents were tolerated though higher yields were obtained for products **3c** and **3d** having halo substitutions. Nitro group containing product **3e** was isolated in 48% yield and with excellent enantioselectivity. Then 3-chloro and 5-methoxy substituted enones **1f** and **1g** were checked in the reaction. To our delight, the corresponding products were obtained in high enantioselectivities. In particular, a high yield of 81% was attained for product **3f** having 3-chloro substitution. Enone **1h** having a 6-ethoxy group, also took part in the reaction to deliver product **3h** in good yield with high enantioselectivity. The presence of 4,6-disubstitution in the enone motif did not alter the reaction outcome though longer reaction times were required both for Michael addition and in ketal formation. For example, 4,6-dichloro and 4,6-dibromo enones **1i** and **1j** delivered the desired products **3i** and **3j** with excellent enantioselectivities. Slightly less yield was observed for 4,6-dibromo substituted product **3j** because of the bulky nature of the substituent. 4-Chloro-6-bromo enone **1k** also participated in the reaction and delivered the product **3k** under the optimized reaction conditions in good yield with high diastereo- and enantioselectivity.

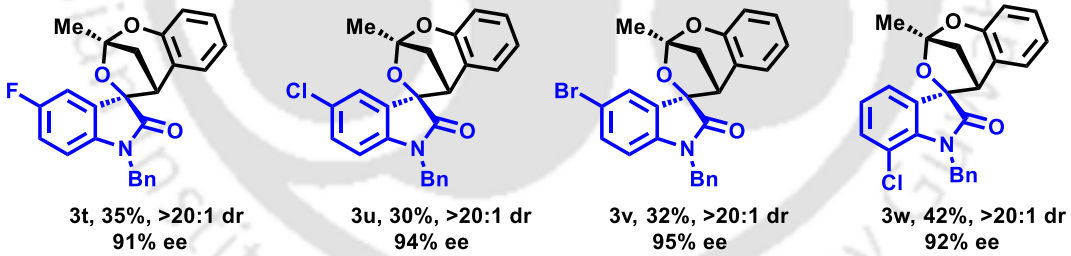
We then applied our protocol to different dioxindoles having diverse *N*-substitutions as well as substitutions on the aryl ring, and the results are shown in Scheme 11. Initially, different *N*-substitutions were checked, and to our delight, decent yields were observed with excellent diastereo- and enantioselectivities. Different alkyl groups were tolerated, and the outcome was independent of the chain length and branching of the group. For example, the same 96% ee was obtained for products **3l-3o** having *N*-methyl, *N*-ethyl, *N*-propyl, and *N*-*iso*-butyl groups, respectively. Similarly, dioxindole **2f** having *N*-allyl group and **2g** having *N*-prenyl group delivered products **3p** and **3q** respectively in the same 97% ee though yields varied slightly. Exposure of dioxindole **2h** having *N*-crotyl group in the reaction led to the formation of **3r** in good yield with excellent enantiomeric excess. Then dioxindole **2i** having *N*-4-CF_3benzyl group was employed in the reaction to obtain the product **3s** in 94% ee. Consequently, we decided to put substitutions on the

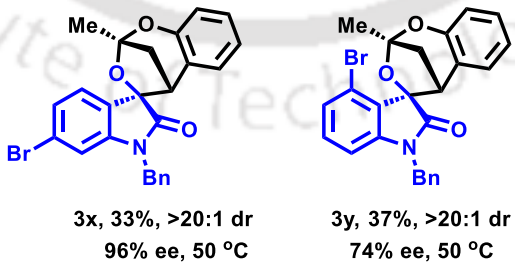
Scheme 11. Scope of dioxindoles[a]









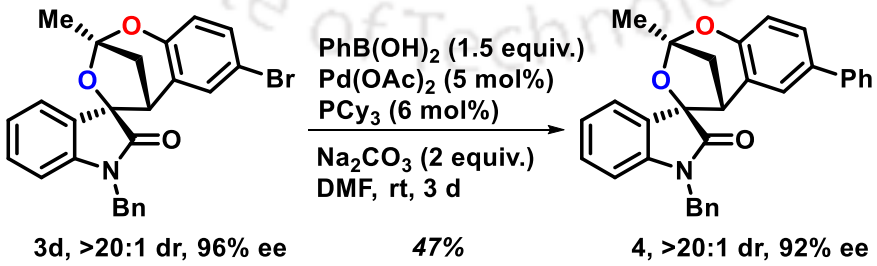


[a]All reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2** in 0.5 mL of THF and 1.5 equiv. of TFA and 2.0 mL of CH_2Cl_2. Yield corresponds to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees was determined by chiral HPLC.

aryl part of the oxindole motif, and here also, the results were excellent. The reactions are found to be slower for substitutions on the aryl part of the oxindole motif because of their bulky nature due to which lower yields were observed. Nevertheless, the level of diastereo- and enantioselectivities remained unaffected to the electronic nature of the aryl substituents. In most of the cases, the reaction temperature for the ketal formation step was increased to 50 °C to obtain acceptable yields. Initially, reactions were carried out with 5-halo substituted *N*-benzyl dioxindoles **2j–2l** and gratifyingly, the desired products **3t-3v** were isolated in moderate yields with excellent enantioselectivities. Then dioxindoles **2m** having 7-chloro substitution was engaged in the reaction, and interestingly, the yield got improved, and excellent enantioselectivity was achieved. Finally, 6-bromo and 4-bromo substituted dioxindoles **2n** and **2o** were prepared and employed; however, in both cases, the Michael reaction was slow at room temperature. Thus, the reactions were performed at 50 °C, and delightfully the desired products were obtained in acceptable yields. Though product **3x** having 6-bromo substitution was attained in high enantioselectivity, slightly less ee was seen for product **3y** having 4-bromo substitution.

4.4.3 Synthetic transformations of 3d

To show the synthetic utility of our method, a Suzuki coupling reaction was performed on **3d** (Scheme 12). Thus, phenylboronic acid was mixed with **3d** in the presence of palladium acetate, and tricyclohexyl phosphine under basic conditions, and the corresponding product **4** was isolated in moderate yield with almost preservation of enantiopurity.



Scheme 12. Synthetic transformations

4.4.4 Determination of product stereochemistry

The absolute configuration of product **3f** (Figure 2) was derived from X-ray crystallography[19] and was found to be (2′*S*,3*R*,5′*R*). The configuration of other products is expected to be same by analogy.

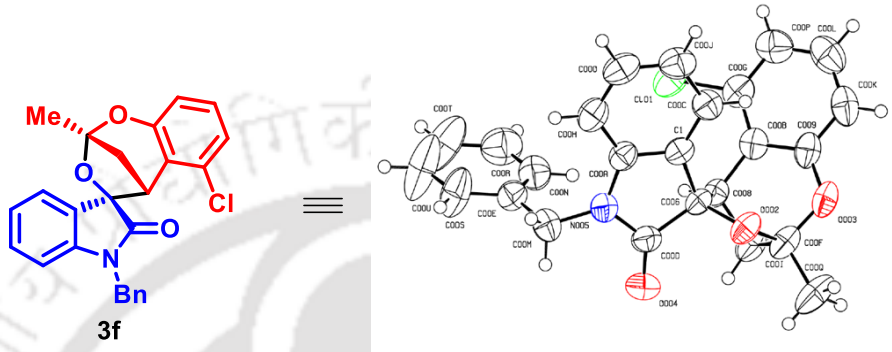


Figure 2. X-ray crystal structure of **3f**

4.4.5 Proposed TS

A plausible mechanism has been shown in Figure 3 to understand the stereochemistry of the product.

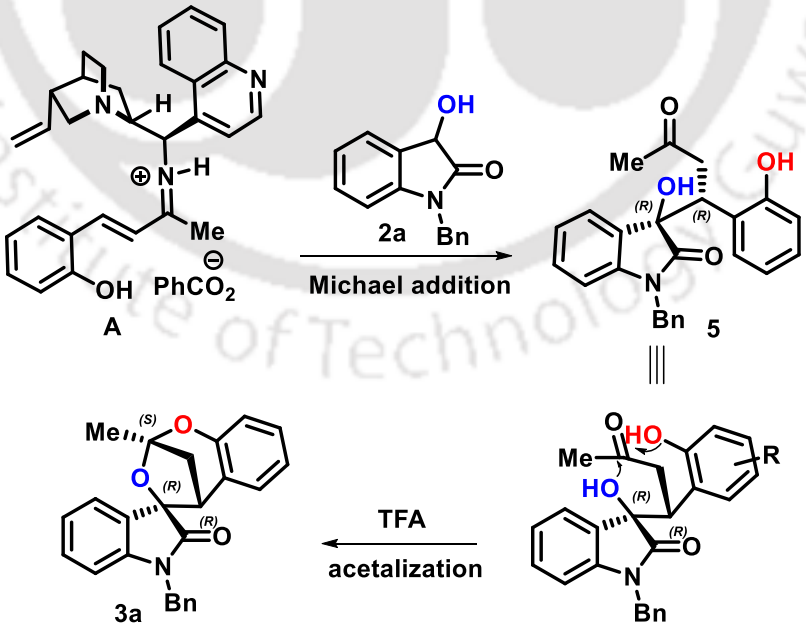


Figure 3. Proposed TS

It is expected that catalyst **V** reacts with **1a** in the presence of benzoic acid to generate iminium ion **A**. As the *Si* face of the chiral iminium ion is blocked by the quinoline motif, the conjugate addition of dioxindole **2a** takes place from the *Re* face to provide intermediate **5** after hydrolysis. Intermediate **5** then undergoes ketalization reaction diastereoselectively in the presence of TFA to deliver product **3a**.

4.5 Conclusion

In summary, we have developed the first organocatalytic asymmetric synthesis of bridged *O,O*-ketals with a spirooxindole skeleton. The methodology proceeds through primary amine catalyzed conjugated addition, followed by diastereoselective ketalization with TFA. The spirooxindole products were isolated in good to high yields with high diastereo- and enantioselectivities under mild and operationally simple reaction conditions.

4.6 Experimental section

4.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, Daicel Chiralpak ID Column and Phenomenex LUX C1 Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

4.6.2 General procedure for the synthesis of *ortho*-hydroxy-benzylidene acetones

Ortho-hydroxy-benzylidene acetones were prepared according to reported procedure.[20]

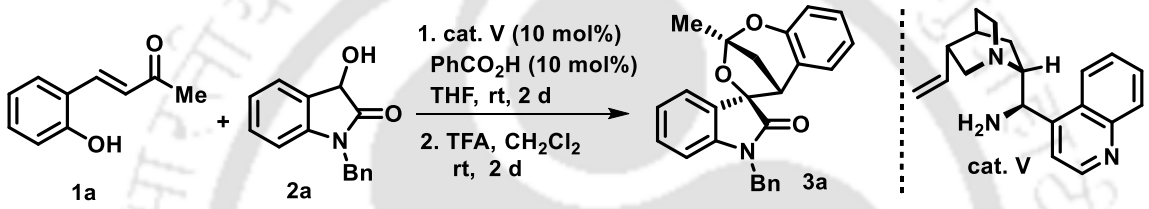
4.6.3 General procedure for the synthesis of dioxindoles

Dioxindoles were prepared according to reported procedures.[21]

4.6.4 General procedure for the synthesis of catalyst

The catalysts (**III**, **IV** and **V**) were prepared according to reported procedures.[22]

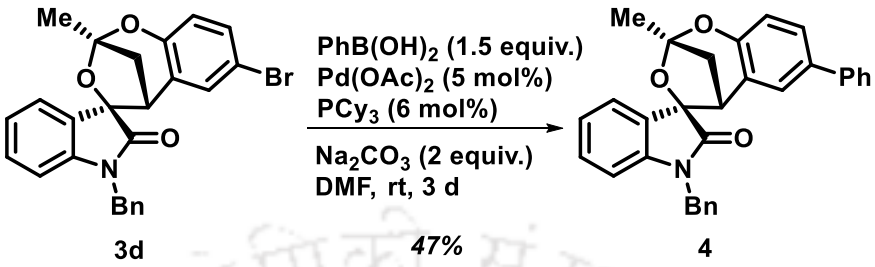
4.6.5 General procedure for the synthesis of compound 3a-3y



In an oven-dried round-bottomed flask, **1** (19.5 mg, 0.12 mmol), **2** (23.9 mg, 0.1 mmol), 10 mol% of catalyst (**V**), and 10 mol% of $PhCO_2H$ were taken. 0.5 mL of THF was added to the reaction mixture and stirred at rt for 2 d. Completion of the reaction was checked by TLC. After the completion of the reaction, solvent was concentrated, and the reaction mixture was directly subjected to TFA.

Second step: To the vacuum dried reaction mixture, CH_2Cl_2 was added to the reaction mixture of the first step and allowed to stir at rt. 1.5 equiv. of TFA was added; the reaction mixture was allowed to stir for 2 d. Progress of the reaction was monitored by TLC. After the completion of the reaction, solvent was concentrated, and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ ethyl acetate (10%) to afford the desired product **3a**.

4.6.6 General procedure for the preparation of derivatives 4



In an oven-dried round-bottomed flask, compound **3d** (50 mg, 0.1 mmol), phenylboronic acid (1.5 equiv.), palladium(II) acetate (0.05 equiv.), tricyclohexylphosphane (0.06 equiv.) and Na_2CO_3 (2 equiv.) were taken, flushed with argon and then dry DMF (0.1 mL) was added. The reaction mixture was allowed to stir for 3 d under the argon atmosphere. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography using EtOAc–hexane (1–2%) as eluent to afford compound **4**.

4.6.7 Crystal structure of compound 3f[19]

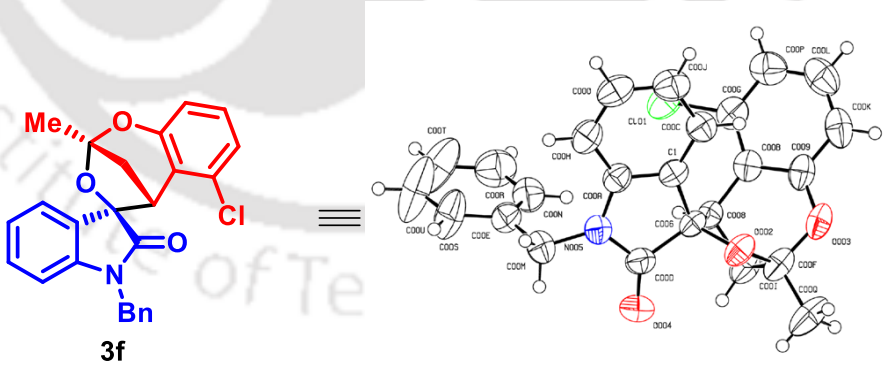
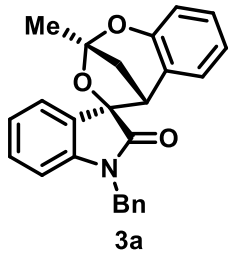


Table 2. Crystal data and structure refinement for compound 3f

Parameters	3f
CCDC No.	1888711
Empirical formula	$C_{25}H_{20}NO_3Cl$
Formula weight	417.87
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.36× 0.33 × 0.33
Temperature, T	296 K
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	*'P 21 21 21'*
Unit cell dimensions	a = 9.6104(17) Å b = 9.8202(18) Å c = 22.509(4) Å α = 90°, β = 90°, γ = 90°
Volume, V ($Å^3$)	2124.3(7)
Z	4
Calculated density, Mg/m^3	1.307
Absorption coefficient, μ (mm^{-1})	0.206
F(000)	872
θ range for data collection	1.809° to 26.685°
Limiting indices	$-12 \le h \le 12$, $-12 \le k \le 12$, $-28 \le l \le 28$
Reflection collected/unique	4482/ 3809
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data/restraints/parameters	4482/0/272
Goodness of fit on F^2	1.099

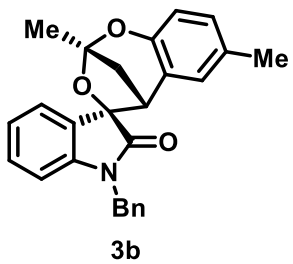
Final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0474, wR2 = 0.1471
R indices (all data)	R1 = 0.0588, wR2 = 0.1596

4.7 Characterization data of products



3a

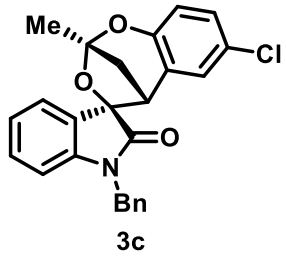
((2'S,3R,5'R)-1-benzyl-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3a) was obtained as a white solid in 80% yield (30.7 mg) after column chromatography. M.P. = 177-179 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36 – 7.22 (m, 6H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.67 – 6.60 (m, 3H), 5.85 (d, *J* = 7.4 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.68 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.31 (d, *J* = 3.9 Hz, 1H), 2.40 (d, *J* = 11.6 Hz, 1H), 1.90 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.8, 153.0, 143.0, 135.7, 130.0, 129.5, 129.0, 128.9, 127.9, 127.4, 125.9, 125.9, 125.1, 122.6, 120.5, 116.3, 109.0, 108.7, 90.8, 47.1, 43.9, 35.5, 23.5. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.0 min, t_{minor} = 7.9 min). **FT-IR (thin film):** 2922, 1638, 1485, 1362, 1332, 1179, 1077, 1030, 750, 704 cm–1 ; **ESI HRMS**: calcd. For $C_{25}H_{22}NO_3[M+H]^+$ 384.1594, found 384.1603.



3b

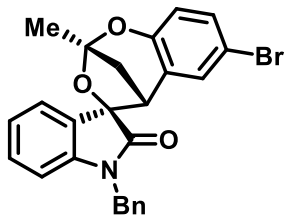
((2'S,3R,5'R)-1-benzyl-2',7'-dimethyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3b) was obtained as a white solid in 40 % (15.9 mg) yield after column chromatography. M.P. = 136–138 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36–7.26 (m, 6H), 7.09 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 14.8, 7.7 Hz, 2H), 6.42 (s, 1H), 5.87 (d, J = 7.5 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 3.66 (dd, J = 11.5, 4.1 Hz, 1H),

3.25 (d, J = 3.9 Hz, 1H), 2.37 (d, J = 11.5 Hz, 1H), 2.15 (s, 3H), 1.88 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.8, 150.7, 143.0, 135.7, 130.0, 129.9, 129.8, 129.4, 129.0, 127.9, 127.4, 126.1, 126.0, 124.7, 122.6, 116.0, 108.9, 108.6, 90.7, 47.1, 43.9, 35.6, 23.5, 20.5. **HPLC Analysis:** ee = 96 %, Phenomenex LUX C1 Column, n-hexane/ iPrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm (tmajor = 7.9 min, tminor = 7.3 min). **FT-IR (thin film):** 2923, 2853, 1637, 1493, 1466, 1362, 1252, 1183, 1141, 1112, 1076, 998, 869, 740, 698 cm–1; **ESI HRMS:** calcd. For $C_{26}H_{24}NO_3$ [M + H]+ 398.1751, found 398.1781.



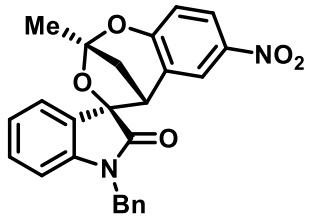
3c

((2'S,3R,5'R)-1-benzyl-7'-chloro-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3c) was obtained as a white sticky solid in 68% (28.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.21 (m, 5H), 7.17 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 5.91 (d, *J* = 7.5 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.6 Hz, 1H), 3.65 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.24 (d, *J* = 3.9 Hz, 1H), 2.31 (d, *J* = 11.7 Hz, 1H), 1.84 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.5, 151.6, 142.9, 135.6, 130.3, 129.3, 129.1, 128.5, 127.9, 127.4, 126.6, 125.7, 125.5, 125.3, 122.8, 117.6, 109.2, 108.8, 90.6, 46.9, 43.9, 35.2, 23.3. **HPLC Analysis:** ee = 94%, Chiralpak ID Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.6 min, t_{minor} = 6.1 min). **FT-IR (thin film):** 2924, 2853, 1721, 1613, 1480, 1363, 1257, 1157, 1073, 864, 750, 699, 496 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}ClNO_3$ $[M+H]^+$ 418.1204, found 418.1203.



3d

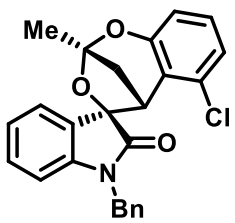
((2'S,3R,5'R)-1-benzyl-7'-bromo-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3d) was obtained as a light yellow sticky solid in 60% (27.7 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.37 – 7.32 (m, 3H), 7.30 (d, *J* = 7.5 Hz, 3H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.78 – 6.71 (m, 2H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.69 (dd, *J* = 11.7, 4.1 Hz, 1H), 3.27 (d, *J* = 3.9 Hz, 1H), 2.35 (d, *J* = 11.7 Hz, 1H), 1.88 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.4, 152.2, 143.0, 135.6, 132.3, 131.3, 130.3, 129.1, 127.9, 127.4, 127.1, 125.7, 125.5, 122.8, 118.1, 112.5, 109.2, 108.8, 90.6, 46.8, 43.9, 35.2, 23.3. **HPLC Analysis:** ee = 96%, Chiralpak ID Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.3 min, t_{minor} = 5.6 min). **FT-IR (thin film):** 2848, 1637, 1468, 1349, 1254, 1164, 1110, 854, 752, 696 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{20}BrNNaO_3$ $[M+Na]^+$ 484.0519, found 484.0535.



3e

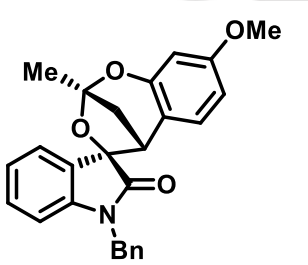
((2'S,3R,5'R)-1-benzyl-2'-methyl-7'-nitro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3e) was obtained as a yellow sticky solid in 48% (20.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.19 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.59 (d, *J* = 2.7 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.32 – 7.28 (m, 3H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 16.5, 7.9 Hz, 2H), 5.90 (d, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 3.80 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.45 (d, *J* = 4.0 Hz, 1H), 2.38 (d, *J* = 12.0 Hz, 1H), 1.92 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.1, 158.7, 143.0, 141.0, 135.4, 130.7, 129.1, 128.0, 127.4, 125.9, 125.8, 125.2, 124.9, 124.7, 122.9, 116.9, 109.8, 109.6, 90.6, 46.8, 44.0, 35.2, 23.0, 22.9. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm (t_{major} = 16.2 min, t_{minor} = 13.1 min). **FT-IR (thin film):** 2923, 2853, 1721, 1614,

1518, 1484, 1339, 1267, 1180, 1090, 852, 751, 699, 550, 495 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}N_2O_5$ $[M+H]^+$ 429.1445, found 429.1471.



3f

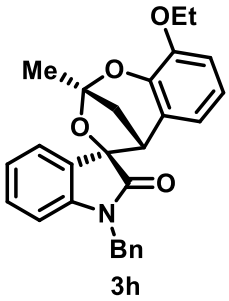
((2'S,3R,5'R)-1-benzyl-6'-chloro-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3f) was obtained as a white solid in 81% (33.8 mg) yield after column chromatography. M. P. = 137-139 ^oC. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.29 (m, 2H), 7.27 – 7.23 (m, 3H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.82 (dd, *J* = 15.1, 8.1 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.92 (d, *J* = 7.5 Hz, 1H), 4.98 (d, *J* = 15.9 Hz, 1H), 4.75 (d, *J* = 15.9 Hz, 1H), 3.91 (d, *J* = 4.1 Hz, 1H), 3.64 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.30 (d, *J* = 11.8 Hz, 1H), 1.88 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.5, 154.1, 142.8, 135.5, 133.5, 130.1, 129.7, 129.0, 127.8, 127.0, 125.5, 124.7, 123.4, 122.8, 121.2, 115.0, 109.2, 108.8, 90.7, 44.0, 43.7, 34.7, 23.2. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.4 min, t_{minor} = 6.6 min). **FT-IR (thin film):** 2919, 2825, 1637, 1452, 1360, 1261, 1179, 1125, 1076, 984, 750, 699, 485 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}ClNO_3$ $[M+H]^+$ 418.1204, found 418.1208.



3g

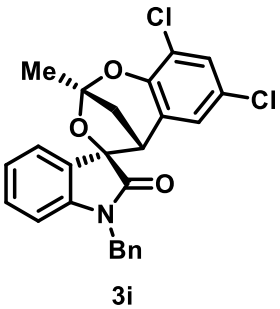
((2'S,3R,5'R)-1-benzyl-8'-methoxy-2'-methyl-5'H-spiro [indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3g) was obtained as a yellow sticky solid in 45% (18.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.35 – 7.31 (m, 2H), 7.31 – 7.27 (m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 2H), 6.34 (dd, *J* = 8.3, 2.5 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 3.81 (s, 3H), 3.66 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.27 (d, *J* = 3.9 Hz, 1H), 2.35 (d, *J* = 11.5 Hz, 1H), 1.88 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.8, 160.7, 153.9, 143.0, 135.7, 130.0, 129.4, 129.0, 127.9, 127.4, 126.1, 126.1, 122.6, 117.5, 109.0, 108.7, 106.5, 101.7,

90.9, 55.5, 46.5, 43.9, 35.9, 23.5. **HPLC Analysis:** ee = 95%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.9 min, t_{minor} = 10.7 min). **FT-IR (thin film):** 2925, 2836, 1637, 1462, 1387, 1261, 1149, 1098, 979, 697, 406 cm^{-1}; **ESI HRMS:** calcd. For $C_{26}H_{23}NNaO_4$ $[M+Na]^+$ 436.1519, found 436.1515.



3h

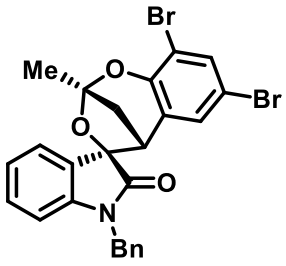
((2'S,3R,5'R)-1-benzyl-9'-ethoxy-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3h) was obtained as off-white sticky solid in 41% (17.5 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.31 (dt, *J* = 28.2, 7.8 Hz, 5H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.70 (t, *J* = 7.8 Hz, 1H), 6.65 (dd, *J* = 15.8, 7.8 Hz, 2H), 6.23 (d, *J* = 7.3 Hz, 1H), 5.91 (d, *J* = 7.4 Hz, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.72 (d, *J* = 15.7 Hz, 1H), 4.20 – 4.11 (m, 2H), 3.68 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.29 (d, *J* = 3.8 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 1.96 (s, 3H), 1.49 (t, *J* = 7.0 Hz, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.8, 147.4, 143.0, 142.7, 135.7, 130.0, 129.0, 127.9, 127.4, 126.1, 126.0, 125.9, 122.5, 121.2, 120.3, 114.1, 108.9, 108.8, 90.8, 65.0, 47.1, 43.9, 35.3, 23.6, 15.0. **HPLC Analysis:** ee = 86%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 14.9 min, t_{minor} = 13.6 min). **FT-IR (thin film):** 2924, 2854, 1732, 1613, 1467, 1273, 1180, 1062, 995, 868, 738, 697, 550, 462 cm^{-1}; **ESI HRMS:** calcd. For $C_{27}H_{26}NO_4$ $[M+H]^+$ 428.1856, found 428.1868.



3i

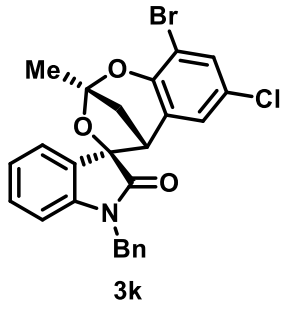
((2'R,3R,5'R)-1-benzyl-7',9'-dichloro-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3i) was obtained as a yellow sticky solid in 72% (32.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.21 (m, 6H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 5.95 (d, *J* = 7.5 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H),

4.71 (d, *J* = 15.6 Hz, 1H), 3.69 (dd, *J* = 11.9, 4.1 Hz, 1H), 3.27 (d, *J* = 3.9 Hz, 1H), 2.32 (d, *J* = 11.9 Hz, 1H), 1.91 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.2, 148.0, 143.0, 135.5, 130.5, 129.7, 129.1, 128.0, 127.6, 127.4, 127.0, 125.7, 125.1, 125.1, 122.9, 122.1, 109.5, 109.4, 90.5, 47.0, 44.0, 35.1, 23.2. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 7.2 min). **FT-IR (thin film):** 2924, 2853, 1722, 1613, 1457, 1363, 1262, 1164, 1098, 985, 874, 773, 699, 550, 463 cm^{-1}; **ESI HRMS:** calcd. For $C_{25}H_{19}Cl_2NNaO_3$ $[M+Na]^+$ 474.0634, found 474.0626.



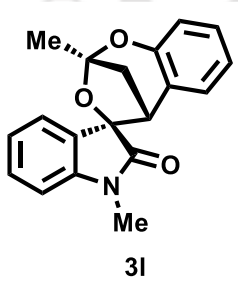
3j

((2'R,3R,5'R)-1-benzyl-7',9'-dibromo-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3j) was obtained as a yellow sticky solid in 35% (18.9 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.62 (d, *J* = 2.3 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.26 (m, 3H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.69 (dd, *J* = 12.3, 5.0 Hz, 2H), 5.97 (d, *J* = 6.9 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 3.72 (dd, *J* = 11.9, 4.1 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.34 (d, *J* = 11.9 Hz, 1H), 1.94 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.2, 149.6, 143.0, 135.5, 135.3, 130.6, 130.5, 129.1, 128.0, 127.4, 125.8, 125.1, 122.9, 112.4, 111.2, 109.7, 109.4, 90.6, 47.0, 44.0, 35.2, 23.1. **HPLC Analysis:** ee = 92%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.1 min, t_{minor} = 7.2 min). **FT-IR (thin film):** 2924, 2854, 1722, 1613, 1450, 1364, 1262, 1180, 1156, 1080, 981, 869, 753, 701, 619 cm^{-1}; **ESI HRMS:** calcd. For $C_{25}H_{20}Br_2NO_3$ $[M+H]^+$ 541.9784, found 541.9777.



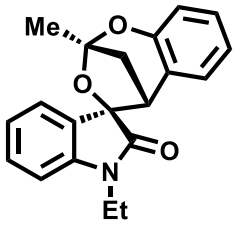
3k

((2'R,3R,5'R)-1-benzyl-9'-bromo-7'-chloro-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3k) was obtained as off-white sticky solid in 70% (34.8 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.45 (d, *J* = 2.4 Hz, 1H), 7.28 (dt, *J* = 22.0, 11.8 Hz, 5H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.54 (d, *J* = 2.3 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.6 Hz, 1H), 3.68 (dd, *J* = 11.9, 4.1 Hz, 1H), 3.25 (d, *J* = 3.9 Hz, 1H), 2.31 (d, *J* = 11.9 Hz, 1H), 1.91 (s, 3H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.2, 149.0, 143.0, 135.5, 132.5, 130.5, 129.1, 128.0, 127.7, 127.4, 125.7, 125.5, 125.1, 122.9, 110.7, 109.6, 109.4, 90.5, 47.0, 44.0, 35.1, 23.1. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.2 min, t_{minor} = 7.0 min). **FT-IR (thin film):** 2924, 2853, 1721, 1613, 1453, 1363, 1262, 1159, 1077, 870, 762, 699, 619, 549, 462 cm^{-1}; **ESI HRMS:** calcd. For $C_{25}H_{20}BrClNO_3$ $[M+H]^+$ 496.0310, found 496.0323.



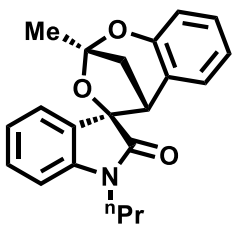
3l

((2'S,3R,5'R)-1,2'-dimethyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3l) was obtained as a yellow semi solid in 70% (21.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 – 7.18 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.81 – 6.65 (m, 3H), 6.59 (d, *J* = 7.4 Hz, 1H), 5.84 (d, *J* = 7.5 Hz, 1H), 3.64 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.26 (d, *J* = 4.0 Hz, 1H), 3.16 (s, 3H), 2.36 (d, *J* = 11.5 Hz, 1H), 1.86 (s, 3H**). ^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.7, 153.1, 143.9, 130.1, 129.5, 128.8, 126.0, 125.9, 125.2, 122.6, 120.4, 116.3, 108.6, 108.0, 90.8, 46.9, 35.5, 26.3, 23.5. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.8 min, t_{minor} = 12.2 min). **FT-IR (thin film):** 2927, 2857, 1718, 1613, 1458, 1360, 1259, 1148, 1104, 1075, 968, 869, 706, 654, 519, 460 cm^{-1}; **ESI HRMS**: calcd. For $C_{19}H_{18}NO_3$ $[M+H]^+$ 308.1281, found 308.1290.



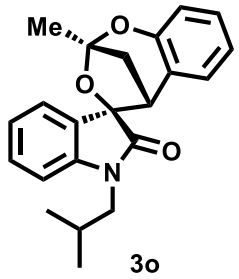
3m

((2'S,3R,5'R)-1-ethyl-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3m) was obtained as a white semi solid in 72% (23.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.20 (dd, *J* = 16.3, 8.5 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 8.0 Hz, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.5 Hz, 1H), 3.70 (dt, *J* = 14.1, 7.0 Hz, 2H), 3.64 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.25 (d, *J* = 4.0 Hz, 1H), 2.35 (dd, *J* = 11.5, 0.6 Hz, 1H), 1.87 (s, 3H), 1.26 (t, *J* = 5.3 Hz, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.3, 153.1, 143.0, 130.0, 129.5, 128.9, 126.3, 126.1, 125.3, 122.3, 120.4, 116.3, 108.6, 108.1, 90.8, 47.0, 35.5, 34.9, 23.5, 12.7. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.4 min, t_{minor} = 10.6 min). **FT-IR (thin film):** 2927, 2855, 1717, 1613, 1458, 1463, 1368, 1257, 1100, 1013, 868, 802, 751, 601, 578, 494 cm^{-1}; **ESI HRMS**: calcd. For $C_{20}H_{20}NO_3$ $[M+H]^+$ 322.1438, found 322.1448.



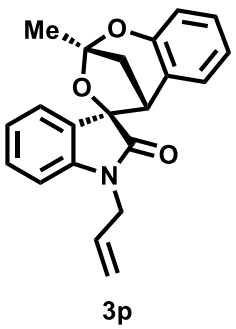
3n

((2'S,3R,5'R)-2'-methyl-1-propyl-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3n) was obtained as a white semi solid in 59% (19.8 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 – 7.15 (m, 2H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.5 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.55 (dt, *J* = 14.1, 7.1 Hz, 1H), 3.24 (d, *J* = 4.0 Hz, 1H), 2.35 (d, *J* = 11.5 Hz, 1H), 1.86 (s, 3H), 1.71 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.7, 153.1, 143.4, 130.0, 129.5, 128.9, 126.2, 126.0, 125.3, 122.3, 120.4, 116.3, 108.6, 108.3, 90.8, 47.1, 41.7, 35.5, 23.5, 20.8, 11.6. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.9 min, t_{minor} = 10.4 min). **FT-IR (thin film):** 2926, 2856, 1717, 1613, 1462, 1364, 1259, 1201, 1135, 1099, 1035, 858, 750, 603, 493 cm^{-1}; **ESI HRMS**: calcd. For $C_{21}H_{22}NO_3$ $[M+H]^+$ 366.1594, found 366.1608.



3o

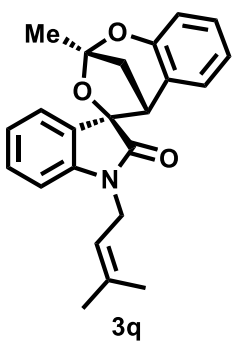
((2'S,3R,5'R)-1-isobutyl-2'-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3o) was obtained as a light yellow semi solid in 74% (25.9 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26 – 7.15 (m, 2H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.76 (dd, *J* = 16.1, 7.6 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.5 Hz, 1H), 3.64 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.55 (dd, *J* = 13.9, 8.0 Hz, 1H), 3.35 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.23 (d, *J* = 4.0 Hz, 1H), 2.36 (d, *J* = 11.5 Hz, 1H), 2.19 – 2.07 (m, 1H), 1.86 (s, 3H), 0.98 (dd, *J* = 6.7, 4.0 Hz, 6H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.9, 153.1, 143.7, 130.0, 129.5, 128.9, 126.1, 126.0, 125.3, 122.3, 120.4, 116.3, 108.7, 108.5, 90.7, 47.6, 47.3, 35.5, 27.2, 23.5, 20.5, 20.4. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.8 min, t_{minor} = 7.6 min). **FT-IR (thin film):** 2916, 2852, 1716, 1614, 1454, 1334, 1261, 1200, 1133, 1096, 1026, 850, 777, 612, 586, 462 cm^{-1}; **ESI HRMS**: calcd. For $C_{22}H_{24}NO_3$ $[M+H]^+$ 350.1751, found 350.1755.



3p

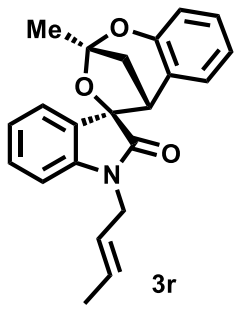
((2'*S*,3*R*,5'*R*)-1-allyl-2'-methyl-5'H-spiro[indoline-3,4'-[2,5] methanobenzo[d][1,3]dioxepin]-2-one) (3p) was obtained as a pale yellow sticky solid in 40% (13.3 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26 – 7.22 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.76 (dd, *J* = 16.2, 7.6 Hz, 4H), 6.67 (t, *J* = 7.6 Hz, 2H), 6.60 (d, *J* = 7.4 Hz, 2H), 5.84 (qd, *J* = 10.5, 5.4 Hz, 4H), 5.30 – 5.21 (m, 4H), 4.35 (dd, *J* = 16.2, 5.4 Hz, 2H), 4.21 (dd, *J* = 16.2, 5.4 Hz, 2H), 3.64 (dd, *J* = 11.6, 4.1 Hz, 2H), 3.27 (d, *J* = 4.0 Hz, 2H), 2.37 (d, *J* = 11.6 Hz, 2H), 1.87 (s, 6H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.4, 153.1, 143.1, 131.4, 130.0, 129.5, 128.9, 126.0, 125.2, 122.5, 120.5, 118.0, 116.3, 108.9, 108.7, 90.7, 47.1, 42.5, 35.5, 23.5. **HPLC Analysis:** ee = 97%, Chiralpak LUX C1 Column n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.6 min, t_{minor} = 12.3 min). **FT-IR (thin film):**

2957, 2858, 1714, 1613, 1474, 1331, 1260, 1231, 1109, 1054, 985, 842, 712, 601, 536, 494 cm^{-1}; **ESI HRMS**: calcd. For $C_{21}H_{20}NO_3$ $[M+H]^+$ 334.1438, found 334.1445.



3q

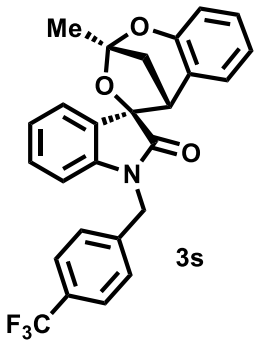
((2'S,3R,5'R)-2'-methyl-1-(3-methylbut-2-en-1-yl)-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3q) was obtained as a white semi solid in 60% (21.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.24 (dd, *J* = 11.0, 4.6 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 5.84 (d, *J* = 7.5 Hz, 1H), 5.17 (t, *J* = 6.7 Hz, 1H), 4.32 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.18 (dd, *J* = 15.4, 6.7 Hz, 1H), 3.64 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.26 (d, *J* = 3.9 Hz, 1H), 2.35 (d, *J* = 11.5 Hz, 1H), 1.86 (s, 3H), 1.82 (s, 3H), 1.73 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.2, 153.1, 143.3, 137.0, 130.0, 129.4, 128.9, 126.2, 125.9, 125.3, 122.4, 120.4, 118.3, 116.3, 108.6, 90.9, 47.0, 38.3, 35.5, 25.8, 23.5, 18.3. **HPLC Analysis:** ee = 97%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.2 min, t_{minor} = 8.1 min). **FT-IR (thin film):** 2955, 2858, 1710, 1619, 1434, 1386, 1253, 1135, 1107, 1056, 1001, 898, 745, 599, 545, 494 cm^{-1}; **ESI HRMS**: calcd. For $C_{23}H_{24}NO_3$ $[M+H]^+$ 362.1751, found 362.1754.



3r

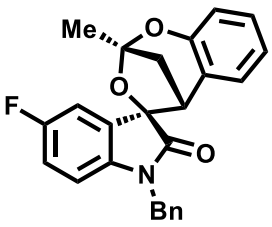
((2'S,3R,5'R)-1-((E)-but-2-en-1-yl)-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3r) was obtained as off-white sticky solid in 63% (21.9 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 – 7.20 (m, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.5 Hz, 1H), 5.73 (dq, *J* = 13.0, 6.5 Hz, 1H), 5.52 – 5.37 (m, 1H), 4.27 (dd, *J* = 15.6, 5.9 Hz, 1H), 4.14 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.64 (dd, *J* = 11.5, 4.1 Hz, 1H), 3.26 (d, *J* = 3.8 Hz, 1H), 2.36 (d, *J* = 11.2 Hz, 1H), 1.87 (s, 3H), 1.70 (d, *J* =

6.5 Hz, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.3, 153.1, 143.2, 130.0, 129.7, 129.5, 128.9, 126.1, 125.9, 125.2, 124.2, 124.1, 122.4, 120.4, 116.3, 108.9, 108.6, 90.8, 47.0, 47.0, 41.9, 35.4, 23.5, 17.8. **HPLC Analysis:** ee = 96%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.5 min, t_{minor} = 10.6 min). **FT-IR (thin film):** 2925, 2856, 1717, 1614, 1464, 1361, 1255, 1183, 1079, 1033, 971, 860, 750, 580, 494 cm^{-1}; **ESI HRMS**: calcd. For $C_{22}H_{22}NO_3$ $[M+H]^+$ 348.1594, found 348.1603.



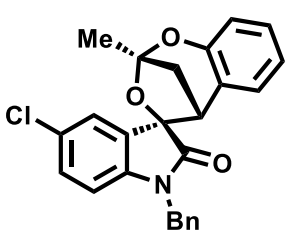
3s

((2'S,3R,5'R)-2'-methyl-1-(4-(trifluoromethyl)benzyl)-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3s) was obtained as off white sticky solid in 47% (21.3 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.60 (t, *J* = 7.8 Hz, 2H), 5.88 (d, *J* = 7.5 Hz, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.83 (d, *J* = 16.0 Hz, 1H), 3.66 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.41 (d, *J* = 11.6 Hz, 1H), 1.89 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.9, 153.1, 142.6, 139.8, 130.1, 129.6, 128.9, 127.7, 126.3, 126.1, 126.1, 126.1, 126.0, 125.0, 122.9, 120.5, 116.4, 108.8, 108.7, 90.7, 47.2, 43.5, 35.5, 23.5. **HPLC Analysis:** ee = 94%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.8 min, t_{minor} = 11.4 min). **FT-IR (thin film):** 2925, 2854, 2081, 1637, 1462, 1376, 1323, 1260, 1165, 1103, 1019, 750, 693, 488 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{21}F_3NO_3$ $[M+H]^+$ 452.1468, found 452.1482.



3t

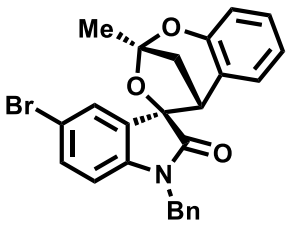
((2'S,3R,5'R)-1-benzyl-5-fluoro-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3t) was obtained as a yellow semi solid in 35% (14.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.33 (d, *J* = 6.5 Hz, 2H), 7.31 – 7.26 (m, 4H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.79 (dt, *J* = 8.8, 5.5 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.53 (dd, *J* = 8.6, 4.1 Hz, 1H), 5.55 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.92 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 21.2 Hz, 1H), 3.66 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.31 (d, *J* = 4.0 Hz, 1H), 2.41 (d, *J* = 11.1 Hz, 1H), 1.89 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.6, 160.1, 152.9, 138.9, 135.4, 129.9, 129.4, 129.1, 128.9, 128.9, 128.8, 128.0, 127.4, 124.6, 120.7, 116.5, 116.4, 116.1, 114.3, 114.0, 109.6, 109.5, 108.9, 47.3, 44.1, 35.5, 23.4. **HPLC Analysis:** ee = 91%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.5 min, t_{minor} = 11.8 min). **FT-IR (thin film):** 2924, 2854, 1716, 1627, 1487, 1341, 1259, 1164, 1076, 1030, 860, 755, 607, 493. 430 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}FNO_3$ $[M+H]^+$ 402.1500, found 402.1527.



3u

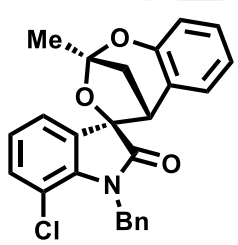
((2'S,3R,5'R)-1-benzyl-5-chloro-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3u) was obtained as a brown semi solid in 30% (12.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.26 (m, 6H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 5.72 (d, *J* = 2.1 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 3.64 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.43 (d, *J* = 11.6 Hz, 1H), 1.89 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.4, 152.9, 141.4, 135.3, 129.8, 129.1, 128.9, 128.1, 128.1, 127.8, 127.4, 126.6, 124.6, 120.7, 116.6, 109.9, 108.9, 90.7, 47.3, 44.0, 35.4, 23.4. **HPLC Analysis:** ee = 94%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.9 min, t_{minor} = 11.3 min). **FT-IR (thin film):** 2924,

2853, 1716, 1637, 1483, 1339, 1259, 1175, 1078, 1029, 859, 750, 698, 602. 550 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}ClNO_3$ $[M+H]^+$ 418.1204, found 418.1200.



3v

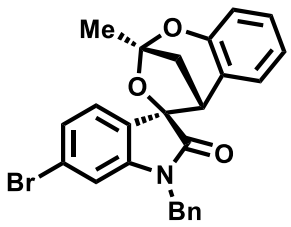
((2'S,3R,5'R)-1-benzyl-5-bromo-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3v) was obtained as an orange semi solid in 32% (14.8 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.26 (m, 6H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 5.84 (d, *J* = 1.9 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 3.63 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.43 (d, *J* = 11.6 Hz, 1H), 1.89 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.2, 152.9, 141.9, 135.3, 132.7, 129.8, 129.4, 129.1, 128.9, 128.1, 128.0, 127.4, 124.6, 120.7, 116.6, 115.5, 110.4, 108.9, 90.7, 47.3, 44.0, 35.3, 23.5. **HPLC Analysis:** ee = 95%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 14.8 min, t_{minor} = 11.9 min). **FT-IR (thin film):** 2966, 2855, 1638, 1481, 1426, 1387, 1260, 1175, 1139, 1077, 1027, 798, 751, 698, 413 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}BrNO_3$ $[M+H]^+$ 462.0699, found 462.0655.



3w

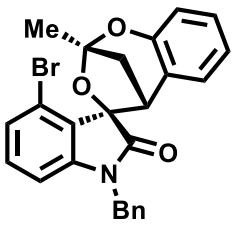
((2'S,3R,5'R)-1-benzyl-7-chloro-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3w) was obtained as a light yellow sticky solid in 42% (17.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 (t, *J* = 7.2 Hz, 3H), 7.23 (d, *J* = 7.4 Hz, 3H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.59 (t, *J* = 7.8 Hz, 2H), 5.84 (d, *J* = 7.5 Hz, 1H), 5.31 (s, 2H), 3.64 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.29 (d, *J* = 3.9 Hz, 1H), 2.39 (d, *J* = 11.1 Hz, 1H), 1.88 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 176.5, 153.0, 138.9, 137.4, 132.6, 129.7, 129.1, 129.0, 128.8, 127.4, 126.6, 124.7, 124.5, 123.4, 120.6, 116.4, 115.3, 108.9, 90.1, 47.6, 45.0, 35.4, 23.4. **HPLC Analysis:** ee = 92%, Chiralpak IE Column, n-Hexane/i-

PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.4 min, t_{minor} = 5.7 min). **FT-IR (thin film):** 2959, 2854, 1710, 1632, 1479, 1404, 1382, 1258, 1170, 1131, 1075, 1014, 863, 797, 730, 644, 560, 443 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}ClNO_3$ $[M+H]^+$ 418.1204, found 418.1210.



3x

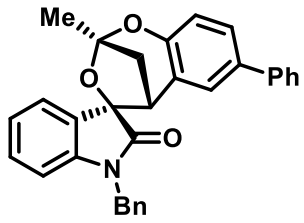
((2'S,3R,5'R)-1-benzyl-6-bromo-2'-methyl-5'H-spiro [indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3x) was obtained as a light orange solid in 33% (15.2 mg) yield after column chromatography. M.P. = 150-152 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (dd, *J* = 15.7, 8.2 Hz, 3H), 7.29 (t, *J* = 6.4 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 3H), 6.60 (d, *J* = 7.4 Hz, 1H), 5.71 – 5.64 (m, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 3.63 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.39 (d, *J* = 11.7 Hz, 1H), 1.88 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.6, 153.0, 144.3, 135.2, 129.7, 129.2, 128.9, 128.1, 127.4, 127.2, 125.5, 125.0, 124.8, 123.9, 120.6, 116.4, 112.4, 108.8, 90.4, 47.2, 44.0, 35.4, 23.4. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.6 min, t_{minor} = 8.4 min). **FT-IR (thin film):** 2925, 2853, 1714, 1634, 1451, 1356, 1214, 1185, 1124, 1068, 989, 874, 784, 496, 468 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}BrNO_3$ $[M+H]^+$ 462.0699, found 462.0706.



3y

((2'S,3R,5'R)-1-benzyl-4-bromo-2'-methyl-5'H-spiro [indoline -3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3y) was obtained as a light yellow semi solid in 37% (17.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 7.2 Hz, 1H), 7.28 – 7.20 (m, 5H), 7.13 (dd, *J* = 13.7, 6.3 Hz, 1H), 6.85 (d, *J* = 3.8 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.53 (ddd, *J* = 18.2, 13.5, 7.7 Hz, 2H), 4.87 (dd, *J* = 30.6, 12.7 Hz, 1H), 4.66 (t, *J* = 18.3 Hz, 1H), 3.62 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.15 (d, *J* = 3.7 Hz, 1H), 2.10 (d, *J* = 11.7 Hz, 1H), 1.93 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 176.8, 154.8, 144.5, 135.4, 130.4, 130.0, 129.1, 128.5, 128.4, 128.3, 128.2,

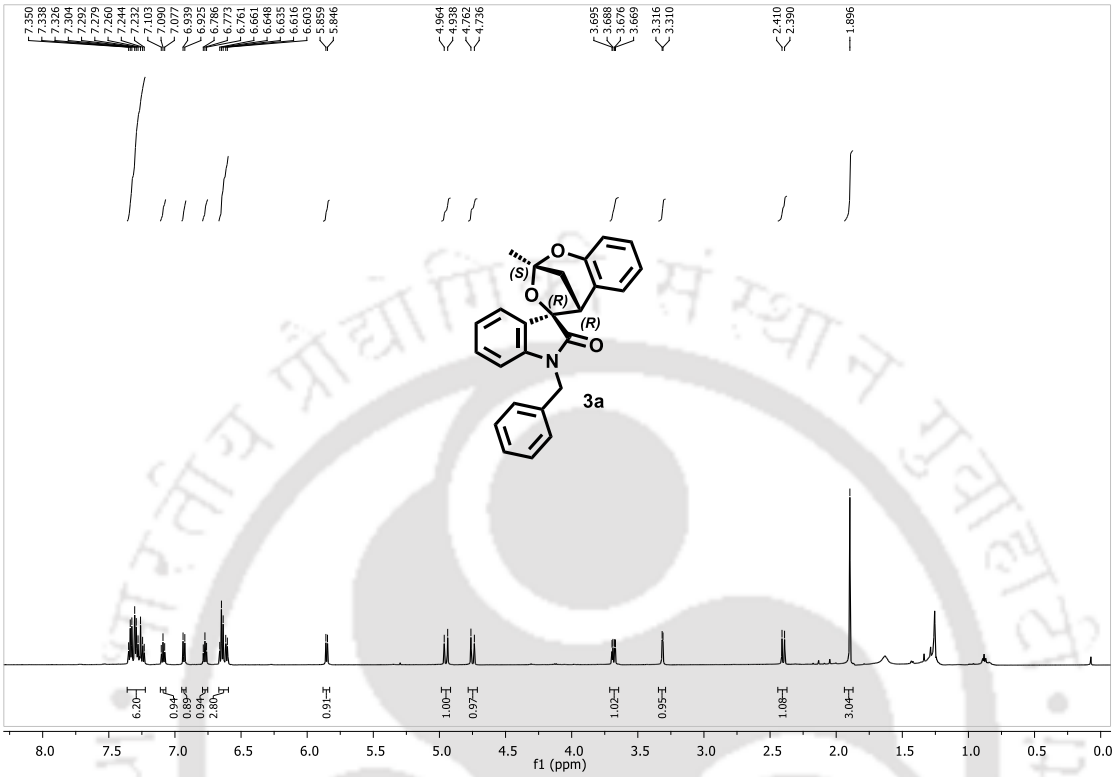
128.1, 127.8, 127.4, 125.6, 121.5, 120.5, 116.8, 109.9, 108.1, 94.1, 49.2, 44.1, 33.9, 23.6. **HPLC Analysis:** ee = 74%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 19.6 min, t_{minor} = 13.0 min). **FT-IR (thin film):** 2924, 2853, 1638, 1447, 1384, 1260, 1094, 1023, 863, 751, 699, 589, 532, 474 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{21}BrNO_3$ $[M+H]^+$ 462.0699, found 462.0708.

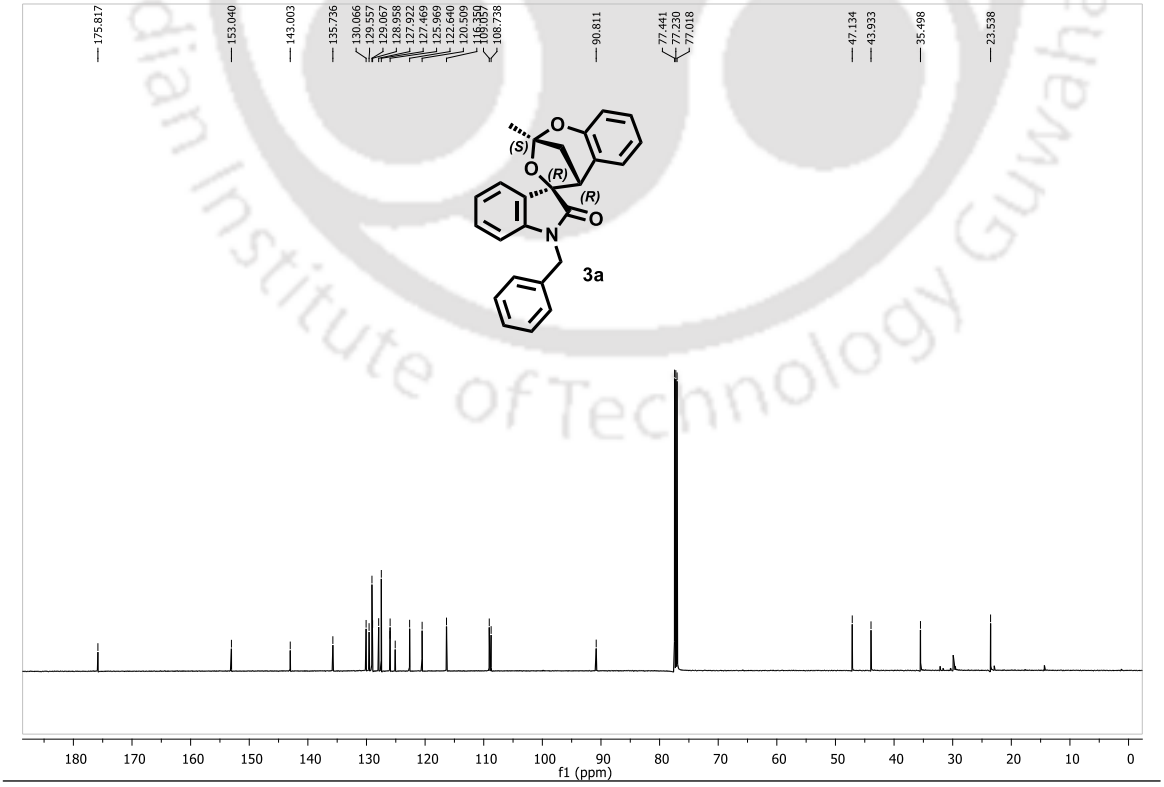


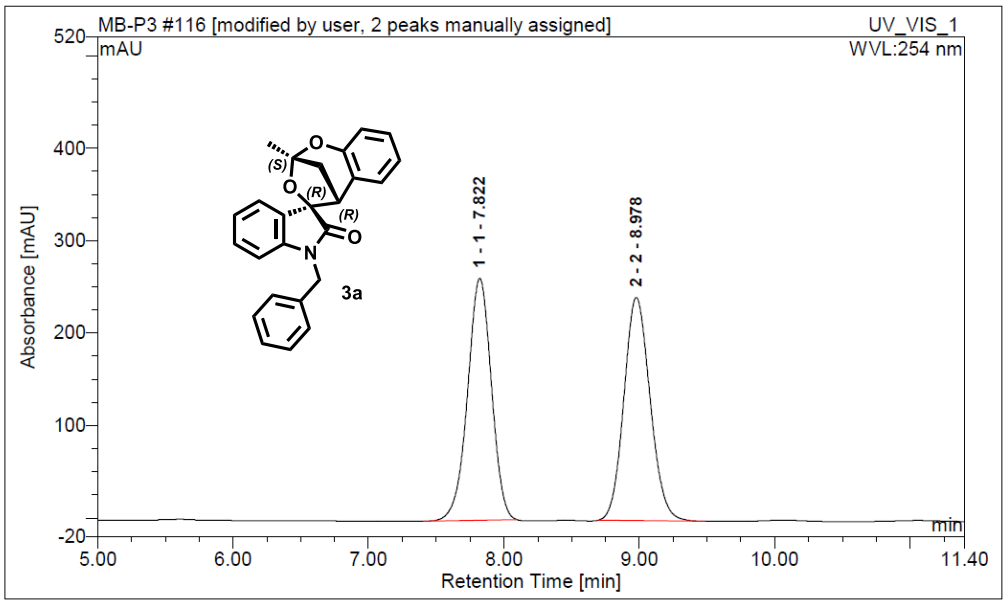
4

((2'S,3R,5'R)-1-benzyl-2'-methyl-7'-phenyl-5'H-spiro [indoline -3,4'-[2,5]methano benzo[d][1,3]dioxepin]-2-one) (4) was obtained as a light yellow sticky solid in 47% (21.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.44 – 7.17 (m, 10H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.64 (dd, *J* = 12.3, 7.7 Hz, 2H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.96 (d, *J* = 15.6 Hz, 1H), 4.76 (d, *J* = 15.7 Hz, 1H), 3.73 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.36 (d, *J* = 3.8 Hz, 1H), 2.44 (d, *J* = 11.6 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 175.8, 152.6, 143.0, 140.8, 135.8, 133.9, 130.1, 129.1, 128.8, 128.3, 127.9, 127.7, 127.5, 126.9, 126.1, 125.9, 125.4, 122.6, 116.7, 109.1, 108.9, 90.8, 47.3, 44.0, 35.6, 23.5. **HPLC Analysis:** ee = 92%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.9 min, t_{minor} = 13.1 min). **FT-IR (thin film):** 2924, 2854, 1717, 1618, 1480, 1362, 1257, 1182, 1142, 1077, 977, 863, 750, 697, 595, 554, 497 cm^{-1}; **ESI HRMS**: calcd. For $C_{31}H_{22}NNaO_3$ $[M+Na]^+$ 482.1727, found 482.1727.

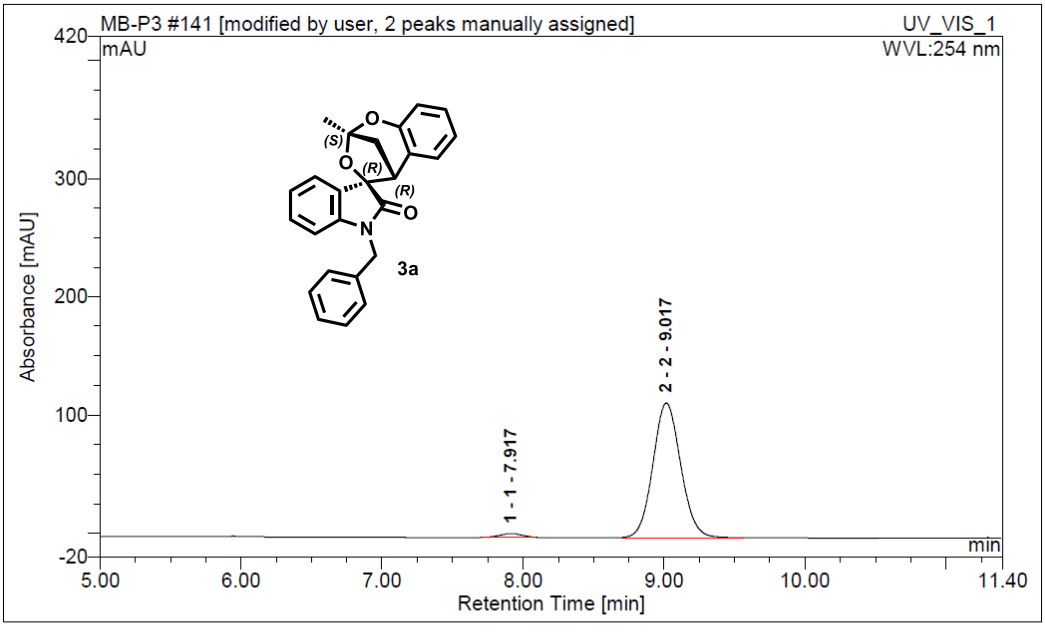
4.8 Selected NMR and HPLC spectra of products



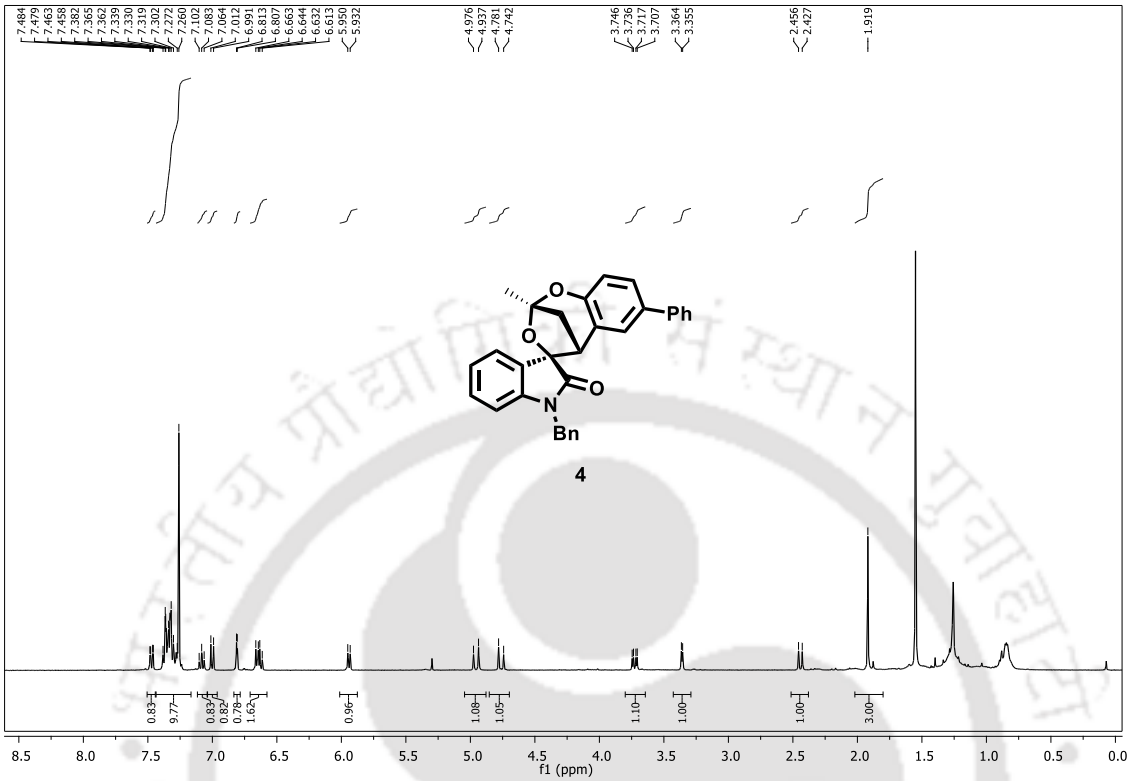


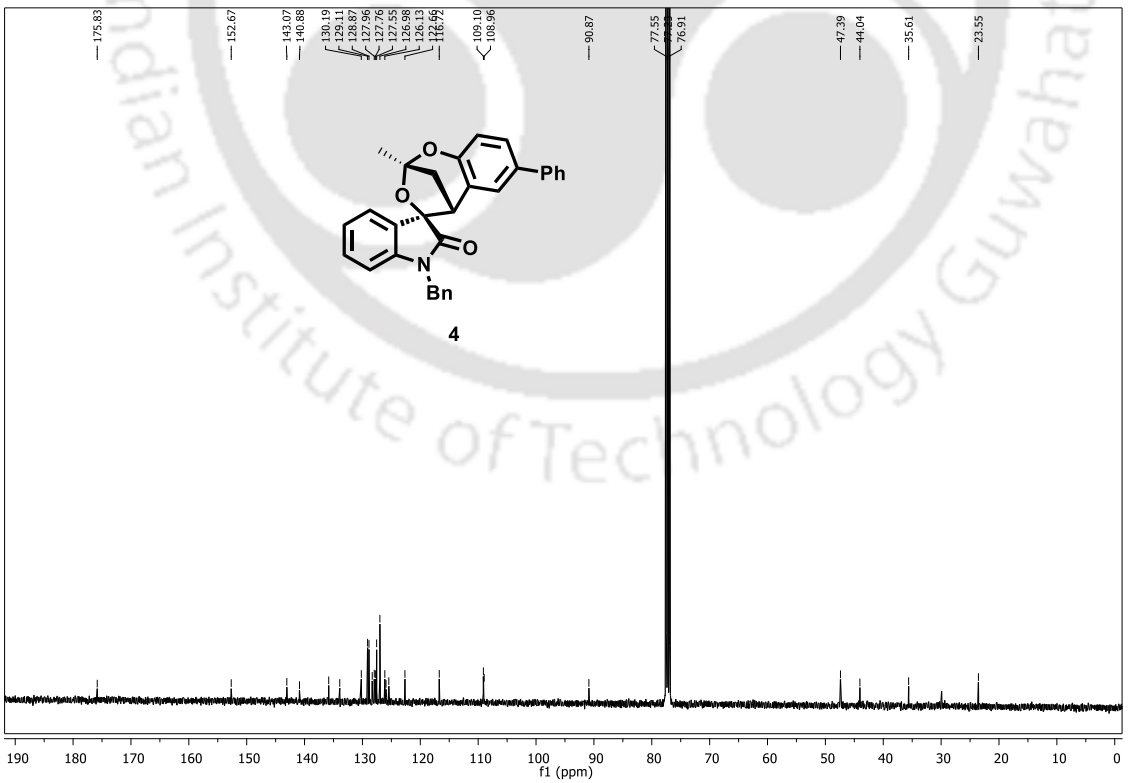


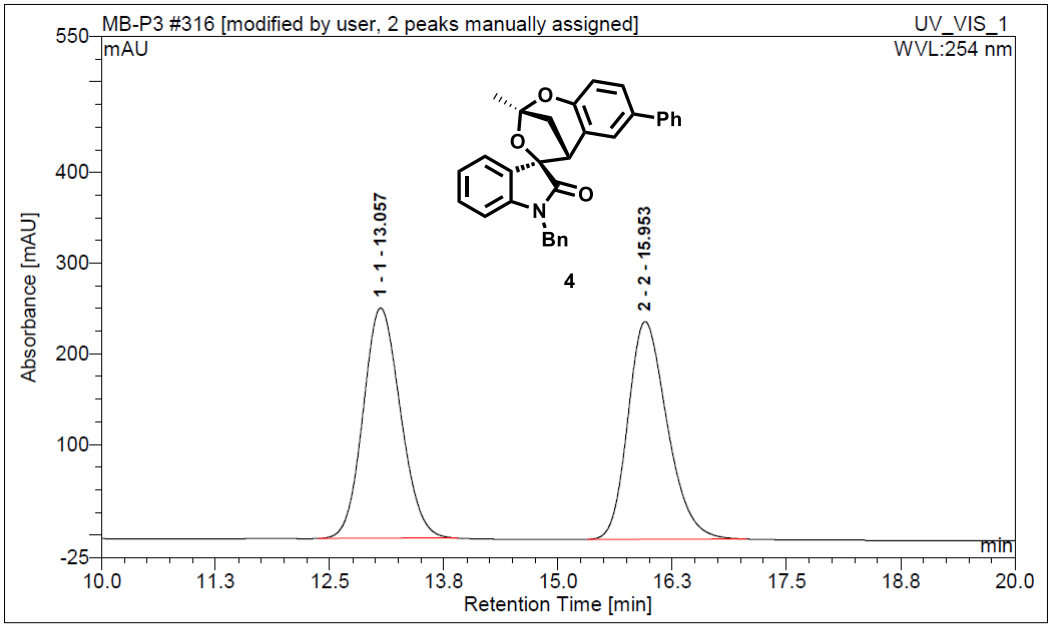
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	7.82	53.40062	49.6566315	261.3188	n.a.
2	2	8.98	54.139	50.3433685	241.072	n.a.



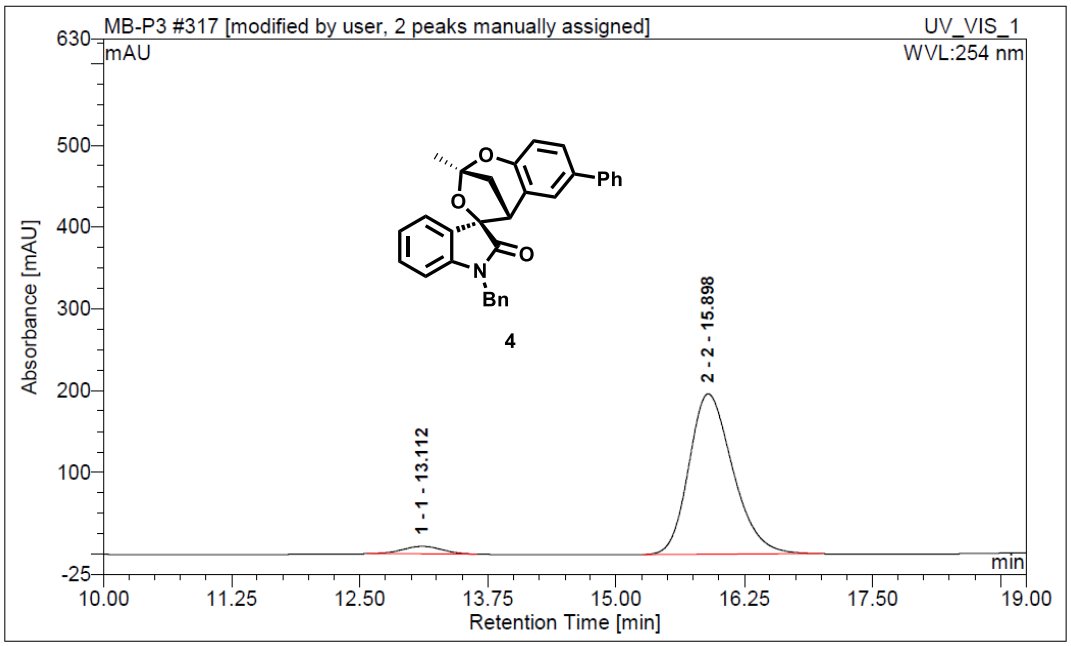
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	7.92	0.561779	2.12127239	3.10656	n.a.
2	2	9.02	25.921	97.87872761	113.728	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	13.06	120.7074	50.14501742	254.0844	n.a.
2	2	15.95	120.009	49.85498258	240.176	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	13.11	4.164335	4.095559545	9.2653	n.a.
2	2	15.90	97.515	95.90444046	196.137	n.a.

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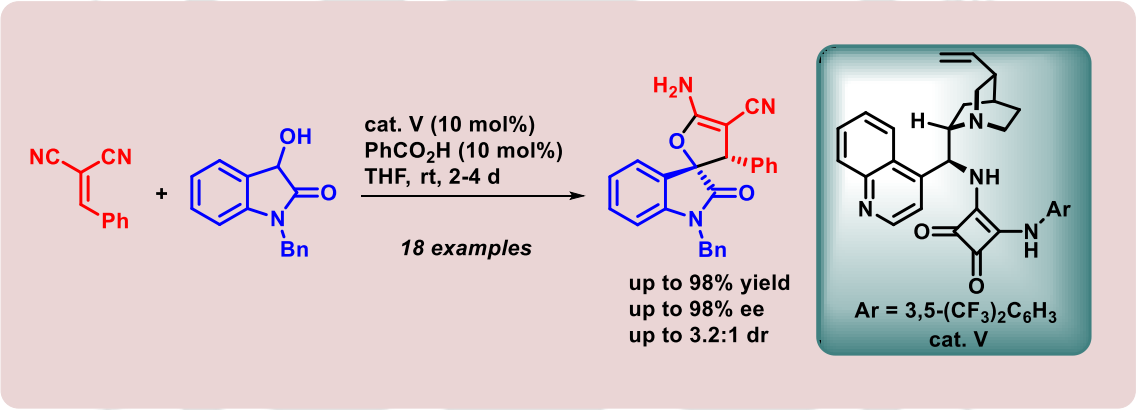
Chapter 5

Organocatalytic Asymmetric Synthesis of Dihydrofuran-Spirooxindoles from Benzylidene Malononitriles and Dioxindoles



Org. Biomol. Chem. **2019**, *17*, 6557.

5.1 Introduction

Spirooxindoles are important structural intermediates present in many natural products and frequently observed in a plethora of pharmaceutical agents.[1] Thus, spirooxindole motif has drawn significant attention to the synthetic organic chemists, and a large number of chemists are engaged for the development of efficient and practical synthetic methods for this class of structural frameworks. In particular, spirooxindolyl five-membered oxaheterocycles including spirooxindole-dihydrofurans have drawn attention because of their presence in a variety of artificial and natural bioactive substances (Figure 1).[2]

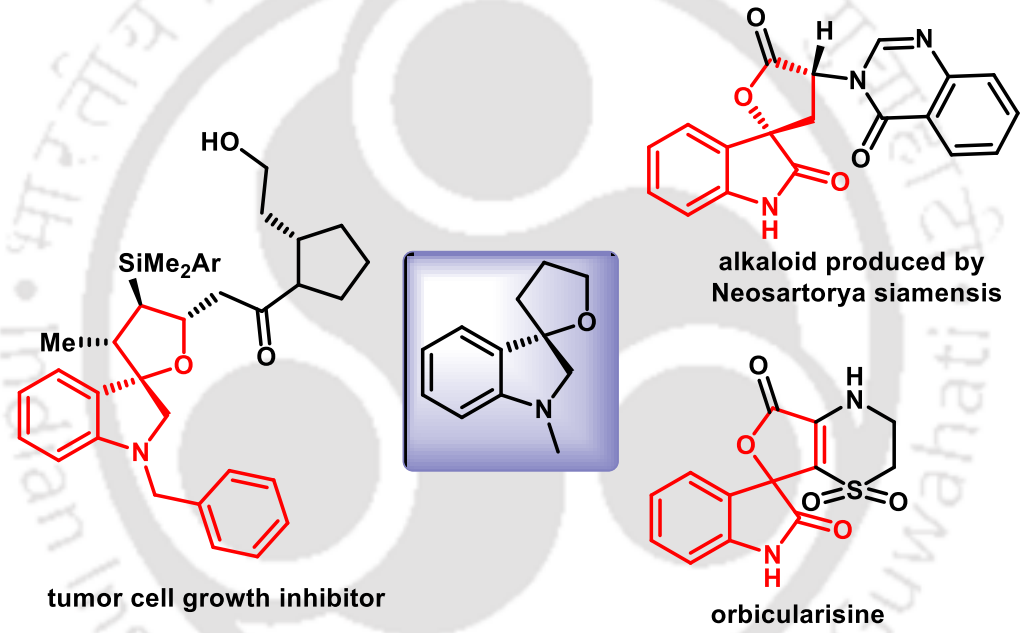


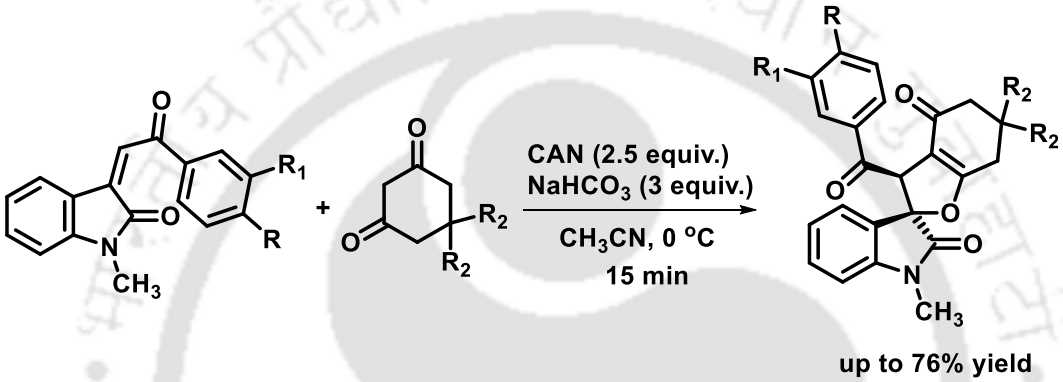
Figure 1. Bioactive spirooxindolyl five-membered oxaheterocycles

In recent years, few effective achiral methods of spirooxindole-dihydrofurans preparation have been documented in the literature,[3] whereas, asymmetric catalytic reports are very few[4] although such skeletons are present in a variety of natural products like orbicularisine, alkaloid produced by neosartorya siamensis, etc.

5.2 Known strategies for the synthesis of spirooxindole-dihydrofurans

5.2.1 Synthesis of spiro dihydrofuran oxindole *via* [3+2] oxidative cycloaddition mediated by CAN

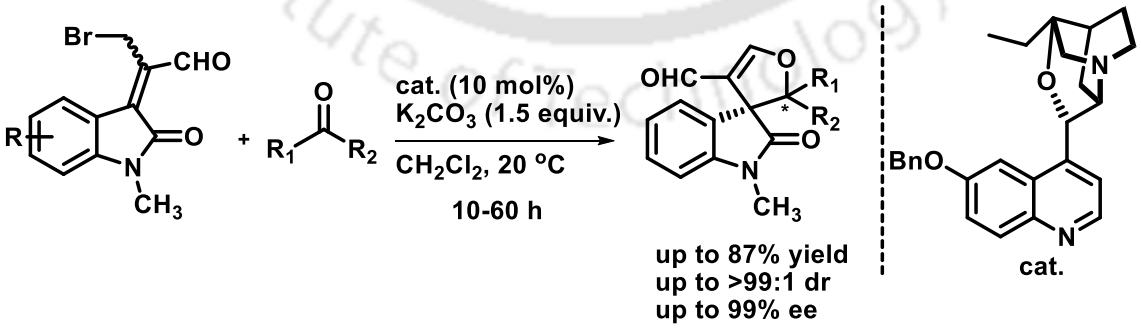
In 2007, Perumal *et al.* reported an efficient one-pot method for the synthesis of spiro dihydrofuran oxindole derivatives *via* [3+2] oxidative cycloaddition of cyclic 1,3-dicarbonyl compounds to 3-(phenyl-2-oxoethylidene)-1-methyloxindole derivatives mediated by ceric ammonium nitrate. The desired spiro dihydrofuran oxindole derivatives were obtained in moderate yields (Scheme 1).[5]



Scheme 1. Synthesis of spiro dihydrofuran oxindole derivatives by Perumal *et al.*

5.2.2 One-Pot Tandem Approach to Spirocyclic Oxindoles

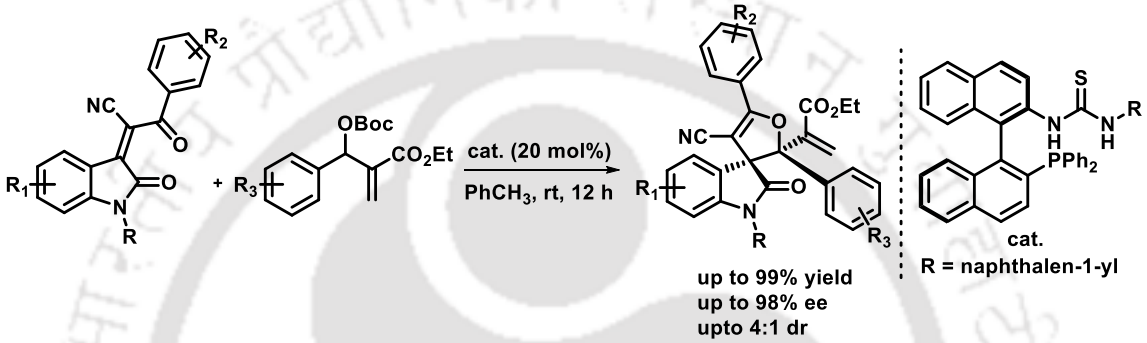
In 2013, Zhou and co-workers developed a novel organocatalytic asymmetric [3+2] annulation of brominated MBH adducts for the facile preparation of dihydrofuran-spirooxindoles featuring two adjacent spiro-stereocenters in good yields and excellent stereoselectivities. This protocol was catalyzed by tertiary amine (Scheme 2).[6]



Scheme 2. Asymmetric [3+2] annulation for the Synthesis of dihydrofuran-spirooxindoles by Zhou *et al.*

5.2.3 Phosphine-catalyzed asymmetric [4+1] annulation for the synthesis of spirooxindoles

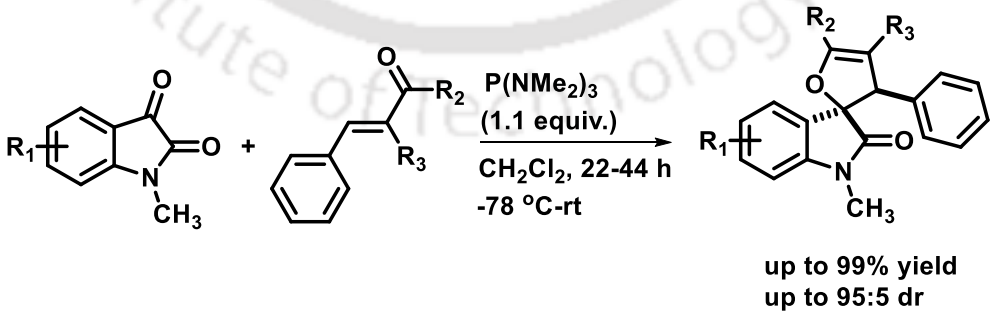
In 2014, Shi *et al.* revealed a convenient synthesis of spirooxindole-dihydrofurans *via* asymmetric [4+1] annulation of isatin derived *α,β*-unsaturated ketones with MBH carbonates catalyzed by bifunctional thiourea–phosphine catalysts. Spirooxindoles scaffolds with two adjacent quaternary stereocenters were isolated in good yields with high enantioselectivities and moderate diastereoselectivities (Scheme 3).[7]



Scheme 3. Enantioselective synthesis of spirooxindole by Shi *et al.*

5.2.4 $P(NMe_2)_3$-mediated synthesis of spirooxindole-dihydrofurans

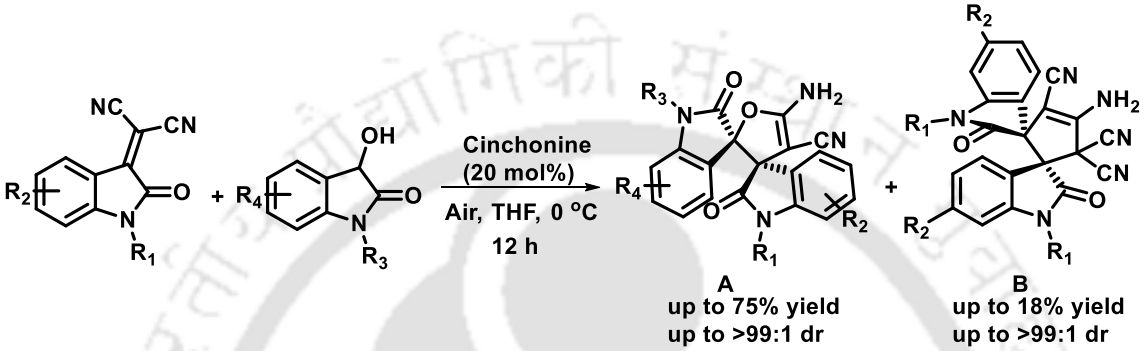
In 2015, Zhou *et al.* reported a novel $P(NMe_2)_3$-mediated reductive [1+4] annulation of isatins with enones for the synthesis of desired spirooxindole-dihydrofurans in good yields with moderate diastereoselectivities. This methodology provided five-membered cyclic motifs *via* a Kukhtin-Ramirez adduct involved [1+4] annulation mode (Scheme 4).[8]



Scheme 4. [1+4] annulation for the synthesis of spirooxindole-dihydrofurans by Zhou *et al.*

5.2.5 Stereoselective construction of bi-spirooxindole frameworks

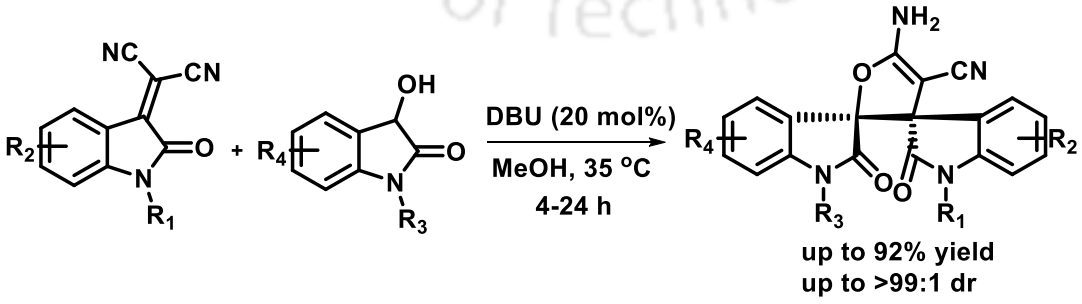
In 2016, the Xie group disclosed a facile and mild synthesis of bi-spirooxindole frameworks, including 2,3-dihydrofuranyl bi-spirooxindole and 1,5-cyclopent[2]ene bi-spirooxindole. 2,3-dihydrofuranyl bi-spirooxindoles were synthesized *via* Michael addition/cyclization and 1,5-cyclopent[2]ene bi-spirooxindoles were developed through an unexpected redox/oxidative coupling/cyclization (Scheme 5).[9]



Scheme 5. Stereoselective synthesis of bi-spirooxindole frameworks by Xie *et al.*

5.2.6 Construction of bispirooxindoles containing a fully substituted dihydrofuran motif

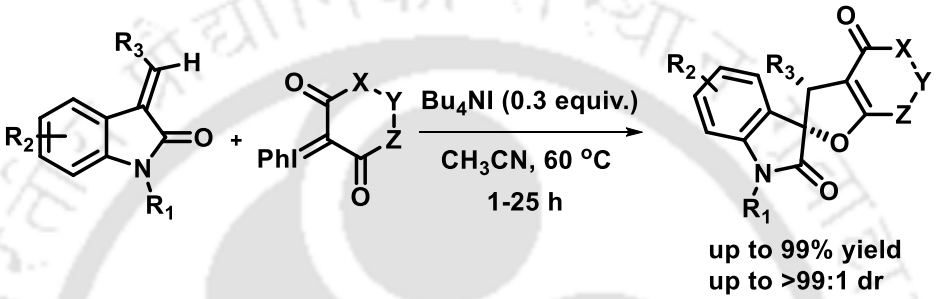
In 2017, Bu *et al.* reported the first DBU-catalyzed Michael/Pinner/isomerization cascade reaction of 3-hydroxyoxindoles with isatylidene malononitriles. The corresponding highly functionalized bispirooxindoles containing a fully substituted dihydrofuran motif were isolated in good yields. The asymmetric version of the cascade reaction was also performed using cinchonidine derived thiourea catalyst, and the desired product was obtained in 75% yield and 72% enantiomeric excess (Scheme 6).[10]



Scheme 6. Synthesis of highly functionalized bispirooxindoles by Bu *et al.*

5.2.7 Iodide-Mediated Synthesis of Spirooxindolo Dihydrofurans

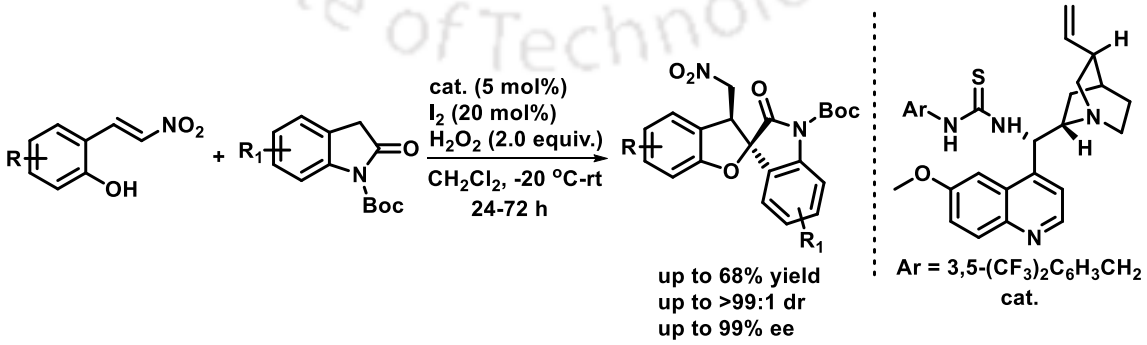
In 2017, Murphy *et al.* developed a metal-free synthesis of spirooxindolo dihydrofurans from substituted 3-alkylidene-2-oxindoles and iodonium ylides of 1,3-dicarbonyls. The reaction was catalyzed by Bu_4NI, and the desired spirocycles were obtained in excellent yields. In this methodology, for the formation of spirocycles, variations in the iodonium ylide were well tolerated, with ylides derived from cyclic 1,3-diketones, 1,3-ketoesters, and pyrimidines (Scheme 7).[11]



Scheme 7. Synthesis of spirooxindolo dihydrofurans by Murphy *et al.*

5.2.8 Organocatalytic synthesis of chiral spirodihydrobenzofuran oxindoles

In 2018, Xu *et al.* reported a one-pot Michael/iodization/SN_2 nucleophilic substitution for sequential catalytic synthesis of spirodihydrobenzofuran oxindole derivatives. This strategy combined both the asymmetric organocatalysis and iodine catalysis involving the combination of a catalytic amount of molecular iodine and 30% aqueous solutions of H_2O_2. The desired products were obtained in moderate to high yields with excellent enantio- and diastereoselectivities. (Scheme 8).[12]

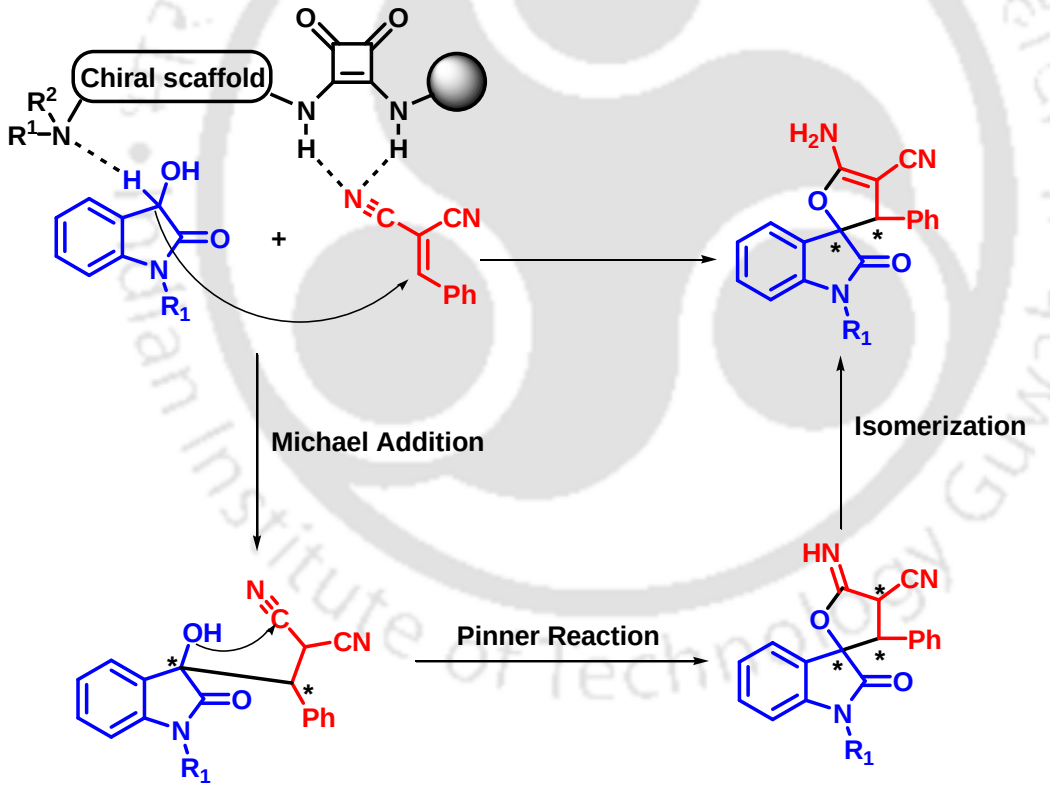


Scheme 8. Synthesis of chiral spirodihydrobenzofuran oxindoles by Xu *et al.*

5.3 Concept

Chiral spirooxindole-dihydrofurans are versatile structural motifs that are prevalent in many biologically active molecules, and due to its wide applicability, we thought of developing a useful strategy for the synthesis of spirooxindole-dihydrofurans. Our plan was to develop an organocatalytic direct asymmetric synthesis of dihydrofuran-spirooxindoles having linkage at 2-position by performing a Michael-cyclization cascade reaction[13] between dioxindoles[14] and benzylidene malononitriles[15] (Scheme 9).

We used benzylidene malononitrile and *N*-benzyl dioxindole as the substrates. The cyano functionality of benzylidene malononitrile will be activated by the thiourea or the squaramide motifs. The tertiary amine part of the catalyst will abstract the proton from *N*-benzyl dioxindole, and the corresponding cascade reaction will take place to deliver the desired product.



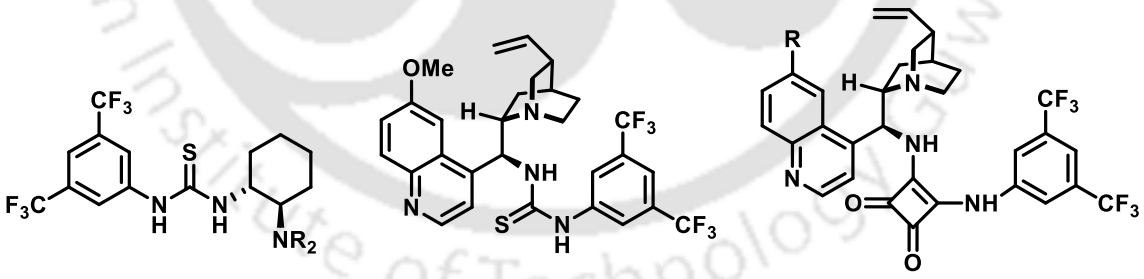
Scheme 9. Michael-cyclization cascade reaction between dioxindoles and benzylidene malononitriles

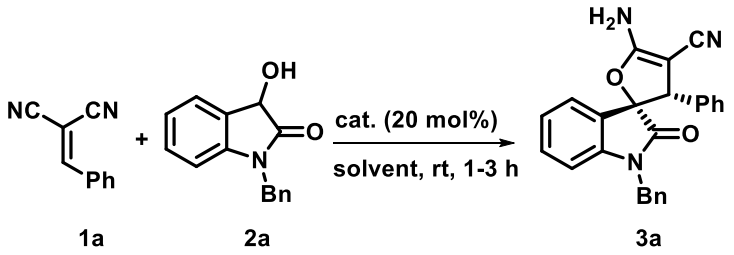
5.4 Results and discussion

5.4.1 Optimization of catalyst and reaction conditions

To validate the strategy, a model reaction between benzylidene malononitrile **1a** and *N*-benzyl dioxindole **2a** was performed with Takemoto catalyst **I** in toluene at room temperature (Table 1). After stirring for 2 h, the desired Michael-Pinner isomerization cascade reaction took place to form the oxindole-dihydrofuran **3a** in 78% yield. However, the diastereoselectivity was less (1:1 dr), and the enantiomeric excesses were 94% and 54%, respectively (entry 1). Replacing the dimethylamino group of catalyst with the diethylamino group did not alter the outcome of the reaction (entry 2). Then quinine derived thiourea catalyst **III** was screened (entry 3). Though the diastereoselectivity of product **3a** got increased slightly, the enantioselectivity decreased. Then we turned our attention to employ cinchona alkaloid derived squaramide catalysts, and this found to be beneficial. A similar level of diastereoselectivity but enhanced enantioselectivity was attained with catalyst **IV,** and also, the reaction was found to be faster (entry 4). Finally, the best catalyst turned out to be cinchonidine derived squaramide **V,** which afforded the product **3a** in 80% yield with 1.7:1 dr (entry 5). The enantiomeric excesses of the diastereomers were 95% and 86%, respectively.

Table 1. **Catalyst screening and solvent optimization**





entry[a]	catalyst	solvent	yield (%)[b]	dr[c]	ee[d]
1	**I**	$PhCH_3$	78	1:1	95/54
2	**II**	$PhCH_3$	72	1:1	94/54
3	**III**	$PhCH_3$	70	1.5:1	64/66
4	**IV**	$PhCH_3$	76	1.4:1	78/63
5	**V**	**$PhCH_3$**	**80**	**1.7:1**	**95/86**
6	**V**	$PhCF_3$	71	1:1	88/47
7	**V**	*o*-Xylene	73	1:1	88/50
8	V	Et_2O	78	1.3:1	94/80

[a]All reactions were carried out with 0.06 mmol of **1a** with 0.05 mmol of **2a** in 0.2 ml solvent at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC using a stationary phase chiral column.

After having the optimum catalyst **V** in hand, we focused on the optimization of other reaction parameters. We checked the influence of different solvents in this reaction, but better results were not observed (Table 1, entries 6-8). For example, in *α*,*α*,*α*-trifluoro toluene, and in *o*-xylene, both the diastereo- and enantioselectivity got reduced (Table 1, entries 6-7). Though high enantioselectivity was detected in diethyl ether solvent, diastereoselectivity was low (Table 1, entry 8).

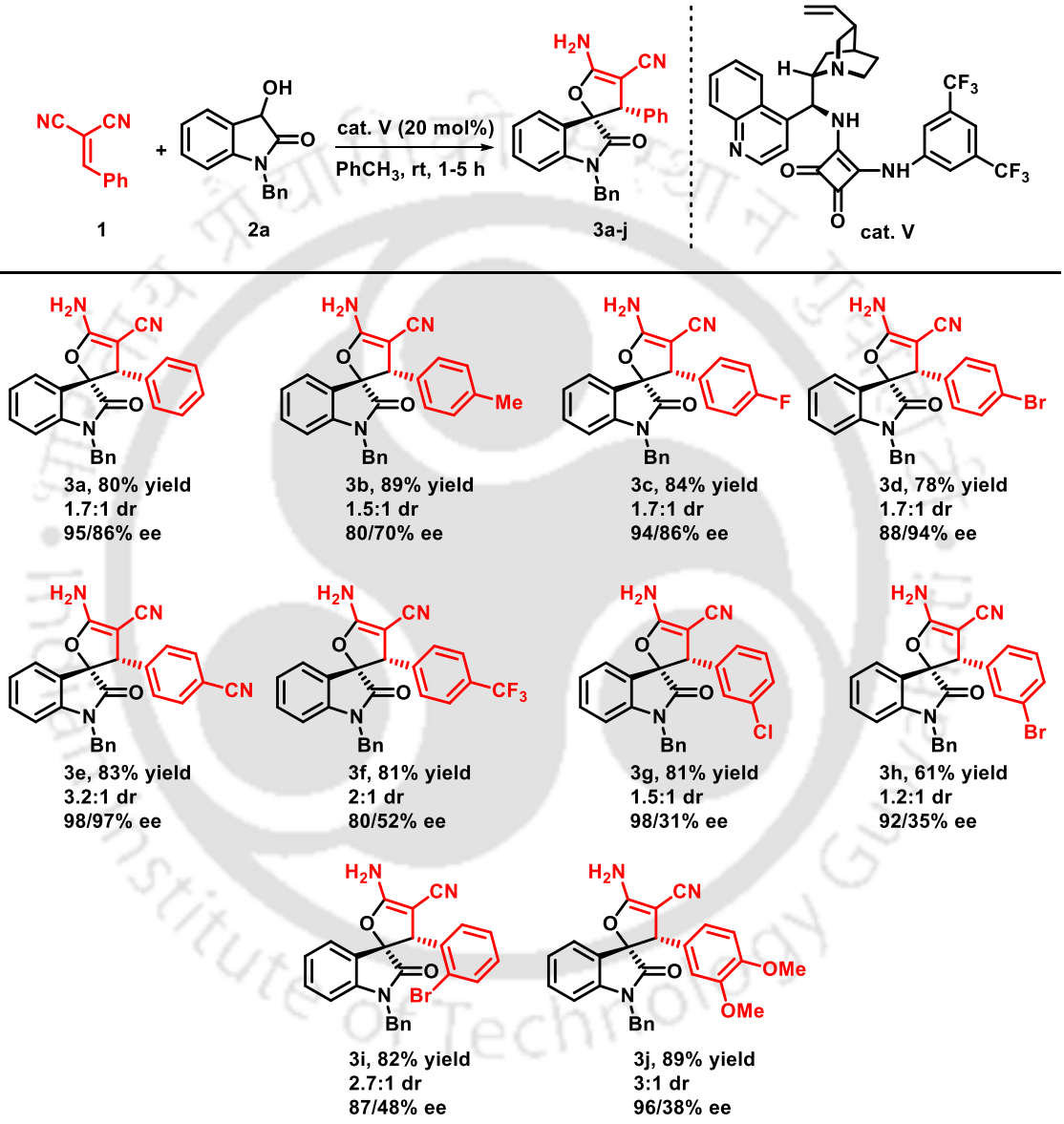
5.4.2 Substrate scope

After establishing the optimal condition for the corresponding Michael-cyclization cascade reaction, the scope and generality of the reaction have been explored.

We first examined the scope of benzylidene malononitrile by varying different substituents on the aromatic ring (Scheme 10). It can be seen from Scheme 10 that the desired corresponding products were obtained in moderate yields with excellent enantioselectivities and moderate diastereoselectivities. For unsubstituted benzylidene malononitrile, product **3a** was obtained in 80% yield with 1.7:1 diastereomeric ratio and

95% enantiomeric excess. Delightfully, different substitutions on the aryl groups were tolerated to afford the desired spirooxindole-dihydrofurans derivatives with good to excellent enantiomeric excesses. Initially, different 4-alkyl-substituted aryl groups

Scheme 10. Substrate scope of benzylidene malononitrile[a]



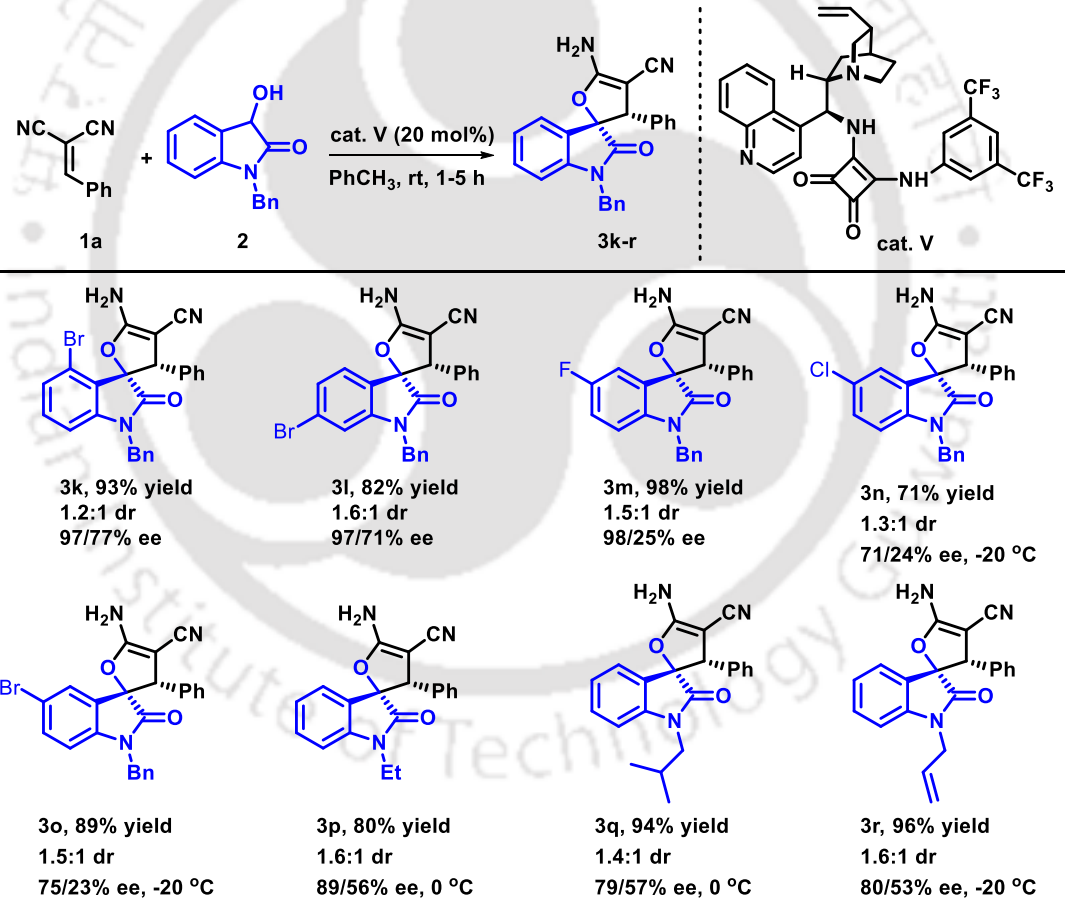
[a]All reactions were carried out with 0.05 mmol of **1** with 0.06 mmol of **2a** in 0.2 ml $PhCH_3$ at room temperature. Yields correspond to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees was determined by HPLC using stationary phase chiral column.

containing benzylidene malononitriles were engaged in the reaction. Benzylidene malononitrile having *para*-methyl moiety delivered the product **3b** with 89% yield in 1.5:1 diastereomeric ratio and 80% enantiomeric excess. Then benzylidene malononitrile having *para*-halo substitutions reacted smoothly to give the expected products **3c** and **3d** with moderate diastereoselectivities and high enantioselectivities. In the case of 4-substituted electron-withdrawing substituents, products were obtained with slightly high diastereoselectivities and excellent enantioselectivities. For example, with 4-cyano substitution, both the diastereomeric and enantiomeric excesses were enhanced for product **3e,** and the major diastereomer was obtained in 98% ee. 4-CF_3 substituted spirooxindole-dihydrofuran **3f** was obtained in good yield with 2:1 diastereomeric ratio. In the next part of the substrate scope study, different *meta*-substituted benzylidene malononitriles were investigated. Pleasingly, excellent enantioselectivities, and moderate diastereoselectivities were obtained for products. For example, *meta*-Cl and *meta*-Br substituted benzylidene malononitriles provided the corresponding products **3h** and **3i** with 98% and 92% enantiomeric excess, respectively. Then *ortho*-substituted benzylidene malononitrile was also screened, and gratifyingly, satisfactory result was achieved. 2-Bromo-substituted malononitrile **1i** delivered product **3i** in 82% combined yield with 87% ee for the major diastereomer. Interestingly, the scope of the reaction was further extended by employing disubstituted benzylidene malononitrile. For example, 3,4-dimethoxy-substituted malononitrile **1j** was engaged in the reaction, and gratifyingly the desired product **3j** was isolated in 3:1 dr having 98% ee for the major diastereomer.

We then extended the scope by employing different dioxindoles having substitutions on the aryl ring and on the *N*-atom (Scheme 11). Initially, different substitutions on the aryl ring of the oxindole motif were incorporated and checked under the reaction conditions. 4-Bromo-substituted oxindole **2b** was first screened, and the major diastereomer **3k** was isolated in 97% ee. Similar enantioselectivity was obtained for product **3l** having 6-bromo substitution, though the diastereoselectivity was improved. Then, 5-halo substituted *N*-benzyl dioxindoles **2d–2f** were checked, and varying results were obtained for the products **3m–3o**. Though the diastereoselectivity was almost the same, the enantioselectivity varied significantly. Excellent enantioselectivity was attained for the

major diastereomer **3m** having 5-fluoro substitution, whereas moderate enantioselectivities were detected for **3n** and **3o** having 5-chloro and 5-bromo substitutions, respectively, even at -20 ^{o}C. Also, longer reaction times were required for **3n** and **3o** to achieve reasonable conversions. Then *N*-substitutions were varied, and gratifyingly, smooth conversions were detected with good enantioselectivities for different *N*-alkyl substitutions. For example, 89% ee was obtained for product **3p** having an *N*-ethyl group. Similarly, dioxindole **2h** having an *N*-isobutyl group and **2i** having an *N*-allyl group delivered products **3q** and **3r**, respectively, in acceptable enantioselectivities.

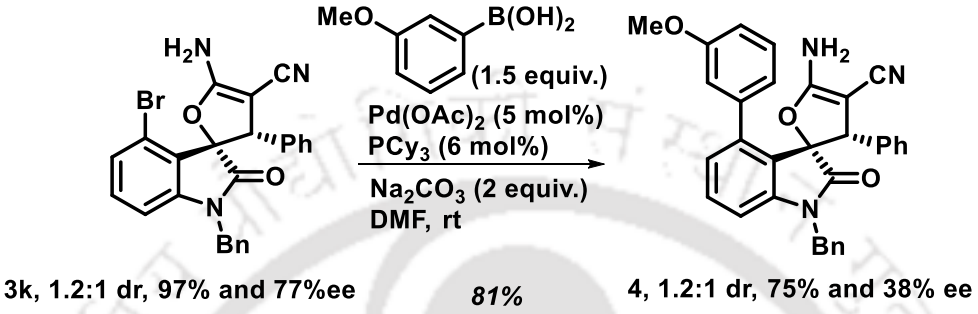
Scheme 11. Substrate scope of dioxindoles[a]



[a]All reactions were carried out with 0.05 mmol of **1a** with 0.06 mmol of **2** in 0.2 ml $PhCH_3$ at room temperature. Yields correspond to isolated yield after silica gel column chromatography. Diastereoselectivity was determined by ^{1}H NMR. ees was determined by HPLC using stationary phase chiral column.

5.4.3 Synthetic transformation

To demonstrate the synthetic potential of our method, a Suzuki coupling reaction was carried out on **3k** (Scheme 3). Thus, 3-methoxy phenylboronic acid was mixed with **3k** and palladium acetate, and tricyclohexyl phosphine was added, and consequently, the reaction mixture was stirred under basic conditions to deliver product **4** in good yield.



Scheme 12. Synthetic transformation

5.4.4 Determination of product stereochemistry

The absolute configuration of product **3i** (Figure 2) was determined to be (2*S*, 3*S*) from X-ray crystallography.[16] The configuration of other products is expected to be the same by analogy.

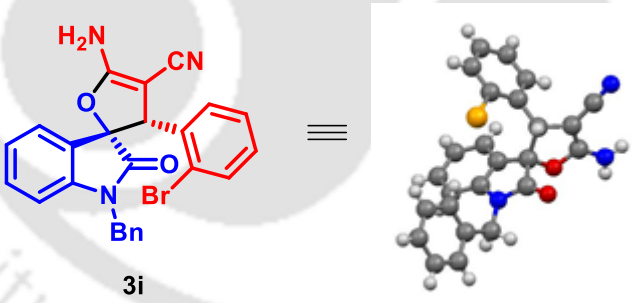


Figure 2. X-ray crystal structure of **3i**

5.4.5 Proposed TS

A plausible mechanism has been shown in Figure 3 to understand the reaction pathways and the stereochemistry of the product. It is anticipated that the squaramide N–H moieties of catalyst **V** bind with a cyanide group of **1a** and thus the *Si* face of **1a** is blocked by catalyst **V**. Also, it is expected that dioxindole **2a** could tautomerize to its enol form **2a′** by the quinuclidine part of the catalyst and the desired Michael addition

takes place from the *Re* face to deliver intermediate **5**, which consequently undergoes the Pinner reaction to provide **6**. Finally, the isomerization of intermediate **6** generates product **3a.**

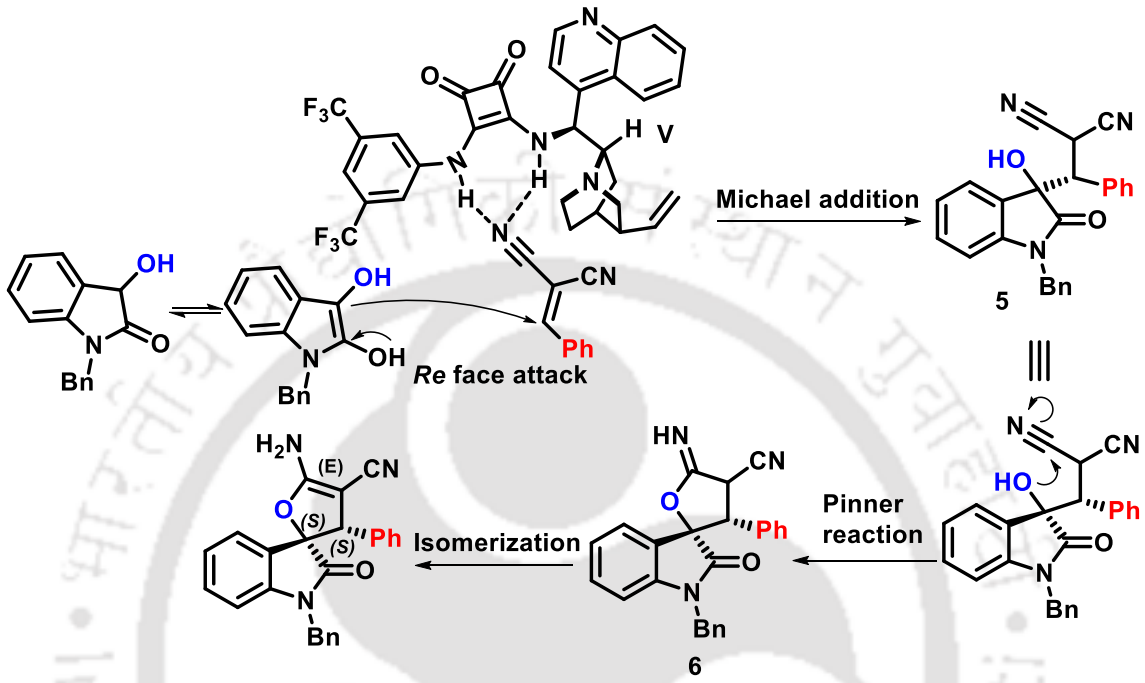


Figure 3. Proposed TS

5.5 Conclusion

In summary, this chapter reports the first organocatalytic asymmetric synthesis of dihydrofuran-spirooxindoles having a linkage at the 2-position of the dihydrofuran motif. The desired products are formed *via* the Michael reaction, Pinner reaction, and isomerization steps. The spirooxindole products were achieved in good to high yields with moderate diastereoselectivity and good to high enantioselectivities under mild reaction conditions. Given the high medicinal importance of spirooxindoles and dihydrofurans, our products are expected to be useful in drug discovery.

5.6 Experimental section

5.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (J) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Phenomenex LUX C1 Column. For visualizing the products, UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

5.6.2 General procedure for the synthesis of benzylidene malononitriles:

Benzylidene malononitriles **(1a-1j)** were prepared according to reported procedure.[17]

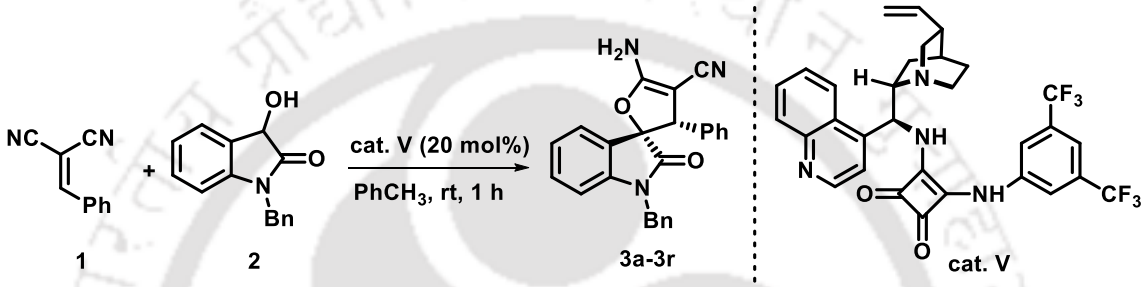
5.6.3 General procedure for the synthesis of dioxindoles:

Dioxindoles **(2a-2i)** were prepared according to reported procedures.[18]

5.6.4 General procedure for the synthesis of catalysts:

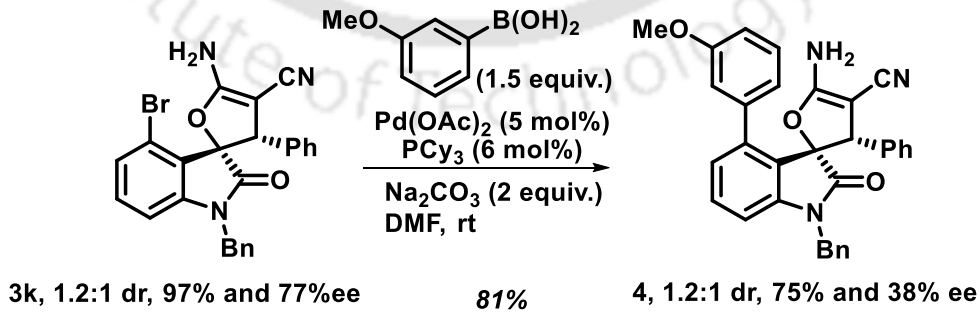
The catalyst (**I, II, III, IV,** and **V**) was prepared according to reported procedures.[19]

5.6.5 General procedure for the synthesis of compound 3a-3r



In an oven-dried round bottom flask, **1** (11.96 mg, 0.05 mmol), **2** (9.25 mg, 0.06 mmol) and 20 mol% of catalyst **V** were taken. 0.2 mL of $PhCH_3$ was added to the reaction mixture and stirred at rt for 1 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, solvent was concentrated, and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (20 %) to afford the desired product **3a-3r**.

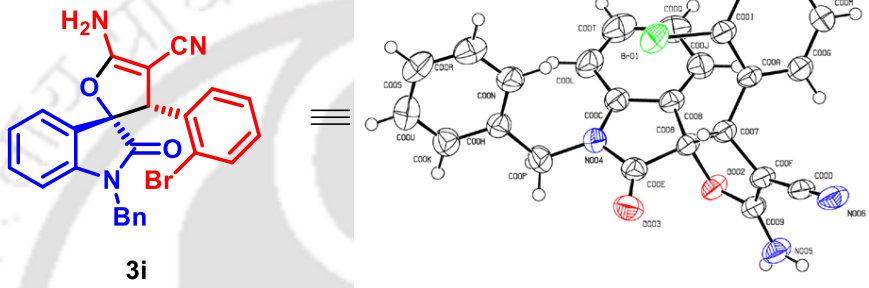
5.6.6 General procedure for the preparation of derivative 4



In an oven-dried round bottom flask, compound **3k** (47.2 mg, 0.1 mmol), phenylboronic acid (1.5 equiv.), palladium (II) acetate (0.05 equiv.), tricyclohexylphosphine (0.06

equiv.) and Na_2CO_3 (2 equiv.) were taken, flushed with argon and then dry DMF (0.1 mL) was added. The reaction mixture was allowed to stir for 2 d under the argon atmosphere. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography using EtOAc-Hexane (10%) as eluent to afford compound **4**.

5.6.7 Crystal Structure of 3i[16]



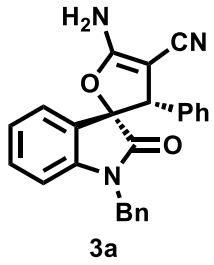
3i

Table 2. Crystal data and structure refinement for compound 3i

Parameters	3i
CCDC No.	1915125
Empirical formula	$C_{25}H_{18}BrN_3O_2$
Formula weight	472.32
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.36× 0.33 × 0.33
Temperature, *T*	296 K
Wavelength, λ (Å)	0.71073
Crystal system	Monoclinic
Space group	*'P 21/c'*
Unit cell dimensions	a = 9.925(4) Å b = 13.094(5) Å c = 16.855(6) Å α = 90°, β = 105.01°, γ = 90°

Volume, V (Å^3)	2115.8(14)
Z	4
Calculated density, Mg/m^3	1.483
Absorption coefficient, μ (mm^{-1})	1.971
F(000)	960
θ range for data collection	1.996° to 25.000°
Limiting indices	$-11 \le h \le 11$, $-15 \le k \le 15$, $-20 \le l \le 20$
Reflection collected/unique	3733/ 2729
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data/restraints/parameters	3733/0/280
Goodness of fit on F^2	0.962
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0391, wR2 = 0.1219
R indices (all data)	R1 = 0.0637, wR2 = 0.1437

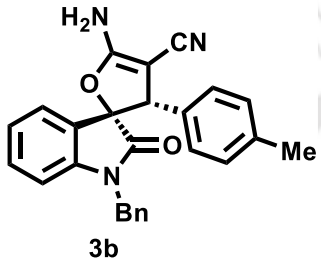
5.7 Characterization data of products



3a

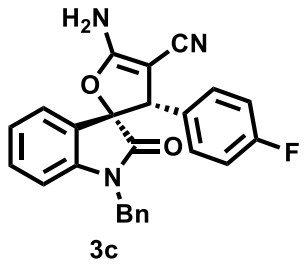
(2S,3S)-5-amino-1'-benzyl-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3a) was obtained as a yellow solid in 80% yield (15.7 mg) after column chromatography. M.P. = 197-198 °C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.81 (d, J = 7.2 Hz, 0.6H), 7.63 (s, 3H), 7.32 (qd, J = 14.9, 7.4 Hz, 8H), 7.21 – 7.07 (m, 7H), 7.02 (t, J = 7.9 Hz, 3H), 6.84 (d, J = 7.9 Hz, 1H), 6.69 – 6.59 (m, 3H), 6.47 (d, J = 7.1 Hz, 1H), 5.03 (s, 0.6H), 4.92 (q, J = 15.8 Hz, 2H), 4.78 (d, J = 16.0 Hz, 0.6H), 4.72 (s, 1H), 4.31 (d, J = 16.0 Hz, 0.6H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.5, 170.8, 170.3, 168.1, 168.0, 142.9, 142.3, 137.0, 135.8, 135.1, 134.4, 131.2, 130.5, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 127.6,

127.6, 127.2, 12.13, 126.4, 125.9, 125.6, 125.1, 123.6, 123.3, 122.2, 118.9, 109.5, 109.4, 88.5, 87.3, 59.7, 56.2, 53.8, 51.9, 51.5, 42.8, 42.3. **HPLC Analysis:** 95% ee (t_{major} = 32.5 min, t_{minor} = 53.7 min) and 86% ee (t_{major} = 36.9 min, t_{minor} = 81.4 min); Daicel Chiralpak ID Column, n-Hexane/ i-PrOH = 80/20, flow rate 1.0 mL/min, 25 ^{o}C, λ = 220 nm. **FT-IR (thin film):** 3435, 2187, 1647, 1489, 1468, 1454, 1421, 1376, 1301, 1265, 1178, 1118, 1078, 1011, 735, 699 cm^{-1}; **ESI HRMS:** calcd. For $C_{25}H_{20}N_3O_2[M+H]^+$ 394.1550, found 394.1556.



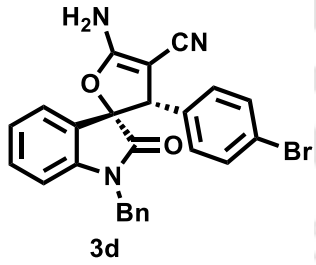
3b

(2S,3S)-5-amino-1'-benzyl-2'-oxo-3-(p-tolyl)-3H-spiro [furan-2,3'-indoline]-4-carbonitrile (3b) was obtained as a yellow sticky solid in 89% yield (18.1 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.80 (d, *J* = 7.2 Hz, 0.7H), 7.60 (s, 3H), 7.33 (dt, *J* = 13.1, 7.1 Hz, 6H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.13 – 7.05 (m, 3H), 7.00 (d, *J* = 7.9 Hz, 2H), 6.95 – 6.88 (m, 3H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.68 (dt, *J* = 12.7, 7.6 Hz, 2H), 6.51 (d, *J* = 7.4 Hz, 1H), 4.97 (s, 0.7H), 4.90 (dd, *J* = 18.0, 12.3 Hz, 2H), 4.80 (d, *J* = 16.0 Hz, 0.7H), 4.68 (s, 1H), 4.32 (d, *J* = 16.0 Hz, 0.7H), 2.30 (s, 2H), 2.18 (s, 3H). **^{13}C {1H} NMR (100 MHz, DMSO-d_6)** δ 174.0, 171.4, 168.5, 168.3, 143.3, 142.8, 137.6, 137.2, 136.2, 135.6, 134.4, 131.8, 131.6, 130.9, 129.2, 129.1, 129.0, 128.7, 128.0, 127.7, 127.6, 126.9, 126.4, 125.5, 124.2, 123.7, 122.7, 119.4, 110.0, 109.9, 89.0, 87.8, 56.5, 54.0, 52.6, 52.2, 43.3, 42.8, 21.2, 21.0. **HPLC Analysis**: 80% ee (t_{major} = 47.4 min, t_{minor} = 74.4 min) and 70% ee (t_{major} = 57.6 min, t_{minor} = 109.8 min); Daicel Chiralpak ID Column, n-Hexane/ i-PrOH = 75/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3449, 2923, 2187, 1660, 1468, 1077, 1019, 751, 704 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{22}N_3O_2[M+H]^+$ 408.1707, found 408.1716.



3c

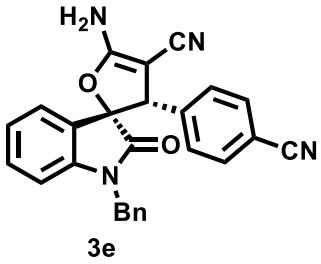
(2S,3S)-5-amino-1'-benzyl-3-(4-fluorophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3c) was obtained as a yellow solid in 84% yield (17.3 mg) after column chromatography. M.P. = 186-187 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.81 (d, J = 7.3 Hz, 0.6H), 7.66 (s, 3H), 7.39 – 7.28 (m, 6H), 7.19 (t, J = 7.4 Hz, 1H), 7.11 (dd, J = 12.2, 7.4 Hz, 4H), 7.08 – 7.00 (m, 5H), 6.86 (d, J = 7.9 Hz, 1H), 6.71 (t, J = 7.3 Hz, 2H), 6.61 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 7.3 Hz, 1H), 5.03 (s, 0.6H), 4.97 – 4.86 (m, 2H), 4.79 (d, J = 16.1 Hz, 0.6H), 4.74 (s, 1H), 4.36 (d, J = 16.0 Hz, 0.6H). **^{13}C {1H} NMR (150 MHz, DMSO-d$_6$)** δ 173.5, 170.8, 168.1, 168.0, 162.3, 161.2, 160.6, 142.8, 142.4, 135.8, 135.2, 133.5, 131.3, 130.6, 130.3, 130.2, 128.7, 128.3, 127.6, 127.3, 126.5, 125.9, 123.5, 123.4, 122.3, 118.9, 115.2, 115.1, 115.0, 109.7, 109.5, 88.4, 87.2, 55.4, 52.9, 51.9, 51.6, 42.9, 42.4, 40.0. **HPLC Analysis**: 94% ee (t_{major} = 45.8 min, t_{minor} = 59.8 min) and 86% ee (t_{major} = 51.5 min, t_{minor} = 92.2 min); Daicel Chiralpak IA Column, n-Hexane/ i-PrOH = 93/7, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3433, 2924, 2193, 1718, 1655, 1490, 1344, 1172, 1078, 969, 736, 655, 557 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{18}FN_3O_2[M+H]^+$ 412.1456, found 412.1460.



3d

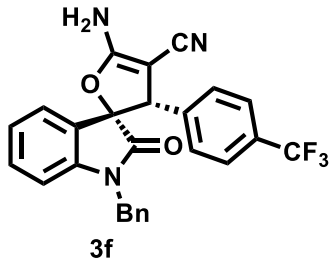
(2S,3S)-5-amino-1'-benzyl-3-(4-bromophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3d) was obtained as a yellow solid in 78% yield (18.4 mg) after column chromatography. M.P. = 184-185 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.86 (d, *J* = 7.1 Hz, 0.6H), 7.74 (s, 3H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.34 (m, 6H), 7.24 (t, *J* = 6.2 Hz, 3H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.80 – 6.74 (m, 2H), 6.69 (d, *J* = 7.1 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 5.08 (s, 0.6H), 5.02 – 4.91 (m, 2H), 4.88 (d, *J* = 16.0 Hz, 0.6H), 4.78 (s, 1H), 4.40 (d, *J* = 16.0 Hz, 0.6H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.3, 170.7, 168.1, 168.0, 142.8, 142.4, 136.7, 135.7, 135.2, 134.0, 131.3, 131.2, 131.1, 130.8, 130.7, 130.5, 128.7, 128.3, 127.6, 127.2, 127.0, 126.5, 125.9, 125.4, 125.2, 123.4,

122.3, 121.4, 120.7, 118.7, 109.7, 109.5, 88.2, 87.0, 55.5, 53.1, 51.6, 51.3, 42.9, 42.4, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.8. **HPLC Analysis**: 88% ee (t_{major} = 54.9 min, t_{minor} = 81.5 min) and 94% ee (t_{major} = 70.2 min, t_{minor} = 121.9 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 90/10, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3430, 2924, 2853, 2188, 1731, 1663, 1486, 1373, 1178, 1062, 1011, 813, 727, 639, 514 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{18}BrN_3O_2[M+H]^+$ 472.0655, found 472.0654.



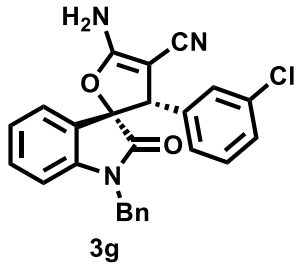
3e

(2S,3S)-5-amino-1'-benzyl-3-(4-cyanophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3e) was obtained as a pale white sticky solid in 83% yield (17.4 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.75 (d, *J* = 7.0 Hz, 3H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.15 (dd, *J* = 16.2, 7.6 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 0.4H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 2H), 5.15 (s, 0.3H), 4.93 (s, 2H), 4.87 (s, 1H), 4.77 (d, *J* = 15.9 Hz, 0.3H), 4.38 (d, *J* = 15.9 Hz, 0.3H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.2, 170.5, 168.3, 143.3, 142.8, 142.4, 140.5, 135.7, 135.3, 132.2, 131.5, 130.8, 129.6, 129.4, 128.7, 128.3, 127.3, 126.6, 125.8, 125.3, 123.5, 123.0, 122.3, 118.6, 118.5, 110.9, 110.4, 109.8, 109.6, 88.0, 86.9, 55.8, 53.3, 51.2, 50.9, 42.9, 42.5. **HPLC Analysis**: 98% ee (t_{major} = 56.2 min, t_{minor} = 30.4 min) and 97% ee (t_{major} = 40.1 min, t_{minor} = 35.2 min); Phenomenex Chiralpak LUX C1 Column, n-Hexane/ i-PrOH = 80/20, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3465, 2078, 1640, 1467, 1377, 1179, 699, 475, 458 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{19}N_4O_2[M+H]^+$ 419.1503, found 419.1521.



3f

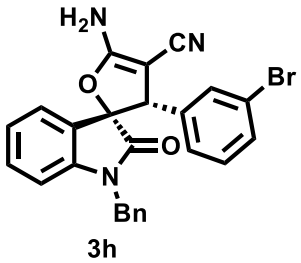
(2S,3S)-5-amino-1'-benzyl-2'-oxo-3-(4-(trifluoromethyl) phenyl) -3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3f) was obtained as a light yellow solid in 81% yield (18.7 mg) after column chromatography. M.P. = 186-187 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.84 (d, *J* = 6.9 Hz, 0.5H), 7.72 (d, *J* = 5.3 Hz, 3H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.31 (m, 5H), 7.30 – 7.13 (m, 6H), 7.13 – 7.06 (m, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 0.5H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.58 (dd, *J* = 13.7, 7.1 Hz, 2H), 5.16 (s, 0.5H), 4.97 – 4.88 (m, 2H), 4.87 (s, 1H), 4.80 (d, *J* = 15.9 Hz, 0.5H), 4.36 (d, *J* = 16.0 Hz, 0.5H. **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.3, 170.5, 168.2, 168.1, 142.8, 142.4, 142.1, 139.6, 135.7, 135.2, 131.4, 130.7, 129.6, 129.2, 128.7, 128.2, 127.6, 127.2, 126.4, 125.8, 125.4, 125.1, 123.5, 123.2, 122.2, 118.7, 118.6, 109.7, 109.6, 88.0, 87.0, 55.6, 53.3, 51.6, 51.1, 42.9, 42.5 **HPLC Analysis**: 80% ee (t_{major} = 13.6 min, t_{minor} = 19.0 min) and 52% ee (t_{major} = 21.9 min, t_{minor} = 28.9 min); Daicel Chiralpak ID Column, n-Hexane/ i-PrOH = 80/20, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3448, 2925, 2854, 2188, 1718, 1655, 1488, 1469, 1325, 1273, 1169, 1067, 1016, 752, 699, 630 cm^{-1}; **ESI HRMS**: calcd. For $C_{26}H_{19}F_3N_3O_2[M+H]^+$ 462.1424, found 462.1429.



3g

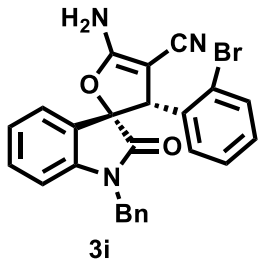
(2S,3S)-5-amino-1'-benzyl-3-(3-chlorophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3g) was obtained as a light yellow sticky solid in 81% yield (17.3 mg) after column chromatography. **^{1}H NMR (600 MHz, DMSO-d$_6$)** δ 7.80 (d, *J* = 7.3 Hz, 0.6H), 7.72 (s, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.1 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 4.6 Hz, 2H), 7.19 (dd, *J* = 14.2, 7.1 Hz, 2H), 7.16 – 7.12 (m, 2H), 7.07 (s, 2H), 7.05 – 7.02 (m, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 14.5, 7.5 Hz, 2H), 6.62 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 5.05 (s, 0.6H), 4.92 (dd, *J* = 39.9, 15.8 Hz, 2H), 4.82 (d, *J* = 15.9 Hz, 0.6H), 4.78 (s, 1H), 4.37 (d, *J* = 16.0 Hz, 0.6H). **^{13}C**

{1H} NMR (150 MHz, DMSO-d_6) δ 173.3, 170.6, 168.2, 168.1, 142.7, 142.4, 139.9, 137.2, 135.7, 135.2, 133.0, 131.4, 130.7, 130.1, 128.7, 128.5, 128.3, 128.1, 127.7, 127.6, 127.4, 127.2, 127.1, 126.4, 125.8, 125.4, 125.2, 123.5, 123.3, 122.3, 118.8, 109.7, 109.6, 88.2, 87.1, 55.5, 53.1, 51.4, 51.1, 42.9, 42.4, 40.0. **HPLC Analysis**: 98% ee (t_{major} = 64.2 min, t_{minor} = 17.9 min) and 31% ee (t_{major} = 32.9 min, t_{minor} = 14.2 min); Daicel Chiralpak IC Column, n-Hexane/ i-PrOH = 80/20, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3435, 2925, 2854, 2188, 1650, 1488, 1433, 1376, 1263, 1178, 1118, 1078, 1011, 793, 734, 698, 552 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}ClN_3O_2[M+H]^+$ 428.1160, found 428.1163.



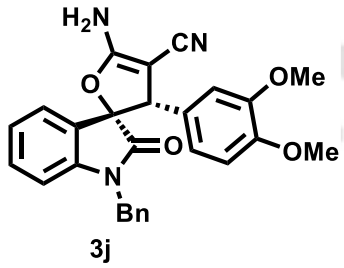
3h

(2S,3S)-5-amino-1'-benzyl-3-(3-bromophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3h) was obtained as an orange solid in 61% yield (14.4 mg) after column chromatography. M.P. = 183-184 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.79 (d, *J* = 7.2 Hz, 0.8H), 7.71 (s, 3H), 7.54 (d, *J* = 8.9 Hz, 0.8H), 7.34 (dd, *J* = 14.4, 7.2 Hz, 6H), 7.20 (d, *J* = 8.7 Hz, 3H), 7.18 – 7.12 (m, 4H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.73 (t, *J* = 7.9 Hz, 2H), 6.61 (d, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 6.4 Hz, 2H), 5.04 (s, 0.8H), 4.92 (q, *J* = 15.8 Hz, 2H), 4.82 (d, *J* = 16.0 Hz, 0.8H), 4.77 (s, 1H), 4.36 (d, *J* = 15.9 Hz, 0.8H). **^{13}C {1H} NMR (100 MHz, DMSO-d_6)** δ 173.3, 170.6, 168.2, 168.1, 142.8, 142.4, 140.1, 137.4, 135.7, 135.2, 131.4, 131.0, 130.7, 130.6, 130.4, 128.8, 128.5, 127.8, 127.6, 127.5, 127.2, 126.4, 125.8, 125.4, 123.3, 122.3, 121.6, 118.7, 109.7, 109.5, 88.2, 87.1, 55.4, 53.1, 51.5, 51.1, 42.9, 42.4. **HPLC Analysis**: 92% ee (t_{major} = 51.9 min, t_{minor} = 58.3 min) and 35% ee (t_{major} = 47.5 min, t_{minor} = 109.2 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 90/10, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3433, 2923, 2853, 2187, 1729, 1665, 1486, 1426, 1372, 1178, 1121, 1078, 1011, 846, 727, 698, 590, 561 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}BrN_3O_2[M+H]^+$ 472.0655, found 472.0652.



3i

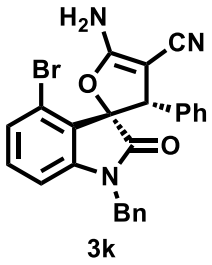
(2S,3S)-5-amino-1'-benzyl-3-(2-bromophenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3i) was obtained as a light yellow solid in 82% yield (19.4 mg) after column chromatography. M.P. = 189-191 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.73 (dd, *J* = 17.3, 8.9 Hz, 3H), 7.57 (d, *J* = 6.1 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.28 (m, 4H), 7.18 (dd, *J* = 9.9, 5.3 Hz, 3H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.79 (dd, *J* = 12.3, 6.0 Hz, 1H), 6.62 (t, *J* = 7.6 Hz, 1H), 6.22 (d, *J* = 7.4 Hz, 1H), 5.25 (s, 0.4H), 4.97 – 4.86 (m, 2H), 4.84 (s, 1H), 4.76 (d, *J* = 15.9 Hz, 0.4H), 4.47 (d, *J* = 15.9 Hz, 0.4H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.2, 170.3, 167.9, 167.9, 143.5, 142.6, 136.6, 135.6, 135.4, 134.7, 132.5, 131.1, 130.8, 130.0, 129.8, 128.6, 128.4, 127.9, 127.9, 127.7, 127.4, 127.3, 127.2, 126.8, 125.8, 125.1, 124.2, 123.4, 122.7, 122.1, 118.7, 109.6, 87.3, 86.1, 54.9, 52.5, 51.9, 50.9, 49.6, 43.0, 42.6. **HPLC Analysis**: 87% ee (t_{major} = 61.5 min, t_{minor} = 77.9 min) and 48% ee (t_{major} = 33.8 min, t_{minor} = 67.7 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 90/10, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3445, 2924, 2853, 2187, 1729, 1659, 1486, 1426, 1372, 1262, 1178, 1121, 1062, 1011, 812, 727, 698, 640, 419 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}BrN_3O_2[M+H]^+$ 472.0655, found 472.0656.



3j

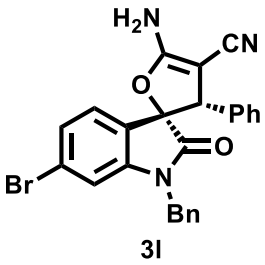
(2S,3S)-5-amino-1'-benzyl-3-(3,4-dimethoxyphenyl)-2'-oxo-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3j) was obtained as a light yellow sticky solid in 89% yield (20.2 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.79 (d, J = 6.9 Hz, 0.3H), 7.59 (s, 3H), 7.37 – 7.28 (m, 5H), 7.20 – 7.06 (m, 3H), 6.84 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.74 – 6.71 (m, 2H), 6.66 (dd, J = 8.0, 3.0 Hz, 1H), 6.52 (d, J = 6.5 Hz, 2H), 6.43 (d, J = 1.8 Hz, 1H), 5.00 (s,0. 3H), 4.95 (d, J = 3.7 Hz, 1H), 4.89 – 4.83 (m, 1H), 4.81 (s, 0.3H), 4.68 (s, 1H), 4.33 (d, J = 16.0 Hz, 0.3H), 3.73 (s, 1H), 3.65 (s, 3H), 3.46 (s, 3H), 3.45 (s, 1H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.7,

171.0, 170.3, 168.0, 167.8, 148.7, 148.3, 148.1, 143.0, 142.2, 135.8, 135.1, 131.1, 130.4, 129.2, 128.7, 128.2, 127.6, 127.2, 127.1, 126.3, 125.9, 125.7, 125.1, 123.9, 123.2, 122.3, 120.8, 120.2, 119.0, 112.1, 111.2, 109.5, 88.6, 87.5, 59.7, 56.1, 55.4, 55.3, 55.2, 55.2, 53.7, 52.1, 51.6, 42.8, 42.4. **HPLC Analysis**: 96% ee (t_{major} = 96.7 min, t_{minor} = 34.5 min) and 38% ee (t_{major} = 58.8 min, t_{minor} = 20.7 min); Daicel Chiralpak IC Column, n-Hexane/ i-PrOH = 70/30, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3437, 2925, 2853, 2185, 1633, 1496, 1425, 1376, 1260, 1210, 1178, 1079, 800, 751, 699, 636, 551 cm^{-1}; **ESI HRMS**: calcd. For $C_{27}H_{24}N_3O_4[M+H]^+$ 454.1761, found 454.1760.



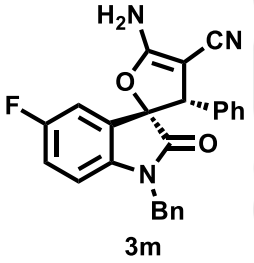
3k

(2S,3S)-5-amino-1'-benzyl-4'-bromo-2'-oxo-3-phenyl-3H-spiro [furan-2,3'-indoline]-4-carbonitrile (3k) was obtained as a creamy coloured solid in 93% yield (22.0 mg) after column chromatography. M.P. = 177-179 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.68 (d, *J* = 2.6 Hz, 3H), 7.38 (dd, *J* = 8.5, 3.9 Hz, 5H), 7.29 (t, *J* = 7.9 Hz, 3H), 7.18 – 7.11 (m, 3H), 7.06 – 7.00 (m, 7H), 6.95 (d, *J* = 7.2 Hz, 0.8H), 6.89 (d, *J* = 8.0 Hz, 0.8H), 6.73 (d, *J* = 7.5 Hz, 0.8H), 6.50 (d, *J* = 6.8 Hz, 2H), 5.23 (s, 0.8H), 4.96 (dd, *J* = 35.6, 15.6 Hz, 2H), 4.87 (s, 1H), 4.74 (d, *J* = 15.9 Hz, 0.8H), 4.29 (d, *J* = 16.0 Hz, 0.8H). **^{13}C {1H} NMR (100 MHz, DMSO-d_6)** δ 174.1, 170.2, 168.2, 167.8, 144.9, 144.1, 135.5, 135.4, 134.8, 134.4, 133.0, 132.0, 128.8, 128.7, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 127.5, 127.2, 127.1, 126.8, 126.5, 124.0, 123.8, 119.4, 119.2, 118.8, 118.6, 109.1, 108.9, 88.9, 88.7, 55.8, 53.2, 51.6, 51.4, 43.3, 42.6. **HPLC Analysis**: 97% ee (t_{major} = 42.8 min, t_{minor} = 48.0 min) and 77% ee (t_{major} = 39.3 min, t_{minor} = 55.2 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 85/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3433, 2924, 2853, 2188, 1732, 1662, 1486, 1454, 1373, 1262, 1178, 1121, 1062, 810, 727, 698, 639, 514 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}BrN_3O_2[M+H]^+$ 472.0655, found 472.0655.



3l

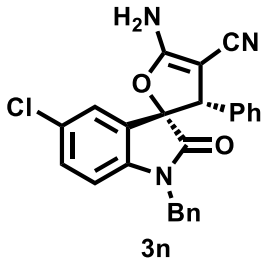
(2S,3S)-5-amino-1'-benzyl-6'-bromo-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3l) was obtained as a yellow solid in 82% yield (19.4 mg) after column chromatography. M.P. = 176-178 ^{o}C. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.80 (d, *J* = 8.0 Hz, 0.6H), 7.66 (d, *J* = 5.4 Hz, 3H), 7.41 – 7.36 (m, 3H), 7.30 (dd, *J* = 18.3, 7.5 Hz, 5H), 7.24 – 7.10 (m, 7H), 7.04 (d, *J* = 7.4 Hz, 3H), 6.94 – 6.85 (m, 2H), 6.54 (d, *J* = 8.0 Hz, 1H), 6.47 (d, *J* = 7.1 Hz, 1H), 5.04 (s, 0.6H), 4.94 (q, *J* = 15.8 Hz, 2H), 4.77 (d, *J* = 16.1 Hz, 0.6H), 4.73 (s, 1H), 4.37 (d, *J* = 16.0 Hz, 0.6H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.4, 170.7, 167.9, 167.8, 144.4, 143.9, 136.8, 135.5, 134.8, 134.1, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.2, 127.1, 126.4, 126.0, 124.9, 124.1, 123.5, 122.9, 118.7, 112.7, 112.4, 87.9, 86.7, 56.0, 53.7, 51.9, 51.4, 42.8, 42.3. **HPLC Analysis**: 97% ee (t_{major} = 31.8 min, t_{minor} = 35.0 min) and 71% ee (t_{major} = 42.6 min, t_{minor} = 58.4 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 85/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3436, 2925, 2854, 2187, 1663, 1486, 1454, 1427, 1372, 1262, 1178, 1121, 1062, 1011, 727, 698, 665, 443 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}BrN_3O_2[M+H]^+$ 472.0655, found 472.0656.



3m

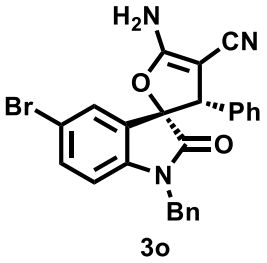
(2S,3S)-5-amino-1'-benzyl-5'-fluoro-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3m) was obtained as a yellow sticky solid in 98% yield (20.2 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.84 (d, *J* = 8.0 Hz, 0.7H), 7.66 (d, *J* = 5.3 Hz, 3H), 7.32 (qd, *J* = 14.7, 7.4 Hz, 8H), 7.23 – 7.10 (m, 6H), 7.05 (t, *J* = 6.6 Hz, 4H), 6.97 (t, *J* = 9.0 Hz, 1H), 6.86 (dd, *J* = 8.6, 4.2 Hz, 1H), 6.65 (dd, *J* = 8.6, 4.1 Hz, 0.7H), 6.44 (dd, *J* = 17.0, 7.7 Hz, 2H), 5.07 (s, 0.7H), 4.92 (q, *J* = 15.8 Hz, 2H), 4.79 (s, 0.7H), 4.74 (s, 1H), 4.31 (d, *J* = 16.0 Hz, 0.7H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.4, 170.7, 170.3, 168.0, 167.8, 159.9, 158.9, 157.5, 156.5, 139.1, 138.5, 136.8, 135.6, 134.9, 134.1, 128.7, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.6, 127.2, 127.1, 126.4, 125.3, 125.2, 118.8, 117.7, 117.4, 117.0, 116.7, 113.8, 113.5, 113.2, 110.6, 88.4, 87.0, 59.7,

56.1, 53.8, 51.9, 51.4, 43.0, 42.4. **HPLC Analysis**: 98% ee (t_{major} = 29.5 min, t_{minor} = 34.7 min) and 25% ee (t_{major} = 37.6 min, t_{minor} = 55.8 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 85/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3433, 2922, 2853, 2193, 1718, 1670, 1455, 1424, 1343, 1276, 1172, 1119, 1078, 1029, 880, 797, 736, 699, 611, 556, 468 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}FN_3O_2[M+H]^+$ 412.1456, found 412.1460.



3n

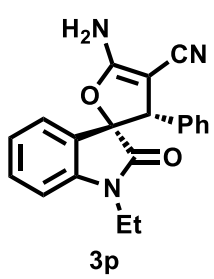
(2S,3S)-5-amino-1'-benzyl-5'-chloro-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3n) was obtained as a yellow sticky solid in 71% yield (15.2 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.99 (d, *J* = 2.1 Hz, 0.8H), 7.66 (d, *J* = 9.7 Hz, 3H), 7.41 – 7.26 (m, 9H), 7.24 – 7.15 (m, 4H), 7.12 (dd, *J* = 14.5, 7.1 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 3H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 0.8H), 6.52 (d, *J* = 2.1 Hz, 0.8H), 6.46 (d, *J* = 7.1 Hz, 2H), 5.08 (s, 0.8H), 4.93 (q, *J* = 15.8 Hz, 2H), 4.77 (d, *J* = 16.1 Hz, 0.8H), 4.73 (s, 1H), 4.32 (d, *J* = 16.1 Hz, 0.8H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.1, 170.5, 167.9, 167.8, 141.7, 141.2, 136.9, 135.4, 134.8, 134.1, 131.0, 130.3, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.4, 127.2, 127.2, 126.4, 125.9, 125.5, 125.4, 118.7, 111.1, 111.0, 88.1, 86.8, 59.7, 56.0, 53.7, 51.9, 51.4, 43.0, 42.4. **HPLC Analysis**: 71% ee (t_{major} = 30.4 min, t_{minor} = 33.1min) and 24% ee (t_{major} = 40.1 min, t_{minor} = 49.7 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 85/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3443, 2925, 2854, 2189, 1715, 1666, 1488, 1469, 1377, 1262, 1178, 1118, 1078, 1012, 794, 752, 698, 633, 552, 469 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}ClN_3O_2[M+H]^+$ 428.1160, found 428.1160.



3o

(2S,3S)-5-amino-1'-benzyl-5'-bromo-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (3o) was obtained as a yellow sticky solid in 89% yield (21.0 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 8.09 (d, *J* = 1.9 Hz, 0.7H), 7.66 (d, *J* = 11.1 Hz, 4H), 7.53 (d, *J* = 8.4 Hz, 0.7H), 7.39 – 7.27 (m, 9H),

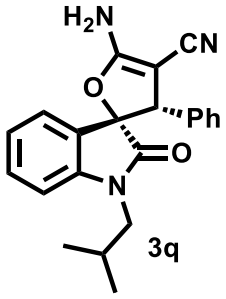
7.23 (dd, *J* = 16.4, 9.1 Hz, 3H), 7.13 (dt, *J* = 14.3, 7.6 Hz, 3H), 7.04 (d, *J* = 6.9 Hz, 4H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.64 – 6.59 (m, 2H), 6.45 (d, *J* = 7.2 Hz, 2H), 5.09 (s, 0.7H), 4.92 (q, *J* = 15.8 Hz, 2H), 4.77 (d, *J* = 16.1 Hz, 0.7H), 4.73 (s, 1H), 4.31 (d, *J* = 16.0 Hz, 0.7H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 173.0, 170.4, 167.9, 167.9, 142.1, 141.6, 136.9, 135.4, 134.7, 134.2, 133.9, 133.1, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.2, 127.2, 126.4, 125.6, 118.8, 118.7, 115.1, 114.0, 111.5, 111.4, 88.1, 86.8, 56.0, 53.7, 51.9, 51.4, 42.9, 42.4. **HPLC Analysis**: 75% ee (t_{major} = 31.1 min, t_{minor} = 33.8 min) and 23% ee (t_{major} = 40.6 min, t_{minor} = 50.1 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 85/15, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3434, 2923, 2853, 2187, 1729, 1664, 1486, 1426, 1372, 1262, 1178, 1121, 1062, 1011, 845, 813, 727, 639, 590, 561, 514, 458 cm^{-1}; **ESI HRMS**: calcd. For $C_{25}H_{19}BrN_3O_2[M+H]^+$ 472.0655, found 472.0654.



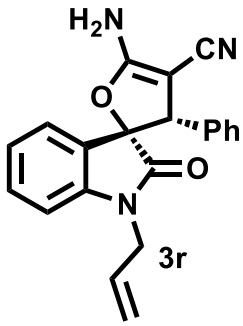
3p

(2S,3S)-5-amino-1'-ethyl-2'-oxo-3-phenyl-3H-spiro [furan-2,3'-indoline]-4-carbonitrile (3p) was obtained as a light yellow sticky solid in 80% yield (13.3 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.75 (d, *J* = 7.1 Hz, 0.6H), 7.59 (d, *J* = 7.5 Hz, 3H), 7.42 (t, *J* = 7.3 Hz, 0.6H), 7.23 – 7.14 (m, 7H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.99 – 6.94 (m, 2H), 6.92 – 6.87 (m, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 7.0 Hz, 1H), 4.89 (s, 0.6H), 4.63 (s, 1H), 3.71 (tt, *J* = 14.1, 7.0 Hz, 2H), 3.41 – 3.36 (m, 0.6H), 3.16 (dd, *J* = 14.1, 7.1 Hz, 0.6H), 1.15 (t, *J* = 7.2 Hz, 3H), 0.49 (t, *J* = 7.1 Hz, 2H). **^{13}C {1H} NMR (100 MHz, DMSO-d$_6$)** δ 172.9, 170.3, 168.3, 168.0, 142.6, 142.3, 137.2, 134.5, 131.2, 130.5, 128.2, 128.1, 128.1, 127.9, 127.7, 127.6, 126.0, 125.8, 124.8, 123.7, 123.0, 121.9, 119.0, 118.9, 108.9, 108.7, 88.6, 87.2, 56.7, 53.6, 51.4, 51.3, 34.3, 33.4, 12.2, 11.6. **HPLC Analysis**: 89% ee (t_{major} = 55.9 min, t_{minor} = 16.7 min) and 56% ee (t_{major} = 29.4 min, t_{minor} = 10.8 min); Daicel Chiralpak IC Column, n-Hexane/ i-PrOH = 70/30, flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm. **FT-IR (thin film):** 3442, 2979, 2189, 1714, 1666, 1489, 1469, 1422, 1374, 1269, 1208, 1160,

1103, 1029, 1010, 750, 700, 617, 554 cm^{-1}; **ESI HRMS**: calcd. For $C_{20}H_{18}N_3O_2[M+H]^+$ 332.1394, found 332.1398.

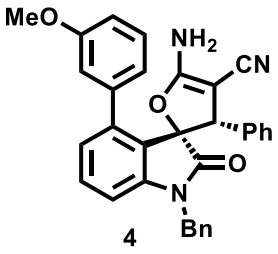


(2S,3S)-5-amino-1'-isobutyl-2'-oxo-3-phenyl-3H-spiro [furan-2,3'-indoline]-4-carbonitrile (3q) was obtained as a pale yellow sticky solid in 94% yield (16.9 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.76 (d, *J* = 7.1 Hz, 0.7H), 7.58 (d, *J* = 7.4 Hz, 3H), 7.41 (t, *J* = 7.3 Hz, 0.7H), 7.23 – 7.13 (m, 7H), 7.04 (d, *J* = 7.0 Hz, 2H), 7.00 – 6.93 (m, 3H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 6.8 Hz, 1H), 4.94 (s, 0.7H), 4.62 (s, 1H), 3.54 (dd, *J* = 13.8, 7.3 Hz, 1H), 3.44 (dd, *J* = 13.8, 7.5 Hz, 1H), 3.22 (dd, *J* = 13.8, 7.2 Hz, 0.7H), 2.97 (dd, *J* = 13.8, 7.4 Hz, 0.7H), 2.04 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.46 – 1.40 (m, 0.7H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.52 (d, *J* = 6.6 Hz, 2H), 0.35 (d, *J* = 6.7 Hz, 2H). **^{13}C {1H} NMR (100 MHz, DMSO-d_6)** δ 173.6, 170.9, 168.1, 168.0, 143.8, 143.1, 137.1, 134.6, 131.2, 130.5, 128.4, 128.2, 128.2, 128.0, 127.8, 127.6, 125.8, 125.8, 124.9, 123.5, 122.9, 121.9, 118.9, 109.3, 109.2, 88.3, 87.2, 56.2, 53.9, 51.7, 51.5, 46.7, 46.4, 26.5, 26.5, 19.8, 19.8, 19.7, 19.1. **HPLC Analysis**: 79% ee (t_{major} = 9.7 min, t_{minor} = 19.4 min) and 57% ee (t_{major} = 8.7 min, t_{minor} = 22.1 min); Daicel Chiralpak ID Column, n-Hexane/ i-PrOH = 70/30, flow rate 1.0 mL/min, 25 ^oC, λ = 254 nm. **FT-IR (thin film):** 3448, 2961, 2927, 2188, 1718, 1655, 1488, 1468, 1421, 1376, 1268, 1201, 1145, 1108, 1031, 1012, 752, 699, 611, 537 cm^{-1}; **ESI HRMS**: calcd. For $C_{22}H_{22}N_3O_2[M+H]^+$ 360.1707, found 360.1709.



(2S,3S)-1'-allyl-5-amino-2'-oxo-3-phenyl-3H-spiro[furan -2,3'-indoline]-4-carbonitrile (3r) was obtained as a yellow sticky solid in 96% yield (16.5 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 7.78 (d, *J* = 6.9 Hz, 0.6H), 7.60 (s, 3H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.24 – 7.13 (m, 7H), 7.05 (d, *J* = 6.9 Hz, 2H), 6.94 (dd, *J* = 6.4, 2.9 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 0.6H), 6.68 (t, *J* = 7.3 Hz, 1H), 6.57 (d,

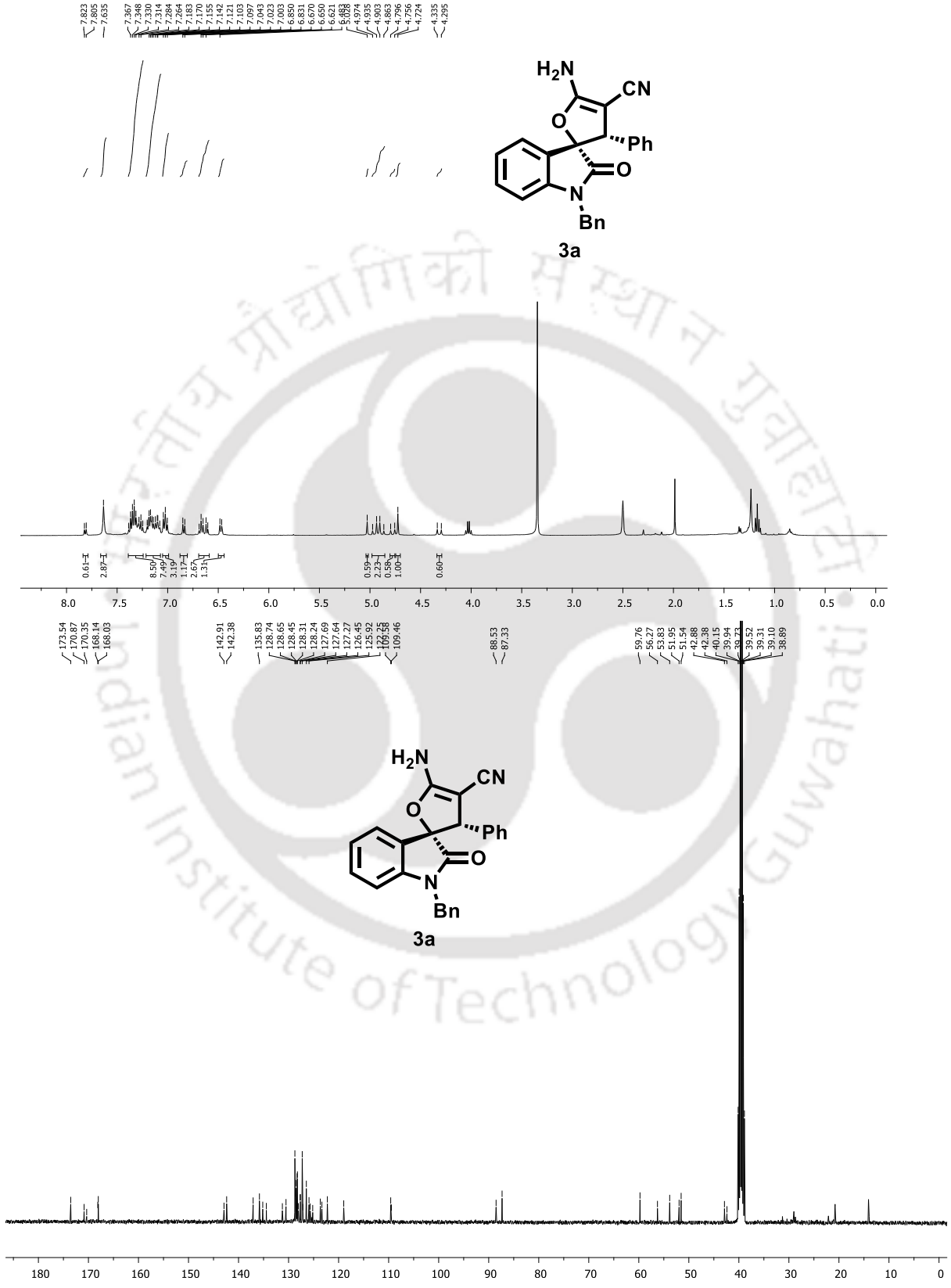
J = 6.9 Hz, 1H), 5.86 (ddt, *J* = 20.4, 10.2, 5.0 Hz, 1H), 5.28 – 5.21 (m, 0.6H), 5.16 (ddd, *J* = 18.5, 13.8, 1.2 Hz, 2H), 4.95 (s, 0.6H), 4.78 (d, *J* = 10.4 Hz, 0.6H), 4.65 (s, 1H), 4.42 – 4.25 (m, 3H), 4.07 – 4.01 (m, 0.6H), 3.77 (dd, *J* = 16.7, 5.4 Hz, 0.6H). **^{13}C {1H} NMR (100 MHz, DMSO-d_6)** δ 173.1, 170.5, 168.2, 168.0, 142.8, 142.4, 137.2, 134.5, 131.3, 131.1, 130.7, 130.4, 128.3, 128.2, 128.2, 128.0, 127.8, 127.6, 125.8, 125.7, 124.9, 123.5, 123.1, 122.1, 118.9, 118.9, 117.0, 116.2, 109.5, 109.3, 88.6, 87.2, 56.5, 53.6, 51.6, 51.5, 41.6, 41.0. **HPLC Analysis**: 80% ee (t_{major} = 11.0 min, t_{minor} = 21.8 min) and 53% ee (t_{major} = 10.0 min, t_{minor} = 23.6 min); Daicel Chiralpak ID Column, n-Hexane/ i-PrOH = 65/35, flow rate 1.0 mL/min, 25 °C, λ = 254 nm. **FT-IR (thin film):** 3433, 2924, 2186, 1637, 1488, 1468, 1422, 1381, 1278, 1182, 1134, 1009, 930, 725, 699, 611, 448 cm^{-1}; **ESI HRMS**: calcd. For $C_{21}H_{18}N_3O_2[M+H]^+$ 344.1394, found 344.1394.

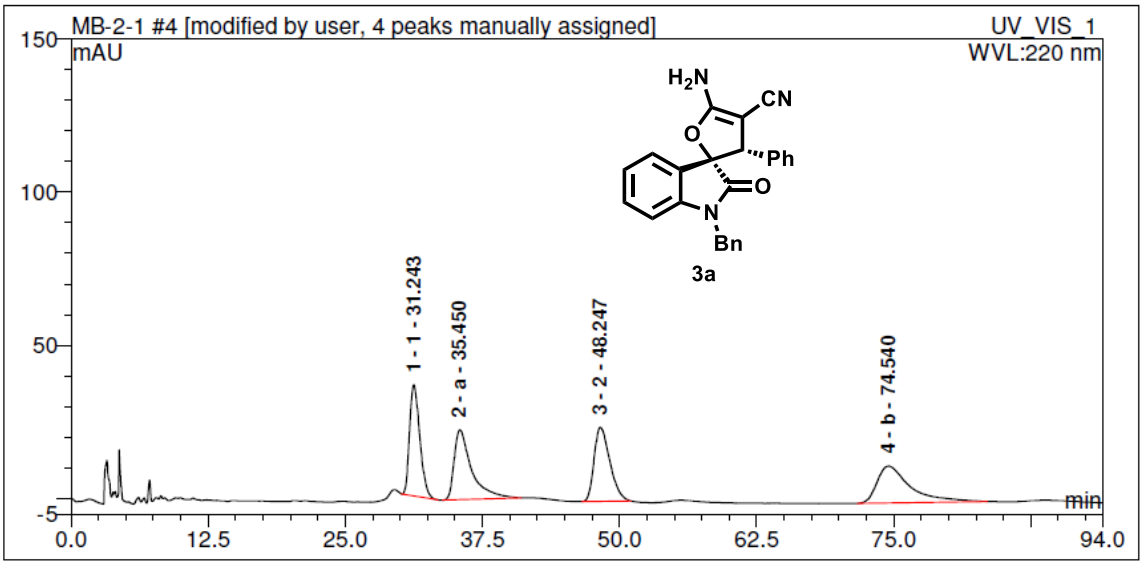


4

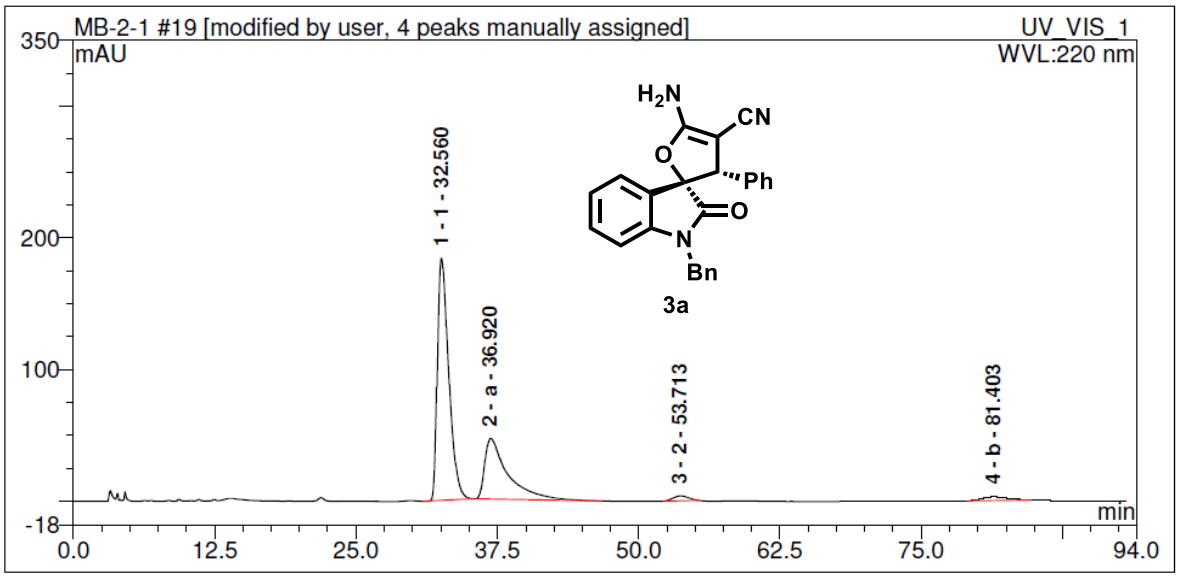
(2S,3S)-5-amino-1'-benzyl-4'-(3-methoxyphenyl)-2'-oxo-3-phenyl-3H-spiro[furan-2,3'-indoline]-4-carbonitrile (4) was obtained as a pale yellow sticky solid in 81% yield (20.2 mg) after column chromatography. **^{1}H NMR (400 MHz, DMSO-d_6)** δ 8.02 (s, 4H), 7.67 (s, 3H), 7.40 – 7.33 (m, 10H), 7.31 – 7.22 (m, 6H), 7.19 – 7.11 (m, 4H), 7.04 (t, *J* = 3.4 Hz, 6H), 6.95 (d, *J* = 7.0 Hz, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.53 – 6.48 (m, 2H), 5.23 (s, 0.8H), 4.96 (dd, *J* = 35.3, 15.6 Hz, 2H), 4.86 (s, 1H), 4.74 (d, *J* = 16.0 Hz, 0.8H), 4.29 (d, *J* = 16.0 Hz, 0.8H), 3.74 (s, 6.6H). **^{13}C {1H} NMR (150 MHz, DMSO-d_6)** δ 174.1, 170.2, 168.2, 167.8, 158.5, 144.8, 144.1, 135.5, 135.3, 134.7, 134.4, 133.0, 132.0, 128.8, 128.7, 128.7, 128.4, 128.3, 128.1, 127.8, 127.8, 127.6, 127.4, 127.2, 127.0, 126.8, 126.5, 126.3, 125.2, 124.0, 123.8, 119.4, 119.1, 118.9, 118.7, 118.5, 115.7, 109.0, 108.9, 88.8, 88.7, 55.8, 54.8, 53.3, 51.6, 51.5, 43.3, 42.6. **HPLC Analysis**: 75% ee (t_{major} = 80.3 min, t_{minor} = 89.8 min) and 38% ee (t_{major} = 72.5 min, t_{minor} = 104.5 min); Daicel Chiralpak IF Column, n-Hexane/ i-PrOH = 90/10, flow rate 1.0 mL/min, 25 °C, λ = 254 nm. **FT-IR (thin film):** 3434, 2925, 2189, 1807, 1730, 1666, 1605, 1495, 1453, 1424, 1343, 1282, 1169, 1143, 1079, 1030, 863, 770, 700, 632, 580 cm^{-1}; **ESI HRMS**: calcd. For $C_{32}H_{26}N_3O_3[M+H]^+$ 500.1969, found 500.1977.

5.8 Selected NMR and HPLC spectra of products

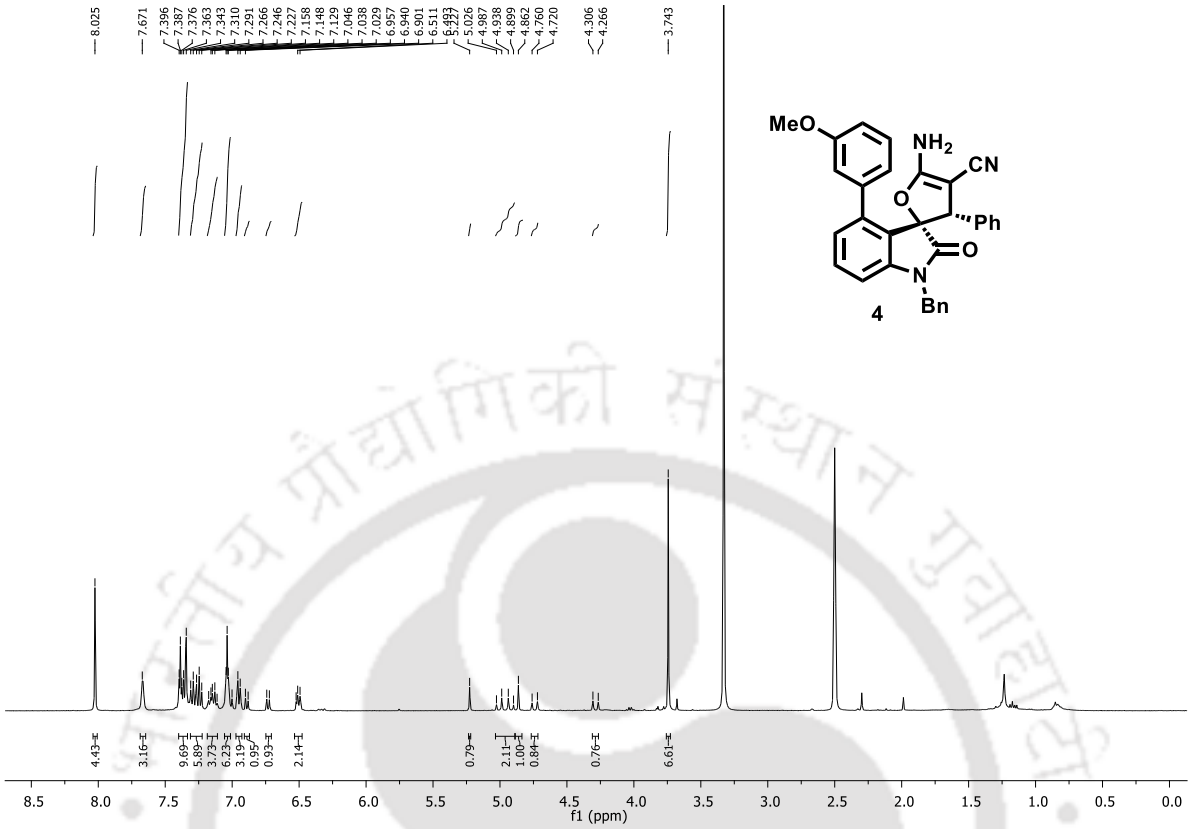


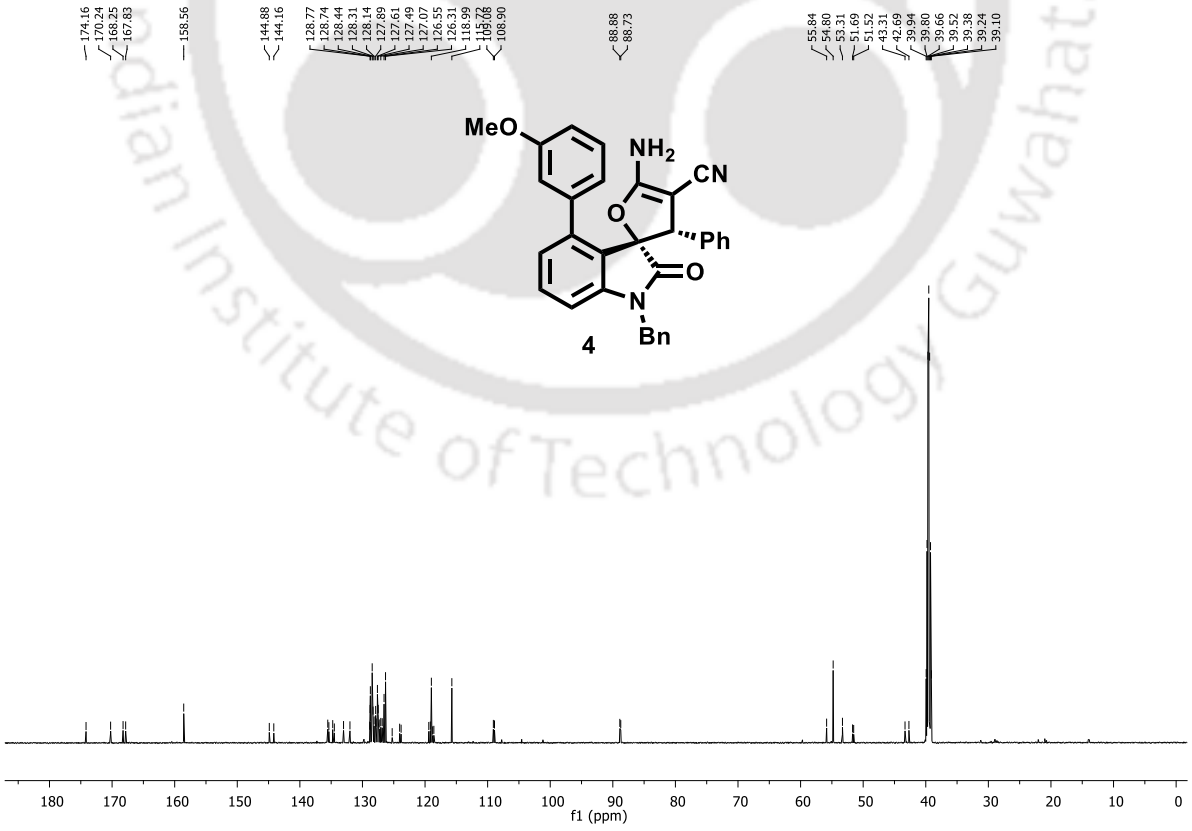


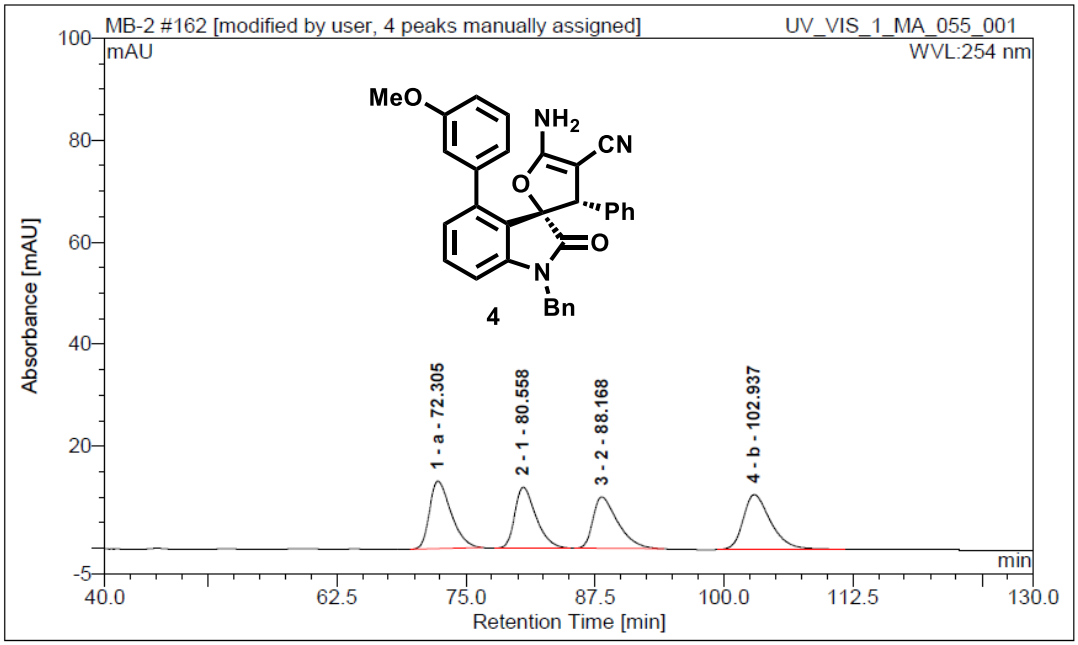
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	31.24	39.39308	24.066092	36.26502	n.a.
2	a	35.45	41.94765	25.62673197	22.6853	n.a.
3	2	48.25	40.30739	24.62465964	24.14593	n.a.
4	b	74.54	42.039	25.6825164	11.992	n.a.



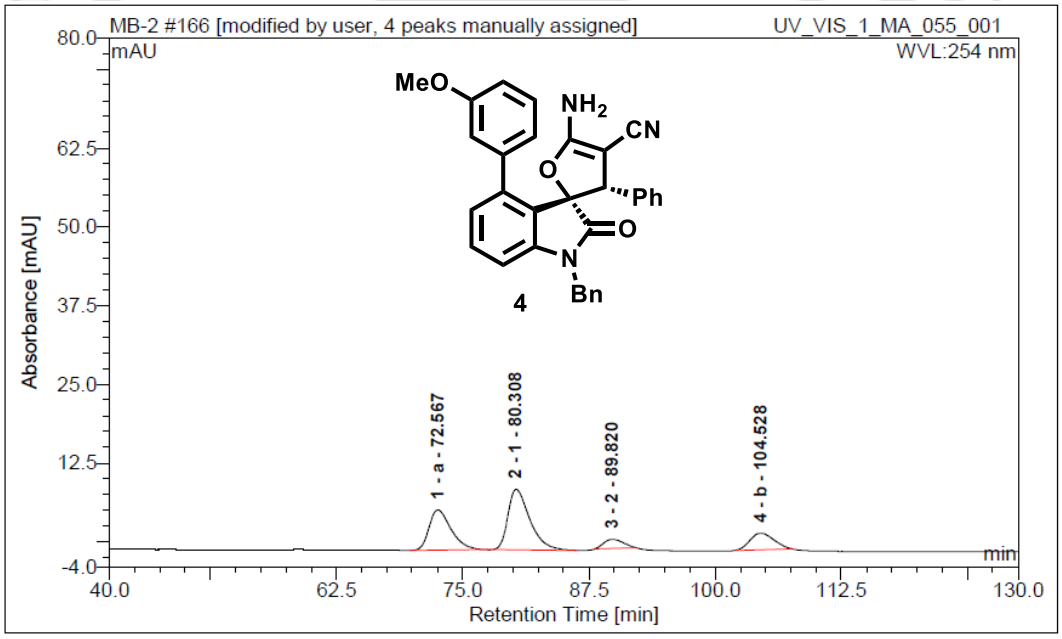
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	32.56	213.9057	63.59374561	183.7942	n.a.
2	a	36.92	108.8183	32.35146641	45.99431	n.a.
3	2	53.71	5.75005	1.709478435	3.61176	n.a.
4	b	81.40	7.889	2.345309546	2.744	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	72.31	32.14397	26.27168845	13.25209	n.a.
2	1	80.56	28.58012	23.35891001	11.93825	n.a.
3	2	88.17	28.28625	23.11872247	10.09305	n.a.
4	b	102.94	33.342	27.25067907	10.738	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	72.57	16.11166	31.66369477	6.37993	n.a.
2	1	80.31	24.21518	47.58927105	9.65086	n.a.
3	2	89.82	3.30546	6.496107787	1.48544	n.a.
4	b	104.53	7.251	14.2509264	2.625	n.a.

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List of publications

1. Organocatalytic Asymmetric Michael-Hemiacetalization Reaction Between 2-Hydroxyacetophenones and Enals: A Route to Chiral β,γ-Disubstituted γ-Butyrolactones, Balha, M.; Mondal, B.; Sahoo, S. C.; Pan, S. C. *J. Org. Chem.* **2017**, *82*, 6409.
2. Organocatalytic Asymmetric Synthesis of Highly Substituted Tetrahydrofurans and Tetrahydropyrans via Double Michael Addition Strategy, Mondal, B.; Balha, M.; Pan, S. C. *Asian J. Org. Chem.* **2018**, *7*, 1788.
3. Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton, Balha, M.; Pan, S. C. *J. Org. Chem.* **2018**, *83*, 14703.
4. Organocatalytic Asymmetric Synthesis of Bridged *O,O*-Ketals with Spirooxindole Motif, Balha, M.; Soni, C.; Pan, S. C. *Eur. J. Org. Chem.* **2019**, 2552.
5. Organocatalytic asymmetric synthesis of dihydrofuran-spirooxindoles from benzylidene malononitriles and dioxindoles, Balha, M.; Mondal, B.; Pan, S. C. *Org. Biomol. Chem.* **2019**, *17*, 6557.
6. Organocatalytic asymmetric spirocyclization reactions of cyclic 2,4-dienones with cyanoketones: synthesis of spiro-dihydropyrano cyclohexanones, Mondal, B.; Balha, M.; Pan, S. C. *Org. Biomol. Chem.* **2019**, *17*, 7849.

Conferences Attended

1. Presented a poster in **CRSI National Symposium in Chemistry-2017** held at Gauhati University, Guwahati, India.
2. Presented a poster in **International Conference on Chemistry for Human Development (ICCHD-2018)** held at Heritage Institute of Technology, Kolkata, India.
3. Presented a poster in **National Organic Symposium Trust (JNOST-2018)** held at CSIR- Indian Institute of Chemical Technology Hyderabad, India.